Chapter 1
Epidemiology and risk assessment
The word epidemiology is derived from Greek: epi means on, above, over, demos means people and logos means study. It is the science of understanding factors related to the occurrence of disease among groups of people. Cancer epidemiology is an analytical discipline focusing on the pattern of distribution of neoplasia in humans and primarily is concerned with disease as it manifests itself in populations rather than individuals.

**NATURAL HISTORY**

The natural history of breast cancer is characterized by long duration and marked heterogeneity within and among patients. Breast cancer is among the slower growing tumors, and the preclinical period before diagnosis and the clinical phases after initial treatment and even after the appearance of metastasis are measured in years or decades.

**MAGNITUDE OF THE PROBLEM**

Breast cancer is the most common cause of cancer death among women worldwide. Incidence rates are high in more developed countries, whereas rates in less developed countries and in Japan are low but increasing (Figure 1.1). In the world, each year more than 1 million women are diagnosed with breast cancer and more than 400,000 die from it. Breast cancer represents 30% of cancer new cases in developed countries and 14% in developing countries.

![Figure 1.1. Worldwide variation in breast cancer rates (data from Globocan 2002)](image)

Among migrants from low-risk to high-risk countries, the rates increase and eventually become similar to those among the rest of the population in the new country. In western
countries, rates of breast cancer increased from the early 1900s to the late 1990s, and rates in Japan have increased during the past 30 years. A very recent stop in the increase is observed in the USA and in some North European countries. The more recent increase could be partially due to the introduction of screening by mammography, because similar changes have also been observed in non-western countries where screening for breast cancer was introduced.

By contrast, mortality from breast cancer in the western life style countries, and several other countries fell since the 1990s. This fall is probably due mainly to improvements in diagnosis and treatment rather than changes in the underlying epidemiology of the disease.

In Egypt, data reported by the Gharbiah population based cancer registry (2001) indicated that breast cancer ranked first among females (37.6%), with an age-standardized rate of 49.6/100000. On the other hand, carcinoma of the male breast was only 0.5% (figure 1.2). A study of migrant from the Middle East to Australia did indicate that the Egyptian women had the highest breast cancer rates of Middle Eastern immigrants.

![Figure 1.2](image)

**Figure 1.2** Incidence of breast cancer by age in Egypt (*from the Gharbiah registry*)

**RISK FACTORS**

1. **Menarche and Menstrual Cycle**
The older the age of menarche is, the lower the risk of breast cancer. For each one-year delay in menarche, the risk decreases by around 5%. Other menstrual factors such as cycle length and regularity have not been consistently related to breast cancer risk.

2. Parity and Age at First Birth
Compared with nulliparous women, women with at least one full-term pregnancy have, on average, around a 25% reduction in breast cancer risk. Increasing protection is also seen with increasing numbers of full-term pregnancies, so that women with five or more children have about half the risk of nulliparous women.

The younger the age at first birth the greater the protection against breast cancer, this effect is independent of the total number of pregnancies. The exposure of the mammary gland to sex hormones before a full-term pregnancy is critical because the breast tissue is especially susceptible to carcinogens due to the immaturity of the cells. A first child after 38 years old increases the risk by 2 fold as compared to nulliparous women. The tendency, in western countries, to delay the 1st pregnancy explains a part of the growing incidence of the last 30 years. Evidence about incomplete pregnancies, is less clear but suggests no large effect on breast cancer risk.

3. Breast Feeding
The relation between breast-feeding and breast-cancer risk has been examined in many studies; some have reported no association and others a reduced risk, particularly among pre-menopausal women. Recent studies in less developed countries where the total duration of breast feeding can be very long, have reported clear protective effects. Protection has also been seen in some, but not all, studies in more developed countries. For example, the US Cancer and Steroid Hormone Study found that breast feeding for a total of 25 months or more reduced the risk of cancer by 33% in over 4500 women studied.

4. Menopause
The age-specific incidence curve of female breast cancer suggests that the menopause has a protective effect. The relative risk of developing breast cancer for a woman with natural menopause before age 45 is 0.73 compared with a woman with natural menopause between the ages of 45 and 54. The risk increases by about 3% for each year older at menopause. The magnitude of this effect is similar whether menopause occurs naturally or as a result of bilateral oophorectomy.
5. **Endogenous Hormones**
For menopausal women, studies examining the relation between serum concentrations of hormones and breast cancer have shown a positive association. Postmenopausal women with high serum free estradiol levels have a risk around twice that of women with lower concentrations. Few data are available for pre-menopausal women, and the results are inconclusive. A positive relation has also been observed in some studies with other sex hormones, prolactin, and insulin-like growth factor 1.

6. **Oral Contraceptives**
A 25% increase in the risk of breast cancer is being observed in users of oral contraceptives, particularly when used before the first pregnancy during more than 4 years. But this risk drops after cessation of use so that at 10 years post use, there is no significant increase in risk.

7. **Hormonal Therapy for the Menopause**
Hormone replacement therapy (HRT) long term users (>5 years) are at higher risk (1.5-2 fold) than women who have never used these treatments. The risk is higher with combined regimen of estrogen and progestin than with estrogen alone (if any) and increases with increasing duration of use. Excess risk diminishes after cessation of use to be nullified at 5 years post use of hormonal therapy for the menopause. Recent estimates suggest that 10 years of use of hormonal therapy for the menopause from age 50 to 60 would result in a cumulative excess incidence of 6 breast cancer cases per 1000 women from age 50 to age 70. This estimate relates largely to the use of estrogen alone, and use of combined estrogen and progestagen preparations have a greater effect. The use of other exogenous hormones for treatment of fertility such as clomiphene citrate, human menopausal gonadotropins, and gonadotropin releasing hormone, has been examined in many studies. Most studies have not detected any increase in risk, but they have been hampered by small numbers and inability to account for important confounding factors.

8. **Benign Breast Disease and Mammographic Parenchymal Patterns**
Benign breast disease may be classified into non-proliferative and proliferative lesions. Proliferative lesions may be without or with atypia. Non-proliferative lesions are generally associated with little or no increase in breast cancer risk. Proliferative lesions without atypia confer a two-fold increase in risk, while atypical hyperplasia confers an increase of at least four-fold risk when compared
with women without benign breast disease. High breast density, as reflected on mammography films, has been shown to be one of the most significant markers of breast cancer risk. Dense breast tissue probably reflects high hormonal exposure and is typical of young women, women using hormone replacement therapy, and those who are BRCA gene carriers.

9. Diet
The best data on the hypothesis that higher-fat diet increases breast cancer risk come from a pooled analysis of seven prospective studies and they do not indicate any association. Other possible dietary factors such as consumption of meat, fiber, fruit and vegetables, and phyto-estrogens have also been studied, there may be a moderate protective effect for a high consumption of vegetables but results for meat, fiber, and fruit are inconsistent. Alcohol consumption, on the other hand, is associated with an increase of 25-40% in the risk of breast cancer. Many studies have examined the relation between smoking and breast cancer risk. A recent meta-analysis showed a risk for passive smoking exposure of 1.7 in pre-menopausal breast cancer and 1.3 in postmenopausal. If active smoking is added the risks slightly increase.

10. Body size and weight
Adult heights show a positive association with breast cancer risk. In postmenopausal women, obesity increases the risk of breast cancer by 2% per unit of BMI. The effect of large gain weight after the age of 18 years has been shown to be an independent risk factor. A few studies have reported that pre-menopausal breast cancer risk is increased in women whose birth weight was high.

11. Exercise
A women’s level of physical activity can have an impact on breast cancer risk. Moderate physical activity is associated with a lower risk of post-menopausal breast cancer so that there is a 30% reduction in risk in association with a few hours/week of vigorous activity versus none.

12. Ionizing Radiation
Epidemiologic studies have shown that women exposed to ionizing radiation due to nuclear war or medical diagnostic and therapeutic procedures are at increased risk for the development of breast carcinoma. There is a long latent period for radiation induced breast cancer, and the risk of developing the disease is related
to the age at radiation exposure (risk is greater <20 years old), or before a full-term pregnancy.

Girls irradiated during infancy for thymic enlargement had a linear dose-response risk for subsequent breast cancer development. A cumulative effect due to repeated chest scan or even mammography cannot be eliminated particularly in mutated genes carriers.

13. Electromagnetic Fields
Increased exposure to extremely low frequency electromagnetic fields and to artificial light at night have been suggested as factors for increased breast cancer risk, by decreasing nocturnal melatonin secretion. However, current evidence is not persuasive of an increase.

14. Environmental Estrogens
Some man-made chemicals, such as organochlorines e.g. DDT and PCBs have structural similarities to endogenous estrogens, and can bind to estrogen receptors. However, several studies could not prove any association between these compounds and increased risk of breast cancer.

15. Family History and Genetic Factors
Environmental and life style factors rather than inherited genetic factors accounts for most cases of familial breast cancer (75% in a recently published Nordic study on 45,000 pairs of twins). However, familial aggregation can also be attributed in part due to shared physical environmental and lifestyle factors. In most studies, there is a two-fold increase in risk for first-degree relatives i.e. mother, sister, daughter, and a lesser increase in second-degree relatives i.e. grand-mother, aunt, grand-daughter. An established proportion (5%) of all breast cancer cases is caused by mutations in specific genes. At least five germ line mutations predisposing to breast cancer have been identified. These include BRCA1, BRCA2, p53, PTEN and ATM.

High-risk alleles probably account for most of the families with four or more breast cancer cases, for around 20%-25% of the familial breast cancer risk overall, and for about 5% of all breast cancers.

**PREVENTION OF BREAST CANCER**
1. Life Style
Behavioral risk factors could be modified, and these changes would reduce the risk of breast cancer. So, avoidance of obesity and late pregnancy (after 35 years), limitation of alcohol intake, increase of breast feeding, and keeping of at least moderate physical activity throughout life may reduce breast cancer risk.

2. Hormonal Therapies
The overall effect of long oral contraceptive use in young women before a 1st child and of women using hormone replacement therapy can be kept to a minimum by using the smallest possible dose, and shortest duration of both estrogens and progestagens to produce only the positive effects when necessary. Two years after the reduction by more than 60% of the use of HRT in the USA, a decrease in the incidence of post menopausal breast cancer has been observed (2004); such a decline is now observed in France (2007).

3. Chemoprevention
During the past century, a link has been established between estrogen and breast cancer. However, the development of anti-estrogenic drugs over the past few decades has changed the prospects for prevention, and the target for intervention became the estrogen receptors. But if estrogen is also essential for women to maintain bone density, then the long-term administration of an antiestrogen would provide no overall health benefit, despite breast cancer prevention. Tamoxifen was selected for testing for chemoprevention in high-risk women in early 1990s. For women who have already had one primary breast cancer, the risk of a second primary in the contralateral breast has been shown to be reduced by as much as 40% with the use of adjuvant tamoxifen. The NSABP P-1 Project compared prophylactic tamoxifen with placebo in high risk females assessed by the Gail’s model, and found that tamoxifen reduced the risk of invasive cancer by 49% during a median follow-up of 55 months. Conversely, recent interim report of two European trials showed that tamoxifen prophylaxis did not reduce the incidence of breast cancer significantly. Possible explanations for those conflicting data include the use of different numbers of patients, their ages, their risk levels, lengths of follow up, and the allowance of the use of hormone replacement therapy in the European studies. So, the larger number of patients in NSABP P-1 trial and its prohibition of hormone replacement therapy add to the strength of its findings. However, the study also confirmed the association between tamoxifen and the increase incidence of endometrial carcinoma (2.3/1000 per year) and of various other side effects (cardio-vascular, hepatic,…).
Of note, in a recent study, the risk of invasive breast cancer was decreased by 76% during 3 years of a new selective estrogen receptor modulator (SERM) called raloxifene amongst postmenopausal women with osteoporosis. Another randomized clinical trial on postmenopausal volunteers determined to be at elevated risk for breast cancer has shown a reduction of the breast cancer rate in women with positive estrogens receptors, after 8 years of follow-up (RR= 0.34), but side effects (endometrial cancer and stroke) are still observed. New molecules (anti-aromatase) are now tested, but they have also side effects (muscular and articulation pains) and are not active on osteoporosis.

4. Prophylactic Mastectomy
For women at high genetic risk of breast cancer, it is not all uncommon for surgeons dealing with breast disease to be confronted with the issue of prophylactic mastectomy. The recent advances in understanding the genetic basis of susceptibility to breast cancer and a better identification of the histological factors affecting a women’s lifetime risk of developing breast cancer have contributed to placing prophylactic mastectomy in a proper clinical perspective. Prophylactic mastectomy is the surgical removal of the breasts, when no breast cancer is present, to reduce the risk of breast cancer. A bilateral prophylactic mastectomy refers to the removal of both breasts; a contralateral prophylactic mastectomy refers to the removal of unaffected, contralateral breast in a woman who had a therapeutic mastectomy for a first breast cancer. Reconstruction??

Existing data suggest that prophylactic total mastectomy significantly reduces, but does not totally eliminate the risk of subsequent development of cancer. However, the benefit of prophylactic mastectomy over alternative strategies (surveillance and chemoprevention) remains to be proven. Currently, prophylactic mastectomy may be considered in a few carefully selected patients. The decision to perform a prophylactic mastectomy should be a multidisciplinary one. Detailed patient counseling is very important; the patient should understand the limitations of prophylactic mastectomy and the need for postoperative follow-up. Furthermore, she should be well informed about the alternative strategies. In the following table (1.1), each of the options available as breast cancer risk reduction strategies for women with high risk of developing the disease is listed with its unique advantage and disadvantages.
<table>
<thead>
<tr>
<th>Approach</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Surveillance</td>
<td>• Preserves breast tissues</td>
<td>• Does not prevent disease</td>
</tr>
<tr>
<td></td>
<td>• Allows other options</td>
<td>• Effectiveness in detecting disease early in young, high-risk women is unknown</td>
</tr>
<tr>
<td></td>
<td>• No intervention for those who do not develop cancer</td>
<td>• Adherence is unknown</td>
</tr>
<tr>
<td>Prophylactic mastectomy</td>
<td>• Reduces breast cancer risk significantly, apparently long-term</td>
<td>• Loss of breast tissue</td>
</tr>
<tr>
<td></td>
<td>• Tissue-specific intervention</td>
<td>• Irreversible decision: reconstruction?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Major surgical intervention</td>
</tr>
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<td></td>
<td></td>
<td>• Treats women who would not have developed cancer</td>
</tr>
<tr>
<td>Prophylactic oophorectomy</td>
<td>• Reduce breast cancer risk</td>
<td>• Premature menopause with systemic effects</td>
</tr>
<tr>
<td></td>
<td>• Preserves breast tissue</td>
<td>• Replacement estrogen may affect breast cancer risk; SERMs have attendant side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Treats women who would not have developed cancer</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>• Reduces risk, but results conflicting</td>
<td>• Systemic side effects</td>
</tr>
<tr>
<td>Raloxifen Anti-aromatase</td>
<td>• Preserves breast tissue</td>
<td>• Magnitude of risk reduction in women with inherited risk is unclear</td>
</tr>
<tr>
<td></td>
<td>• Allows other options</td>
<td>• Duration of risk reduction unclear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Treats women who would not have developed cancer</td>
</tr>
</tbody>
</table>

*Table 1.1.* Breast cancer risk reduction strategies for high genetic risk women
Chapter 2
Breast Cancer Screening
Breast cancers account for about 30% of cancer deaths in women in developed countries, and about 15% in developing countries, this is therefore an important public health problem. Primary prevention should be given highest priority in the fight against cancer; however, the reduction in breast cancer incidence, which can be achieved by primary prevention, based on present knowledge of risk factors, is limited. The early detection of cancer encompasses the detection of cancer in individuals who exhibit signs and symptoms in the evolution of the disease, as well as the detection of cancer (or precancerous lesions) in apparently healthy populations.

**Early detection programs for cancer have two components:**

1) early diagnosis, based on awareness (by the public or health professionals) of the signs and symptoms of cancer which can result in substantial improvement in the outcome of persons destined to develop cancer if they are adequately treated,

2) screening, based on the presumptive identification in an apparently asymptomatic population of either precancerous lesions or very early stage cancers by means of tests, followed by effective treatment for the lesions detected. Both approaches involve costs to the individual (in terms of time spent, distance traveled, possible cash payments for detection/diagnosis) and the health services (manpower, subsidies for detection/diagnosis, treatment, follow-up), and may be associated with undesired harm. It is important to establish that the benefits of early detection outweigh complications and harmful effects before implementation of one or the other type of early detection as a cancer control policy.

Thus a decision to implement early detection of cancer should be evidence-based, depending on the burden of the disease, efficacy and cost-effectiveness of each early detection solution and the level of development of health services in a given setting. The latter is particularly important in low resource settings, as the whole process may involve substantial costs and risk diversion of resources from other health-care activities. It is important to bear in mind that interventions for the early detection of cancer can help reduce mortality from cancer only if they are part of a wider cancer control strategy that offers individuals appropriate diagnostic procedures and effective treatment and follow-up.
These activities need to be integrated at appropriate levels of health services and specific additional investments in health service infrastructure are required to cater for the additional cases resulting from early detection.

Systematic mammographic screening (any radiographic examination of the breasts of asymptomatic women) to detect breast cancer is a public health measure, which has aroused increasing interest in many countries of the world. Apart from mammography, physical examination by a physician or nurse, breast self-examination, ultrasound, thermography, diaphanography, computed tomography and magnetic resonance imaging have been used to detect breast cancer.

Evidence of the efficacy of breast cancer screening by mammography for post-menopausal women has been provided by several randomized trials, but the effectiveness of screening on the reduction of deaths from breast cancer in pre-menopausal women is still controversial.

Furthermore the question remains as to whether the benefit of screening, when applied in routine to large asymptomatic populations, justifies the risks and the costs. Most of these women would not in their lifetime have developed breast cancer and therefore, would not benefit individually from reduction of breast cancer mortality but may well experience adverse effects. The numerous pilot programs undertaken throughout the world will undoubtedly provide the experience indispensable for the implementation of routine wide spread programs. Policy recommendations should be established after a three dimensional evaluation: epidemiologic, medical and economic.

**Epidemiology: Potential Efficiency**

The first requirement for the justification of a population based screening program is the importance of the public health problem caused by the disease, i.e. the disease should be relatively frequent and have serious consequences.

Before implementation of a breast cancer screening program, national morbidity and mortality rates should be considered. Cost-effectiveness of screening clearly depends on the prevalence of the disease (number of undiagnosed cases in the population at the time of screening). The higher the prevalence, the higher the detection rate at the same cost. A low incidence rate will give a low prevalence and then, the cost for the whole population could become unacceptable. Many countries, would exclude breast cancer screening programs with mammography from their priorities on the simple grounds of efficiency, due to the epidemiological
situation. Society should not use resources for cancer screening programs unless there is strong evidence showing that there is a clear benefit for the population. Another important indicator to consider is the stage at diagnosis: if the majority of breast cancers are advanced cases (stage 3 or 4) at first presentation it is not appropriate to undertake a screening program, but to promote measures for earlier diagnosis, referral and access to care.

**Medical: Effectiveness**

The aims of mammographic screening are to detect cancer at “stage 0” (before symptoms) where more effective and less aggressive treatment can be offered. Any medical evaluation should cover, reduction of the number of cases of late-stage disease, deaths from breast cancer, side-effects such as unnecessary check-ups or treatments, and potential impact of the program on the general health of the target population, such as potential years of life saved weighed by quality of life.

The evaluated screening tests for breast cancer include mammography, physical examination of the breasts (Breast Clinical Examination: BCE), and Breast Self Examination (BSE). These 3 types of test for Breast cancer screening have been evaluated by randomized control trials and case-control studies. The 2002 IARC review concluded that there was sufficient evidence that mammography alone in women age 50-69 reduced mortality from breast cancer. The expert also concluded that the evidence in women age 40-49 is limited. In fact the cut off point is the menopause which influences the sensitivity and specificity of the mammography due to change in the density of the breasts.

The magnitude of the reduction using mammography alone in risk of breast cancer death ranges from 6%, to 48%, with an overall estimate of +25% (95% CI: +33% to +15%), for women aged 50 to 69 years. The overall estimate of reduction in risk for women aged 40 to 49 years is +19% (95% CI: +35% to -1%), and ranges, in the different studies, from +42% to -48%. The results in women aged 50-69 years were statistically significant regardless of, the number of views per screen (one or two), the screening interval (18 to 33 months), the duration of follow up, or the addition of a clinical breast examination. For women aged 40 to 49 years followed for 7 to 9 years, there was no significant risk reduction in breast cancer mortality as well as for women followed for more than 10 years.

Thus, it appears that no benefit is observed for younger women until 10 to 12 years of follow-up, by which time women who were 40 to 49 years when entering the
study are 50 to 61 years of age and mostly in a post-menopausal phase when a mammography becomes more sensitive.

These findings suggest that it might be possible to begin mammographic screening of menopausal women only of women aged 50 or more. This is a major problem for many developed countries where, because of their populations pyramids, breast cancer is relatively more frequent in women age 40-49.

Detection by Clinical Breast Examination tends to diagnose breast cancer at an earlier stage than those not detected by screening. Some epidemiological studies (in Japan) suggested that CBE reduces mortality from breast cancer. In the Canadian breast screening trial (CNBSS2) mortality from breast cancer was similar among women who received combined screening (mammography + CBE) and those who had only CBE. The CNBSS2 trial demonstrated that mammography results in the diagnosis of in situ carcinomas and good prognosis small invasive carcinomas that do not impact upon breast cancer mortality, providing a woman is having regular good breast physical examination. This result was re-enforced by a model-base evaluation, that suggested that CBE resulted in a 20% reduction in breast cancer mortality. There is preliminary indication from the Egyptian trial that stage shift towards more limited disease is being achieved by such screening (A.Miller).

Breast self examination (BSE) has intuitive appeal since it should result in earlier diagnosis if practiced regularly. However, it has proved to be difficult to adequately perform it and 2 large randomized trials using BSE have yield disappointing results.

Apart from the impact on breast cancer mortality, another potential benefit of breast cancer early detection is the increased use of conservative surgery such as partial mastectomy, segmental excision or lumpectomy. The results of the prospective studies showed, in the screened group, an increased proportion of women undergoing conservative surgery.

**Adverse Effects**

Adverse effects of screening for breast cancer have also to be considered. In the first place a screening program could create an over “medicalisation of healthy people”: by being confronted with too many preventive and diagnostic procedures, women belonging to the target population could be over concerned with health and medical issues. In the second place, participation in screening programs might
cause undue anxiety: the confrontation with the possibility of having breast cancer is frightening; anxiety is particularly increased in women presenting with a false-positive result, i.e. when abnormalities detected by mammography are subsequently found to be benign. However, documentation on these aspects is scarce. The few studies dealing with worry and anxiety show that such reactions seem relatively infrequent and tend to regress rapidly. The prevalence of anxiety has been reported to be significantly greater in women with false-positive results (29%) than in those with negative results (13%).

Furthermore, mammography involves compression of the breasts, which can cause physical discomfort: 10% to 20% of women reported moderate or severe discomfort. Surgical biopsy, when necessary, involves a risk of infection, scaring, hematoma, pain and breast abnormalities are also possible:

Firstly, some screen-detected cancers would never have become clinically apparent during the woman’s lifetime. The possible magnitude of this effect is uncertain but predictions give as many as 70% of breast cancers remaining clinically unapparent. Secondly, it is certainly possible that not all in situ cancers become invasive. Thirdly, false-positives based on histology have been reported for small lesions.

The difficulty to classify minimal or borderline lesions as benign or malignant is now recognized and should result in the review of pathological procedures. It has been suggested that women with a false-negative result, might subsequently delay seeking treatment if symptoms develop, because of a false sense of security. This could ultimately result in greater morbidity and poorer prognosis.

The increase of life time risk of radiation-induced breast cancer from mammography (if the dose is 0.12 rad per two-view film-screen examination), has been estimated to be less than 1%. Finally, screening can result in a large burden of unnecessary investigations and treatments when the quality of such interventions is not assured.

**Economical Cost**

Effects on health should be considered in relation with the resources allocated for establishing those effects. The main aim of an economic assessment is to assist the relevant decision makers for an optimal use of the available health care resources.

The analysis of the costs components should take into account, the size of the target population, the investments (equipment), the operating costs (mammography,
diagnostic examinations, quality control, call-recall system, data collection and analysis, information and training, evaluation ...). Generally, in developed countries, organized screening would replace current “spontaneous” practices. Considering the problem from this angle totally modifies the approach of costs and their evaluation. In France, the estimate of the yearly cost of screening considering a population of 860,000 women aged 50-69 a 50% participation rate, a 3-year periodicity and a 10% recall rate reached Francs 33.4 million Euro, i.e. 35 Euro per woman screened. In comparison, an estimate of the cost of spontaneous screening made in the late eighties and based on an observed annual activity of 1.12 million mammographic examinations (40% of such mammographies presently concern French women less than 50 years of age) reached 45.9 millions Euro, i.e. 41 Euro per woman screened. The possible decrease in cost with the organized program should be due to the targeting of the program to a limited population for whom breast cancer screening has proved effective on one hand; and on the second hand a better use of quality controlled health structures, thus reducing false positive and unnecessary examinations to the minimum.

Furthermore, the cost of breast cancer screening could be partly compensated, by the subsequent decrease in the costs of management of late-stage diagnosed breast cancers.

These estimations for France, should have been correct if the individual spontaneous screening had been strongly reduced, which is not the case presently in France where the participation rate to the organize screening is far too low (45%) and the spontaneous mammographic screening still high (35-40%). An important item, which does not facilitate the problem, is that costs occur long before favorable effects and savings are observed.

**Benefits and Risks: Efficiency**

The decision to screen part of the population on a routine basis must be taken only after careful assessment of the risks and benefits. Several factors play an important role and contribute to the success of a programme. The reduction of mortality rates obtained with clinical trials will be difficult to reach with population-based routine programmes; that is mainly due to lower participation rates and difficulties in obtaining high quality level of procedures: mammography (technique and reading), follow-up of women with abnormalities, biopsies, pathological interpretation and adequate treatments.
The rate of participation depends mainly on the woman’s age, the place of residence, the socioeconomic status and modalities of screening (call-recall system, facilities and access to mammography). The rates of 65% to 93% observed in the trials will be impossible to reach and this will result in a lower level of detection in the target population. Compliance is also of crucial importance in women with mammographic abnormalities, if there are women lost to follow-up after the mammographic test, then the benefit of the program will be null and the intervention in itself will become unethical. All the women with an abnormality have to be recalled, diagnosed and treated if necessary.

Quality control of all steps of the screening process is, thus, mandatory; high quality mammographical testing requires not only modern equipment but also trained radiologists who need to acquire equilibrium between sensitivity and specificity, i.e. to balance the need to find all cancers with that of keeping the number of unnecessary biopsies as low as possible. Pathology, including cytopathology and histopathology, are basic to achieve screening objectives. Pathologists should be able to make accurate diagnoses when assessing clinically occult lesions revealed by mammography. Any screening program should include experts (radiologist and pathologist) in charge of maintaining high quality standards of diagnosis, teaching of colleagues, and organization of quality control. Quality-assurance requirements and objectives have already been assessed and well documented.

Effectiveness of treatment of women with screen-detected cancer is of major influence on the results and, inadequacy, may drastically reduce the expected benefit.

Therefore, the efficiency of a program strongly depends on the organization of the program, which should include the improvement of the participation rate, the quality control of each step of the process, and data collection for evaluation.

**Evaluation**

Two levels of evaluation have to be checked: the first one will assess the general procedures in terms of participation rate, compliance (lost follow up), and quality. Such an evaluation will allow the identification and correction of the dysfunctions in the course of the program if any; the second will estimate the results in terms of health benefits and costs. The benefits can be expressed as the number of prevented breast cancer deaths or potential years of life saved; the change in the distribution of advanced stages of the disease can also be used as a surrogate indicator (table 3.1).
<table>
<thead>
<tr>
<th>Indicator</th>
<th>Acceptable</th>
<th>Desirable</th>
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<tbody>
<tr>
<td>Participation rate</td>
<td>&gt;70%</td>
<td>&gt;75%</td>
</tr>
<tr>
<td>Inadequate mammography</td>
<td>&lt;3%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Recall rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial (1st round)</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Subsequent</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Lost of follow up with mammographic abnormality</td>
<td>&lt;3%</td>
<td>0%</td>
</tr>
<tr>
<td>Cancer detection rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>3xIncidence</td>
<td>&gt;3xIncidence</td>
</tr>
<tr>
<td>Subsequent</td>
<td>1.5xI</td>
<td>&gt;1.5xI</td>
</tr>
<tr>
<td>In situ ductal carcinoma</td>
<td>10%</td>
<td>10-20%</td>
</tr>
<tr>
<td>% of node negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>70%</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Subsequent</td>
<td>75%</td>
<td>&lt;75%</td>
</tr>
<tr>
<td>% of invasive cancer≤10mm in size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>≥20%</td>
<td>≥25%</td>
</tr>
<tr>
<td>Subsequent</td>
<td>≥25%</td>
<td>≥30%</td>
</tr>
<tr>
<td>Benign to malignant open surgical biopsy ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>≤1/1</td>
<td>≤0.5/1</td>
</tr>
<tr>
<td>Subsequent</td>
<td>≤1/1</td>
<td>≤0.2/1</td>
</tr>
</tbody>
</table>

*Table 2.1* Major European key performance indicators

Quantitative assessment of the comparative risks and benefit of screening is difficult due to the diversity of screening effects. The benefit-risk balance can be calculated as the number of breast cancer deaths prevented per women-years (number of women x number of years of follow-up), per number of mammographic examinations, per number of biopsy, and per number of cancers detected. For example, the Swedish two-country study investigators calculated that for women aged 50-69 years at entry, one breast cancer death was prevented per 4000 woman-years, per 1460 mammographies, per 13.5 biopsies, and per 7.4 breast cancers detected. This type of evaluation incorporates the reduction from the baseline risk of breast cancer death, and the increase in risk of undesirable investigations. It
Breast Cancer screening

could be extended to include adverse effects such as pain, false reassurance, overtreatment, psychological morbidity and economical costs.

A second way of measuring the risk-benefit balance is to calculate the cost per quality-adjusted life-years saved. This measure weighs the increase in life expectancy according to quality of life and years. Such a calculation implies to estimate the weight of the various types of undesirable events. The results of these calculations vary considerably according to studies. This is due to the variations in the health care systems of each country, the screening programs designs, the compliance of the target population, the weighing of adverse effects, and finally in the cost analysis methodology.

The decision in terms of public health to implement a breast cancer screening program should be based on country specific assessments taking into account the epidemiology of the disease, the current practice (average stage of breast cancer at diagnosis, mammographic equipment and practice, training of professionals, treatments possibilities...) and the available resources (table 3.2). Once the decision has been taken, all efforts have to be implemented to ensure high quality at each level of the program in order to minimize the risks and maximize the benefits.

<table>
<thead>
<tr>
<th>Table 3.2 Questions to be answered before deciding what type of detection program for breast cancer to implement in a country</th>
</tr>
</thead>
<tbody>
<tr>
<td>- What is the breast cancer burden in the country?</td>
</tr>
<tr>
<td>- Are accurate diagnosis and effective treatment available and accessible to the whole targeted population?</td>
</tr>
<tr>
<td>- What proportion of cancer cases presents with potentially curable disease?</td>
</tr>
<tr>
<td>- Are there already programs for early detection running and evaluated?</td>
</tr>
<tr>
<td>- What are the resources needed and available (humans, structures, economic…)?</td>
</tr>
</tbody>
</table>

**Update**

More is probably known about breast cancer screening than about screening for any other malignancy. WHO did not recommend that developing countries implement screening for breast cancer, because it believes that, the focus for any screening efforts should be on screening for cervical cancer. Other resources should be devoted to palliative care or diagnosis and treatment.
Similarly, the Global Summit Early Detection Panel concluded that mammographic screening is not currently a realistic goal for most countries with limited resources and recommended that early detection efforts first be focused on the education of patients and physicians and increasing general social awareness about breast cancer.

The Summit Panel suggested the following sequential approach: 1) promote the empowerment of women to obtain health care, 2) develop the infrastructure to diagnose and treat breast cancer, 3) begin early detection efforts through breast cancer education and awareness, and 4) when resources permit, expand early detection efforts to include mammographic screening if breast cancer treatment is available for all detected cancer.

The Panel argued that although such programs will first provide care to a portion of the population and could serve as pilot programs for more extensive programs covering larger populations, and ultimately the entire population, as resources becomes available.

As completely new technologies emerge, such as the ability to identify genetic risk factors, new challenges also emerge. We cannot be satisfied with simply identifying women at particularly high risk. We must be prepared to counsel them about the risk and to propose them some solution.

Within the past 10 years, work defining the basis of genetic susceptibility to breast cancer in general and the identification of \textit{BRCA1} and \textit{BRCA2} specifically has enhanced the accuracy of breast cancer risk prediction. The subsequent diffusion of risk prediction tools, such as genetic susceptibility testing and the National Cancer Institute's “Risk Disk” have resulted in the identification of many women at increased risk of breast cancer. Although this information has implications for many areas of medical care, its potential impact is particularly great in the area of cancer screening. In theory, the ability to stratify breast cancer risk allows intensive screening regimens to be targeted to women at high risk who are most likely to benefit, with more limited screening for women at lower risk. This approach both reduces complications associated with low-risk biopsies and saves health care resources. The challenges now are translating this approach into practice.

In a recent study by Brekelmans et al., the effectiveness of breast cancer surveillance in \textit{BRCA1}/2 gene mutation carriers and women with high familial risk was demonstrated.
These results provide a rationale for tailoring screening recommendations to breast cancer risk, as rates of cancer detection were 10-fold higher among *BRCA1* and *BRCA2* mutation carriers than among women at moderately increased risk of breast cancer. Moreover, Brekelmans et al., observed a substantial risk of interval cancers in *BRCA1* and *BRCA2* mutation carriers undergoing annual screening beginning some time between the ages of 25-35, suggesting that current approaches may be insufficient in this very high-risk group. Moreover it has not been proven that screening of this predisposed group reduces their mortality from breast cancer and because the *BRCA1* and *BRCA2* genes participate in the repair of radiation-induced DNA breaks, it has been suggested that women who carry these mutations are at greater risk for radiation-induced breast cancer than are women in the general population. The sensitivity of magnetic resonance imaging has been reported to be greater than that of mammography for women at high risk because of *BRCA* mutation or a family history. Prospective studies of alternative screening regimens are clearly needed.
Chapter 3
Staging of Breast Cancer
and end result of therapy
Breast examination is an essential component of the evaluation of the patient with Breast Cancer.

**The Technique of Breast Self-Examination**

The physician has to teach his patient, before anything else, the careful breast inspection at the mirror. Many women have inequality in the size of the breasts and they may discover it for the first time, when they inspect their breasts. Asymmetries of the contour, dimpling of the skin, chronic redness and thickening of the nipple epithelium or erosion of its surface have to be looked for. Nipple inversion, especially if difficult to be erected, is an important sign of malignancy, and the same for spontaneous serous or bloody discharge.

The woman should lie supine on bed, with a small pillow placed under the shoulder. This flattens her breast, making palpation of the lateral half much easier. At the supine position, palpation begins with the flat of the fingers of the opposite hand (Fig. 4.1). The whole extent of the inner half of the breast is explored by transverse movements; extending from the nipple line to sternal edge and from the clavicle to the inframammary fold.

![Figure 3.1.](image-url)
On examining the outer half, the examining hand starts at the inframammary fold ascending to the axilla and in transverse lines. It is better to discourage women to palpate their breasts in a sitting position. In the erect position, the lower dependent half is folded upon itself and small tumors might be masked.

Haagensen advised women who do not want to practice breast self-examination and are at a high risk of developing cancer (positive family-history, gross cystic disease, multiple intraductal papilloma and those who have had carcinoma in one breast) to go, regularly, every four months, to be breast-examined by a physician, who is skilled in that field.

**PHYSICAL EXAMINATION OF THE BREAST**

**Inspection of the Breast**

Good light is needed. Inspection has to be done first with the patient’s arms at her sides and then high above her head. Redness, ulceration, edema, dilated veins and surface erosion have to be looked for.

Changes in the nipples such as deviation, flattening, retraction and inversion are signs of diagnostic importance. The fibrosis in and about the lesion pulls on the duct system and tilts the nipple.

**Palpation of the Breast**

The patient is asked to lie supine on the examining table. The nipple has to be examined first for thickening, redness or erosion. Sometimes, there is a pre-erosion stage that begins with slight reddening of its epithelium.

Next, place the nipple between your index finger and thumb and gently apply pressure to elicit discharge. Palpation has to be started over the medial half of the breast, better with the patient’s arm above the head to tense the pectoral muscles (Fig. 4.2).

Palpation of the lateral half of the breast is best carried out with the patient’s arm at her side, so it lies more caudal and its lateral half is more accessible to palpation. Note the general characteristics of the breast: smooth, granular or nodular. Any mass has to be recorded and checked whether it is fixed to the skin or pectoral fascia. Also press together the skin to elicit dimpling or flattening.
Supraclavicular and Axillary Regions
The patient sits on the examining table, in front of the physician. He must search for the sentinel nodes at the confluence of internal jugular and subclavian veins; hidden deep behind the medial end of the clavicle. Laterally situated nodes are more superficial and usually involved by retrograde permeation from the sentinel nodes (Fig. 4.3).

Figure 3.2.

Figure 3.3.
For examination of the axilla (Fig. 4.4), the examiner supports the patient’s arm by his own hand to relax the pectoral muscles. The number, consistency and movability of axillary nodes should be noted; also their diameter in centimeters. In obese patients, axillary palpation is difficult. Palpation of both axillae is essential.

![Figure 3.4.](image)

**DIAGNOSIS OF BREAST CANCER**

Different breast lesions commonly appear in patients in certain age groups. Cancer of the breast is unusual under the age of thirty. Nevertheless, all symptomatic women are suspect. The longer the delay in diagnosis and treatment of breast cancer, the more ominous is the outlook for survival.

Clinical examination remains indispensable for detection and clinical staging of breast cancer. Detectability increases with the increase in mass size and with care given in examination. The overall diagnostic accuracy of physical examination does not exceed 75%.

A lump or mass in the breast is the most common initial sign of mammary cancer. The mass is not always painless. Donegan, in 1979, reported that about 15% of cancers are painful. The upper outer quadrant of the breast is the most common site for mammary carcinoma.
Nipple discharge, particularly the serosanguineous type is an occasional sign. Nipple changes, including retraction, division, or elevation, can be due to benign lesions but are usually due to an underlying cancer. The changes known as Paget’s disease can present a variety of appearances from moist and eczematoid to dry and psoriatic or it may appear as red granular erosion. The characteristic lesion may exist with or without a palpable tumor mass.

Skin retraction or dimpling was once considered diagnostic of mammary cancer, but some benign lesions can produce this change, notably fat necrosis, plasma cell mastitis and chronic infections. Skin changes including fixation to the skin, peau d’orange, edema, ulceration, satellite nodules, marked retraction of the entire breast and edema of the arm are signs of advanced malignancy.

Halsted in 1907 pointed out that enlarged axillary lymph nodes could be the only sign of occult mammary carcinoma, one per cent or less of all cases present in this fashion. Cancer is the probable etiologic factor if the axillary nodes are firm to hard, slightly irregular, matted, fixed, or larger than 2 cm. The presence of supraclavicular nodes, fixed axillary nodes or edema of the arm indicates an advanced regional disease. Complaints at distant sites may have their origin in the breast and represent metastasis to bones or viscera (e.g. liver or lung).

Careful physical examination is the primary resource for evaluating the local and regional extent of the disease. Extensive preliminary investigations are not appropriate when it is unlikely that a lesion of the breast is cancer.

For practical purposes, the diagnosis and clinical staging of a patient without signs or symptoms suggesting dissemination might include a complete history and physical examination, a complete blood picture that may detect an anemia indicative of extensive bone marrow involvement and a roentgenogram of the chest, which may detect pulmonary metastasis in asymptomatic patients.

A radiographic survey of the skeleton, ribs, skull, spine, pelvis, femurs and humerus is generally unrewarding unless the patient has symptoms suggesting osseous metastasis.

Besides clinical palpation, the techniques of mammography, thermography, galactography ultrasonic examination of the breast and aspiration cytology have been used in the detection of early breast tumors.
It is to note that with the breast cancer detection screening, more and more cases (about 20% of cases in the country in which there is this type of program which concern only patients between 50 – 74 y.o.) are detected by mammography without any symptomatic disease.

Mammography has an accuracy of approximately 80-90%. Ultrasound mammography is somewhat useful as an ancillary procedure to mammography in selected patients for evaluating deep seated lesions, especially in premenopausal women whose dense glandular breasts may obscure masses on mammography. Mammary RMI can help to objective intramammary spread.(see chapter 6)

It is a useful advice that breast cancer should be considered as a systemic disease until proved otherwise. The methods for search for distant metastases can be broadly subdivided into physical techniques and biochemical methods.

Physical techniques include the conventional chest X-ray, skeletal scans, hepatic scan, brain scan, computerized tomography scans and, now PET SCAN. The conventional chest X-ray should be a routine investigation for all cases with early carcinoma of the breast. The development of isotopic skeletal scanning has improved the accuracy for detecting bony metastases, followed by specific radiology for the areas of abnormal uptake. A negative scan would exclude, in the majority of cases, the presence of skeletal metastases.

However, a so called positive scan needs to be further evaluated since healing fractures, Paget’s disease and areas of osteoarthritis can also show up as hot spots on the scan image. Having confirmed the presence of skeletal metastases by X-raying the area of abnormal uptake on the scan, the patient falls into the stage 4 category. There remains a considerable confusion as how to handle a group of patients who have an apparently early breast cancer with hot spots on their scan and no radiologically detectable metastases. It was advised that the optimum way of handling this problem would be to carry out a bone biopsy on suspicious areas shown up by the scan.

Haagensen in 1971 reported that approximately 35 to 65 per cent of autopsied patients with breast cancer have hepatic metastases. Ultra-sonic exploration or CT are the more common investigations. used to detect an hepatic lesion.

Positron Emission Tomography (PET) (associated or not with a CT Scan) is not used routinely. It can be of a great help for the diagnosis of an abnormal picture founded by an other imaging technique. The newly developed PET Mammo is
cuurently under evaluation with only one machine present in the world at Mazo Clinic.

All physical techniques for detecting metastases have a built-in limitation in that improvements in resolving power are bought at extreme costs with diminished returns.

Improvements in the detection of biochemical markers, which might be released by the tumor itself, can be of help. These markers might be released from normal parenchyma as a result of invasion and destruction by the tumor cells. Elevated liver enzymes, such as alkaline phosphatase are very crude estimates of hepatic invasion. If advanced laboratory facilities are available, additional investigations such as tumor markers [CA15.3, CEA, and MCA] can be considered.

**Clinical Staging**

Since 1905, several systems of classification have been adopted. Steinthal described the first pure clinical estimation of the stage or the extent of disease at the time of treatment.

In 1940, the four stage system for clinical evaluation was adopted at the Christi Hospital in Manchester. This classification was widely accepted, and is still in use in many centers all over the world.

The four stages are:

*Stage 1*: The growth is confined to the breast; *Stage 2*: The growth is confined to the breast, but palpable, mobile lymph nodes are present in the axilla; *Stage 3*: The growth extends beyond the mammary parenchyma: (a) skin invasion or fixation over an area large in relation to the size of the breast or skin ulceration; (b) tumor fixation to the underlying muscle or fascia; axillary nodes, if present, are mobile. *Stage 4*: The growth extends beyond the breast area as shown by fixation or matting of the axillary nodes, complete fixation of the tumor to chest wall, deposits in supraclavicular nodes or in the opposite breast, or distant metastases.

In 1972, according to Denoix, and the committee of clinical staging of the UICC, the new method of clinical staging was widely used by different centers. This classification depends upon the T (Tumor Size), N (Regional Lymph Node Affection), and M (Distant Metastases).
Staging and end results of therapy  35

This classification adopted by the American Joint Committee on Cancer (AJCC) TNM system can be summarized as follows:

TNM Definitions

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. If the measurement is made by physical examination, the examiner will use the major headings (T1, T2, or T3). If other measurements, such as mammographic or pathologic measurements, are used, the subsets of T1 can be used. Tumors should be measured to the nearest 0.1 cm increment.

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Intraductal carcinoma, lobular carcinoma in situ, or Paget disease of the nipple with no associated invasion of normal breast tissue
  - Tis (DCIS): Ductal carcinoma in situ
  - Tis (LCIS): Lobular carcinoma in situ
  - Tis (Paget): Paget disease of the nipple with no tumor. [Note: Paget disease associated with a tumor is classified according to the size of the tumor.
- T1: Tumor not larger than 2.0 cm in greatest dimension
  - T1mic: Microinvasion not larger than 0.1 cm in greatest dimension
  - T1a: Tumor larger than 0.1 cm but not larger than 0.5 cm in greatest dimension
  - T1b: Tumor larger than 0.5 cm but not larger than 1.0 cm in greatest dimension
  - T1c: Tumor larger than 1.0 cm but not larger than 2.0 cm in greatest dimension
- T2: Tumor larger than 2.0 cm but not larger than 5.0 cm in greatest dimension
- T3: Tumor larger than 5.0 cm in greatest dimension
- T4: Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below
  - T4a: Extension to chest wall, not including pectoralis muscle
o T4b: Edema (including peau d’orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast

o T4c: Both T4a and T4b

o T4d: Inflammatory carcinoma

**Regional lymph nodes (N)**

- NX: Regional lymph nodes cannot be assessed (e.g., previously removed)
- N0: No regional lymph node metastasis
- N1: Metastasis to movable ipsilateral axillary lymph node(s)
- N2: Metastasis to ipsilateral axillary lymph node(s) fixed or matted, or in clinically apparent* ipsilateral internal mammary nodes in the absence of clinically evident lymph node metastasis
  o N2a: Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
  o N2b: Metastasis only in clinically apparent* ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis
- N3: Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or, metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
  o N3a: Metastasis in ipsilateral infraclavicular lymph node(s)
  o N3b: Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
  o N3c: Metastasis in ipsilateral supraclavicular lymph node(s)
Pathologic classification (pN)*

- pNX: Regional lymph nodes cannot be assessed (e.g., not removed for pathologic study or previously removed)

- pN0: No regional lymph node metastasis histologically, and no additional examination for isolated tumor cells (ITC)

  [Note: ITCs are defined as single tumor cells or small cell clusters not larger than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but that may be verified on hematoxylin & eosin (H&E) stains. ITCs do not usually show evidence of malignant activity, e.g., proliferation or stromal reaction.]

- pN0(I-): No regional lymph node metastasis histologically, negative IHC

- pN0(I+): No regional lymph node metastasis histologically, positive IHC, and no IHC cluster larger than 0.2 mm

- pN0(mol-): No regional lymph node metastasis histologically, and negative molecular findings (RT-PCR)**

- pN0(mol+): No regionally lymph node metastasis histologically, and positive molecular findings (RT-PCR)**

* [Note: Classification is based on axillary lymph node dissection with or without sentinel lymph node (SLN) dissection. Classification based solely on SLN dissection without subsequent axillary lymph node dissection is designated (sn) for sentinel node, e.g., pN0(I+) (sn).]

- pN1: Metastasis in one to three axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by SLN dissection but not clinically apparent**
  - pN1mi: Micrometastasis (larger than 0.2 mm but not larger than 2.0 mm)
  - pN1a: Metastasis in one to three axillary lymph nodes
• pN1b: Metastasis in internal mammary nodes with microscopic disease detected by SLN dissection but not clinically apparent**

• pN1c: Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by SLN dissection but not clinically apparent** (If associated with more than three positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden.)

• pN2: Metastasis in four to nine axillary lymph nodes, or in clinically apparent** internal mammary lymph nodes in the absence of axillary lymph node metastasis to ipsilateral axillary lymph node(s) fixed to each other or to other structures
  o pN2a: Metastasis in four to nine axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)

  o pN2b: Metastasis in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis

• pN3: Metastasis in ten or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph node(s) in the presence of one or more positive axillary lymph node(s); or, in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or, in ipsilateral supraclavicular lymph nodes
  o pN3a: Metastasis in ten or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); or, metastasis to the infraclavicular lymph nodes

  o pN3b: Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph node(s); or, in more than three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**

  o pN3c: Metastasis in ipsilateral supraclavicular lymph nodes
Distant metastasis (M)

- MX: Presence of distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

AJCC Stage Groupings

Stage 0

- Tis, N0, M0

Stage I

- T1*, N0, M0

Stage IIA

- T0, N1, M0
- T1*, N1, M0
- T2, N0, M0

Stage IIB

- T2, N1, M0
- T3, N0, M0

Stage IIIA

- T0, N2, M0
- T1*, N2, M0
- T2, N2, M0
- T3, N1, M0
- T3, N2, M0

Stage IIIB

- T4, N0, M0
• T4, N1, M0
• T4, N2, M0

Stage IIC**

• Any T, N3, M0

Stage IV

• Any T, Any N, M1

However, these classifications did not satisfy all descriptive clinical conditions, as some of the tumors are biologically active and their clinical behavior differs irrespective of their original tumor measurements or apparent nodal affection. Consequently, an additive system of classification was adopted by the workers at Gustave-Roussy Cancer Institute in France. This system demonstrates staging according to the evolutionary phase PEV (Phase Evolutive).

**The Evolutionary Phase (PEV)**

The characteristics of the evolutionary phase were looked for in the tumor and the lymph nodes. They were present in varying degrees. Two elements: the signs of inflammation and the speed of growth as a function of time, distinguished the three degrees in decreasing severity.

**PEV 3** These are the worst cases, which correspond to the classical acute inflammatory type. The breast is hot, red, and presents diffuse edema of the dermis and subcutaneous tissues. There, almost always, exist a collateral circulation and most often greatly enlarged lymph nodes are hidden in the edematous tissues i.e. acute mastitis carcinomatosa involving the entire breast.

**PEV 2** These are the cases of moderate severity, which correspond to the sub-acute pseudo-inflammatory forms involving only a part of the breast. However, peritumoral and cutaneous edema is more often to be found beyond the limits of the tumor, even though at times, it is difficult to precise its limits. The enlarged lymph nodes are often matted together, and attached to the tumor by an indurated cord of “neoplastic lymphangitis”.
PEV 1. These are the cases which are apparently the least serious but also the most difficult to define. They are differentiated from the usual “chronic” type of breast cancer by one essential and unique characteristic “the rapid rate of growth”.

PEV 0. These are the cases, which correspond to the classic “chronic” type of breast cancer but they lack the previously-mentioned activity signs.

It is therefore admitted that any tumor with its apparent volume doubled in 6 months is to be considered in evolution (progressive). The determination of this characteristic is based on the interrogation of the patient and thus, its appreciation is subjective. Such evaluation is impossible for recently discovered tumors. However, skin biopsy for involvement of skin lymphatics by tumor cells is a more reliable method to assess the stage of evolution.

Inflammatory Carcinoma
Inflammatory carcinoma of the breast was described by Lee as a distinct entity. This disease form is reported to account for 1% to 10% of breast malignancies and can be divided into two types: the primary type, in which inflammatory changes appear simultaneously with the carcinoma in an otherwise normal breast, and the secondary type in which the inflammatory manifestations appear in a breast with long standing carcinoma. The common factor in all such cases is the unusual appearance of widespread redness and edema in the skin, usually without any increase in the patient’s temperature and with no change in the white blood count. This inflammatory type corresponds to types PEV3 and PEV2 mentioned above.

End Results of Therapy (National Cancer Institute, Cairo)
A follow-up study was conducted on a total of 408 female patients with operable breast cancer treated in National Cancer Institute, Cairo (NCI) during the period January 1980-December 1983. All patients except 6 were subjected to radical mastectomy at that time; 224 patients received adjuvant postoperative radiotherapy and 73 patients were treated by adjuvant CMF combination for 6 courses. This adjuvant regimen was conducted in relation to tumor size and lymph node affection. In June 1987 multivariate analysis was carried out where multiple stepwise regression analysis was done on the various prognostic factors to elicit the prognostic index. In our study, age had no effect on survival similar to the results obtained by Rosen et al. and Muscolino et al. This was in disagreement with the results of Palmer et al. who found a better survival rate of patients ranging from 40-49 years of age than older patients in stage I and II of the disease.
Staging had a strong effect on survival as evidenced by the different rates of survival in relation to tumor extent. T1 lesions, had survival of 60.7% in contrast to 19.6% for T4 lesions and clinical nodal affection (N) N0 66.9%; N1a 54.6%, N1b 25.9% and N2 3.5%. The first 3 years were the critical period for patients especially those with T4 lesions and N2 category. Using stage grouping as a prognostic discriminator, it was noticed that Stage I was far better than Stage II which was better than IIIa and IIIb, while 5% of Stage I patients died during the first 6 months; 19.7% of the poorest prognosis group (Stage IIIb) continued alive and free of recurrence for the first 3.5-5 years. Either this was due to the biological heterogeneity effect proven by many reports as Isaacs’, or that staging was not sufficient to predict prognosis. This result was also supported by the multivariate analysis, which showed no independent prognostic effect for the clinical staging. Although PEV showed a significant prognostic value, yet their discriminating power was not like that of staging. This was in agreement with what Contesso et al. and Chevallier had reported.

On the other hand, tumor size showed a prognostic effect on survival, which seems to be indirect through the lymph node metastasis and not through the tumor grades. This, was supported by the non significant relationship detected between tumor size and tumor grade. These results were in agreement with those of the American College of Surgeons in 1979 and Lee who found that the larger the tumor, the more the number of lymph nodes involvement with metastasis, the greater would be the tumor relapse and mortality rates. The histopathologic types (favorable and unfavorable) and grade gave significant discrimination, which was indirect through nodal metastasis. It was found that the favorable group had a lower incidence of nodal metastasis in comparison to the unfavorable group (56.0% vs. 70.6%). Also patients with grade 1 had a survival rate of 65% while those of grade II and III were 30%. This was in accordance with the results of Davis et al. and Fisher et al.

Axillary lymph node metastasis showed the most significant prognostic power of the whole prognostic factors. Our results indicated that patients with (4-9) and (>9) nodes were far worse. These results are supported by those of Fisher et al. and Contesso et al. Capsular invasion was also a powerful prognostic factor in multivariate analysis done. The clinical diagnostic accuracy for axilla nodes was 66.6% and 78.4% for the clinically negative and clinically positive lymph nodes respectively.

A more recent series was conducted at the same institute between 1994 and 1998, and included 400 patients. The median age of this group of patients was 46 years (range 21-76 years). Of these 400 cases, 261 (65%) were postmenopausal, and 139
(35%) were premenopausal. While all cases in the older series conducted between 1980-1984 had modified radical mastectomy as their primary treated option followed by adjuvant radiotherapy in 55% and chemotherapy in 24% of those cases, in the recent series (1994-1998), modified radical mastectomy was the primary treatment option in 333/400 (83%) and conservative surgery was done for the remaining 67 cases (17%). Adjuvant radio-chemotherapy was given to 85% of these cases. Tumor size was below 2 cm in 13%, between 2-4 cm in 54% and >4 cm in 33% of cases. Pathological axillary lymph node involvement was absent in only 14/400 (3.5%) cases examined, while 1-3, 4-6, 6-10, and >10 positive nodal affection was present in 16.5%, 11%, 13%, and 56% of cases respectively.

At a median observation time of 49 months, the 5-year disease free survival rate was 60.1% for the patients included in 1994-1998 series, compared to 37.2% for those reported in 1980-1984 series. Survival rate was significantly adversely affected by postmenopausal status, tumor size more than 2 cm in diameter, grade III tumors, positive axillary lymph nodal affection, and being ineligible for conservative surgery as primary treatment.

In another study using high dose adjuvant chemotherapy with autologous peripheral blood stem cell transplantation in node positive breast cancer, fifty-three premenopausal patients with node positive (≥6) breast cancer were randomly allocated to receive one cycle of high-dose cyclophosphamide 6 gm/m² divided on 3 days, etoposide 1500 mg/m² divided on 3 days and carboplatin 800 mg/m² divided on 2 days (CVCb regimen) versus six cycles of conventional-dose cyclophosphamide 600 mg/m², epirubicin 75 mg/m² and fluorouracil 600 mg/m², all given IV day one, and repeated every 21 days (CEF regimen). The high-dose regimen used peripheral blood stem cells as a stem cell rescue. HDC (n=27) and CEF arms (n=26) were almost comparable with respect to different prognostic factors. In HDC arm, the mean times to neutrophil and platelet recovery were 10.29 and 11 days respectively. The mean time of empiric antibiotic therapy was 8.59 days. The complications of the HDC regimen were mild (grades 2 and 3) and were mainly gastrointestinal (vomiting, diarrhea and mucositis). In both arms of the study, there were no life-threatening complications or treatment-related mortality. At a median follow up period of 30 months, the 3-year disease-free survival of the HDC group (50.5%) was better than that of the CEF group (29.4), but the difference did not reach statistical significance (p = 0.137). The 3-year overall survival of HDC arm (82.8%) was slightly higher than that of the CEF arm (76.9%), but the difference was also statistically insignificant (p=0.763). So, it was concluded that further follow-up and additional studies are required to evaluate the role of high-dose adjuvant chemotherapy in high-risk breast cancer patients.
Chapter 4

Breast Cancer and Genetic Predisposition
The relation between the occurrence of a cancer and the existence of genetic alterations is now well established. In breast cancer as in the majority of cancers, these alterations are mostly somatic. Genetic alterations observed in the course of the malignant transformation are varied: chromosomal deletions, translocations, amplifications and rearrangements, duplications or whole chromosome losses (aneuploidy), and point mutations. Some of these alterations lead to the modification of the expression and/or the structure of the product of the gene implied by these alterations.

It will result in:
- activating genes in a dominant way: the alteration of only one of the two copies of the gene is required and these genes have been called oncogenes.
- inactivating genes whose loss of function participates to tumorigenesis; these genes have been called tumor suppressor genes (TSG).
- activating or inactivating genes whose products interfere with the genome stability: genes regulating the processes of mitosis and DNA repair enzymes. The alteration of these genes will help the occurrence of alterations of the more directly implicated genes (i.e. oncogenes and tumor suppressor genes).
- finally, the above mentioned gene expression modifications can result, not from the direct alteration of the gene itself, but from alteration of genes acting on the “modeling” of the chromatin or on the DNA methylation status. Such mechanisms are called epigenetic.

The activation or inhibition of only one of these genes is not sufficient to convert the phenotype of a normal cell into a tumor one: multiple mutational events are required. The accumulation of these genetic alterations, which interact and cooperate between themselves, is necessary to lead to the tumor phenotype. During this multi-stage process, each new genetic alteration acquired by the cell will give it new properties, favoring the selection of this clone and thus converging to the tumoral phenotype. The understanding of carcinogenesis requires the identification of these numerous genetic alterations or mutations, of which all or part of it is responsible for the initiation and the tumor progression. In due time, the identification of the responsible genetic alterations have repercussions on diagnosis, prognosis and therapeutic.

Somatic alterations in breast tumors
At the chromosomal level, the most frequently observed somatic genetic alterations are deletions affecting in particular the chromosomes 1p, 3p, 6q, 8p, 9p, 11q, 13q, 16q, 17p; these chromosomal regions may thus contain TSGs, with a decreased or lost expression in tumor tissues. Other chromosomal regions are amplified, notably 1q, 8q, 11q13, 17q, 20q13…Several amplified oncogenes have been identified within these regions like HER2 on 17q, MYC on 8q24, or Cyclin D1 on 11q13. Other alterations include point mutations, notably those affecting the tumor suppressor gene TP53, present in 20 to 40% of breast cancer or those of the oncogene PI3K –Phosphatidylinositol 3 Kinase-, in about 25% of breast tumors. Other TSGs are mutated less frequently like PTEN, a tumor suppressor gene inhibiting PI3K, or CDKN2A, a negative regulator of the cell cycle. Epigenetic alterations are frequent in breast tumors; for example the methylation of the promoters of several TSGs results in a loss or decreased of their expression level.

At the RNA level using DNA microarray –also called transcriptomics-, five molecular subtypes with distinct gene expression profiles have been evidenced. One major ER negative class contains HER2 positive, basal-like (HER2 and ER negative) and normal-like breast tumors. The ER positive tumors can be subdivided in luminal and B subtypes. Moreover, this molecular classification clearly influences the prognosis and response to treatments of breast tumors, with the best prognosis for luminal A and the worse for basal-like tumors.
Hereditary cancer predisposition

Genetic alterations may occur by chance, but may be enhanced by mutagenic and/or mitogenic factors, both endogenous and environmental. In 4 to 10% of breast cancers, a germline mutation predisposes to breast cancer, easing the occurrence of specific other somatic genetic alterations. Knudson in 1971 postulated that the development of retinoblastoma results from two mutations in retinoblast. The two-hit model assumed that one mutation spontaneously occurs and the second could be the consequence of a constitutional—also called germ-line—mutation.

Comings in 1973 focused the Knudson hypothesis to a particular gene which should regulate the cellular growth. This explains why a recessive mutation can have a dominant phenotype in cancer predisposition. The analysis of LOH—for Loss of Heterozygosity—in retinoblastoma showed that the wild allele was prone to be more frequently lost in the tumor tissue than the mutated one. That explains also why the probability to a child to inherit a parent’s mutation is 50%. There is no sex discrimination, so risk can be transmitted by either men or women. Some suppressor genes have been implied in inherited predisposition to breast cancer. In genetic susceptibility, all cells carry a mutation responsible for the disease. The transmission mode is mainly autosomal dominant. Then, the offsprings have 50% risk to have the deleterious mutation.

Inherited predisposition to breast cancer and family history

A family history of breast cancer is clearly accepted as a risk factor and for a long time. When there is a family history, the breast cancer risk is increased by 3 to 4 times. And this increase is positively correlated to the number of first and second degree relatives with a breast cancer and the precocity of these cancers. Breast cancer is a very frequent disease and that explains the difficulty to associate multiple breast cancers in a family and predisposition to breast cancer. Familial aggregate and genetic susceptibility to cancer are not synonymous. At the breast cancer diagnosis, 15-20% of women have a first degree parent with a breast cancer and only 5% have a genetic susceptibility. However, in breast cancer, there is, up to now, few other factors than a family history to decide a gene screening. Nowadays, some family histories can be associated to a specific gene. A germline mutation in the BRCA1 and BRCA2 gene is most frequent cause. However, less than 30% of families with solely multiple breast cancers have a mutation in those two genes. The population-based cases of breast cancer and familial clusters have favored the polygenic model where multiple genetic factors act independently. Some studies are assessing the effect of multiple gene alteration.

Genes involved in breast cancer predisposition

Susceptibility genes can be classified by the risk and the penetrance. The penetrance is the frequency of the disease expression associated to a deleterious mutation. In high penetrance genes, individuals with a deleterious mutation have a risk in the lifetime close to 80%. Schematically, the breast cancer risk is by 80% at 80 years old.

High penetrance genes: BRCA1 and BRCA2

Discovery

Linkage studies were used to find those two genes. Linkage studies the transmission of some markers in families with a predisposition to cancer. Some significant marker can identify a sensible area in genome which transmitted exclusively to the individual with a phenotype of breast cancer. The correlation with the BRCA1 and BRCA2 genes has been between 35% and 50% of the familial cases. The attempt to find another genes to explain the families without any mutation in BRCA1/2 failed. BRCA1 gene was localized at the chromosome 17q21 in 1990 and identified in 1994. This gene can explain the majority of familial predisposition. BRCA2 gene, localized in chromosome 13p12.1 have been identified in 1995. This gene is mainly associated to families with solely breast cancer and/or with male breast cancer.
Molecular function

BRCA1 and BRCA2 are genetically distinct but both of them are involved in the maintenance of genome stability. The role of BRCA1 looks complex: E3 ubiquitin ligase involved in the DNA damaging signal, reparation of double stranded DNA breaks, chromatin remodelling and implication in the transcription. There is no biallelic mutation reported and no viable animal with null BRCA1 allele. BRCA2 intervenes also in the reparation of double stranded DNA breaks and homologous recombination in the direct association of RAD51. A biallelic mutation in BRCA2 have been associated Fanconi’s anemia (FANC-D1). In this disease, the consequences are an extreme sensitivity to chemotherapy and irradiation with spontaneous chromosomal instability.

Epidemiology

In general population with breast cancer, the proportion of mutations in those two genes are very low. One women by 400 is a BRCA1/BRCA2 mutation carrier. The average frequency is between 2 and 6% in young onset of breast cancer in different population. In a british study, 6% of women with a breast cancer diagnosed before 36 years have a mutation either in BRCA1 or BRCA2. With the most penetrance estimates, the respective proportions of BRCA1 and BRCA2 mutation carriers are 3% of patients with breast cancer and younger than age 50 years, 0.4-0.8% of patients with breast cancer and age 50 years or older, and 0.1% of women in the general population. All those statistics have been evaluated on Caucasian women in Europe and United States, African women seem to have a lower rate of deleterious mutations, but much more unclassified variants with unknown significance and have a higher frequency of young onset of the disease (studies on African American women). In all ovarian cancer, BRCA1 and BRCA2 mutations occur in 10-20% in unselected patients.

Risk

In familial aggregate, BRCA1 and BRCA2 are the two archetypes for high penetrance genes. In Breast Cancer Linkage Consortium, those two genes were responsible for 95% of families with ovarian and breast cancers (at least 4 cases before 60 years old). Recent estimates of breast-cancer risk by the age of 80 years are 90% for BRCA1 mutation carriers and 40% for BRCA2 mutation carriers. Some studies have tried to identify genotype-phenotype correlation. For BRCA2, there is the ovarian cancer cluster region, central region between nucleotide 3035 and 6629. There, the risk of ovarian cancer is multiplied twice and breast cancer risk divided. Other attempt to find other correlation was unsuccessful. Now, some studies try to understand the reason why some positive BRCA1/2-mutation families have a higher incidence of breast cancers. Some polymorphisms in other genes could facilitate the increase in the breast cancer risk. RAD51 have been the first gene identified as a modifier of risk among BRCA1/2 mutation carriers. The gene RAD51, a partner of both BRCA1 and BRCA2 in the double-stranded DNA-repair mechanisms, have a polymorphism in the 5' untranslated region (UTR) 135G>C which has been suggested as a possible modifier of breast cancer risk in BRCA1 and BRCA2 mutation carriers. For CC homozygotes in BRCA1/BRCA2 mutations carriers, the hazard ratio is increased by 1.92. Moreover, in BRCA2 mutations carriers and CC homozygote, the hazard ratio is 3.18. A single nucleotide polymorphism have reported for the MDM2 gene to increase the risk for breast and ovarian cancer in the Ashkenazi BRCA1 and BRCA2 mutation carriers. There are also strong evidences to suggest increases in penetrance of breast cancer related to BRCA1 and BRCA2. Environmental and lifestyle factors could play a role in this trend.

High penetrance genes with a specific spectrum of cancer

Other genes have been implied in predisposition to breast cancers with a high penetrance rate. In those genes, breast-cancer is not the main phenotype. No other high penetrance genes have been found through large genome-wide association study.

TP53 gene (17p13) is responsible for Li-Fraumeni syndrome with the following associated cancers: soft-tissue sarcoma, osteosarcoma, brain tumors, adrenocortical carcinoma, leukemia and colon cancers. In this type of familial aggregation, a mutation in TP53 is found in 50% of cases. 1% of breast-cancer before 40 years old would be associated to a mutation in this gene. The relative risk of
Breast cancer is 1.46 overall, but from 5.46 between 15 and 29 year-old. The risk by age of 70 years is more than 90.

**PTEN gene** is responsible for several syndromes: Cowden’s disease, Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome and Proteus like syndrome. Major cancers associated are thyroid, endometrial and genito-urinary cancers. Breast-cancer cover 0.1%. PTEN is associated to cutaneous and muquous hamartome. Half of mutation carriers have mastopathie which lead in 50% of cases to breast cancer. The relative risk of breast cancer is 2-4. The risk by age of 70 years is more than 25-50.

**STK11/LKB1** gene is responsible for Peutz-Jeghers syndrome. The spectrum of tumours are from small intestine, colorectal, uterine, testicular, ovarian sex cord and others. The relative risk of breast cancer is 15 and the risk by age of 70 years is 45-54.

**CDH1**, E-cadherin, is responsible mainly for hereditary diffuse gastric carcinoma. The risk of breast cancer is 3.25 and the risk by age of 70 years is 39. The cytology of the breast cancer associated to CDH1 is very specific with a lobular type. Some family have been described without any diffuse gastric carcinoma.

**Intermediate penetrance genes**
Four intermediate-penetrance breast cancer genes have been identified: CHEK2, ATM, BRIP1 and PALB2. Mutations are rare and confer a relative risk to breast cancer of 2 to 4. Those four genes are implied in the cell cycle regulation and DNA reparation. They interact directly or indirectly with **BRCA1** or **BRCA2**.

CHEK encodes CHK2 protein implied in the phosphorylation of both p53 and **BRCA1** during DNA double-strand breaks reparation. The mutation reported is 1100delC. A meta-analysis conclude to a direct odds ratio of breast cancer between 1.72 and 3.2. Some studies associated this gene with other cancers as prostate and Li-Fraumeni syndrome, but without any convincing evidence.

ATM occupies a central role in the response to double-strand DNA breaks. It is associated to ataxia telangetasia when biallelic mutations. However, the heterozygous women have an increase in breast cancer between 1.51 and 3.78.

BRIP1 and PALB2, both encodes for proteins which interacts one with **BRCA1** and the other with **BRCA2**. In case of biallelic mutation, both result in Fanconi Anemia. BRIP1 mutations have a relative risk close to 2 (95% CI 1.2-3.2). PALB2 mutations have a relative risk close to 2.3 (CI 95% 1.4-3.9).

**Low-penetrance genes and alleles**
Other pathways have been reported sterodien hormone (AR), hormonal metabolism (CYP17, CYP19) detoxification system (GSTM1, GSTP1, NAT2). In recent publications, some specific single nucleotide polymorphisms could increase the breast-cancer risk or protect carriers to this cancer as the gene CASP8. An interesting review have explored all the variant described in those gene and the level of risk associated. In candidate gene studies and genome-wide association studies, many polymorphisms were studied and some new genes were connected to BC susceptibility. Unfortunately, the odd ratio were all close to 1 to 2 (as the following table).

<table>
<thead>
<tr>
<th>Locus</th>
<th>Gene</th>
<th>Homozygote OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10q26</td>
<td>FGFR2</td>
<td>1.63 (1.53-1.72)</td>
</tr>
<tr>
<td>16q12</td>
<td>TNRC9</td>
<td>1.64 (1.45-1.85)</td>
</tr>
<tr>
<td>2q35</td>
<td></td>
<td>1.44 (1.30-1.58)</td>
</tr>
<tr>
<td>2q33</td>
<td>CASP8</td>
<td>0.74 (0.62-0.87)</td>
</tr>
<tr>
<td>11p15</td>
<td>LSP1</td>
<td>1.17 (1.08-1.125)</td>
</tr>
<tr>
<td>6q22.33</td>
<td>ECHDC1</td>
<td>1.41 (1.25-1.59)</td>
</tr>
</tbody>
</table>

**Table**: Summary of known low-penetrance breast cancer predisposition variants
The increase is so moderate that they cannot be used alone. One can imagine a combination of several SNP to determine an individual risk. Since the penetrance can be modulated by external factors, a notion of individual susceptibility is now assumed to explain a risk of cancer associated to many factors in which there is the genetic factor.

Finally, only BRCA1/2 is proposed as a routine screening in a breast/ovarian cancer familial history, but high penetrance genes with specific phenotype.

**BRCA1/BRCA2 tumor characteristics**

Infiltrating ductal carcinoma is the most common histological subtype in hereditary breast cancers, although several subtypes are associated with hereditary breast tumors. This is the case of medullary breast carcinoma that is observed in 11% of BRCA1 tumors, whereas only 1-2% of sporadic and BRCA2 tumors belong to this subtype.

BRCA1 tumors have characteristic pathological features. They often show atypical medullary features, ‘pushing margins’ and lymphocytic infiltrate, and are less likely to have coincident in situ carcinoma. BRCA1 tumors are usually of high histological grade, highly proliferative, and ER/PR and HER2 negative (referred to as ‘triple-negative’ tumors).

At the biological level, frequent somatic mutations of TP53 and/or p53 immuno overexpression are observed. BRCA1 tumors often express basal cytokeratins (CK 5/6 and/or 14 and 17) and EGFR. Altogether BRCA1 tumors share morphological and immunohistochemical features of basal-like breast tumors. Also at the RNA level using DNA microarray, the tumors arising in BRCA1 carriers segregate together with sporadic basal-like breast cancers.

Unlike BRCA1 tumors, BRCA2 tumors do not have specific morphological and biological properties. They are of a low or intermediate grade (60%). They express ER and PR in the same proportion than not otherwise specified sporadic breast tumors and are mainly HER2 negative.

**Oncogenetic consultancy**

**Organization and role**

Some important points should be stressed during the consultancy: best limits, impact on social life and personal point of view, medical management, information diffusion in the family…The time to get the result should be clearly described. Time for reflection and decision should also be given to the patient.

Consultancy is an important time to discuss about the familial history and disease risk. Now it should be also a point of entry for a multidisciplinary carryover.

**Family test is well codified:**

- General information and family history discussion
- Information about a genetic test and its limits
- A choice given with an informed consent
- Two independent blood samples collected at two different days
- A psychological and multidisciplinary management

**Indications**

A molecular screening should be proposed when a family history can evoke a predisposition to breast or ovarian cancers. Two levels of clinical intervention can be assessed. For healthy patient, the detection of a deleterious mutation in a family can help to assess their own risk toward the cancer. For cancer patient, that can also be a help to decide a surgery intervention and to plan a regular surveillance.
Since \textit{BRCA1} and \textit{BRCA2} have a very high penetrance, a molecular screening should be prescribed specifically to those two genes. In fact, genes associated to low-to-moderate risk have no clear management guideline up to now. In case of asymptomatic individual, the decision to perform a molecular screening should be assessed in a multidisciplinary staff to take into account all the impact connected to this analysis.

Several models exist for the decision to screen those genes. Family history remains the main factor to select individual for a genetic screening. Some model were developed but no have been fully validated. Moreover, the population used for those models were mainly occidental (BRACAPRO, MANCHESTER). BRACAPRO appears to perform with the best performance, but in small families, it is necessary to have direct criteria of selection.

\textbf{The indicators can include with a 10\% detection probability of mutations :}
- early age of cancer onset before 35 years-old
- multiple affected individuals within a family :
  - at least 3 cases of breast or ovarian cancer in the same parental branch and with first degree relative. If the first degree relative is a male, the second degree can be taken into account.
  - Two cases of breast cancer in first degree relatives in whom one breast cancer occur before 40 years-old, or one cancer is ovarian cancer, or one breast cancer is for a male.
- bilateral disease
- association of a breast cancer and an ovarian cancer
- males with breast cancer

\textbf{Here, a rapid table for compute the best indication:}

| \textit{BRCA1}/2 mutations identified | 5 |
| Breast cancer in a woman under 30 years-old | 4 |
| Breast cancer in a woman between 30-39 years-old | 3 |
| Breast cancer in a woman between 40-49 years-old | 2 |
| Breast cancer in a woman between 50-70 years-old | 1 |
| Breast cancer in a man | 4 |
| Ovarian cancer | 3 |

In a parental branch, all the event have to be added with the weight associated. If it is superior to 5, it is an excellent indication. Between 3 and 4, indication is possible. Under 3, the medical use is reduced. As quoted before, ovarian cancer is an important weight in any assessment for a mutation in families. Deleterious mutation in \textit{BRCA1}/\textit{BRCA2} account for 1 to 30\% of family with those indicators. The screening of mutations should characterise the mutation responsible for the familial aggregate of cancer. Due to the large spectrum of mutations, many families bear its own private mutation. Any strategy to screen only a panel of specific mutation in a country has not been generalised.

\textbf{Confirm a genetic predisposition}

To maximise the the yield, the first analysis should be performed only with a person getting the most reliable clinical history to predisposition. If possible, the person with the breast cancer should be the first person to undergo a genetic testing. Some medical doctors can be directly contact by someone in the family with healthy. In those cases, it is better to ask for contacting the person with breast cancer.

Detection strategy begins mostly with a rapid first screening to select suspicious exons. Since all mutations are heterozygous, the techniques performed in routine look for heteroduplex (dHPLC, HRM). Then, a direct sequence of some suspicious exons can be done. Two independent blood samples should be collected to check any positive result on another independent sample from the patient. The result should be given only to the person associated to the medical consultation. What ever the result, there given directly to the patient. Any mail, fax or e-mail should be avoided.
If positive, the patient is encouraged to diffuse the result toward his family. Specific surveillance and preventive treatment can then be proposed to the patients. If the result is negative, the existence of the genetic predisposition cannot be cancelled only with these results. The interpretation to a negative result is either the lack of sensibility in the technique used or the responsibility laid on another unknown gene. Some case without any mutation can also be phenocopy that means they have a non hereditary cancer. That is why, it can be valuable to test an other patient with a breast or ovarian cancer in the family. With a negative result, the residual risk of predisposition has then to be assessed only with the family history.

In between, some result would conclude to a polymorphism which has no impact on the disease history. There is would get an unclassified variant which should be analysed further to conclude to any responsibility. Some methods have proposed to better classify those unclassified variants with unknown significance in the risk of cancer. Only deleterious mutation will lead to genetic tests for all the family members.

Test other family members
When a deleterious mutation is found in a family, the genetic tests proposed to other members of the family is only focused on the deleterious mutation identified. The time to get the result is shortened. In those other member of the family if the test is negative, they can be considered with a risk equal to the risk of the general population. However, a recent study have raised a disturbing possibility that even with a negative-mutation result, women in those families still have between two and five times more risk to develop a cancer than women in general population. In fact, since there are a large number of individuals with a breast cancer in those families, individuals are usually under a high level of surveillance and often fully aware of the risks.

If the test is positive, medical follow-up can be proposed. Then a negative test result is a very important information for an individual in family with a deleterious mutation.

Database and interpretations
In the international database (Breast Information Cancer / http://research.nhgri.nih.gov/bic/), a large panel of mutations has been described. For BRCA1, 1643 different mutations have been reported with 52% reported once. For BRCA2, 1643 mutations have been reported with 54% reported once.

For both BRCA1 and BRCA2, there is a large diversity. In some populations, one or few mutations are associated with the large majority of predisposition breast cancer associated to BRCA1 and BRCA2. For instance, in the Dutch families, two large rearrangements represent 36 per cent of the described mutations. This phenomenon is described as a founder effect. In the Ashkenazic families, they are three recurrent mutations. In Iceland, BRCA2, 999del5 covers most of the mutations.

Usually, clearly deleterious BRCA1 and BRCA2 mutations are frameshift or non-sense mutations. Because the real function of those two genes just begins to be understood, there is few clues to classify missense mutations.

Surveillance of a inherited breast-cancer background
The follow-up of individuals at risk is managed after a precise quantification of the cancer risk. Generally, those preventive actions target only individuals bearing in BRCA1/BRCA2 mutation and those with a high probability to bear any mutation. It should be mentioned here that the use of an oral contraceptive is allowed. Up to now, no clear increase in breast cancer has been associated to in general population. In contrast, hormone replacement therapy (HRT) should be discussed in this population. Certainly, high level of estrogens/progestins should be avoided in this population, but the exact consequences are undefined. However, short term HRT for women who undergo prophylactic bilateral salpingo-oophorectomy at early age should be considered. Short term HRT does not seem to decrease the risk reducing effect of PBSO.
**Screening for breast cancer**

The surveillance of women with high risk of Hereditary Breast Cancer should be done in multidisciplinary state-of-the-art breast centers. Monthly self-breast examination starting at age 18 has been recommended, although no significant reduction in breast cancer mortality has been shown. Semiannual clinical breast examination at age of 25 is usually recommended; the proportion of cancers detected by clinical breast exam varies from 0 to less than 5%. Until recently, only clinical breast exam and annual mammography from age 25 was recommended. Nowadays, the most sensitive screening approach uses four modalities to detect breast tumors early on: clinical breast exam, mammography, breast ultrasonography, or MRI. The screening interval is usually 6 months and combines one or more of these modalities.

**Mammography**

A meta-analysis of the efficacy of screening mammography had shown a reduction in breast cancer mortality by 16% in women whatever their age. The first criteria to measure the efficacy of screening mammography is the number of interval cancers which raise in between two screenings and present as a palpable mass after a normal screening examinations. Among 10 series, 29% of incident tumors were interval cancers. Those interval cancers were found more commonly in the women younger than 40 years of age. The sensitivity of mammography is influenced by age, breast density and the time of development of breast tumors.

In BRCA mutation carriers, the sensitivity of mammography is low, with a high risk to have interval cancer, of up to 50%. One explanation may be the rapidly growing “basal-like” phenotype found in BRCA1-associated cancers. Due to its high specificity, from 90 to 100%, annual mammography is recommended in high-risk women, but in association with other modalities of surveillance.

**Ultrasonography**

Annual screening ultrasonography has been found to add sensitivity to mammography, particularly for women with dense breasts.

**Magnetic Resonance Imaging**

Unlike mammography, breast density does not influence magnetic resonance image quality. Contrast-enhanced MRI has been reported to have 70 to 100% sensitivity in BRCA mutation carriers (compared to about 40% for mammography) and a specificity ranging from 80 to 95%. Annual bilateral MRI starting at age 25, as an adjunct to mammography, is now recommended. Using these modalities interval breast cancers are equal or less to 10%.

**Screening for ovarian cancer**

Twice-yearly transvaginal ultrasonography and serum CA 125 measurements are usually performed although they have not shown to downstage ovarian tumors or improve survival. The management of Hereditary Breast Cancer as well as ovarian cancer has been reviewed.

In France, the modalities for the follow-up of predisposed women were proposed by a group of experts in 1998 and revised in 2004:

- Clinical breast examination two to three time a year, from the age of 20
- Yearly bilateral mammography from the age of 30 -year-old, even 25
- Yearly breast ultrasonography, moreover with high density breast
- Yearly MRI. Due to its high sensitivity, bilateral MRI every year in comparison to mammography, has been introduced in routine practice in 2004.
**Strategy for reducing risk**

Other preventive options than surveillance include chemoprevention and surgery.

**Surgery**

Preventive surgery aims to reduce cancer risk and mortality. Risk-reducing options are prophylactic bilateral mastectomy (PBM) and prophylactic bilateral salpingo-oophorectomy (PBSO).

No randomised, controlled trials of prophylactic surgery have been conducted. Most of studies are retrospective or prospective cohort studies.

Mastectomy cut the risk of breast cancer by 90% in mutation carriers. Other studies of prophylactic bilateral mastectomy in high-risk women have been published. All studies results are consistent with a high risk reduction of breast cancer, ranging from 85-100%.

Salpingo-oophorectomy is an important preventive intervention for mutation carriers and cut the risk of gynaecologic cancer by 80 to 96 per cent. Furthermore, with this intervention, the risk of breast cancer is approximately cut by 50 per cent probably due to the induction of premature menopause. This intervention is recommended for women older than 40 years old and with a familial project closed. However the earlier the PBSO is performed, the greater is beneficial effect. Hormone replacement therapy should be considered in these young women. A short hormone replacement therapy after a salpingo-oophorectomy does not seem to modify the risk reduction.

Although highly effective, PBM and PBSO do not entirely prevent the risk of subsequent breast or ovarian cancer. For example, a 0.2% annually risk of peritoneal cancer after PBSO has been reported.

**Chemoprevention**

The development of SERMs like Tamoxifen has improved survival in breast cancer. In the primary prevention setting, Tamoxifen given for five years was shown to reduce the incidence of breast cancer by 43% in woman at increased risk. Other trials have shown a reduction in breast cancer incidence in high risk women. There is some evidence in the reduction in the risk of contralateral breast cancer both in BRCA1 and BRCA2 carriers. The results of trials tamoxifen are contradictory and several studies have not proven a risk reduction in breast cancer incidence. Moreover, concerns over the side effects discourage widespread implementation of tamoxifen. All trials indicated increased risk for thromboembolic events (OR = 2.21 [CI 1.01-2.24]), endometrial cancer (OR=2.42 [CI 1.46-4.03]) and stroke (OR = 1.50 [CI 1.01-2.24]). Another SERM, Raloxifen may confer a similar risk reduction with lower side effects.

In France, no official indication has been approved by a national drug agency. In contrast, the FDA has approved the use of Tamoxifen as a preventive agent for high risk women only. Other anti-estrogens like Aromatase Inhibitors (AIs) have been proposed in control trials. They seem to surpass Tamoxifen in terms of both efficacy and tolerance. However, it should be underscored that AIs will be effective only in post-menopausal women. Randomized trials are in development.

No randomised controlled trials of oral contraceptives to prevent breast and ovarian cancer have been published. Observational studies indicate associations between oral contraceptives and reduced ovarian cancer in the general population as well as BRCA1/2 mutation carriers. Case-control studies have demonstrated a substantially lower risk in women with have had three or more years of exposure to oral contraceptives (up to 60%).

**Treatment**

The great majority of studies on survival in hereditary breast cancer do not identify a survival difference between mutation carriers and non carriers. Currently, mutation carriers are treated with the same protocols than all the patients with breast cancer, particularly with adjuvant therapy. The
existence of a mutation does not seem to have an impact on the efficacy or on toxicity of treatment. However, due to the high incidence of in-breast tumor recurrence as well as of second ipsilateral primary tumor, the indication of a full mastectomy should be discussed.

The high risk of contralateral breast cancer –25 to 30% at 10 years- shall be taken into account and a prophylactic mastectomy can be also proposed, although this risk may partly be reduced by PBSO and/or chemoprevention.

Novel therapeutic approaches are now proposed. Several preclinical data support the hypothesis that BRCA-deficient cells are more sensitive to particular chemotherapies. The reason for that may be the role of BRCA genes in DNA repair, especially DNA double-strand break repair. Thus, BRCA deficient cells may be more sensitive to alkylating-agents like cisplatin and mitomycin. Clinical trials addressing these issues are ongoing. Other strategies that may also take advantage of the specific DNA repair defect in BRCA-deficient cells are currently being tested, like poly(ADP)-ribose polymerase (PARP) inhibitors. Actually, the inhibition of PARP results in accumulation of double-strand breaks in BRCA-deficient cells. Phase I and II studies are in development.

Altogether, BRCA-associated cancers should be treated like sporadic breast cancers bearing comparable clinical and pathological features. However, local treatment should be discussed regarding the high of second primary breast tumors.
Chapter 5
Breast Imaging
Breast Imaging

Breast Cancer is the most frequent cancer in women in western countries where it accounts for 27% of all female cancers. Imaging techniques play a major role in early diagnosis, evaluation and look out for treated breast. Early detection of breast cancer allows a decrease in the mortality rate by 20–30% in women aged 50 or older. Current screening practice is based on conventional or digital mammography. Ultrasound may be complementary to explore masses. MRI plays a major role in the detection of breast cancer recurrence in treated patients, in the diagnosis of homolateral multifocality extension or contralaterality and in the screening of women with high risk of breast cancer BRCA1 and 2. Biopsy under stereotactic, ultrasound or MRI guidance have been developed in order to optimize the diagnosis and to organize the best treatment.

BREAST IMAGING MODALITIES

MAMMOGRAPHY

Techniques

High quality mammography requires efficient equipment and trained radiologic teams. All mammographs need approximately the same designed generators (tungsten anod system, molybden target or rhodium target for dense breast photo-timing, small focal spot sizes) but there are two types of signal reception: Classical Screen Field Mammography (SFM) that requires scatter-reducing grid, and high definition films, and more recently Full field digital mammography (FFDM): this technique is divided in CR (Computed radiology) where ERLM Screens receive the signal that is then read by laser spot or DR (Digital Radiology); in this former the detector transmits the signal to a numerical reading system. FFDM permits acquisition, storage and facilitates the comparison. It has been demonstrated that FFDM offers quite the same accuracy in terms of detection and diagnosis of breast pathology, especially for the examination of dense breast tissue and for the microcalcifications. FFDM and SFM offer the same specificity (almost 92%) and quite the same sensibility except in the subgroup of dense breasts (BIRADS 3-4) of women under 50 years old. FFDM is now also available for the Breast cancer screening, subject to quality control as in SFM. Physical examination should always precede mammography.

Mammography in every technique uses compression of the breast between parallel rigid plates, permitting projection of the breast unto the surface film. The dose delivered to the breast should remain within acceptable limits and seems to be lower with FFDM. Usually crano-caudal and oblique views of both breasts are obtained. For the cranio-caudal view the breast must be well drawn, centered, the nipple perpendicular projecting out of the breast. The oblique view compresses the breast along a 45 to 60-axis (the beam parallel to the pectoralis muscle extending from the axilla to the lower quadrants of the breast) and projects more breast tissue than straight lateral view. Additional views are obtained completing the check: Mediolateral side view permits to localize an abnormality. We will choose mediolateral or lateromedial access depending if the image is in the outer or in the inner quadrant (minimal distance between the image and the receptor); the magnified views in SFM and high resolution, if possible magnified views in FFDM complete microcalcifications analysis. For the examination of a densification or a mass it could also be useful to rotate the breast or to use a small compression plate to differentiate normal breast tissue from a true mass. The analysis of microcalcifications require magnified views in high resolution to identify the morphology and shape of the group.

Some techniques are developing like Digital Breast Tomosynthesis: In Tomosynthesis the breast is compressed in the same manner but the X-ray tube allows the acquisition of many low dose images rather than only one on FFDM. Then these slices are reconstructed by 3D software. This new technique is in evaluation for analysis of densification and geometry of clusters of microcalcifications.
**Normal mammographic pattern**
On mammography, breast parenchyma is separated from the skin by a radiolucent layer of subcutaneous fat. The glandular elements are prominent in the upper outer quadrant with the ductal structures converging to the nipple. The parenchymal cone of the breast is delineated from the chest wall by the retromammary fat. Curvilinear dense structures coursing through the breast are seen and correspond to connective tissue and vessels. In premenopausal women, the breast appears dense on mammography. After menopause, the breast is often more radiolucent and it could become easier to detect abnormalities.

**Diagnosis in mammography**
In mammography, mass developed in the three following locations are more suspicious for malignancy: Internal quadrant, Retroglandular lipomatous region and no man’s land. The main etiologies of round opacities are given in table.

**Opacities** can be masses and density, or architectural distortion. A mass is a lesion that occupies a volume. It can be qualified by its shape round, oval, lobular or irregular. The Density of a mass is important only when lipomatous composant is seen permitting the diagnosis of intramammary lymph node, hamartoma, lipoma, galactocele, steatonecrosis. Small cancer is often not very dense. The margin (FIG 1) is also pejorative when not circumscribed but microlobulated, obscured by adjacent tissue, indistinct or spiculated. The margin of the mass is often obscured by surrounding tissue and localized view with small compression can be useful for a better analysis. Benign lesions often provide well-circumscribed margins but this former can also be seen in 8% of malignant tumors especially in medullary or mucinous carcinomas. The margin of a mass is the most important factor in breast diagnosis: PPV for cancer increases from circumscribed (less than 10%) to spiculated (VPP more than 95%). Architectural distortion is rupture of normal architecture with no visible mass.

![Figure 5.1: Margin of a Mass](image)

**Microcalcifications** are the best tool for the diagnosis of infra-clinical cancer in the in situ form (that is contained in the duct without breach of the basement membrane). The microcalcifications are described by their distribution in the breast tissue (diffuse ou grouping), their number, their morphology and their size. Numerous calcifications throughout the breast with a diffuse distribution are usually due to benign nature. Regional, segmental or linear distribution is often suspicious for malignity (FIG 2). Fine pleiotrophic calcifications and fine-linear or branching calcifications are the most suspicious for malignity. Mme Le Gall described a classification based on the morphology of the microcalcifications in relation to the risk of cancer.
Type I Microcalcifications (rim-like and tea-cup calcifications) are always associated with benign lesions. The type V corresponds to intraductal linear or branching microcalcifications and is associated with carcinoma in more than 90% of cases. Histologically, they represent intraductal calcifications of necrosis. The other types of microcalcifications are associated with variable risk of carcinoma. Another important criterion is the shape of the cluster as described by Lanyi: linear, triangular oriented towards the nipple or angular outline are suspect of cancer. Associated signs can be useful like macrocalcifications, skin abnormalities, nipple retraction.

ULTRASONOGRAPHY
Ultrasound is an important complementary imaging technique to physical examination and mammography. Mammography will always be first acquired for breast diagnosis. The only exception can sometimes be the case of a young woman with no past history, whose prior ultrasonography shows a palpable cyst or a mass typical of fibroadenoma. But one must always keep in mind the possibility of breast cancer also in very young women.

High frequency linear array transducers must be used (from 7 to 14 MHz) to correctly explore this superficial organ. New sonography units are performing with new software like Spatial or Frequency compound, Doppler imaging and Harmonic Imaging and Elastography. The examination is performed with the patient in supine position, sometimes slightly oblique to permit the lateral part of the breast to be scanned with the arm raised. The major indications of breast ultrasound are the differentiation between cyst and solid mass, the exploration of a palpable abnormality not clearly visible on mammogram (dense breast, protheses, mammographic opacity seen on only one incidence) or when the lesion cannot be radiographed (axillary or submammary locations). Guided aspiration, biopsy, or needle localization can be performed under ultrasound guidance.

Diagnosis in Ultrasonography
Ultrasound is essential for diagnosis of masses. It enables to characterize a cyst as simple, complicated or complex (FIG 4). When this mass is not a cyst, Ultrasound permits to evaluate the degree of suspicion with description of shape, margins, orientation, boundary, internal echo pattern and posterior
acoustic feature. It will appreciate the shape which can be oval, round or irregular. The margins can be circumscribed, angular, microlobulated or spiculated. The orientation of the mass is parallel or non-parallel to the cutaneous surface, parallel axis of the mass being an argument for benignity. The boundary of the lesion is also important, abrupt interface is often benign, but more or less hyperechogenic halo can be seen in malignant lesions or abscess. The type of internal echo pattern is also important as posterior acoustic feature (no features, enhancement or shadowing). Shadowing is not a specific sign of malignant lesions and enhancement can also be observed. Macro or microcalcifications can sometimes be seen especially if they are included in a mass but ultrasonography is not a good exam for calcifications.

**Figure:** Vacuum Assisted Breast Biopsy guided by Ultrasonography

**GALACTOGRAPHY**

Galactography is a retrograde injection of water-soluble contrast material (2 ml) into a duct followed by magnified views. This procedure is indicated to explore a unilateral spontaneous serous or bloody nipple discharge localized in a single duct.

The procedure is always performed after an initial mammographic, ultrasonographic study and after samples of discharge for cytologic analysis. The injection provides an opacification of the ductal cavity. Pathologic signs are ectasias, stenosis, cut off, intraluminal defects and rigidity or deviation of the duct. Unfortunately these signs can be observed in benign and in malignant conditions so that surgery is often required. The main interest of galactography remains in pointing out the causal duct to program pyramidecotomy or to identify peripheral lesions that could be missed by standard surgical duct excision.

**Pre-operative needle localization procedure**

When a non-palpable doubtful lesion is detected by mammography, accurate guidance for the surgeon is necessary to permit the excision of this lesion while sacrificing the smallest amount of surrounding tissue (minimal cosmetic defect for benign lesions). Localisation techniques can require the introduction of a needle in close proximity of the lesion. It can usually be performed under mammographic or ultrasonic guidance; sometimes CT or even when available MR can be used. Sometimes with surgeon’s agreement a simple skin marking can be sufficient. When preoperative localisation is made by mammographic procedure, the lesion must be seen on two prior orthogonal views. The view with the shortest mammographic distance to the lesion is chosen. Stereotactic devices permit to work out the space-coordinates of the lesion. Then the needle is passed in the direction of the beam and a wire hook can be left in place. The two next mammographic views control the good position of the needle tip which optimally is within 10 mm of the lesion. After removal of the lesion, an excised breast tissue radiograph must be done to control the complete removal of the abnormal tissue. (FIG 5)
Helical computed tomography with iodine contrast injection is often used with success in quite the same indications of Breast MRI, the main limitation of its use being exposition to radiation. However this seems not to be a limitation in examination of the tumoral size and diagnosis of multifocality in breast cancer, in diagnosis of the recurrence in the treated breast, in the pre-operative location of lesion without mammo or ultrasonographic translation. The advantage of CT is the supine position of the patient like in ultrasonography, in opposition to MRI. It allows an easier comparison of the two methods and to complete an eventual positive CT by a targeted ultrasonography. Dedicated breast CT are actually in developpement.

Contrast breast MRI has been shown to have very high sensitivity in the detection of breast cancer, superior to 95 % but also varying specificity depending on the type of examined breast ranging from 40 to 80 %. False positive diagnoses are proliferative fibrocystic disease, adenomatous fibroadenomas, radial scars, fat necrosis, intramammary lymph nodes and breast parenchyma after surgery (during 6 months) or radiation therapy.

The main indications are screening in high risk women, search for primary breast cancer in patients with metastatic axillary lymph nodes, differenciation between benign post therapeutic changes and local recurrence in a breast treated for cancer, monitoring neoadjuvant treatment efficacy. Sometimes
it is used for the assessment of difficult cases after standard imaging. Diffusion weighted MR or Proton Spectroscopic Imaging following dynamic contrast breast MR are in evaluation for the diagnosis of masses and in monitoring of the tumoral size with neoadjuvant treatment indications.

**MRI technique**

Patients are studied in prone position with a dedicated coil and the exam is uni or bilateral. MRI with contrast injection brings to light tumoral neoangiogenesis. The exam includes T2 slices, T1 slices before and after bolus administration of contrast medium, with or without fat suppression. Some post-processing techniques can be used like image substraction, maximum image intensity... High resolution spatial technique is very important for assessing morphological features but kinetic informations about enhancement are also considered.

**MRI diagnosis**

Abnormal enhancement is defined as enhancement of higher signal intensity compared to the normal glandular tissue on contrast-enhanced images. It will be defined as a mass or a non-mass like enhancement. Masses are defined by their shape, margin and internal enhancement. Malignant lesions typically have an irregular shape, spiculated margins and heterogenous or rim internal enhancement. Benign lesions are more often round or oval, with smooth margins homogenous internal enhancement or sometimes dark internal septations. Abnormal enhancement can be a non mass. When its size is less than 5 mm, it is called focus and cannot be taken into account when there is no concordant mammographic or sonographic sign. Non mass enhancement can be described by its spatial distribution as ductal, segmental, regional or diffuse distribution and its internal enhancement pattern (homogenous or heterogenous, punctuate, clustered...). Kinetic analysis includes initial enhancement and time intensity-curve shapes that can be described as three types: a persistent curve (continuous enhancement increasing with time) often seen in benign lesions, a “plateau curve” or a “washout” curve defined as a decrease in signal intensity after an initial peak often suggestive of malignity.

**ISOTOPIC BREAST IMAGING**

Positron Imaging Tomographic Scanning is usually used with 18F-fluorodeoxyglucose (FDG) as early evaluation for neoadjuvant therapy efficacy. Some new markers like FES (16alpha 18 F-fluoroestradiol-17béta) are in evaluation in some indications. Some teams use PET scan for the initial evaluation of neoadjuvant therapy effect.

**GUIDED BREAST SAMPLING**

Imaging modalities are very useful to guide biopsy of non palpable suspicious lesions. The goal remains to avoid useless surgical approach for many benign lesions but also to prove invasiveness and to specify pathologic and immunohistochimic features of carcinoma. This procedure implies efficient collaboration between clinician, surgeon, radiologist and pathologist. Patient information and acceptance is required before each procedure. After biopsy multidisciplinary consultation is necessary to verify radiologic and clinical comptatibility with the pathologic result and for consensual management of images especially when the result is benign.

The sampling can be simple fine needle aspiration (FNA) for cytologic analysis and core needle biopsy (CNB). FNA provides cytologic information that is often sufficient for palpable lesions especially depending on the experience of pathologic and radiologic teams but in certains types of lesions, the sensitivity is very low. Biopsy provides better sensitivity (more than 95 %) especially with the technique of vacuum assisted breast biopsy.

The modality of biopsy guidance is chosen depending on the accessibility and the best imaging of the lesion. It can be stereotactic guidance which is especially efficient for the diagnosis of microcalcifications, with 11 or 8 vacuum core. Ultrasound-guided biopsy can be performed with 14 G automated gun biopsy but also more recently with vacuum-assisted core 11 and 8 G with very good results. (FIG 6). MR guided needle localization and now biopsy system are developing but it still is a time and machine consuming procedure.
Breast Imaging

Breast diagnosis

The Breast Imaging Report and Data System (BIRADS) of the American College of Radiology (ACR) is today largely used in most of the countries where breast cancer screening is implemented. At the beginning, BIRADS was only devoted to mammography but the fourth version of the American edition, published in 2003 is completed by ultrasonographic and MRI lexicon. BIRADS lexicon includes a list of mammographic, ultrasonographic and MRI terms and an atlas containing illustrations of each feature. In France the Société Française de Radiologie translated the BIRADS lexicon in classification “ACR” The aim of this classification is to standardize the terminology in each report, to deliver recommendations of the action to be taken, according to the probability of breast cancer risk. It permits also assessment of the findings and audit of screening programs.

The first item concerns the composition of the breast: type 1: fatty breast (less than 10% of dense tissue), type 2: fibroglandular (10-49% dense tissue), type 3: heterogeneous dense (49-90% of dense tissue), type 4 dense and homogenous (more than 90% dense tissue). Breast density is an independent risk factor for breast cancer and also decreases mammographic sensitivity. Additional ultrasonography is often useful to complete the mammographic examination in type 3 or 4 breasts. Then report describes each breast according to breast lexicon in mammography, ultrasonography or MRI when done, and the final conclusion is delivered according to the following BIRADS categories, taking into account the worst classification.

<table>
<thead>
<tr>
<th>BIRADS 0</th>
<th>Incomplete, need for an additional imaging evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIRADS 1</td>
<td>Normal. Normal interval follow up</td>
</tr>
<tr>
<td>BIRADS 2</td>
<td>Typically benign. Normal interval follow up</td>
</tr>
<tr>
<td>BIRADS 3</td>
<td>Probably benign. A short interval follow up is recommended: 4 month follow up for masses and 6 months follow up for microcalcifications</td>
</tr>
<tr>
<td>BIRADS 4</td>
<td>Suspicious abnormality: a biopsy should be considered</td>
</tr>
<tr>
<td>BIRADS 5</td>
<td>Highly suggestive of malignancy. Surgery should be performed. Sometimes with prior Biopsy for neoadjuvant therapy or when sentinel node imaging is included in treatment</td>
</tr>
<tr>
<td>BIRADS 6</td>
<td>Histologically proven malignancy. Imaging is performed for cancer staging or evaluation after neoadjuvant therapy</td>
</tr>
</tbody>
</table>

However this classification doesn’t take into account extra-technical elements important in breast diagnosis like the patient’s age, past or familial history, risk factors for breast cancer like BRCA 1 or 2 mutations nor does it give elements of clinical examination. These elements can change the management of an image.

MAMMOGRAPHY:

TYPICAL BENIGN ASPECTS BIRADS 2

Some masses and clusters of calcifications may be qualified of typically benign, and necessitate no subsequent control

BENIGN MASSES

Normal intramammary lymph nodes are usually small (less that one centimeter) and located in the upper outer quadrant of the breast, near a vessel. It is typical when it has a central or lateral lucency corresponding to the hilar notch. In sonography it can be an oval mass, normal when large hilar hyperechogenicity and fine homogenous cortex are seen. In MRI it is often an oval mass with circumscribed margin with hilar hyper T1 and T2, hypo T1 with fat saturation. But enhancement can be early and intense. Masses with fatty components (FIG 7) can be identified as benign like Hamartoma (as breast in breast in mammography and in ultrasonography). It can also be oil cyst, lipoma or
galactocele. Architectural distortion can be also classed BIRADS2 when it is clearly related to prior surgery and not modified on successive mammograms.

![Intramammary lymph node](image1.png) ![Hematoma](image2.png)

**Figure:** Typical Benign Breast Mass with lipomatous changes

For diagnosis of a well circumscribed mass, ultrasonography is necessary to distinguish between cyst and tissue mass. Cysts may be round, oval or flat, well circumscribed with abrupt interface with the normal breast tissue and often anechoic with posterior enhancement. A typical cyst can be classified BIRADS 2 (FIG 8). Atypical cyst because complex (association of anechogetic and solid parts) or complicated (not anechogetic) is classified as suspicious (BIRADS 4) and may necessitate aspiration with cytologic analysis.

![Circumernal mass](image3.png) ![Pneumographic mass](image4.png)

**Figure:**

![Multiple Cysts, BIRADS 2](image5.png)
TYPICAL BENIGN CALCIFICATIONS, BIRADS 2
Calcifications that can be identified as always benign on mammography are typically large, coarse, round. It can be skin, suture, vascular calcifications, “eggshell type” calcifications in cysts, coarse or pop-corn like of fibroadenoma. Linear Macrocalcification are often associated with ductal ectasia but at the early stage it can be difficult to distinguish them from ductal cancer. Round calcifications associated with lucent centered calcifications, diffuse distribution of punctuate calcifications are also benign in aspect. Deposit of calcic milk in microkystic dystrophy will give the aspect of curvilinear upwards appearance on mediolateral view or tea-cup aspect.

PROBABLY BENIGN IMAGES, BIRADS 3
The primary rationale behind probably benign assessments is to reduce false-positive recommendations for biopsy while maintaining an acceptably high detection rate of early-stage cancer. The likelihood of malignancy in these lesions is defined to be under 2%. These lesions must be controlled over a period of at least two years. Neither age of the patient nor size of the lesion modify the attitude of surveillance of these images as demonstrated by Sickles. On the other hand if this surveillance may be impossible or difficult (pregnancy, hormonal treatment ..), biopsy may be indicated. The same is true of such lesions for women with high risk for breast cancer. Three types of mammographic lesions can be assessed as probably benign: circumscribed masses, small clusters of round (or punctate) or oval calcifications and focal asymmetry.

Fibroadenoma (FAD) is the main tumor of the young woman (FIG 9). Well circumscribed in mammography and in ultrasonography, the mass will often be homogenous, oval or macrolobulated (3 or less lobulations), the main axis being parallel to the cutaneous surface. This aspect is sufficient to evoke a FAD that should be controled 4 months later. Sometimes MRI is performed for another cause and typical aspect of ADF in MRI must be known: a circumscribed mass with smooth margins hyper or iso on T2 weighted sequence, hypo T1 with homogenous or heterogenous pattern with dark septationsand enhancement. Kinetic analysis of enhancement curve often shows persistent curve (continuous enhancement increasing with time). If a mass suggestive of FAD changes, it should be classified BIRADS 4 and be biopsied in order to permit differential diagnosis of round benign or malignant tumors (FIG 10)

Figure: Fibroadenoma, BIRADS 3

SUSPICIOUS ABNORMALITIES, BIRADS 4
This category groups together many images with various levels of risk for cancer but likehood of carcinoma more than 2 % makes histologic study necessary. This former will be done with percutaneous biopsy. In this class are included: New clusters of few fine pleomorphic calcifications (FIG 11), amorphous or indistinct calcifications, numerous punctate regular microcalcifications which shape of cluster is not round nor oval, coarse heterogenous calcifications, Architectural distortion without known scar, Assymetry of density with convex margins, Non cystic mass with microlobulated margins, obscured or recently increased, Spiculated images without dense center that are sometimes due to a radial scar but which can be associated with carcinoma like tubular carcinoma
Figure: BIRADS 4 Metaplastic carcinoma

Figure: Suspicious Image, BIRADS 4, Biopsy : In Situ Carcinoma

HIGHLY SUGGESTIVE OF MALIGNANCY IMAGES, BIRADS 5
In these images, the likelihood of malignancy is high and the biopsy before surgery has strategic interest to precise the pathologic, immuno-histochimic or even genomic charateristics of the tumors. But sometimes such BIRADS 5 aspects can be observed in some benign lesions like FAD. Highly suggestive of malignancy are spiculated masses with dense centers (FIG 12), III defined masses with irregular margins (FIG 13), irregular spiculated masses with associated pleomorphic calcifications. For the calcifications, numerous fine pleomorphic calcifications, fine linear or fine-linear branching calcifications (FIG 14), linear or segmental distribution of calcifications whatever their morphology, are very suspect of malignancy.

Figure: Suspicious malignant mass, BIRADS 5
**IMAGING OF BREAST CANCER**

Invasive ductal carcinoma is the most common breast cancer histologic type (70-80% of all cases). Invasive lobular carcinoma is the second most common histologic type (5-10%). This form is associated with a high rate of multifocality and bilaterality. Other less common cancers are the tubular, papillary, medullary and mucinous cancers. Sarcomas, Phyllod tumors grade 3, Angiosarcomas and Lymphomas are other types of malignant tumors. When basement membrane is intact, the carcinoma is called in situ: ductal in situ (DCIS) or lobular in situ carcinoma (LCIS). 30-50% of DCIS will develop invasive form in the next 10 years. LCIS is considered to be a marker of increased risk for invasive cancer of all forms.

**Preoperative staging.**

Mammography is always the first exam to be done. In women with dense breasts, the sensitivity of mammography can be low (around 68%). About 10% of cancers are mammographically occult. Ultrasonography is a good complement to mammography especially in the case of dense breasts. Questions to be checked are tumoral size, multifocality or multicentricity and controlaterality.

**Tumoral size:**

Mammography is performant to determine the tumoral size when the breast is fatty or little dense. The measure is more accurate when the opacity is round than when it is spiculated and in that case the measure must take into account the dense center and the spiculated continuations, where tumor can also...
be seen. But mammography fails to determine exact size of a tumor when the breast is dense or when the tumor is inflammatory. In these cases, Ultrasonography gives better correlation for tumoral size with pathologic correlations. MRI is good exam for the evaluation of tumoral size because of good correlations with histologic size. In the case of Microcalcifications, size of focus in mammography is very important but in the in situ carcinoma the tumoral size is often underestimated (especially if for low grade tumors). MRI doesn’t offer better size evaluation because of false negatives for CCIS (low or high grade) and can also overrate lesion extension. MRI will offer information about pectoral or chest wall invasion.

**Multifocality- multicentricity- Controlaterally**

When mastectomy was performed instead of lumpectomy for unifocal breast cancer; pathologic analysis found that 20% of cancers had additional focus of carcinoma in less than 20 mm away of the known cancer, 27% had in situ carcinoma and 14% invasive carcinoma at a distance superior to 20 mm; for this reason it appears important to search for other lesions.

The association of mammography and ultrasonography is sufficient in fatty breasts for this approach and MRI doesn’t offer any supplementary aid. But when breasts are dense, MRI is able to detect additional mammographically occult lesions in 30% of cases permitting the diagnosis of multifocality (within different quadrants) or multifocality (within the same quadrant of the breast), more often when the patient has a familial history for breast cancer or in lobular invasive carcinoma (FIG15-16).

Controlateral associated cancer can also be detected in approximately 3-5 percent of cases with normal clinical exam and mammography. However, MRI is a very sensitive technique but not specific enough; so detection of suspicious enhancement must be proved as malignant because it could lead to surgical modification (mastectomy instead of lumpectomy in 17% of cases). Secondly targeted sonography after MRI can find an abnormality in approximately 30% of cases, allowing a biopsy procedure. When there is no sonographic or mammographic translation, histologic analysis should be done by Biopsy under MRI guidance or by surgical approach after CT or MRI localisation procedure. The population that could benefit of this MRI extension assessment could be when cancer is not correctly analyzed (dense breast) or not seen (palpable masses without mammo or ultrasonographic translation, carcinoma lobular invasive, suspicion of multifocality, when a parietal extension is suspected, when radiotherapy could be contraindicated or before beginning a neo-adjuvant therapy.

**Neoajuvant therapy response**

Response to Neoajuvant therapy is important because a complete pathologic response is a good predictor of long term survival. It can be appreciated with Conventional imaging especially for evaluation of unifocal lesion in fatty breasts. Delineation of the lesion is important and there is a high correlation with the size when more than 50% of the tumor margin is seen. When microcalcifications due to the association to in situ carcinoma are present, they can persist even in good responders or they
can appear under treatment secondary to necrosis. The question of surgeons is to identify patients who could have a breast-conserving surgery. MRI is a better exam for the estimation of residual disease than mammography or ultrasonography. But sensitivity for evaluating residual tumor must still be studied because it seems to be perfectible. In some small series, patients without residual enhancement on MRI still had residual lesions on pathologic analysis. On the other hand, MRI is good for detection of non-responder or progression. In broad outline, at the end of the treatment, MRI can depict three types of response: Tumoral stability or progression, Concentric shrinking of the tumor leading to disappearance of the visible tumor, fragmentation of the tumor that is contre-indication for conservative surgery. For predicting early response after initiation of the treatment, MRI, FDG-PET Imaging and MRI Spectroscopy seem to be promising.

**Tumor recurrence after lumpectomy**

Tumor recurrence after lumpectomy occurs at the rate of 10-15% in 20 years, almost 2% per year during the five first years. Follow up consists in a first mammography 6 months after the end of therapy and then annually. Ultrasonography is useful to precise mammographic abnormalities. The comparison of successive mammographies is a precious aid. Normal Aspect: During the first mammographic controls skin thickening and architectural distortion due to surgical scar can be observed. Ultrasonography may be useful to eliminate mass syndrome but doubtful images can be created by post-therapeutical fibrous tissue. Fat necrosis can appear after treatment and the early form can be confusing. Typically it presents like a densification or architectural distortion associated with a fine limited lipomatous image. Calcification can appear in the periphery, typical when clear at the center macrocalcifications, sometimes ambiguous at the early stage and needing an earlier control.

Abnormal aspect: A mass or microcalcifications emergence are usual aspects but can also only be scar modification or densification increase. In these cases, MRI can be very helpful: Indeed in the treated breast, MRI is more specific than in the non treated breast because with radiotherapy, normal or dystrophic breast tissue often does not enhance anymore. So the VPN and the specificity of MRI is very high and allows not to biopsy treated breast if there is no enhancement. When enhancement is observed, biopsy will be performed according to the best radiologic translation.

**Breast cancer Screening**

Mass screening for early detection of breast cancer is available in many countries. In the general population, the risk of breast cancer is 0.6% per ten-years period before 40 years and 2.8% for the fifth ten years period, so one woman per 8 can be concerned. The aim of early detection is to treat earlier and to decrease mortality. The international quality criterions of a screening campaign are a participation rate up to 70%, a reconvocation rate inferior to 7%, a PPPV of biopsy superior to 50% and a rate of interval cancer inferior to 2%. In the general population, screening procedure rests on high quality mammograms and permanent quality control of the complete chain of mammography from the technical acquisition to the radiologist. Clinical examination improves detection. Sensitivity of mammography is better in breast type 1 or 2 than in type 3 or 4 (respectively 98, 85, 83, and 68%). The use of CAD does not improve detection rate and can’t take the place of second reading. The association of ultrasonography in dense breasts clearly improves sensitivity of mammography. There is no indication of MRI in screening of the general population because MRI is less performant than mammography for microcalcifications and it is sensitive but not very specific and the rate of recall may be to important.

On the other hand, it is now demonstrated that screening in the population of women with a high risk of cancer and with genetic mutations like BRCA1 or 2, rests on association of annual mammogram, ultrasonography and MRI, because these young women, who often have dense breasts, also may have round cancer, high grade cancer or interval cancer (FIG 17). The sensitivity of mammography alone is lower and needs the adjonction of ultrasonography if possible targeted after MRI.
Conclusion

During the past ten years, technical improvements have been essential for breast imaging: Evaluation of digital mammography proved to be competent for breast cancer screening, improvement of sonographic installations, extension and evaluation of Breast MRI, diversification of percutaneous biopsy with all modalities of guidance, new technical developments like tomosynthesis, MRI spectroscopy. If primary senologic evaluation always lies on clinical exam, mammography and ultrasonography, it’s now relatively clear that MRI can be essential in care of breast cancer for preoperative staging, evaluation of neoadjuvant therapy response, supervision of treated breasts, but also for screening of women with high risk for breast cancer like genetic mutations BRCA1 and 2 carriers.
Chapter 6
Pathology of Breast Carcinoma
and methods of analysis
Microscopic examination is the definitive means of evaluation of breast disease. The ultimate method of treatment of the patients with breast carcinoma may be determined on the bases of the pathologic findings in the initial breast biopsy. The following sampling techniques are used singly or in combination:

1) **Cytopuncture and Fine Needle Aspiration (FNA)**

Cytopuncture or FNA may constitute the initial diagnostic procedure for palpable breast masses. This technique has been also used to evaluate non-palpable mammographically detected lesions under stereotactic or ultrasound guidance. This method has two limitations: first its accuracy which depends upon the skill and experience of the personnel who perform the puncture, the radiologic guidance for the non palpable lesion, and also the microscopical analysis. Second, the inability to permit a reliable distinction between in situ and invasive ductal carcinoma except when the puncture concerns metastatic lymph nodes.

This technique is the simplest and the cheapest diagnostic method, only little material is required. It is immediately done and gives the possibility to have a nearly instant diagnosis. By being that easy to perform, this has allowed its integration to the consultations associating radiologist and clinicians to ensure a complete diagnosis in one visit. It equally allows a rapid evaluation of the efficacy of neo-adjuvant chemotherapy. This material guarantees the diagnosis of carcinoma, the evaluation of its type but also the measurement of its grade. The immunohistochemistry staining is possible thanks to the cytobloc techniques. The material, formed essentially of tumor elements, is especially adapted to the techniques of cytometry, molecular biology and even the microarray.

2) **Core needle biopsies**

The biopsied material has considerably progressed thanks to multiple technological improvements. First, the development of aspiration needles having variable calibers, starting from 18G, then the aspiration systems which guarantees the possibility to achieve multiple aspiration materials through only one entry site to the lesion and finally the instrument and technique of stereotactic detection or ultrasound allowing the precise millimetric targeting of non palpable lesions.
Today, it represents for most of the countries, where an organized mammographic screening was developed, the first diagnostic method thus allowing the surgical resections to be only limited to patients having malignant lesions (therapeutic surgery) or doubtful lesions (diagnostic surgery).

The handling of the specimens by the pathologist requires learning both for: their management that requires a severely strict protocol having multiple levels of cut sections and also for their microscopic analysis. The pathologist has a double role, performs the most precise microscopic diagnosis on the small size and fragmented material, then confirming the correct representation of the biopsy in relation to the doubtful image.

3) **Incisional or excisional open biopsy**

The pathologic evaluation of the primary excision specimen is a crucial component in the selection and implementation of breast conservative surgery. The following recommendations should be adopted for proper evaluation of the breast specimens:

- The specimen should be presented to the pathologist intact and carefully oriented by means of the suture tags or fixed to a support where the anatomical marks are indicated (Fig. 6.1).
- After measurement, it is inspected for gross margin involvement. If there is evidence that the specimen contains a grossly suspicious lesion that extends to the surface of the specimen, the surgeon, if still operating, is immediately notified about the precise location of the margin involved so that additional tissue can be excised. Prior to cutting the breast excisional biopsy, the surface should be blotted dry and then painted with marker (India ink), which will be visible on the permanent section.

The subsequent steps in processing will depend upon the nature of the specimen, whether it is obtained because of the presence of a palpable mass, and if carcinoma is suspected clinically or radiographically. For these specimens, the specimen should be cut in such a way as to permit examination of the resected margins on histologic sections. The steps of handling of the specimen are outlined in figure 7.1. Briefly, the tumor and the specimen are bisected transversely. The anteroposterior and mediolateral diameters of the tumor are measured. Aliquots of the tumor are systematically conserved in cryopreserved tumor bank when its size is sufficient. The standard method of sectioning varies, depending upon the size of excised specimen.
For evaluating the margins of a breast excision specimen, the specimen is oriented, the margins are painted with India ink, and the specimen is sectioned in various planes (modified from Fisher B et al., 1986, 57: 1717-1724).

**Figure 6.1.**

(A) **Coat surface with India ink**

(B) **Blot Dry**

Palpate for tumor Bisect & specimen & specimen diameters of tumor and transversely partial SI measurement (a) tumor

(C) **Fix remaining hemispheres 1-2 hours**

(D) 7 Place cut surface down

Take sagittal blocks through superior and inferior portions

Blocks viewed from side, each may be transected to give SA, SP, IA, IP margins.

Measure SI diameter of tumor: a+b+c.
For small excisions specimen, the whole tissue is totally included. For larger specimens, a sampling is necessary. After inking the specimen, single incision is made through the center of the palpable mass where it most closely approaches the margin in this way, the size of the tumor and the relationship to the nearest margin can be quickly determined. The remaining margins can then be entirely removed from the specimen and submitted for permanent sections so that representative sections from each of the six surfaces of the specimen are submitted. Multiple sections can then be made through the remainder of the specimen at 3 to 5 mm intervals and several sections to the tumor and the adjacent parenchyma or fat should be submitted for microscopic evaluation. Segments of skin and muscle should be systematically sampled in order to demonstrate their relationship with the tumor.

For the specimen excised because of the presence of mammographic abnormality, in the absence of a palpable mass, the most frequent mammographic abnormalities promoting biopsy are microcalcifications, mass with or without associated microcalcifications, and focal asymmetry. These specimens are usually excised using the hook wire or needle localization technique. Specimen radiography is an essential component in the evaluation of these specimens in order to both, document the presence of the lesion detected by mammography or the clip and localize the suspicious area for histologic examination. The use of frozen sections is limited because many lesions have been previously evaluated by core needle biopsy and for the others; their small size renders difficult or even impossible the realization of a frozen section. After fixation, the entire specimen is submitted for permanent sections. The specimen can be cut perpendicular or parallel to its main axis in serial cut sections.

4) **Mastectomy**

The skin and the nipple are assessed, with sampling of any isolated cutaneous lesions. The tumor size is measured and any evidence of multicentricity is recorded. Adequate histologic sections should be obtained from the tumor mass, any other identified lesion, the nipple parallel and perpendicular to the axis of the main lactiferous ducts and systematically each quadrant.

5) **Axillary lymph nodes**

In mastectomy specimens, the axillary nodes are removed in contiguity with the breast tissue. In patients treated with breast conserving therapy, an axillary dissection usually comprises a specimen containing the lymph nodes which is
Pathology and methods of analysis

separate from the breast excision specimen and requires orientation by the surgeon. The number and size range of the lymph nodes should be recorded. After fixation, once lymph nodes have been grossly identified, they may be bisected or sectioned in slides of 1-1.5 mm and submitted in totality in separate cassettes (fig 7.2). The technique of analysis is critical and directly influences the number and size of metastases identified (fig 7.3). This is crucial car avec la diminution de la taille tumorale induite par le dépistage de masse, parallèlement le nombre et la taille des metastases ganglionnaires diminuent. Lors de l’analyse microscopique, toute zone suspecte doit faire l’objet d’un immunomarquage pour distinguer les envahissements ganglionnaires minimes de lésions bénignes comme les inclusions glandulaires bénignes ou neuronaeviques. Les métastases des carcinomes lobulaires sont particulièrement difficiles à détecter, constituées de cellules isolées et régulières, s’insinuant entre les cellules lymphoïdes normales selon un mode réticulé. Les immunomarquages anti cytokératines réalisés systématiquement pour ce type histologique, identifient dans plus de 10% des cas des métastases non vues avec les colorations standard. Toutefois ceux-ci ne seraient pas associés à un pronostic péjoratif, à la différence des autres types de carcinomes notamment la forme canalaire.

Figure 6.2: Macroscopic axillary lymph node dissection
6) Sentinel lymph node biopsy

In this technique, the lymph node analysis is limited only to the lymph node (or nodes) draining the tumor area. These nodes are detected by injecting a dye or radioactive plotter in the peri tumorale zone, the injection is done in the subcutaneous layer facing the tumor or in peri-areolar region. The sentinel nodes are the first lymph node relay identified by these markers.

The detection of metastasis in the sentinel lymph node, even minimal, leads to a complementary axillary dissection. On the other hand, in case of absence of metastasis in the sentinel node, the risk of finding metastasis in the remaining axillary dissection is so minimal that no excision is done.

These sentinel nodes, requires a rigorous and extensive examination to be perfectly representative of the of the remaining axillary dissection state. Their size, number and color are registered and the suspected zones are systematically looked for.
They are immediately examined, by opposition, and/or by cryostat cut sections with the possibility of immunohistochemical examination thanks to the presence of rapid analysis kit.

Then, they are totally included in separated cassettes and examined on staged cut section levels stained by immunohistochemistry. As required for their identification, their management by the pathologist also requires learning.

7) Frozen section
Despite the obvious limitations, frozen section diagnosis remains to be the most useful tool in the evaluation of breast lesions and sentinel lymph nodes. The clinical data, gross morphology, specimen consistency and mammographic findings, if available, should be taken into consideration. False negative results may be encountered with sampling error or when dealing with a well differentiated tubular carcinoma. False positive results may be obtained in lesions exhibiting sclerosing adenosis and like lesions. In frozen sections of lymph nodes, the largest and firmest nodes should be selected for sampling. Diagnostic difficulties arise in the setting of small intrasinusoidal-subcapsular micrometastases, or nodal deposits of infiltrating lobular carcinoma with pseudoreticular forms.

8) Investigational Tools
As an adjuvant to routine histopathologic examination of breast tumors, additional investigational tools can help improve the evaluation. These tools include immunohistochemistry, cytogenetics and molecular biopsy tests.

Many protein products can be detected by immunohistochemistry, some including estrogen and progesterone receptors, HER-2/Neu oncogene done on a routine basis; other like p53 tumor suppressor gene, proliferation markers, angiogenesis, apoptosis, basal and luminal cytokeratins, EGFR etc. as a complement or for research purpose. Their application should be perfectly controlled and in the frame of using automation, calibrated internal and external control, as part of the quality assurance in order to ensure constant precision and reproducibility. Different European organisations suggest a quality control program.

Molecular biology methods have been developed and adapted in order to be able on fixed and embedded tissues. Fluorescent in situ hybridization (FISH) technique is today the gold standard method for the determination of amplification of her2 gene. Research of deletion and mutation of different genes such as EGFR, K-ras are
possible by PCR and more recently prognostic and predictive molecular signature determined by microarray has been developed.

**Proliferative disease and in situ carcinoma**

<table>
<thead>
<tr>
<th><strong>Table 6.1.</strong> Simplified WHO Histologic Classification of epithelial proliferation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lobular neoplasia</strong></td>
</tr>
<tr>
<td>- lobular carcinoma in situ</td>
</tr>
<tr>
<td><strong>Intraductal proliferative lesion</strong></td>
</tr>
<tr>
<td>- usual ductal hyperplasia</td>
</tr>
<tr>
<td>- flat epithelial atypia</td>
</tr>
<tr>
<td>- atypical ductal hyperplasia</td>
</tr>
<tr>
<td>- ductal carcinoma in situ</td>
</tr>
<tr>
<td><strong>Intraductal papillary neoplasms</strong></td>
</tr>
<tr>
<td>- central papilloma</td>
</tr>
<tr>
<td>- peripheral papilloma</td>
</tr>
<tr>
<td>- atypical papilloma</td>
</tr>
<tr>
<td>- intraductal papillary carcinoma</td>
</tr>
<tr>
<td>- intracystic papillary carcinoma</td>
</tr>
</tbody>
</table>

**1- Lobular Neoplasia**

This type of lesion occurs during a woman’s period of sexual activity, that is to say while the lobules are fully active, and disappears after the menopause. Its incidence represents about 1 to 4% of breast carcinoma. Lobular neoplasia is nearly always diagnosed by incidental microscopic discovery on surgical specimen of patients with microcalcifications or other abnormal radiographic images connected with benign pathology. Microscopically, there is a proliferation of globular cells, which are of the same shape and a little bigger than the neighboring cells, which have slightly bigger nuclei and slightly more irregular chromatin, with vacuolised cytoplasm in places. They fill in the center of terminal ectasic ducts and are able to propagate between the layers of neighboring extralobular ducts in a “Paget” spreading way. The absence of expression of E-Cadherin facilitates their
recognition. About 80% of lesions are multifocal and multicentric and 30% bilateral. Despite their name, they finally represent risk lesions as about 20% of patients treated by lumpectomy alone develop an infiltrating carcinoma after 10 to 25 years.

According to the intensity of the proliferation and the cytology 3 different groups are distinguished:

**Atypical lobular hyperplasia**
This lesion is characterized with small and irregular cells which incompletely filled in the acini, or involved less than half the acini of a lobule. The relative risk is estimated about 4 times the risk of the general population. This lesion could be more associated with an homolateral rather than a bilateral risk of cancer.

**Lobular in situ carcinoma**
The cells are more homogeneous and completely filled the lumen of the majority of acini of lobules in at least a minimum of 2 lobules. Despite the term of carcinoma, this lesion is only associated with a high risk of cancer. After conservative surgery, about 20% of the patients developed homo or contralateral carcinoma. LCIS’s multifocality is brought to light by all authors, and is estimated at 50 to 70% depending on the series.

**Pleomorphic lobular in situ carcinoma or LIN3**
This recently variant of LCIS associates LCIS with specific features
- large distension of the lumen
- presence of comedonecrosis sometimes calcified
- neoplastic cells with large and irregular nuclei

These features might be isolated or more often associated. This variant of LCIS is considered more aggressive, with 20 to 60% of microinvasive areas and unlike the classic LCIS is generally treated by complete surgical excision.

**2- Ductal Carcinomas In-Situ (DCIS)**
Until the 1980’s, this type of cancer was detected either by bleeding of the nipple or a mastosic lump in the breast in which DCIS was discovered, or by Paget’s nipple disease. In even rarer cases, a focus of microcalcifications was found accidentally. Today, it is the opposite, for the majority of DCIS’s are discovered due to an isolated cluster of microcalcifications. In microscopic terms, DCIS corresponds to a proliferation of cells, which vary in shape and size. These cells
proliferate within the lumina of the ducts and do not go beyond the myoepithelial border, which can be proven by appropriate immuno-staining. At the center of certain formations, necrotic areas form with some calcareous degeneration as in comedo-carcinoma. They are characterized by “stick-like” radiological images. Many microscopic forms of DCIS have been reported, both architectural (massive, comedomatous, papillary, cribriform, clinging ...), and cytologic (with big, small, apocrine or clear cells ...).

Until 1970, mostly comedomatous forms were discovered due to bleeding and/or tumoral masses and the treatment chosen for breast cancers in general, and in situ forms in particular, was mainly surgical, by mastectomy according to Patey or Halsted due to widespread diffusion to the mammary gland. But the development of screening campaigns has gradually brought about patients being operated on due to radiological signs alone, without any clinical symptoms. These infraclinical forms are the subject of this chapter, and the proportion of in situ carcinomas is increasing more and more, parallel to a decrease in size.

At the same time, came the idea of women, with early cancers, keeping their breast. This brought about a revision of therapeutic protocol. Moreover, after proving that small infiltrating carcinomas could benefit from “conservative” treatment, it seemed unethical that women with carcinomas with even better prognoses “intraductal forms” should continue to undergo mammary amputation. The first studies carried out confirmed the validity of conservative treatment but also observed a high number of relapses, linked to different factors like the size of the carcinoma and its histologic shape. Consequently, from 1988 onwards when EORTC held an initial consensus meeting, the separation of DCIS into 2 different types was recommended: the large cell type, or “comedomatous”, and the small cell type or “non-comedomatous”. This distinction was made from biological and evolutive characteristics: in fact the comedomatous type is pejorative, as shown by the over-expression of C-erb B-2, which is much higher (77%) than in the non-comedomatous type (15%).

Thereafter, another classification was suggested which put forward 3 groups divided up according to nuclear features and the architectural pattern (polarization of cells): the well differentiated type, clinging; the intermediate type, and the poorly differentiated comedo type. Finally in 1995, another classification divided into 3 groups came about, “Van Nuys classification”, based on nuclear grade and necrosis (fig). It was separated into: group 1, with neither high nuclear grade nor necrosis; group 2, without high nuclear grade but with comedomatous necrosis; and
group 3 with high nuclear grade, whatever its architectural shape. This classification is based on a prognostic report study, which confirms the wisdom of certain radical treatment of comedematous types.

Differential diagnosis of DCIS is difficult, from atypical hyperplasia to one hand to invasive carcinoma. L’identification d’une assise de cellules myoépithéliales par immunohistochimie (smooth muscle actine, p63...) facilite le diagnostic de micro infiltration. Par contre malgré les espoirs placés dans l’immunohistochimie, comme l’identification de cytokératines de différents poids moléculaire, pour aider la distinction entre lésions proliférante, atypique et in situ, il n’existe pas à ce jour de marqueurs utiles en cas de difficulté diagnostique.

Clinically, and in relation to infiltrating carcinomas, average age is variable, sometimes significantly younger (50 vs. 54), which gives value to the idea of a “continuum” between in-situ and infiltrating carcinoma, and sometimes nondifferent if there is a high proportion of comedematous forms in the group studied. Moreover, asymptomatic forms “T0” are ten times more numerous than in general breast cancers (55 vs. 5%).

This high multifocality is often underlined in old series which mainly reported comedematous DCIS: it reached nearly 80% in an IGR study. More recently following the work of R. Holland in correlation with radiologists, there appeared a distinction between multicentricity which, is rare and characterized by the presence of multiple neoplastic areas, at a distance from the initial tumor and independent of it; and multifocality, which is more frequent, and corresponds to areas in direct liaison with the tumor, less than 2 cm from it in 40% of cases, and more than 2% from it in 10% of cases, suggesting a segmentary distribution or a gradual invasion (Table 15.3), which reinforces the development of conservative surgery. These observations contrast with the usual absence of axillary node invasion at this stage. As far as evolution is concerned, relapse rate is, on the one hand, connected to histologic classification, which is based on nuclear size and the presence of necrosis, as shown in the majority of recent studies, and on the other hand, to the quality of resection. Les rechutes se font pour moitié sous forme infiltrante et pour moitié reste in situ. Elles comportent les mêmes caractéristiques moléculaires. Ceci souligne l’importance du choix initial de traitement local et la difficulté à trouver un consensus pour sélectionner les patientes pouvant bénéficier d’une résection chirurgicale sans radiothérapie associée, qui représentent de 5% à 30% des patientes selon les pays.
In conclusion, the pathologist in direct liaison with the radiologist and the surgeon, play a capital role both in the diagnosis of DCIS, distinguishing it from atypical hyperplasia or micro-invasive carcinomas, as well as in treatment, by giving details of its boundary of the specimen. However, in reality it is very difficult, even impossible, in spite of the claims of certain authors, to evaluate the size of these DCIS, even if the tumor foci are placed as precisely as possible on the glass slides. The pathologist’s role is to broaden the field, using new techniques offered by modern biology, and to attempt to forecast the forms, which stay local and may benefit from “conservative” treatment, and those which will become multifocal and/or multicentric and which justify mastectomy. Thus, individual treatment of each patient will be better programmed through communal decision.

### 3- Histologic classification of invasive breast carcinomas

#### Epithelial tumors
- invasive ductal carcinoma, not otherwise specified
- invasive lobular carcinoma
- tubular carcinoma
- invasive cribriform carcinoma
- medullary carcinoma
- mucinous carcinoma
- neuroendocrine tumours
- invasive papillary carcinoma
- invasive micropapillary carcinoma
- apocrine carcinoma
- metaplastic carcinoma
- lipid-rich carcinoma
- secretory carcinoma
- oncocytic carcinoma
- adenoid cystic carcinoma
- acinic cell carcinoma
- glycogen-rich clear cell carcinoma
- sebaceous carcinoma
- inflammatory carcinoma

| Table 6.1. |
| Simplified WHO Histologic Classification of breast carcinoma |

**Invasive Duct Carcinoma (NOS)**
This represents the most frequently encountered histologic type of breast carcinoma. Grossly, the tumor appears either well circumscribed, stellate, or shows a combination of both. The stellate variant is associated with extensive fibrosis (scirrhus carcinoma). The size of the tumor is variable and its assessment constitutes an important prognostic parameter. Microscopically, the tumor is characterized by the presence of irregular or rounded solid clusters of tumor admixed with single cells and cords of tumor cells. Based on the degree of tubule formation, nuclear appearance and mitotic activity, the tumor should be graded. In some tumors, an in-situ ductal carcinoma may be found; alternatively both ductal and lobular types of in-situ carcinoma may be present.

**Infiltrative Duct Carcinoma with Extensive In-situ Component**
This variant has been defined as invasive tumor in which 25% of the overall area involved by the invasive carcinoma is composed of intraductal carcinoma. The presence of abundant intraductal carcinoma within the tumor was associated with a tendency to have in-situ component beyond the tumor margin and multicentric carcinoma. However the risk of local relapse as other tumor type is directly dependant of the status of the resection margins.

**Microinvasive Carcinoma**
These are tumors that are predominantly intraductal but focally the tumor cells have barely broken through the basement membrane, invading the stroma immediately adjacent to the defective portion of the duct wall but measuring less than 1mm.

**Infiltrating Carcinoma Presenting as an Axillary Mass**
Breast carcinoma may present as axillary mass in the absence of a clinically, detectable breast tumor. It is possible that some of these tumors actually arise from either the axillary tail of the breast, accessory breast tissue in the axilla, or heterotopic breast tissue in an axillary lymph node.

**Invasive Lobular Carcinoma**
The tumor tends to present either as an irregular infiltrating or well circumscribed, indurated mass. Originally the invasive lobular carcinoma is characterized by a linear growth pattern of small cells in “Indian file” of one cell width. Subsequently, additional patterns of invasive lobular carcinoma were defined including: solid pattern, alveolar pattern, and a mixed group composed of an admixture of one or more of these patterns. Another pattern designated tubulo-lobular has been described. In this variant, tubules formations are arranged along with cords of cells
arranged in “Indian files”. Cytologic variants such as apocrine, histiocytoid and pleomorphic have been also described. This latter form differs from the classic type by its aggressiveness. Infiltrating lobular carcinoma can closely simulate a lymphoma. Immunostains for cytokeratin and leucocyte common antigen (LCA) are helpful in establishing the nature of the neoplastic cells. E cadherin, a membranous antigen which expression is typically absent in lobular carcinoma is helpful for the recognition of these rare variants.

**Tubular Carcinoma**
A distinctive variant of mammary carcinoma characterized by proliferation of angulated tubules separated from each other by a reactive fibroblastic stroma. The tubules display open lumens and are lined by a single layer of epithelial cells. A minimum of 75% of the lesion should display this morphology in order to call this tumor a tubular carcinoma. When such arrangement is present as a minor component the tumor is referred to as a mixed tubular carcinoma. The recognition of tubular carcinoma is important because of its good prognosis and the rarity of axillary node metastases. Tubular carcinoma can be mistaken for sclerosing adenosis, microglandular adenosis and radial scar.

**Invasive cribriforme carcinoma**
This rare type grows mainly in a cribriform pattern similar to that seen in intraductal carcinoma but without any myo-epithelial cells. A minor tubular component is frequently seen. This form is associated to an excellent prognosis. Immunohistochemistry is important to distinguish it from an adenoid cystic carcinoma and intraductal carcinoma.

**Medullary Carcinoma**
Medullary carcinomas are distinctive tumors with pushing expansile margins. Occasionally, they may appear encapsulated. The tumors have fleshy soft consistency and composed of a syncytium of anastomosing cords and sheets of tumor cells separated by loose connective tissue. The tumor cells are round with abundant cytoplasm, round vesicular nuclei, containing one or more prominent nucleoli. Mitosis is common. Squamous metaplasia and atypical tumor giant cells have been noted in some of these tumors. Typically, the tumor cells in medullary carcinoma are accompanied by moderate to pronounced lympho-plasmocytic infiltrate in the supporting and surrounding stroma. Microglandular or tubular formations are absent. The constant lymphocytic reaction seen in medullary carcinoma may be linked to the favorable prognosis of medullary carcinoma and low frequency of nodal metastasis. This form is rare since strict histologic criteria
have been used to its identification. It is frequently observed in predisposed patients for breast carcinoma with BRCA1 germ line mutation.

**Mucinous Carcinoma**
In this form, the uniform tumor cells are accompanied by large amounts of extracellular mucin lakes. Pure and mixed variants of mucinous carcinoma have been recognized. An infiltrating duct carcinoma is the most common associated tumor in the mixed tumors. It is important to differentiate the pure form from the mixed type because of the favorable prognosis of the former.

**Neuroendocrine Tumours**
These are mammary carcinomas that display any growth patterns similar to those of carcinoid tumors that occur in other organs. They express neuroendocrine markers in more than 50% of the cell population. Hormonal receptors are frequently identified. If neuroendocrine markers are frequently found in other breast carcinomas, they are limited to scattered cells. This group comprises different subtypes, solid neuroendocrine carcinoma, atypical carcinoid, oat cell carcinomas and large cell neuroendocrine.

**Invasive papillary carcinoma**
This tumor is generally well delineated, frequently cystic and associated with hemorrhage. Myoepithelial cells are completely absent. It is now considered that many of the intra cystic carcinoma published may represent invasive papillary carcinoma. As they share an excellent prognosis, they have been called also papillary encapsulated carcinoma.

**Invasive micropapillary carcinoma**
This newly identified form of carcinoma is characterized by the presence of small clusters of tumours cells lying in clear stromal spaces mimicking vascular channels. This is an aggressive form, with frequent and numerous axillary lymph node metastases and poor prognosis. It may be pure or associated with a ductal component.

**Metaplastic Carcinoma**
Several metaplastic forms may be encountered in this category. Pure squamous or epidermoid carcinoma is rare, a more common presentation being foci of squamous differentiation in vicinity of necrotic areas in other histologic patterns of tumor. Spindle cell differentiation and metaplasia such as cartilagenous or osseous metaplasia are rare in pure form.
**Adenoid Cystic Carcinoma**
In this histologic subtype, a cribriform pattern is seen with rounded hyaline spaces enclosed in between cellular masses. It associated two cell components one expressing cytokeratin the other actin. Perineural invasion is a peculiar feature to this pattern of growth. Generally, this type of neoplasm exhibits a slow rate of growth and a favorable prognostic outcome.

**Lipid Rich Carcinoma**
This histologic variant has a particularly unfavorable prognosis. Large tumor cells exhibit lipid material, best demonstrated in frozen tissue material.

**Juvenile (Secretory) Carcinoma**
It occurs primarily in children and adolescents. This neoplastic variant is highly differentiated exhibiting excessive PAS positive secretory products.

**Inflammatory Carcinoma**
This type of breast carcinoma has been given a variety of terms such as mastitis carcinoma, carcinoma mastitoides, or acute mammary carcinoma. It is considered as the most malignant type of breast carcinomas, and of high proliferative activity (PEV 3). It represents 1% to 2% of breast carcinoma in Western literature, however, in Egypt, North Africa and Tunisia such mammary carcinoma is not uncommon. Characteristically, the skin of the breast is reddened, warm, edematous and thickened. During early stage, an underlying breast mass may not be palpable, and this may cause an erroneous diagnosis of inflammatory non-neoplastic process. Histologically, the skin dermis is filled with many lymphatic tumor cell emboli. Blocking of lymphatics causes skin edema.

**Clinical Versus Pathologic Definition**
The criteria for clinical diagnosis of inflammatory carcinoma include diffuse erythemaedema extending to greater than two thirds of the breast, “peau d’orange”, tenderness, engorgement, and diffuse breast involvement. The pathologic diagnosis requires the presence of tumor emboli in the dermal lymphatics, in addition to the presence of invasive carcinoma with spontaneous necrotic foci. In majority of cases, the clinical picture and the pathologic picture of dermal lymphatic involvement coincide. However, all patients with the clinical disease have demonstrable dermal lymphatic involvement, and there are also cases with dermal lymphatic involvement but without the clinical inflammatory features. It was found that clinically occult inflammatory carcinoma i.e. patients without clinical signs of inflammatory carcinoma but with tumor emboli in the dermal lymphatics followed
rapidly deteriorating clinical course, and wide spread metastases similar to clinically diagnosed inflammatory carcinoma. Furthermore, clinically diagnosed inflammatory carcinoma without demonstrable dermal lymphatic invasion, behave aggressively. Therefore, the use of the term “inflammatory carcinoma” is justified with either the clinical or the pathologic features.

**Pronostic classification**

**Histologic SBR Grade**

Tumor grading regardless of the system used has prognostic importance in breast cancer. Grading systems have been developed based on nuclear features, architectural pattern, mitotic rate or combinations of these features. Its use, initially restricted to the sole invasive ductal carcinoma, now has been extended to every subtype of invasive carcinoma except the medullary carcinoma. The chief difficulty with any of these grading systems is their subjective nature and the resultant poor reproducibility among pathologists, one approach is to use a uniform grading system with distinct criteria that are easy to reproduce among observers (Table 7.2.). For instance, the mitotic count is evaluated on ten consecutive high power fields and adjust according to the microscopic field area (table 7.3.). Studies have indicated that proliferation is the most important prognostic compound of this system. Other investigators have combined morphologic grade with other features, including tumor size and nodal status to calculate a prognostic index that appears to be highly predictive of clinical course.

**Axillary Lymph Node examination**

Involvement of axillary lymph nodes by metastases in patients with cancer breast is one of the important markers of prognosis. Pathologic examination of the axillary nodes in patients with breast cancer is required in order to assess prognosis and determine the need for adjuvant therapy. For sentinel lymph node, serial sectioning and the use of immunohistochemical staining is mandatory to ensure the predictive value for the involvement of the other axillary lymph nodes. One consequence of this method is to increase the detection metastases, in particular those of limited size (micrometastases) whose prognostic value is still under discussion. UICC has modified its classification of these small metastases, based on their size, in order to be able in the future to determine their prognostic value.

<table>
<thead>
<tr>
<th>Features</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubule formation</td>
<td></td>
</tr>
<tr>
<td>Majority of tumor (&gt;75%)</td>
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### Table 6.2. Summary of Semiquantitative Method for Assessing Histologic Grade in Breast Carcinoma

<table>
<thead>
<tr>
<th>Description</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Moderate degree (10-75%)</td>
<td>2</td>
</tr>
<tr>
<td>Little or none (&lt;10%)</td>
<td>3</td>
</tr>
<tr>
<td>Nuclear pleomorphism</td>
<td></td>
</tr>
<tr>
<td>Small, regular uniform cells</td>
<td>1</td>
</tr>
<tr>
<td>Moderate increase in size and variability</td>
<td>2</td>
</tr>
<tr>
<td>Marked variation</td>
<td>3</td>
</tr>
<tr>
<td>Mitotic counts</td>
<td></td>
</tr>
<tr>
<td>Dependent on microscopic field area</td>
<td>1-3</td>
</tr>
</tbody>
</table>

3–5 points: Grade I, well differentiated  
6–7 points: Grade II, moderately differentiated  
8–9 points: Grade III, poorly differentiated

**Figure 6.1** Value of the mitotic count according to the microscopic field area

<table>
<thead>
<tr>
<th>pN0</th>
<th>absence of lymph node metastasis with a routine analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0 i-</td>
<td>absence of lymph node metastasis with a special analysis</td>
</tr>
<tr>
<td>pN0 i+</td>
<td>presence of a metastasis measuring less than 0.2mm</td>
</tr>
</tbody>
</table>
### Table 6.4. UICC classification for the limited metastatic involvement of lymph nodes

<table>
<thead>
<tr>
<th>pNmi</th>
<th>presence of a metastasis measuring between 0.2mm and 2mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN1a</td>
<td>presence of a metastasis measuring more than 2mm</td>
</tr>
</tbody>
</table>

### New classifications

The recent development of molecular biology techniques, in particular the microarray techniques which allows the simultaneous analysis of thousands of genes, has considerably modified our cancer knowledge. One of the first consequences was grouping of infiltrating carcinomas according to their genetic expression similarity (unsupervised analysis) in so called molecular sub types. Five main groups have thus been individualized, **Luminal A** and **B** associated to hormonal receptor related and luminal type cytokeratin expression genes, **basal** related to basal type cytokeratin and absence of genes related to Her2, **Her 2** associated to the genes of the amplicon of this part of the chromosome 17 and **normal** type characterized by normal mammary tissue expression genes.

Their evolution as well as their aggression and their response to treatment could have been different but with some restrictions related to weak stability of this classification; each new incorporated case modifies the distribution of each of the designated class, also by the selected statistical algorithm and the number of selected class. Different groups have tried to characterize these different groups using immune-histo-chemistry.

### Morphologic changes induced by radiation and chemotherapy

Since radiation therapy is being used with increasing frequency as part of the conservative treatment option in the management of women with stage I and II breast carcinoma, it is important to become familiar with morphologic and functional alterations induced by this modality. Familiarity with the range of morphologic alterations induced by radiotherapy will prevent misinterpretation of these changes as atypical or malignant.

One significant change that could result in diagnostic problems that deserve practical attention is the development of epithelial cells with enlarged hyperchromatic nuclei, inconspicuous nuclei, and cytoplasmic vacuolization in the terminal duct lobular unit as well as in areas of adenosis. These changes are not related to age, interval between termination of radiotherapy and the subsequent biopsy, or the usual dosage of radiation. Similar changes may also affect the
epithelial cells in larger ducts, but less frequently. Variable degrees of lobular
sclerosis may also occur. The radiation induced atypia differs from carcinoma
involving the lobules by the absence of epithelial hyperplasia, mitotic activity, and
luminal necrosis. Furthermore, the cytoplasmic vacuolization and a history of prior
radiotherapy should serve as additional clues.

Similar epithelial changes have also been observed secondary to chemotherapy. An
increase in nuclear size, pleomorphism, vacuolization, and chromatin clumping in
residual tumor cells has been described after chemotherapy. Chemotherapy may
induce nodular fibrosis and areas of fibrohistiocytic proliferation in both the breast
as well as in axillary lymph nodes. Chemotherapy does not induce the vascular and
stromal changes. Preoperative chemotherapy can abolish the tumor leaving no
evidence of residual malignancy in the specimen.
<table>
<thead>
<tr>
<th>Size(s):</th>
<th>1) DCIS</th>
<th>5) Mixed NOS/ILC</th>
<th>9) Papillary</th>
<th>2) LCIS</th>
<th>6) Tubular</th>
<th>10) Cribriform</th>
<th>3) Infiltrating ductal (NOS)</th>
<th>7) Mucinous</th>
<th>11) Other. (specify)</th>
<th>4) Infiltrating lobular</th>
<th>8) Medullary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Type</td>
<td>1) DCIS</td>
<td>5) Mixed NOS/ILC</td>
<td>9) Papillary</td>
<td>2) LCIS</td>
<td>6) Tubular</td>
<td>10) Cribriform</td>
<td>3) Infiltrating ductal (NOS)</td>
<td>7) Mucinous</td>
<td>11) Other. (specify)</td>
<td>4) Infiltrating lobular</td>
<td>8) Medullary</td>
</tr>
<tr>
<td>Grade of invasion:</td>
<td>1) I</td>
<td>2) II</td>
<td>3) III</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Gross margin:</td>
<td>1) Free (specify distance)</td>
<td>2) Focal</td>
<td>3) Inevaluable</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Margins invasive (specify type of margin evaluation)</td>
<td>1) Free (specify distance)</td>
<td>2) Focal</td>
<td>3) Inevaluable</td>
<td></td>
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</tr>
<tr>
<td>Margins DCIS (specify type of margin evaluation)</td>
<td>1) Free (specify distance)</td>
<td>2) Focal</td>
<td>3) Inevaluable</td>
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<tr>
<td>DCIS nuclear morphology</td>
<td>1) High grade</td>
<td>2) Intermediate grade</td>
<td>3) Low grade</td>
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</tr>
<tr>
<td>DCIS patterns (specify all that apply)</td>
<td>1) Large areas of central necrosis (comedo)</td>
<td>4) Solid</td>
<td>2) Small areas of central necrosis</td>
<td>5) Micropapillary</td>
<td>3) Cribriform</td>
<td>6) Papillary</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Calcification in situ:</td>
<td>1) Absent</td>
<td>2) Prominent in DCIS</td>
<td>3) Local in DCIS</td>
<td>4) In LCIS</td>
<td>5) Prominent in benign breast tissue</td>
<td>6) Focal in benign breast tissue</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Peritumoral lymphatic invasion:</td>
<td>1) Absent</td>
<td>2) Present</td>
<td>3) Dermal</td>
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<tr>
<td>Peritumoral vascular invasion:</td>
<td>1) Absent</td>
<td>2) Present</td>
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<tr>
<td>Extent DCIS within invasive tumor:</td>
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<tr>
<td>1) Absent</td>
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<tr>
<td>2) Slight</td>
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<tr>
<td>3) Moderate-Marked</td>
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<tr>
<td>4) Tumor primarily DCIS with focal invasion</td>
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</table>

<table>
<thead>
<tr>
<th>Extent DCIS adjacent to invasive tumor:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Absent</td>
</tr>
<tr>
<td>2) Slight</td>
</tr>
<tr>
<td>3) Moderate-Marked</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EIC status:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) EIC negative</td>
</tr>
<tr>
<td>2) EIC positive</td>
</tr>
<tr>
<td>3) EIC intermediate</td>
</tr>
</tbody>
</table>

Note: If a tumor is primarily DCIS with focal invasion or has a moderate or marked amount of DCIS within the infiltrating tumor and in the adjacent tissue it is EIC positive

<table>
<thead>
<tr>
<th>Skin:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Not sampled</td>
</tr>
<tr>
<td>2) Free</td>
</tr>
<tr>
<td>3) Invasive</td>
</tr>
<tr>
<td>4) Dermal lymphatic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nipple:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Not sampled</td>
</tr>
<tr>
<td>2) Free</td>
</tr>
<tr>
<td>3) Invasive</td>
</tr>
<tr>
<td>4) Dermal lymphatic</td>
</tr>
<tr>
<td>5) DCIS</td>
</tr>
<tr>
<td>6) Paget’s</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Muscle:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Not sampled</td>
</tr>
<tr>
<td>2) Free</td>
</tr>
<tr>
<td>3) Involved</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mastectomy tumor location:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Central</td>
</tr>
<tr>
<td>2) UOQ</td>
</tr>
<tr>
<td>3) UIQ</td>
</tr>
<tr>
<td>4) LOQ</td>
</tr>
<tr>
<td>5) LIQ</td>
</tr>
<tr>
<td>6) Axillary tail</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multiple areas involved:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Central</td>
</tr>
<tr>
<td>2) UOQ</td>
</tr>
<tr>
<td>3) UIQ</td>
</tr>
<tr>
<td>4) LOQ</td>
</tr>
<tr>
<td>5) LIQ</td>
</tr>
<tr>
<td>6) Axillary tail</td>
</tr>
<tr>
<td>7) Only one area involved</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lymph nodes (number of involved nodes in relation to total number examined):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Level I Level II Level III Other (specify)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extranodal extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Absent</td>
</tr>
<tr>
<td>2) Present</td>
</tr>
</tbody>
</table>
Chapter 7C
Plastic Surgery
The evolution of the breast cancer treatment is oriented toward a decrease of the surgical mutilations and an association with other methods of treatment. The radical mastectomy proposed by Halsted was the treatment of choice until the 1960's. This surgical procedure had a further extension with the "super radical mastectomy" proposed by Urban, that includes an internal mammary lymphadenectomy. The important mutilation resulting from this operation generated in most cases a psychological trauma to the patients. Lacour and Veronesi proposed an evaluation of the internal mammary lymphadenectomy efficacy by a multicentric randomized trial. This was the first randomized trial in breast cancer and a showed that Patey's mastectomy provided the same survival rates than the super radical mastectomy. It showed also that early metastatic disease could be present which should best be treated by systemic therapy.

In the early sixties, Baciesse had already proposed to replace the mastectomy by an external radiotherapy only. However, half of the patients treated by exclusive radiotherapy had either a secondary local recurrence or no sterilization of the primary tumor. After an evaluation of this method, French and Italian oncologists proposed a treatment combining quadrantectomy with axillary dissection plus radiotherapy. New trials showed the therapeutic efficacy of this treatment allowing a conservation of the breast. Since more than twenty years, breast cancer treatment is performed by a multidisciplinary team: including the general surgeon, the radiologist, the medical oncologist and the pathologist. Today, the epidemiologist, the molecular biologist, the genetician, the psychologist and many others are combining their efforts to improve the chance of cure of breast cancer. The new trends in surgery are trying to reduce as much as possible the mutilation and improve the cosmetic results; such goal explains the role of plastic surgery in the breast cancer treatment.

Plastic surgery can be helpful in a large number of cases:
- To improve the cosmetic results after diagnostic surgery for microcalcifications. (The number of this operations increases with the screening campaigns and they are performed in a large number of cases for young patients).
- To increase the cosmetic results in cases of conservative surgery by association of mammoplasty techniques, implants, local glandular or myocutaneous flaps.
- To perform breast reconstruction when a mastectomy is necessary.
- To ensure thoracic wall covering in cases of large excision for local recurrences or radionecrosis.

Prosthesis updating
Whatever the indication of a plastic surgery procedure, the use of a silicone implant may be required and should be discussed in light of the recent polemics concerning the risk of cancer and autoimmune diseases related to such material.

Types of Prosthesis
Different types of definitive prosthesis are shown in Table 16.1. They are changing frequently following the manufacturer's innovations to get the whole security, the smallest rates of capsular contracture and allows the better cosmetic results.

The different types of expanders are shown in Table 16.2. This type of prosthesis is used when the final volume cannot be allowed with a definitive prosthesis. In our experience, the indications of breast reconstruction using expanders are limited. It is a very expensive technique, requiring two prosthesis and two surgical procedures with general anesthesia.
The safety of gel-filled silicone prosthesis has recently been brought into question, despite their worldwide use for more than 30 years in breast augmentation or reconstruction. An increased risk of cancer and autoimmune disease has been suggested. In order to evaluate these effects, we have studied 146 patients with breast cancer treated by mastectomy at the Gustave Roussy Cancer Institute between 1965 and 1983 and who received a gel-filled silicone prosthesis for immediate or delayed breast reconstruction between 1976 and 1984. These patients were compared with 146 matched controls with breast cancer that were treated in the same center by mastectomy without breast reconstruction and were matched for age at diagnosis (within 10 years), year of diagnosis (within 3 years), stage, histologic type of the tumor, histopathologic grade, and nodal status. The relative risks of death, relapse, and second primary cancer were estimated by means of the Cox proportional hazard model stratified on age at diagnosis.

The risks of distant metastasis and death due to breast cancer were significantly lower in the breast reconstruction group than in the control group. The risks of local recurrence, second breast cancer and second primary cancer in another site than the breast were not significantly different between the two groups of patients. These results do not support the hypothesis of detrimental effect of gel-filled silicone prosthesis in the course of breast cancer (Table 16.3).

In respect of autoimmune disease, the literature showed about a hundred cases around the world of association between silicone use (prosthesis or silicone injection) and autoimmune disease. These rates seem very low in comparison to the total of silicone prosthesis use in the world. However, a valuable statistical study is difficult to apply with such a low incidence of the autoimmune disease. Nowadays, epidemiologic studies have shown that autoimmune disease cannot be related to prosthesis implantation in most cases and most countries.

Capsular contracture is another common problem observed when using an implant. Five to 20% contracture rates are published in the literature. Textured prosthesis seem to give a lower rate of capsular contracture than smooth envelope.

**Surgical procedures**

When a conservative treatment is not recommended, a mastectomy with prosthetic immediate breast reconstruction is the first choice in our experience. This is the simplest procedure and requires the minimum hospital stay. The use of myocutaneous flaps is necessary when the local thoracic or general conditions do not allow the use of simple implant or when such simple reconstruction risks to end up with a poor cosmetic result.

**Delayed Breast Reconstruction Using Prosthesis**

This technique was the outset of the breast reconstruction. It was proposed, in the past, for mastectomised patients after a certain delay free of disease. This delay was decreased progressively down to several months and nowadays the immediate breast reconstruction is more frequent than the delayed in our series. This technique is indicated in cases presenting with adequate skin and muscle coverage after mastectomy. A good cosmetic result can be obtained in cases of small nonptotic breasts. It can also be used in the woman with larger ptotic breast, but symmetry can only be achieved with reduction or pexy of the other breast (photos 1 and 2). The contraindications are pectoralis muscle damage, tight skin closure and special attention should be given to previous thoracic wall radiotherapy.

The reconstruction is performed through an incision along the mastectomy scar then the pectoralis major is undermined. A pocket is created behind this muscle medially and behind the serratus anterior muscle laterally and a definite prosthesis is inserted after drainage. When the skin is well vascularized, it is possible sometimes to insert the prosthesis subpectoral in the inner part and subcutaneously in the outer part.
Expander prosthesis can be used in cases of large breast reconstruction with good quality but insufficient skin laxity. Expander is placed in the submuscular pocket and is inflated sufficiently to permit a good healing without tension. The advantage of this prosthesis is to allow a progressive distention of the skin, thanks to a weekly injection of saline solution. The definitive prosthesis is placed after complete distention of the skin. This procedure provides large reconstructed breast without further scar on the abdomen or on the back. But it is not recommended for women with poor local tissue conditions especially after radiotherapy or when the pectoralis muscle has been removed.

**Immediate Breast Reconstruction Using Prosthesis**

This is the most useful technique in our experience. The advantages are: easy technique, short additional time during the operation and for the hospital stay, reduction of the number of interventions and patient's psychological satisfaction.

**The best indications are:** cases of large tumors where a conservative treatment is not indicated, tumors without skin ulceration or muscle infiltration. The best results are obtained in cases of small nonptotic breasts. In cases of large ptotic breast, the symmetry can be achieved by a contralateral reduction or mastopexy. The contraindications are frequently related to technical problems: when a large skin or a muscle resection is mandatory, when a preoperative radiotherapy has been indicated. In these cases a number of authors proposed a myocutaneous flap as well as in cases of immediate breast reconstruction after mastectomy for conservative treatment recurrences.

Before the operation, the plan and skin marks are drawn together by the oncological surgeon and the plastic surgeon. The prosthesis type and the necessity to perform a contralateral correction to achieve a better symmetry are discussed with the patient.

Both breasts are prepared and the operation can be performed simultaneously, while the mastectomy and axillary dissection are performed by the oncologic team, the plastic surgeon begins to perform the reduction mammoplasty or the mastopexy of the contralateral breast. When the mastectomy is finished, the prosthesis can be inserted into a muscular pocket, made of the pectoralis major and the serratus anterior muscle (photos 3 and 4). It is important that the implant be inserted in a muscular pocket completely closed, in order to avoid the sliding of the implant in the dissected axillary area, and to decrease the risk of secondary exposure and/or capsular contracture.

In cases of serratus anterior atrophy, a partial muscular flap of latissimus dorsi can be taken by the same incision and rotated to the anterior part of the breast to cover the prosthesis laterally otherwise, in cases of excessive skin tension, an expander prosthesis can be used to preserve the skin flaps perfusion, to allow a good healing and a progressive postoperative distention and to obtain the suitable volume.

Nowadays, we are trying a new technique for immediate breast reconstruction with definitive prosthesis using a non absorbable mesh. The abdominal skin is undermined below the inframammary fold and a triangular marlex mesh is sutured on the new inframammary fold inferiorly. Thereafter the mesh is pulled up until the new inframammary fold becomes symmetric to the contralateral side and the mesh is fixed in third and fourth costal cartilage. This technique allows a good esthetic result and reduces the indications of expanders.

The success of the immediate breast reconstruction depends on the close collaboration between the oncological surgeon and plastic surgeon to decide the skin excision, to preserve the skin flaps perfusion at the moment of the mastectomy and to choose the timing and the better reconstruction technique in each case. The main purpose is "no delay for the adjuvant treatment due to plastic surgery complications".
Breast Reconstruction Using Myocutaneous Flaps
This technique is used in cases of poor local skin or muscular conditions of the thoracic wall, and it is performed more frequently in cases of previous thoracic wall radiotherapy.

More recently, some authors propose free flaps (with micro anastomoses of the vessels) to improve the cosmetic results of the breast reconstruction and reduce the morbidity in the donor site. But this technique requests an experimented and trained team of microsurgeons to reduce the length of the intervention and the postoperative complications.

The oldest technique is the latissimus dorsi flap, which is a very safe procedure but requires prosthesis to match the volume of the opposite breast. The TRAM flap has been used in our experience since 1983 and provides the best cosmetic results in what concerns the breast, but gives a high percentage of sequellae on the abdomen. Table 16.4 resumes the advantages and disadvantages of each technique.

The final decision about the flap to be used must be discussed with the patients, presenting to them the different options, and analyzing the risk factors of each technique in function of their cosmetic wishes and physical activities.

In cases of TRAMF reconstruction, the skin marks are performed the day before the operation with the patient in standing position. Just before the operation, a urinary and a peridural catheter are positioned for the postoperative comfort and the analgesia. The abdominal flap is an ellipse designed with the lower incision in the suprapubic crease and the upper incision slightly above the umbilicus. The flap should be pedicled on one or two abdominal rectus muscles, depending on the volume of the breast to be reconstructed and the risk factors of flap blood supply (smoker, scar, etc.). After the flap dissection, the epigastric area should be undermined to allow the flap transposition to the thoracic wall; then the flap is reshaped to look like the contralateral breast. A special attention must be given to the abdominal closure. In our experience this closure is performed with non absorbable stitches and always with a non absorbable mesh. This care decreases the incidence of hernia or bulging (photos 5 and 6).

In cases of LDF reconstruction, the location of the posterior skin island is positioned in order to cover the anterior skin defect. At the same time, the latissimus dorsi muscle completes the muscular pocket of the implant together with the pectoral major muscle. For this reason, the position of the scar on the back depends on the anterior position of the flap. The patient is positioned in middle lateral decubitus to allow preparation of the flap on the back and have a global view of both breasts at the same time.

Generally, the whole latissimus dorsi muscle is taken to make possible a total prosthesis cover without utilization of the pectoralis major muscle. The choice of the prosthesis volume depends on the contralateral breast (photos 7 and 8).

Cosmetic improvement after quadrantectomy
Veronesi showed that a better local control after conservative treatment is obtained by an association of a "large" quadrantectomy and radiotherapy. Petit showed that tumors located in central and lower quadrants give a worst cosmetic results than tumors situated in upper quadrants. For these reasons, immediate mammoplasty techniques permit a large tumor excision and a good cosmetic results. A mammoplasty reduction with superior areolar pedicle permits a large quadrantectomy in the lower pole of the breast (photos 9 and 10), on the other hand, a large quadrantectomy in the upper pole is possible with an inferior areolar pedicle (photos 11 and 12). In cases of central quadrantectomy with areola and nipple resection, the shape can be improved by a rotation of a dermo-glandular flap. Myocutaneous flaps, local skin flaps or prosthesis could be used depending on the tumor characteristics (size and localization) and breast volume and shape.
Contralateral breast management
The actual tendency of breast cancer treatment is to be as large as possible but with preservation of the body morphology. For this reason, a contralateral breast surgery is necessary to achieve symmetry. In our experience, 60% of the breast reconstruction cases required a contralateral correction; and in cases of conservative treatment with mammopla association, the better results are achieved with application of the same technique bilaterally.

Furthermore, the contralateral intervention can be helpful to perform an opposite b screening with a complete bimanual glandular exploration and multiple biopsies. A van incidence from 5% to 11% of clinical and radiological occult tumors was shown.

Areola and nipple reconstruction
This is the final touch after a breast reconstruction. Normally it is recommended to postpone the second stage intervention to avoid a malpositioning of the nipple and areola complex. Tattooing is the most simple technique to areola reconstruction. For the nipple reconstruction, a tattooed skin flap or a partial contralateral nipple graft can be used (photo 13).

Particular indications of large excisions on the thoracic wall can be used for palliative or cleanliness purposes (local recurrence treatment or radionecrotic sequellae). The solutions to cover this area must be discussed case by case and some techniques are most useful: skin grafts, local skin flaps, myocutaneous flaps or omentum flap. The last one is specially used when the internal mammary vessels have been involved in the thoracic ulceration or when pedicled TRAM flap is no more available.

Conclusion
Nowadays, the plastic surgery is a part of breast cancer treatment. It helps the women to preserve their body appearance, their well being and their quality of life. For this reason, a perfect interaction with general surgeons, radiotherapist and chemotherapist allows the better treatment association for each case taking into account the disease phase and patient's wishes.

<table>
<thead>
<tr>
<th>Table 16.1. Different Types of Definitive Prosthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filled Material</td>
</tr>
<tr>
<td>Gel Polyurethane cover</td>
</tr>
<tr>
<td>Capsular contracture rates probably lower than smooth prosthesis.</td>
</tr>
<tr>
<td>Good results with anatomical shape.</td>
</tr>
<tr>
<td>Recommended change every 10 years.</td>
</tr>
<tr>
<td>Prosthesis with the smallest rates of capsular contracture.</td>
</tr>
<tr>
<td>Not recommended by the FDA.</td>
</tr>
<tr>
<td>Saline Solution</td>
</tr>
<tr>
<td>Capsular contracture rates probably lower than smooth prosthesis.</td>
</tr>
<tr>
<td>Good results with anatomical shape.</td>
</tr>
<tr>
<td>Recommended change every 10 years.</td>
</tr>
<tr>
<td>Prosthesis with the smallest rates of capsular contracture.</td>
</tr>
<tr>
<td>Not recommended by the FDA.</td>
</tr>
<tr>
<td>Double Lumen</td>
</tr>
<tr>
<td>Capsular contracture rates probably lower than smooth prosthesis.</td>
</tr>
<tr>
<td>Good results with anatomical shape.</td>
</tr>
<tr>
<td>Recommended change every 10 years.</td>
</tr>
<tr>
<td>Prosthesis with the smallest rates of capsular contracture.</td>
</tr>
<tr>
<td>Not recommended by the FDA.</td>
</tr>
<tr>
<td>Hydrogel Peanut oil</td>
</tr>
</tbody>
</table>

Table 16.2. Different Types of Expanders
Temporary Saline
Distant Round
Site injection uncomfortable. Expensive technique because requires 2 prosthesis and 5 surgeries with general anesthesia.

Anatomical Incorporated
Site injection comfortable. Better shape with anatomical prosthesis. Textured shell probably reduces capsular contracture rates. Expensive technique because requires 2 prosthesis and 5 surgeries with general anesthesia.

Saline and Round Gel
Definitive (Becker)
Distant Injection site can be removed with local anesthesia. Risk of deflation.

236 Breast Cancer
Table 16.3. Risk and 10-year Rate of Death, Relapse, and Second Primary Cancer in 146 Breast Cancer Patients with Gel-filled Silicone Implant as Compared with 146 Matched Controls without Reconstruction.

<table>
<thead>
<tr>
<th>Type of Events</th>
<th>Number of events</th>
<th>Relative Risk (95% CI)*</th>
<th>P</th>
<th>10-year rates (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from any cause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G.Co G.BR</td>
<td>26</td>
<td>1.67</td>
<td>0.07</td>
<td>18%(13%-26%) 10%(6%-16%)</td>
</tr>
<tr>
<td>Breast cancer death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G.Co G.BR</td>
<td>25</td>
<td>1.00</td>
<td>0.05</td>
<td>18%(12%-26%) 9%(5%-15%)</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G.Co G.BR</td>
<td>35</td>
<td>1.50</td>
<td>0.01</td>
<td>24%(18%-32%) 12%(8%-18%)</td>
</tr>
<tr>
<td>Local Recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G.Co G.BR</td>
<td>21</td>
<td>0.67</td>
<td>0.07</td>
<td>15%(0%-21%) 8%(5%-14%)</td>
</tr>
<tr>
<td>2nd primary cancer Breast</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G.Co G.BR</td>
<td>10</td>
<td>1.10</td>
<td>NS</td>
<td>7%(4%-12%) 8%(5%-14%)</td>
</tr>
<tr>
<td>Other site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G.Co G.BR</td>
<td>7</td>
<td>0.80</td>
<td>NS</td>
<td>6%(3%-12%) 4%(2%-01%)</td>
</tr>
</tbody>
</table>

* CI: Confidence interval.
§ Reference category.
# Co Group: stomach, colon, ethmoid, uterine corpus, kidney, malignant melanoma, b
BR group: Duodenum, colon, uterine corpus and ovary.

Chapter 16: Plastic Surgery 237
Table 16.4. Advantages and Disadvantages between TRAMF and Latissimus dorsi Flap

TRAMF

LDF
Advantages
# Good shape with possibility to reconstruct a ptotic breast. # Abdominoplasty in obese patients.
# Shorter length of operation (2-3 hours).
# Smaller muscular morbidity.
# Safe vascular perfusion of the flap.

Disadvantages
# Variable vascular perfusion of the flap.
# Length of operation (4-5 hours).
# Longer hospital stay (5-8 days).
# Longer period of normal activities recuperation (about 1 month).
# Abdominal muscular morbidity.
# More important blood loss.
# Prosthesis is necessary to allow the shape, and this increases the incidence of contractures and contralateral mammoplasty for symmetry.
# Frequent large dorsal scar.
Chapter 8
Radiotherapy of Breast
**Radiotherapy** plays an essential and critical role in the management of breast cancer, it is given for primary carcinoma of the breast to reduce the risk of loco-regional recurrence, and it has also been shown in many studies to improve survival in patients after mastectomy. In a general radiation oncology practice, breast cancer typically comprises approximately 25% of the total patient caseload. The role of radiotherapy after conservative surgery for DCIS remains complex and surrounded by considerable controversy. According to prospectively randomized trials, radiotherapy reduces subsequent breast recurrence in all patient groups irrespective of prognostic risk factors. That is not to say, however, that radiotherapy must be used for all patients with DCIS. In all cases, a realistic and balanced discussion of the relative risks and benefits of treatment options should be presented to the patient.

Clinical T1T2No lesions Breast-conserving surgery followed by radiation therapy to the intact breast is now clearly established as the most acceptable standard of care for the majority of women with early stage invasive breast cancer. Some patients may be treated by simple mastectomy, depending on the site and size of the tumour, the histological type, the grade and extent of in-situ change, and the size of the breast. Consideration of the cosmetic result and patient preference may determine the choice of treatment. Contraindications to conservative surgery and radiotherapy include multifocal breast tumours, extensive DCIS and patients with severe pre-existing cardiac or lung disease. After mastectomy, radiation to the chest wall is recommended for patients at high risk of local recurrence. i.e. if the primary tumour is more than 5 cm in diameter, of high-grade malignancy, involves the skin or axillary nodes, is incompletely excised, or there is tumour close to the excision margin. For inoperable T3 and T4 tumours, primary hormone therapy or chemotherapy may be given before loco-regional radiotherapy and possible subsequent surgery depending on systemic staging. T4d inflammatory carcinomas are treated with primary chemotherapy and radiotherapy.

Patients with operable tumours 3-4 cm or more in diameter have a higher local recurrence rate with conservative surgery and radiotherapy, and may therefore be offered primary chemotherapy. This strategy aims to produce sufficient tumour regression to avoid mastectomy in many patients, and data on its effect on local control and survival are awaited.

Lymph-node irradiation is unnecessary if an axillary dissection up to the lower border of the pectoralis minor (level 1) is negative, since involvement of other nodes is unlikely. If axillary nodes are involved, radiation may be given to the axilla and supraclavicular fossa. If a formal axillary clearance has been performed, subsequent axillary radiotherapy is associated with considerable morbidity but supraclavicular node irradiation alone may be given. For central or medial quadrant tumours, irradiation to the internal mammary nodes may be considered, but isolated local recurrence is rare and routine radiotherapy is not recommended. The role of sentinel node biopsy is currently under investigation, and may allow a policy of axillary dissection only in patients with a positive node biopsy.

**Interstitial implants may be used:**
- to give a boost to the site of excision following lumpectomy and external beam radiation as part of primary breast conservation therapy;
- to give a boost to residual tumour after external beam radiation for bulky inoperable disease;
- for salvage therapy for local recurrence.

**With breast conservation, interstitial implantation may be considered to improve local control in patients with the following high-risk factors for recurrence:**
- incomplete tumour excision;
- extensive intra-duct carcinoma in addition to invasive disease;
- patients under the age of 40 years;
- grade III tumours;
- tumours greater than 3 cm in diameter.
Radiotherapy has a major role in the palliation of locally advanced fungating tumours and symptomatic metastases in sites such as bone, brain and skin.

Primary lymphoma of the breast is usually associated with diffuse histology and is treated by chemotherapy. Where local treatment is required for residual disease, this may be given to the breast by tangential fields as described below.

**Planning technique**

**ASSESSMENT OF PRIMARY DISEASE**

It is important for the radiotherapist to examine the patient pre-operatively. Breast examination includes inspection for nipple or skin retraction, discharge, ulceration or asymmetry, and palpation for site and size of the lump and fixation to adjacent structures. Glandular drainage areas are also assessed and TNM staging recorded on an accurate diagram. A photograph may be useful to show the exact position of the lesion. Mammography is performed to demonstrate the tumour and to detect multifocal or in-situ disease and bilateral involvement. Ultrasound is used to measure the lesion and guide fine-needle aspirate (FNA) cytology or core biopsy for histology.

Examination of the surgical specimen should define the size, site and local extent of the primary lesion and the number and position of axillary nodes in the specimen. Histological review determines size, type of tumour, grade, assessment of excision margins, oestrogen-receptor status and lymph-node involvement. If the breast is preserved, the position of the tumour in relation to the surgical scar must be known and should be obtained from a surgical operative diagram.

Where inoperable primary tumours remain palpable after systemic therapy they can be assessed by palpation and ultrasound, marked on the skin and a photograph taken.

**PATIENT POSITION**

The patient is treated supine, and her position should remain the same during planning, simulation and treatment. The slope of the chest wall can be corrected by insertion of a triangular wedge or inclined plane under the head and shoulders for a simulator or simulator-CT localization (Fig. 1). However, this technique is not CT compatible, and if three-dimensional CT planning is to be used, a supine position with both arms elevated and secured above the head is optimal for entering the CT scanner aperture. An immobilization device commercially available or custom made breast tilt boards with armrests that maintain the patient's daily position with the slope of the chest wall parallel to the table, often in combination with immobilization devices (e.g., alpha cradle, plastic molds), are typically used to reproduce daily positioning and minimize day-to-day set up errors. All patients should be aligned using a system of medial and lateral tattoos and laser lights. When tangential and lymph-node fields are used, careful consideration must be given to matching field edges to avoid inhomogeneity of dose distribution. Any junction between adjacent treatment fields is affected by normal respiration causing some patient movement, and verification should be carried out in each radiotherapy department when multiple diverging beams are used.

Other treatment positions have been used to improve the dosimetry in patients with large, pendulous breasts. A lateral decubitus position has been suggested by investigators at the Institut Curie. Irradiation in the prone position has been proposed, with reduction of dose in the high-dose region to 102% to 103% of the dose to the irradiated breast, as well as reduction of volume and dose to the underlying lung and heart and reduction of scattered dose to the contralateral breast. This technique is being increasingly employed and long-term follow-up data regarding outcomes and cosmesis are awaited.
DEFINITION OF TARGET VOLUME

For this complex treatment several target volumes must be defined.

Breast
The entire breast is included in the target volume, with a 1 cm margin around palpable breast tissue. The aim is to treat down to the deep fascia, but not the underlying muscle, rib-cage, overlying skin or excision scar. The superior border covers as much breast tissue as possible and lies at about the level of the suprasternal notch medially, and just below the level of the abducted arm laterally. The inferior border lies 1 to 2 cm below the breast.

The medial and lateral borders are determined by the site of the primary lesion and the size of the breast. The medial margin, if no internal mammary portal is used, should be at or 1 cm over the midline. If an internal mammary field is used, the medial tangential portal is located at the lateral margin of the internal mammary field. The lateral-posterior margin should be placed 2 cm beyond all palpable breast tissue, which is usually near the mid-axillary line. The inferior margin is drawn 2 to 3 cm below the inframammary fold.

In selected patients these margins can be reduced, provided that the cover of the tumour bed is not compromised, in order to minimize the treatment volume and/or amount of lung in the high dose zone. Irradiation of the rib-cage inferior to the inframammary fold is unnecessary unless the tumour bed encroaches on this margin or the breast is pendulous. The deep margin extends down to the deep fascia.

In patients treated with 6-MV or lower energy photons with wide tangential fields in whom separation is >22 cm there may be significant dose inhomogeneity in the breast; this may correlate with less satisfactory cosmetic results. This problem can be minimized by using higher energy photons (10 to 18 MV) to deliver all or a portion of the breast radiation (approximately 50%) as determined with treatment planning to maintain the inhomogeneity throughout the entire breast to 10% or less. If desired, the buildup of the beam may be modified with a “degrader.” Bolus should be avoided in conservatively managed patients. A variety of immobilizing devices or molds may be constructed to support the breast in the treatment position. A polyvinyl chloride, ring-shaped device, held by a strap, has been used around the breast to aid in positioning of patients with large, pendulous, or flaccid breasts. Skin reactions where material is in contact with the skin should be closely monitored.
**Chest wall**
The target volume includes the skin flaps. Posteriorly, the deep margin extends to the deep fascia, inevitably including underlying muscle and rib-cage. Part of the surgical scar may have to be excluded medially or laterally in order to reduce the dose to the underlying heart and lung to acceptable tolerance limits. This is achieved by allowing a maximum central lung distance of 2 cm on the simulator film.

**Tumour bed**
This volume must be chosen by taking into account the initial site and size of the tumour determined clinically, by photographic record and by mammography, the position of the surgical scar in relation to the tumour from a surgical diagram, the depth of the tumour in relation to skin and chest wall, and histopathological reports. Surgical clips may help to locate the tumour bed if their exact relationship to the tumour is known. A 2 cm margin is allowed around this estimated clinical target volume, with a deep margin extending to the underlying muscle fascia, giving a PTV of 7-9 cm in diameter at the skin surface (i.e. electron applicator 8-10 cm in diameter).

**Lymph nodes**
The lymphatic drainage to the axillary and supraclavicular nodes forms an irregular volume lying anteriorly at its upper border in the supraclavicular fossa, and extending more posteriorly at the lower border to include all groups of axillary nodes. After positive axillary-node sampling, the entire target volume may be treated in continuity. However, after a positive complete axillary clearance, the supraclavicular lymph nodes alone may be treated using the technique described below, in order to avoid unnecessary morbidity. The internal mammary nodes lie 2-3 cm lateral and deep to the mid-line.

Since they cannot be treated satisfactorily with the breast target volume, and the incidence of clinical involvement is low, they are only treated in high-risk patients with large central or medial quadrant tumours with involved axillary lymph nodes.

**Field arrangements**
All fields should be treated with the patient in the same supine position as described above.

**Breast technique**
The patient lies supine with appropriate immobilization, and her position is aligned using laser lights. The borders of the target volume are marked on the skin with the centre points of the medial and lateral fields defined. Two reference tattoos are made at medial and lateral field centres, and a third one is made on the opposite side of the body, corresponding to the lateral field centre, to prevent rotation. Using the simulator, an isocentric technique is planned. The maximum depth of lung included in the tangential field is 2-3 cm (the central lung distance is usually less than 2 cm) as defined by simulation, simulator-CT or CT scanning (Fig. 2). The amount of lung included in the irradiated volume is greatly influenced by the portals used.

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**Figure 8.2.**
Isodose of the breast on the axis tangential field, including internal mammary chain
The anterior border of the field in free air should be at least 1 cm from the skin surface (to ensure a satisfactory dose distribution). A transverse cross-section of the patient is taken through the centre of the planning target volume using an external contour or computerized tomography. Beam divergence into the lung at the posterior border of the field can be reduced by using either independent collimators to block the posterior half of the beam, or a 5° gantry tilt to align the opposing posterior field borders.

A dose distribution is prepared across the target volume using a wedge as compensator to ensure dose inhomogeneity of no more than ±5 per cent (Fig. 4). Lung correction employing a correction factor within the range 0.2-0.3 may be used when calculating the dose distribution. Where the breast is large, outlines are taken through the centre of the volume and 5-8 cm above and below the centre; the simulator-CT facility is ideally suited to collecting these data. Dose distributions are produced at these three levels in order to check homogeneity and prepare tissue compensators if necessary.

**Chest wall technique**

Two tangential fields arranged as for the breast can be used. Bolus is usually only needed when treating recurrent disease, in order to maximize the dose to the skin. An alternative technique is to use a single anterior electron field of appropriate energy for the thickness of the chest wall determined by ultrasound or CT (usually 8-15 MeV).

**Alignment of the Tangential Beam with the Chest Wall Contour**

The anterior chest wall slopes downward from the mid-chest to the neck. To make the posterior edge of the tangential beam follow this downward-sloping contour, the collimator of the tangential beam may be rotated, or the patient placed on a slant so that the slope of the chest wall is parallel to the table. An alternative is to make the deep posterior edge of the tangential beam follow the chest wall contour by means of a rotating beam splitter mounted on a tray without rotation of the collimator or using multileaf collimation. In this way, the superior edge of the tangential beam remains in the true vertical and matches perfectly the vertical inferior edge of the supraclavicular field if used.

**ANTERIOR FIELD**

The irregular three-dimensional target volume of the breast and regional lymph nodes makes it technically difficult to deliver an equal and adequate dose to all areas and to spare the lungs, heart and brachial plexus.

The tangential fields used to treat the breast or chest wall are planned as described above. For irradiation to the supraclavicular nodes only, a single anterior field is used with the patient in exactly the same position. The superior border extends at least 3 cm above the medial end of the clavicle, but leaving a margin of skin clear superiorly in order to reduce reaction. Medially the border is placed 1 cm lateral to the mid-line to avoid the larynx and spinal cord. The lateral border lies at the junction of the medial two-thirds and the lateral one-third of the clavicle. The inferior border is at the lower border of the clavicle.

If the axillary lymph nodes and supraclavicular fossa are to be included in the target volume, then the inferior border of the anterior field is extended caudally to match with the tangential field, with shielding of the apex of the lung where appropriate. The lateral border extends to the outer border of the head of the humerus, with lead shielding of the acromio-clavicular joint and the head of the humerus (Fig. 3).
Various techniques have been developed for matching the inferior border of the supraclavicular field with the superior border of the tangential fields. A gap of 5-10 mm may be left between the fields at the skin. The superior divergence of the tangential beams can be eliminated by rotating the couch through an angle of approximately 5° so that the superior edge of the fields lies horizontal and matches the straight upper border of the target volume. This manoeuvre increases the divergence inferiorly, but this is not usually clinically important. Divergence may then be removed from the inferior border of the anterior nodal field by moving the gantry a few degrees following a 90° couch rotation. Despite these two manoeuvres to remove divergence, matching at a skin junction is not perfect at depth, and movement of the patient due to respiration leads to inhomogeneity at the match line. Independent collimators can be used to produce half-beam blocking at the inferior border of the supraclavicular field and the superior border of the tangential field (Fig. 4).

**Fig. 4** Diagram showing the matching of superior border of tangential fields and inferior border of supraclavicular field using independent collimators.

**ADDITIONAL AXILLARY FIELD**
A single anterior field encompassing the planning target volume is recommended for adjuvant radiotherapy to supraclavicular and axillary lymph nodes. For advanced, palpable axillary disease, an additional posterior axillary field may be needed to ensure an adequate dose to the axillary nodes. When the axillary separation exceeds 15 cm, the mid-plane close to the axilla for a single anterior field falls below 80 per cent for 6-MV photons. An adequate mid-plane dose to the axilla can be achieved using a posterior axillary field treated every day, and weighted according to the separation in the axilla (e.g. for 16-18 cm, 1: 10 weighting of posterior axilla: anterior SCF field applied doses). However, the hot spot at Dmax (2 cm below the anterior skin surface) increases for larger separations to 110 per cent. Care must be taken to stay within the tolerance range of the brachial plexus, and a dose distribution should be produced for each patient when this technique is used. The
posterior axillary field is defined by palpating the apex of the axilla and aligning the infra-medial margin along the upper border of the rib-cage (Fig. 5).

**Fig. 5.** Posterior axillary field with shielding of acromio-clavicular joint and upper humerus, apex of lung and chin to anterior field.

**Single Isocentre, Breast and Nodal Technique**
A technique can be used where a single isocentre is set up at depth on the match-line of the anterior nodal and tangential fields. The gantry is set up to treat the tangential fields by blocking the beam superior to the central axis and thereby shielding the nodal field. When the suprclavicular/axillary field is treated, the inferior part of the beam is blocked. This technique requires asymmetric collimators and good immobilization of the patient so that the isocentre does not move during the entire treatment. It is assumed that the effects of respiration are random. The technique requires large field sizes (a 40 X 40cm field produces a maximum tangential field length of 20cm). Special wedges may be needed for the maximum field length or the tangential half of the beam only. This technique can be time-consuming to simulate, and its accuracy depends on precise abutment of the jaws, as an under- or overlap of 1 mm can lead to significant inhomogeneity of dose.

**INTERNAL MAMMARY NODE FIELD**
The benefit of irradiation of the internal mammary lymph nodes is an unresolved issue because clinical failures at this site are very rare and the majority of patients at risk receive adjuvant therapy. Megavoltage anterior fields are no longer used to treat internal mammary lymph nodes because of the exit dose to the heart. For medial-quadrant disease, the tumor bed may lie so close to the internal mammary nodes that it is impossible to treat both target volumes homogeneously. Treatment may then have to be given to the primary tumor alone by moving the tangential field further across the mid-line on to the contralateral side. Alternatively, an electron field of electron energy 12-16 MeV can be used to treat the internal mammary nodes with a match to adjacent tangential fields. Care must be taken to ensure homogeneity of dose to the primary tumor bed, and attempts must be made to calculate the dose distribution at the electron-photon interface.

The medial border of the internal mammary field is the midline. The lateral border is usually 5 to 6 cm lateral to the midline. The superior border abuts the inferior border of the supraclavicular field and the inferior border is at the xiphoid or higher. If only the internal mammary lymph nodes are to be treated, the superior border of the field is at the first intercostal space (superior border of the head of the clavicle). The dose is calculated at a point 4 to 5 cm beneath the skin surface (depending on the thickness of anterior chest wall and ideally based on CT scan localization).
CT treatment planning is useful for irradiation of the internal mammary lymph nodes. Although the lymph nodes are most often not visible, the internal mammary vessels can be clearly seen and contoured on axial CT slices. This anatomic region can then be visualized in treatment field design and in dosimetry planning.

**Bilateral Breast Irradiation**

Where bilateral breast irradiation is indicated a combination of two- and three-field techniques is used, with particular care to prevent overlap of the tangential fields in the mid-line by leaving an appropriate gap. When a second primary tumour is diagnosed in a contralateral breast and radiotherapy is required, it is important to reconstruct any previous radiotherapy treatment to the original side in order to ensure that there is no risk of overlap, particularly in the mid-line and supraclavicular region. Doses to underlying spinal cord should be estimated.

**Irradiation of Tumor Bed (Boost to Tumor Site)**

The need for a boost to the tumor bed following lumpectomy and whole breast radiation remains an area of debate. In the earlier years of breast-conserving surgery, status of the surgical margins was not always assessed. Recent retrospective data suggest that patients with known negative margins have high local control rates with no boost following whole breast irradiation.

Before the widespread availability of electron beam therapy, interstitial brachytherapy or cone-down photon boost was popular. Currently, most institutions prefer electron beam boost because of its relative ease in setup, outpatient setting, lower cost, decreased time demands on the physician, and excellent results compared with Ir192 implants.

**Electron Boosts**

The patient is positioned with the arm toward the head to flatten the breast contour, and may be rolled so that the tumor bed is parallel to the table and the accelerator head can point straight down onto the target volume. An electron energy is selected that covers the target volume depth (usual range is 9 to 16 MeV electrons), based on review of the physical examination, mammogram, ultrasound, CT, or other imaging used to ascertain the location and depth of the tumor or metallic surgical clips. The 90% prescription isodose line is limited to the chest wall to decrease dose to the lung. The clinical setup for electron boost involves marking the projection of the postlumpectomy volume on the skin and adding 2 to 3 cm in all directions.

Accurate target volume definition is critical with any boost technique. Methods vary from simple and unsophisticated to complex and expensive, such as ultrasound and CT definition of the target volume. The accuracy of using the scar to define the lumpectomy cavity has been questioned.

Surgical clips are ideal for the localization of the tumor bed. The surgical clip method requires the cooperation of the surgical team. Despite the fact that it would theoretically take an infinite number of clips to define every extension of a typical tylectomy cavity, in practice six clips suffice (superficial, deep, medial, lateral, cephalad, and caudal).

CT-guided portal design should be done in the treatment position. This technique gives good definition of the depth of the chest wall, and has been shown to be similar to ultrasound in delineating the lumpectomy cavity. Delineation of the biopsy cavity becomes more difficult with increased interval from surgery. The combination of surgical clips with a treatment planning CT scan to define the lumpectomy site for electron boost is most ideal. In the absence of surgical clips, the CT scan evaluation of the biopsy cavity and/or postsurgical changes, in combination with clinical information including mammography findings, scar location, operative reports, and patient input, will provide accurate information regarding placement of the field and energy of the electron boost.

**Three-Dimensional Conformal or Intensity-Modulated Radiation Therapy**

Standard opposed tangential fields with appropriate use of wedges to optimize dose homogeneity remain the most commonly employed method for delivery of whole breast irradiation. A number of publications have explored the potential advantages of 3D conformal radiation therapy (3DCRT) or intensity-modulated radiation therapy (IMRT) to treat patients with breast cancer. Theoretically, 3DCRT involves a reduction in the volume of normal tissues receiving a high dose, with an increase in dose to the target volume that includes the tumor and a limited amount of normal tissue. IMRT potentially can further improve the dose distribution between the target
and non-target tissue, but may also increase the volume of tissue exposed to lower doses of radiation. As suggested, this may increase the risk of second malignancies, and one must carefully weigh the potential gains and limitations of advanced planning techniques. It is important to recognize that the term IMRT has been used in various ways to describe breast cancer treatment. In some studies, IMRT is described as a method of three-dimensional dose compensation without a change in the gantry angles of predesigned tangential fields. In such instances, dose distribution has been improved, but the fields are not more conformal. Accordingly, low dose to other organs is not an issue. For others, IMRT attempts to improve conformity of the high-dose region by using multiple field angles that increase the volume of normal tissues that receive low radiation doses.

**Accelerated Partial Breast Irradiation**

The current standard of care for women with invasive breast cancer remains whole breast irradiation following breast-conserving surgery. With the notable exception of selected elderly women, omission of radiation therapy has now been proven in numerous randomized trials and meta-analysis to compromise local control, and to a lesser extent breast cancer-related mortality. For some women, the 6-week course of daily radiation with its associated time and travel issues is not feasible. In response to this, a wide variety of accelerated forms of treatment have been developed and proven safe and effective in short-term studies.

These approaches include multicatheter interstitial implants placed around the excision cavity, single balloon catheter that can be afterloaded with a central radiation source (MammoSite, Cytyc Corporation, Marlborough, MA) which is placed into the excision cavity, external beam conformal partial breast irradiation, and intraoperative single-dose irradiation. Although these techniques vary considerably, they share the common strategy of delivering the radiation to a smaller volume of breast tissue around the lumpectomy site, using fewer larger fractions delivered over a shorter time. The rationale behind this approach is that the majority of breast relapses occur at or near the lumpectomy site.

Although the early results clearly demonstrate the feasibility and acceptable toxicity of accelerated partial breast irradiation, this approach has not yet been demonstrated in a randomized trial to be equivalent to whole breast irradiation. There are several ongoing randomized trials that will attempt to answer the question of whether this approach is equivalent to whole breast irradiation for selected patients.

**Interstitial Implantation**

For interstitial implantation, the distribution of sources to cover the target volume is chosen and a suitable perspex template used. Under general anaesthesia, rigid needles are passed through the breast and fixed at each end with a template (Fig. 6). Undue pressure on the templates should be avoided as this can cause severe scarring.

![Fig. 6. Interstitial implant with rigid needles](image)

The length of iridium wire loaded into a needle should position the end of the active wire 5-10 mm from the skin entry point. The superficial plane of wires should be approximately 1 cm below the skin surface. These measures ensure that the high dose rates around the wire do not cause telangiectasia or skin necrosis. For peripheral tumours or chest-wall recurrence where there is only sufficient tissue for a single-plane implant, a straight plastic tube technique can be used. Breast implants can be performed with remote afterloading; if this is done at a high dose rate, the treatment may need to be fractionated.
**Implementation of plan**
Patient alignment is checked using sagittal and coronal laser lights to medial and lateral tattoos. Tangential fields are treated isocentrically, and anterior and posterior nodal and electron fields are treated at the machine FSD. Appropriate shielding is applied to the anterior field. Beam films are taken on the treatment unit in order to check the borders of the tangential fields and to ensure that the central lung distance included does not exceed 2 cm.

**Dose prescription**

**Breast and Chest Wall**
50 Gy in 25 fractions given in 5 weeks.
Using tangential fields, skin doses are adequate for the intact breast, but bolus may sometimes be required for chest-wall irradiation for recurrent disease.

**Tumor Bed**
10-15 Gy in 5 to 7 fractions to the 100 per cent isodose given in 7 to 9 days
or 20-25 Gy at the 85 per cent isodose given in 2 to 2.5 days by implant.

**Residual Tumor**
18-20 Gy given in 6 to 8 fractions
or 30-40 Gy at the 85 per cent isodose given in 3 to 4 days by implant.

**Nodal irradiation**
50 Gy in 25 fractions given in 5 weeks.

The dose from the anterior supraclavicular field is prescribed to the 100 per cent point (build-up depth) on the central axis. The dose received at the midaxillary plane from the anterior supraclavicular field is calculated using the axillary separation, and recorded.

If an additional contribution from a posterior axillary field is considered to be necessary to bring this dose up to 50 Gy, a dose distribution is essential. This additional dose should be given as small daily fractions, and the summated dose at the anterior bronchial plexus should be kept within the tolerance range according to guidance given.

**Patient care**
Patients are instructed to limit washing of the irradiated skin and to use aqueous cream to keep the skin moisturized. One per cent hydrocortisone cream may be used to relieve the discomfort of dry desquamation. If moist desquamation occurs, treatment is temporarily stopped and paraffin gauze or hydrogel applied until healing occurs. Tight-fitting clothes should be avoided as much as possible in order to reduce friction and abrasion of the skin. Loose cotton garments are recommended.
Chapter 9
Systemic Adjuvant Therapy of Breast Cancer
During the last twenty years, the incidence of breast cancer has increased in Europe and in the USA. However, a parallel increase has not been noted in mortality due to breast cancer. In fact, since 1994 there has been a 1% to 2% reduction in mortality in the USA, Canada, Sweden, France, and the UK. This is for two main reasons. First, by the development of early diagnosis, based on radiological and clinical detection and secondly, the use of systemic adjuvant therapy.

The rationale for the use of systemic adjuvant treatment following loco-regional therapy of breast cancer is:

1. The relation between the tumor volume and the risk of metastatic dissemination: this risk is estimated at over 50% for a volume of more than 40 mm;
2. The efficacy of adjuvant therapy, chemotherapy or hormonotherapy, is tumor volume dependent, the greater the volume, the higher the risk of acquiring the drug-resistance phenotype; and
3. Progress in loco-regional therapy does not seem to enhance survival, since it has failed to prevent metastatic dissemination.

A better appraisal of prognostic parameters currently allows a more accurate definition of the groups of patients in whom systemic adjuvant therapy is relevant. Moreover, some of these factors e.g. axillary node status, estrogen, and progesterone receptors, nuclear grade, tumor size and age are decisive for the choice between adjuvant hormonal therapy and chemotherapy.

Before addressing specific adjuvant therapies, it is important to address the necessity, of any adjuvant systemic therapy. Two groups who do not need adjuvant therapy may be suggested. Those who will not benefit, because their prognosis is so favorable and those for whom adjuvant therapy is ineffective.

It appears from the present data that women with node negative breast cancer <1 cm in diameter or 1-2 cm in diameter and have histologic grade 1 tumors (T1a,b N0 or T1c grade 1 N0) have the same survival likelihood as age-matched women without breast cancer. So, adjuvant systemic therapy may not be indicated. The second group, where adjuvant systemic therapy is ineffective includes giving hormonal therapy for women whose tumors lack hormone receptors, trastuzumab for women with low levels of HER-2 expression, and giving cytotoxic chemotherapy for very old women, as they appear to receive only toxicity without benefit.

I. ADJUVANT ENDOCRINE THERAPY

I.1. Selective Estrogen Receptor Modulators [SERMs]
Tamoxifen is the first SERM to be tested. The EBCTCG data clearly demonstrate that 5 years of daily tamoxifen reduces the risk of recurrent breast cancer by 47% in receptors positive women. This reduction is also durable. The benefit of 5 years of tamoxifen appears greater than with 2 years, which is greater than that seen with one year of therapy. But limited data exists on the value of greater duration. A very large international clinical trial of duration (ATLAS trial) including 15V 252 is underway to resolve this issue. Benefits in addition to prevention of metastatic breast cancer include improved local control and prevention of contralateral breast cancer in individuals with a hormone receptor-positive primary tumor.

The detrimental aspects of tamoxifen include menopausal symptoms, endometrial cancer, and thromboemboli. The latter two are seen only (are you sure for thrombo-embolism?) in postmenopausal
women. Very rarely, there may be an accelerated progression of certain types of cataracts, but this is uncertain. However, the benefit of giving tamoxifen greatly outweighs the hazards. The benefit of reduction of contralateral breast cancer is alone able to counterbalance the increased risk of endometrial cancer, quite aside from the other benefits of systemic adjuvant effects.

It is now very clear and conclusive that the benefit of tamoxifen is only for those with hormone receptor-positive tumors, even those with low levels of receptor expression.

A further area of controversy concerns the use of adjuvant tamoxifen in women with tumors overexpressing Her-2; an overexpression to Her-2 is associated in the lab with tamoxifen resistance. However, and based on existing clinical data, it appears appropriate to treat patients only based on hormone-receptor status and not to deny tamoxifen when Her-2 is overexpressed.

The search continues for tailored SERMs that retain only desirable effects of tamoxifen. Other SERMs such as raloxifene have not been tested sufficiently, while the so-called SERM-3 agents are nearing clinical testing. So, at present, tamoxifen is the only SERM used outside adjuvant clinical trials and the most potent adjuvant available for the receptor-positive patient.

I.2. Anti-estrogens

The finding that both steroidal aromatase inhibitors e.g. exemestane (Aromasin®), and non steroidal aromatase inhibitors e.g. letrozole (Femara®), and anastrozole (Arimidex®), can provide major response in the advanced and metastatic disease has suggested about their role in adjuvant therapy. Results of recent clinical trials show a benefit in term of disease free survival of antiarmotase over tamoxifen Others trials are now ongoing to answer whether the use of sequential administration of tamoxifen and antiaromatases either during five years of each treatment, or 2.5 years of each increases the quality of the results. Long term tolerance of antiaromatases in mainly marked by the risk of major osteoporosis. Fulvestrant is a pure anti-oestrogen that reduce markers of hormone sensitivity and proliferation of breast cancer. Up to now it is only used in metastatic situation.

I.3. Ovarian Ablation/Suppression

The clinical trials of ovarian ablation either by surgical means (open or laparoscopic), or by pelvic irradiation antedate selection by hormone receptor status. However, even so, they demonstrated a reduction in the annual odds of death of 25% for women below 50 years of age at the EBCTCG Oxford overview. Also, in presence of chemotherapy, ovarian ablation adds about 10% to the mortality reduction achieved with chemotherapy alone.

The use of gonadotropin-releasing hormone agonists e.g. Goserelin, appears to provide benefit in the overview analysis. However, it has the advantage of being given for a period of time i.e. 2 years, with return to normal hormonal status after stopping the use of the drug. It can be associated with tamoxifen in premenopausal patients.

Conclusion

Endocrine therapy for breast cancer includes selective estrogen receptor modulators (SERMs), antiestrogenic agents, ovarian ablation by surgical means or pelvic irradiation, and gonadotropin-releasing hormone agonists (LHRH agonists). Up to now, the optimal adjuvant hormonal therapy is considered to be 5 years for tamoxifen for anyone with a tumor that is estrogen receptor or progesterone receptor-positive, even if at a low level, and regardless of the possible concurrent overexpression of Her-2. Patients with tumors lacking estrogen and progesterone receptors will not benefit by tamoxifen administration. Also, for patients with node negative cancers less than 1 cm in diameter regardless of histologic grade, or tumors 1 to 2 cm in diameter of low grade (grade 1), evidence of a benefit exceeding the detriments of systemic adjuvant therapy including hormonal therapy is lacking. However, it seems likely that optimal
therapy will be changed by the new ongoing clinical trials now using the new SERMs, aromatase inhibitors, and LHRH agonists.

II. CHEMOTHERAPY IN EARLY BREAST CANCER

II.1. Current Knowledge on Adjuvant Chemotherapy

The first randomized studies of adjuvant chemotherapy were reported more than 20 years ago by Bonnadona in Milan and the NSABP. Although the regimens were very different, the results of these studies were the same. They showed that premenopausal women may procure a greater benefit from adjuvant chemotherapy than postmenopausal women and that the gain in terms of survival was better for patients with minimal axillary lymph node involvement than for patients with more than 4 involved nodes.

So, for a long time, adjuvant chemotherapy was only given to premenopausal women. Since the results of the meta-analysis, chemotherapy is now known to be also efficient in postmenopausal women. When prolonged chemotherapy is given the risks of recurrence and of mortality is reduced by 35% and 18% in premenopausal women, and 39% and 19% in postmenopausal women respectively.

It is also clear from the last overview meta-analysis that:

1. Polychemotherapy is more effective than single agent chemotherapy,
2. There is no significant greater benefit from prolonging polychemotherapy beyond about 3-6 months,
3. Prolonged benefits of polychemotherapy appear to be largely unaffected by axillary nodes, ER, or menopausal status at presentation, or by the use of tamoxifen,
4. Benefits of polychemotherapy are greater among women aged under 50 years (risk reduction of 36% and 27% for disease recurrence and death respectively), but even at age 50-59, and 60-69 years, polychemotherapy resulted in risk reduction of 19% for disease recurrence and 11% for mortality,
5. Anthracycline-containing regimens are more effective than the CMF regimens, with a benefit of 4% in death rates. There are too few non-breast cancer deaths to assess long-term safety mainly linked with the cardiac toxicity.
6. Taxane containing regimens are more effective than regimens without for N+ patients adding about 3.5% benefit for the disease free survival and 2 to 2.8% for N+ patients.

So, overall adjuvant polychemotherapy has produced risk reduction of 23.4% in disease recurrence, and 14.9% in deaths. This risk reduction was clearer in younger ages, and that polychemotherapy adds to the benefits of tamoxifen and vice versa.

Currently a consensus exists regarding the administration of chemotherapy to women with breast cancer (see appendix I and II). Chemotherapy should be enhanced prior radiotherapy.

II.2. Chemotherapy regimens

Adjuvant chemotherapy regimens that include an anthracycline result in a statistically significant improvement in survival compared to non-anthracycline containing regimens and chemotherapy regimen including taxanes seem of a greater interest.

At present time, there is no role for high dose chemotherapy outside the context of a clinical trial. But dose intensity regimen appears of interest in one trial for N+ operable breast cancers. This fact is not confirmed by others studies concerning locally advanced breast cancer.
Table 9.1. Examples of Chemotherapeutic Regimens used in the Adjuvant Setting

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adriamycin</td>
<td>60 mg/m² IV</td>
<td>D1 /3 weeks</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>500 mg (or 600 mg?) /m² IV</td>
<td>D1 /3 weeks</td>
</tr>
<tr>
<td>1. FAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>500 mg/m² IV</td>
<td>D1 /3 weeks x 6 cycles</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>500 mg/m² IV</td>
<td>D1 /3 weeks x 6 cycles</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>500 mg/m² IV</td>
<td>D1 /3 weeks x 6 cycles</td>
</tr>
<tr>
<td>2. CMF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>600 mg/m² IV</td>
<td>D1, 8</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>40 mg/m² IV</td>
<td>D1, 8</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>600 mg/m² IV</td>
<td>D1, 8 /4 weeks x 6 cycles</td>
</tr>
<tr>
<td>3. FEC 60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>600 mg/m² IV</td>
<td>D1 /3 weeks x 6 cycles</td>
</tr>
<tr>
<td>Epidoxorubicin</td>
<td>60 mg/m² IV</td>
<td>D1 /3 weeks x 6 cycles</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>600 mg/m² IV</td>
<td>D1 /3 weeks x 6 cycles</td>
</tr>
<tr>
<td>4. FEC 100*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>500 mg/m² IV</td>
<td>D1 /3 weeks x 6 cycles</td>
</tr>
<tr>
<td>Epidoxorubicin</td>
<td>100 mg/m² IV</td>
<td>D1 /3 weeks x 6 cycles</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>500 mg/m² IV</td>
<td>D1 /3 weeks x 6 cycles</td>
</tr>
<tr>
<td>5 A T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adriamycin</td>
<td>50 mg/m2</td>
<td>D1 /3 weeks x 6 cycles</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>75 mg/m2</td>
<td>D1 /3 weeks x 6 cycles</td>
</tr>
<tr>
<td>6 AC x 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Paclitaxel</td>
<td>AC (cf supra)</td>
<td>4 cycles</td>
</tr>
<tr>
<td></td>
<td>80mg/mé weekly</td>
<td>X 12</td>
</tr>
</tbody>
</table>

* Indicated in cases having more than 10 positive nodes.

II.4. Tolerance of Chemotherapy

Most of the cytotoxic drugs and combination regimens used in breast cancer are with a spectrum of toxicity, but hematological toxicity with neutropenia, thrombocytopenia and anemia is by far the most frequent. Complete blood counts are required before each cycle to verify bone marrow recovery.

Hospitalization with broad-spectrum antibiotics should be mandatory in cases of febrile neutropenia, whereas WHO grade IV thrombocytopenia and anemia may require platelet or red cell transfusions. Other toxicities include nausea and vomiting which are now readily managed with the advent of 5-HT3 antagonists; cardiac failure due to high cumulative doses of anthracyclines (>500 g/m² for doxorubicin); alopecia which is frequently unpopular among young women and, menstruation disorders which are mainly transitory in women < 40 years but frequently definitive in women over 45 years. Neurological toxicity can be observed with use of taxanes Finally, about 50 to 60% of women receiving adjuvant chemotherapy may gain weight, the mechanism of which is unknown.
In practice, several measures are recommended for adequate monitoring of chemotherapy: a complete blood cell count before each cycle, left ventricular function evaluation before the initiation of chemotherapy, the use of a central venous catheter to prevent extravasation of cytotoxic drugs and adequate contraception (excluding estrogens) to avoid pregnancy and fetal risks during therapy.

II.5. Predictive Markers for Response to Chemotherapy
There are many factors associated with a poor prognosis, and these are useful to guide systemic therapy. Predictive factors, on the other hand, help determine the probability of response to a particular drug or drug class.

Although application of these factors in choosing the appropriate systemic chemotherapy for a certain patient appears promising, currently there is no clinical level 1 evidence to support the definitive predictive role of any tumor or patient characteristics for response to cytotoxic therapy. It is now well established that invasive lobular carcinomas are less sensitive to chemotherapy than invasive ductal carcinomas.

However, some markers hold some promise. Analysis of retrospective data suggests that Her-2 overexpression may indicate particular sensitivity to anthracyclines, and less responsiveness to CMF. So, many prospective trials are now exploring these unconfirmed data. p53 represents another potential predictive factor as there are some preclinical and clinical data to suggest that tumors with p53 mutations may be particularly sensitive to taxanes and relatively resistant to anthracyclines. Tumors with amplification of the topoisomerase II alpha gene seem more sensitive to anthracyclins regimens. Other markers include urokinase plasminogen activator, tissue plasminogen activator inhibitor 1, thymidylate synthase, MDR-1 overexpression, and alterations in Ki67 and p27 genes. Exploration of the role of all these markers may help in the future to determine the most appropriate treatment for a particular patient.

III. Targeted therapy:
For patients with HER2/neu overexpression reports of some trials in 2005, and subsequent reports demonstrate that an humanized antibody trastuzumab (Herceptin) (administated evry 3 weeks during 1 year) following chemotherapy improves clearly both diseases free survival and over all survival.

Side effects: In 2-7% of cases, trastuzumab is associated with cardiac dysfunction. As a result, regular cardiac screening with either a MUGA scan or echocardiography are mandatory during the trastuzumab treatment period. Approximately 10% of patients are unable to tolerate this drug because of pre-existing heart problems.

Many questions are still unresolved concerning this type of treatment
1) Duration 1 year or shorter duration?
2) The use of trastuzumab associated with anthracycline containing regimen appears to increase the risk of congestive cardiomyopathy. Is it possible to select patients who could benefit of an association of trastuzumab and a non-anthracycline-based regimen?
3) Should tratuzumab, in adjuvant situation has to be used with or following adjuvant chemotherapy?
4) Do we have to use trastuzumab for tumors < 1cm?

New targeted therapy are effective on metastatic breast cancerds (for lapitinib a novel inhibitor of HER1 and HER2)instance now disponible could have a place in dajuvant situation in addition with trastuzumab.
ADJUVANT SYSTEMIC TREATMENT
As mentioned above in the results of the overview meta-analysis of EBCTCG, adjuvant tamoxifen and adjuvant chemotherapy trials have demonstrated that each of these modalities, used in appropriate patient groups, will greatly reduce the annual odds of recurrence and morality, and that such treatments are not mutually exclusive i.e. polychemotherapy adds to the benefits of tamoxifen and vice versa.

However, other analyses and results of some individual trials have suggested that the added benefits from adjuvant chemotherapy may be considerably smaller in those cases with ER-positive tumors specially when treated with optimal endocrine therapy. These suggestions are most apparent in recent tumors specially when treated with optimal endocrine therapy. These suggestions, however, have not appeared in recent Intergroup and NSABP trials.

In the future, it is possible that LHRH agonists and aromatases inhibitors may replace chemotherapy as an adjuvant therapy of pre- and postmenopausal patients, respectively, with receptors-positive tumors.

II.3. Neo-adjuvant Chemotherapy in Breast Cancer
Neoadjuvant chemotherapy is the use of cytotoxic drugs prior to local treatment. There are several possible advantages with this strategy. Some non-randomized and randomized studies suggest that a reduction in tumor volume in response to primary chemotherapy may limit the extent of surgery required, and particularly the need for mastectomy. But long-term data confirm that less mutilating surgery permit higher local failures without detrimental effect in term of overall survival.

A second objective of neoadjuvant chemotherapy is the early eradication of micrometastases. Any tumor response indicative of chemosensitivity will render aggressive therapy including intensification of chemotherapy conceivable in order to improve survival. Finally, neoadjuvant chemotherapy may inactivate tumor cells and thereby possibly prevent their dissemination during surgery.

In clinical practice, neoadjuvant chemotherapy procures a high clinical and radiological response rate, (higher than 80% in most studies, with a complete response rate of about 20%). As mentioned above this high response rate, and the need for mastectomy after neoadjuvant chemotherapy, as a primary surgical approach is questionable. Currently, conservative surgery is possible after chemotherapy in about 50% to 75% of women who would have been candidates for mastectomy. Most authors recommend 3 to 6 cycles of neoadjuvant chemotherapy with various drug combinations. The FAC or the FEC regimens or regimen including taxanes mainly used. For patients with HER2/neu surexpression , addition of tratstuzumab improves the results. In some studies a complete histological response is, but a good prognostic factor (référence Aberdeen) but this data was not confirmed by the randomized trial NSABP .

In patients with expression of hormonal receptors the neoadjuvant systemic treatment can be an hormonal therapy. This schedule is often preferred in old patients for which neo-adjuvant chemotherapy could be detrimental.

LATE AND LONGTERM COMPLICATIONS
AFTER ADJUVANT THERAPIES OF BREAST CANCER

A particularly important trend has been the increasing application of systemic adjuvant therapies to patients with earlier stage disease even with a lower risk of breast cancer recurrence. Although this strategy extends the absolute benefits of adjuvant therapy to more women, it also exposes a greater proportion of those women with breast cancer to the potential of late complications of adjuvant therapy.
A. Ovarian Failure
Premature menopause is a common outcome after adjuvant therapy in menstruating women. In parallel, hormone replacement therapy is routinely discontinued at the time of diagnosis in postmenopausal patients.

Age and the duration as well as the type of adjuvant therapy are the primary determinants of ovarian failure. The median time to its onset is shorter in older than in younger women (2-4 months vs. 6-16 months). Ovarian failure is less likely to be reversible in older women (≤10% vs. up to 50%). The rate of permanent ovarian failure is lower with regimens like AC than with CMF. Treatment with CMF for 6 months results in permanent ovarian failure in 70% of women over 40 years of age and in 40% of younger women. Short and long term effects of menopause in breast cancer survivors include the following: A-ton des données pour les taxanes ?

1. Vasomotor symptoms
Hot flushes, night sweats, disruption of sleep and irritability may occur in certain situations including postmenopausal patients who are taken off hormone replacement therapy, or started on tamoxifen, and in premenopausal patients who have received adjuvant chemotherapy, or undergone ovarian ablation. These symptoms may occur very early during the course of the disease and its treatment, or may occur many years after treatment. They may be transient, or may be severe and persistent.

2. Vaginal effects
In a study on breast cancer survivors, vaginal dryness was significantly increased in women who had received any form of adjuvant therapy compared to those who had not received adjuvant treatment. Vaginal dryness may lead in some patients to dyspareunia. Also, vaginal discharge was increased in women who received adjuvant tamoxifen but not in women who received chemotherapy alone.

3. Osteoporosis
Ovarian failure early menopause and anti-aromatase treatment in post menopausal patients is a risk factor for osteoporosis increase the risk of osteoporosis. Long term data on fractures in women with chemotherapy-induced ovarian failure are unavailable. To prevent this complication women should have adequate dietary intake of calcium and vitamin D and should perform weight-bearing exercises regularly and have their bone density evaluated. Treatment with bisphosphonates mitigates bone loss in women with breast cancer and chemotherapy-induced ovarian failure. On the other hand, tamoxifen when given as adjuvant therapy preserves bone mineral density in postmenopausal women, but whether it reduces the risk of vertebral or hip fractures is uncertain. However, tamoxifen may increase bone loss in premenopausal women because of its estrogen-antagonist activity.

The administration of estrogen to women with breast cancer for the relief of menopausal symptoms and for the long-term prevention of osteoporosis is contraindicated

B. Cardiovascular Disease

Related with chemotherapy
An important unanswered question is the effect of the induction of premature menopause associated with adjuvant treatment on the cardiovascular system. Long-term studies are essential to evaluate this concern, but preliminary lipid profiles, blood pressure measurements, and waist to hip ratio measured in one study
of breast cancer patients treated by adjuvant therapy at age 50 years and younger, do not show significant
differences among women who received adjuvant therapy and no therapy.

Doxorubicin directly damages the myocardium and can cause cardiomyopathy. However, when the total
dose of doxorubicin is limited to 240 –300 mg/m² the incidence of clinically important cardiomyopathy is
less than 1%. However, in one study 8% of those receiving adjuvant doxorubicin had echocardiographic
evidence of systolic dysfunction or reduced LVEF, compared to less than 1% of women treated with
CMF regimen. Whether such subclinical systolic dysfunction will result in clinically overt cardiac
problems is unknown. Dexrazoxane (cardioxane) as preventive treatment can should be used when a total
dose of adriamycin reaches more than 300 mg/m² (more for epiruclin)

**Related with hormonal treatment**

On the other hand, a potential benefit of adjuvant tamoxifen therapy may be a reduction in cardiac
mortality in postmenopausal women treated with tamoxifen, serum concentrations of total and LD
lipoprotein cholesterol fall by about 10%. Whether tamoxifen reduced the rate of cardiovascular disease
remains to be determined. Retrospective analysis of two randomized trials showed that the risk of
myocardial infarction, and death from cardiac causes were lower among women who received tamoxifen
than among those who did not. However, the NSABP P-1 tamoxifen prevention trial results did not show
such a protective effect.

On the other hand, women treated with tamoxifen have small decreases in plasma concentration of
antithrombin III, protein S, and fibrinogen. The relevance of these findings to the observed very small
excess risks of DVT, pulmonary embolus, and stroke among postmenopausal women taking tamoxifen is
unknown yet. Also, it was observed that concurrent administration of tamoxifen and chemotherapy may
result in a higher incidence of venous and arterial thrombosis than either treatment alone.

**C. Cognitive Dysfunction**

Two or three years after adjuvant treatment, problems with concentration, memory and language were
observed to be more frequent in women receiving chemotherapy than in other women. The mechanism of
this cognitive dysfunction is unknown, but it has been postulated that a direct effect of chemotherapy or
diminished estrogen secretion due to ovarian failure has a role.

**D. Second Cancers**

Tamoxifen treatment is associated with about 80 excess cases per 10,000 of endometrial cancer at 10
years, primarily in women over the age of 50 years. There is no evidence that tamoxifen therapy increases
the risk of other cancers. In most of cases, endometrial cancers are of low grade and early stage that are
curable with surgery alone. There is little evidence that the risk of second cancer is increased among
women who receive adjuvant CMF chemotherapy. Also, there is less information on the risk of second
cancers among women treated with doxorubicin-containing regimens, and there is no information on the
risk with those containing taxanes. The risk associated with 6 months CMF therapy includes acute
myeloid leukemia or myelodysplasia (5 excess cases per 10,000 treated patients at 10 years).
Mitoxantrone used as adjuvant treatment increases the risk of secondary acute leukemia and combined
chemotherapy and radiotherapy may increase the risk of leukemia.

**E. Neurologic Toxicity, Weight Gain, Fatigue and Quality of Life**

The taxanes cause both sensory and motor peripheral neuropathy, myalgia and arthralgia. In rare cases,
tamoxifen is associated with reversible retinopathy and slight increase in cataracts. Tamoxifen is
frequently thought to cause depression and weight gain, but both were similar in incidence in tamoxifen
and placebo groups in several trials. On the other hand, the majority of women with breast cancer who are treated with CMF regimen gain weight while women treated with AC combination gain less weight than those treated with CMF. Weight gain may adversely affect the quality of life. Also, many women with breast cancer who are receiving adjuvant chemotherapy have fatigue. The fatigue appears to resolve after treatment. So, measurements of the quality of life worsen during adjuvant chemotherapy but improve after the cessation of treatment. This may be also attributable to other factors including depression, body image, sexual dysfunction and other treatment related factors.

**Late Effects of Radiotherapy**

Long term side effects of irradiation of the breast, chest wall and regional lymph nodes include cardiac toxicity, second cancers, pneumonitis, lymphedema, brachial plexopathy, skin reactions, and rib fractures. Meta-analysis and registry based studies have shown small long-term increases in mortality from cardiac causes involving coronary artery disease. However, most of these women have been treated with outmoded techniques that exposed the heart to high doses of radiation. Women treated with modern techniques have not been found to suffer from an increased risk of these cardiac complications. However, even when radiation fields are limited to the breast, there still may be a risk of cardiac toxicity when the daily doses are high implicating probably an adverse systemic effect of radiotherapy. Sequentially administered radiotherapy and doxorubicin with higher single doses (75 mg/m$^2$) or higher cumulative doses (450 mg/m$^2$), also increases the risk of cardiac toxicity.

Several case-control studies have found that the risk of contralateral breast cancer was slightly increased among patients treated with radiotherapy after mastectomy, probably as a result of the small dose of scatter radiation to the other breast. Sarcomas are very rarely caused by irradiation. Likewise, angiosarcomas of the skin of the irradiated breast occur in 0.1% to 0.5% of patients. Also, in case-control studies that were mainly limited to smokers, there were very small excess risk of ipsilateral lung cancer, and esophageal cancer among women treated with now outmoded radiation techniques. Symptomatic radiation pneumonitis occurs in about 1% of women. This incidence is higher when chemotherapy and radiotherapy are given concurrently or when a supraclavicular or full axillary field is treated as well.

**Pregnancy after Breast Cancer**

A significant sector of new cases of breast cancer occurs in women of childbearing age and it is natural after completing therapy for the patient to ask about an integral and treasured part of life; pregnancy and childbearing. Although hormonal influence on carcinogenesis, growth rate and metastases of breast cancer is well known, few studies have evaluated women who became pregnant after breast cancer treatment.

There are several retrospective and population-based studies that have been published. Also an ongoing study in the USA will help to address this issue. From all the retrospective studies, it has been generally observed that breast cancer patients who subsequently become pregnant have good survival rates, often the same or sometimes better than patients with no subsequent pregnancy. Three of these retrospective studies have examined the timing of subsequent pregnancy on breast cancer prognosis. In one study patients who became pregnant within 6 months had a comparatively poor prognosis than those who waited 6 months to 2 years to become pregnant after breast cancer diagnosis (5 year survival rates of 54% vs. 78% respectively). Those who waited 5 years or more to become pregnant had a 100% 5-year survival rate from that point. However, these data may be affected with the fact that the longer survival after diagnosis is in itself an indicator of the patient’s better prognosis regardless of the occurrence of pregnancy or not. Although smaller, the other two studies did not find, however, a statistically significant difference between outcomes of patients based on the time interval between diagnosis and pregnancy.
However, certain biases remain inherent in these retrospective studies. For example, as pregnancy is not considered as a disease, it may be noted or added in a patient’s chart. So, four large population-based studies have been published worldwide since 1994 from Finland, Sweden, Denmark and USA. Again all these studies showed that survival of women with breast cancer is not decreased in any of these reports. Still, it is likely that breast cancer patients who choose to become pregnant and give birth were disease-free as opposed to an unknown proportion of controls that had a recurrence at the time of matching for the study, but had not yet died. For this reason, as well as other factors that may affect data interpretation, a prospective study on pregnancy after breast cancer treatment is now being conducted in the USA and funded by the Army Breast Cancer Research Fund.

St-Gallen Consensus 2009

Till page 171
Chapter 12
Management of advanced breast cancer
The clinical course of metastatic breast cancer is variable; this heterogeneity results in large variations in growth rate and responsiveness to systemic therapy. The heterogeneity of patients with metastatic breast cancer must be emphasized. Rarely, patients with metastatic breast cancer succumb to their disease within weeks of a diagnosis; others live with the disease for many years. Many patients have metastatic involvement that is confined to bone or soft tissue, while others have predominantly visceral disease. CNS involvement is relatively unusual as a presenting sign or symptom of metastatic disease. It is important, both in the approach to individual patients and in considering clinical trial results, to have an understanding of the variability of metastatic breast cancer. Table 10.1. outlines the clinical and laboratory characteristics of patients with metastatic breast cancer who have an indolent versus aggressive clinical course. No single factor explains the heterogeneity that is seen clinically. It is uncertain to what extent the administration of prior adjuvant therapy affects a patient's prognosis in the setting of advanced disease. There are reports of patients responding to chemotherapy in the metastatic setting even after receiving the identical therapy in the adjuvant setting. On the other hand, a patient who develops an early recurrence following treatment with an effective adjuvant regimen (i.e. CA: cyclophosphamide and Adriamycin) followed by paclitaxel followed by tamoxifen almost certainly has a relatively poor outlook in the metastatic setting.

<table>
<thead>
<tr>
<th>Favorable Prognosis</th>
<th>Unfavorable Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(Indolent Clinical Course)</strong></td>
<td><strong>(Aggressive Clinical Course)</strong></td>
</tr>
<tr>
<td>Long disease-free interval (usually</td>
<td>Short disease-free interval (usually</td>
</tr>
<tr>
<td>considered at least 2 y from initial</td>
<td>considered less than 2 y from initial</td>
</tr>
<tr>
<td>diagnosis)</td>
<td>diagnosis) a</td>
</tr>
<tr>
<td>Hormone receptor positivity</td>
<td>Hormone receptor negativity</td>
</tr>
<tr>
<td>Response to prior therapy</td>
<td>Lack of response to prior therapy</td>
</tr>
<tr>
<td>Lack of visceral involvement</td>
<td>Presence of visceral involvement, CNS</td>
</tr>
<tr>
<td></td>
<td>involvement, or both</td>
</tr>
<tr>
<td>Limited sites and bulk of disease</td>
<td>Multiple sites of disease and extensive</td>
</tr>
<tr>
<td></td>
<td>involvement at these sites</td>
</tr>
<tr>
<td>HER-2/neu negative</td>
<td>HER-2/neu positive b</td>
</tr>
</tbody>
</table>

a. Although 2 years is often used as an arbitrary cutoff in separating early recurrences, the longer the disease-free interval, the more indolence one can expect in terms of tumor behavior.

b. It is not clear that HER-2/neu positivity remains an adverse prognostic factor with the availability of trastuzumab.

**Table 10.1.** Factors that affect prognosis in patients with metastatic breast cancer
**Diagnostic Workup**

Patients with metastatic breast cancer have organ involvement assessed by symptoms and physical examination. A biopsy to establish metastatic disease provides an opportunity to reassess the hormone receptor status of the tumor. While few tumors evolve from ER negative to ER positive, more frequently there can be loss of hormone receptors over time. With the availability of Herceptin, the result of a HER-2/neu assay is often important in making treatment decisions, although this can often be assessed from specimens of the primary tumor.

Recommendations for the laboratory and radiographic evaluation of patients with newly diagnosed metastatic breast cancer have been established by the National Cancer Center Network. Routine blood work consisting of complete blood counts and liver function tests are recommended. In addition, chest radiographs and bone scans are recommended. The decision to proceed with other-radiographic studies can be based on symptoms, although many physicians obtain a baseline assessment of liver involvement with a CT scan or MRI, particularly if the presence of liver metastases would change treatment. Since intracranial involvement is extremely rare, in newly diagnosed patients in the absence of CNS symptoms, a CT or MRI of the brain is not usually recommended for a woman with a new diagnosis in the absence of symptoms. Sometimes it could be useful to realize a PET to get an overview of metastatic disease. The use of tumor markers in the management of patients with breast cancer remains controversial. It is reasonable to obtain a CA 15-3 and more accessorily carcinoembryonic antigen(CEA), and CA 27-29, level looking for an elevation in either of these proteins. If elevated, they can be followed to determine if rising or falling levels correlate with the patient's disease status. Caution should be used in changing a treatment regimen based on tumor markers alone. If tumor markers are negative at the time of diagnosis, they can be checked again when the patient has disease progression, as they are more commonly elevated in patients with more extensive disease.

**Choice of Systemic Therapy**

The vast majority of patients with metastatic breast cancer receive some form of systemic therapy. Hormonal therapy can be indicated only for patients with hormonal receptor positivity on the primary (or metastatic) tumor. (Patients with both estrogen and progesterone receptor positivity are more likely to respond to hormonal therapy than are those with ER-positive/PR-negative or ER-negative/PR-positive tumors). A trial of hormonal therapy may be justified even in the presence of negative hormone receptors since a small number of patients, with ER-negative/PR-negative tumors respond to a hormonal intervention). Immunotherapy with trastuzumab (anti-HER2 antibody) can be
considered only for patients with strong expression of HER2/neu (+++) on the primary tissue or on a metastatic specimen. (Fig. 12.1).

Hormonal Treatment

Because of the limited toxicity with most hormonal therapies, patients who have hormone receptor-positive tumors and a limited to moderate disease burden should generally receive hormonal therapy. The key issues that the clinician must consider in proceeding with initial hormonal therapy are whether or not the patient is likely to respond to the treatment and whether the patient would be adversely affected if she did not respond to treatment and was started on chemotherapy 2 to 3 months later. Visceral disease, particularly low-volume and asymptomatic disease, is not a contraindication to the use of hormonal therapy; however, the patient with extensive visceral disease is probably better served by chemotherapy. If a patient with a hormone receptor-positive cancer is initially treated with chemotherapy, the clinician should consider returning to hormonal therapy at some point in the future.

Choice of drugs

It depends on the menopausal status and of the kind of the adjuvant treatment given previously to the patient. For premenopausal patient, if the patient did not receive tamoxifen this is the preferred treatment. If yes and if the interval between the end of the adjuvant treatment by tamoxifen and the diagnosis of the relapse is sufficient, it is possible to try again the administration of tamoxifen. If the patient is obviously resistant to tamoxifen, castration (chemical by LHRH agonist (Gosereli) or by radiotherapy) is to be considered, but often chemotherapy is preferred. None of the new SERMs, including idoxifene, droloxifene, and toremifene (Farestone®), has been found to have activity in tamoxifen-refractory patients. We have to wait for the results of randomized trials to know if Fulvestrant can be used in this case. For post menopausal patients and mainly, if the received as adjuvant treatment tamoxifen, one of the aromatase inhibitors (AI) steroidal ( exemestane, formestane) and non-steroidal (anastrozole, letrazole) is indicated. In case of resistance it is possible to shift to another AI, steroidal if the patient breceived initially a nos steroidal AI et and reciprocally. If the patient received an AI as adjuvant treatment, tamoxifen as first line of treatment of metastatic disease is indicated.

Here also, we have to wait for the results of two large prospective randomized trials comparing Fulvestrant to anastrozole in tamoxifen-refractory patients, and to tamoxifen in patients who have never received tamoxifen or not received the drug for at least one year. Fadrozole is being less potent and less specific, and formestane is less convenient and equivalent to tamoxifen and megace. ??
The semisynthetic progestins: medroxyprogesterone acetate and megestrol acetate are the two most active agents of this class of hormones available for treating breast cancer patients and could be used as a third or fourth line of hormonal therapy. In routine there is no place for combination Endocrine Therapy except if we consider the modest improvement in response rate, progression-free survival, and overall survival associated with the combination of LHRH-A plus tamoxifen versus LHRH-A.

**Figure 10.1.** Optimal palliative therapy for women with metastatic breast cancer
**Cytotoxic Chemotherapy for Metastatic Breast Cancer**

**Single agents**
Chemotherapy is the most commonly used palliative treatment for metastatic breast cancer patients whose tumors become hormone refractory and for those patients whose tumors are expected to be hormone resistant from the start with the goal of ongoing symptomatic control and modest prolongation of survival.

A large number of chemotherapeutic agents are available to patients and their physicians: anthracyclines, alkylating agents, antimetabolites and microtubule inhibitors. Response rates for these agents range from 20% to high 60% (Table 12.2).

<table>
<thead>
<tr>
<th>Drug</th>
<th>ORR (%) (mean)</th>
<th>Drug</th>
<th>ORR (%) (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin*</td>
<td>43</td>
<td>Methotrexate*</td>
<td>26</td>
</tr>
<tr>
<td>Cyclophosphamide*</td>
<td>36</td>
<td>Paclitaxel*</td>
<td>36-62</td>
</tr>
<tr>
<td>Fluorouracil*</td>
<td>28</td>
<td>Docetaxel*</td>
<td>52-68</td>
</tr>
<tr>
<td>Capecitabine **</td>
<td>29</td>
<td>Vinorelbine*</td>
<td>40-52</td>
</tr>
<tr>
<td>Mitoxantrone*</td>
<td>27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ORR = objective response rate  
* in First-Line, ** in pretreated patients

**Table 10.2.** Single-Agent Chemotherapy Treatment of Metastatic Breast Cancer

**Anthracyclines** are probably the more often used of chemotherapy in the treatment of breast cancer: the main drug is doxorubicin. Except the hematologic toxicity, the main side effect of this drug is the cardiac one. So some times derivated products can be used: 4-epi adriamycin. Caelyx which is doxorubicin coated with sterically stabilized liposomes and idarubicin, which has oral bioavailability. These drugs should be less toxic and, in particular, less cardiotoxic than the parent compound; their exact role in breast cancer management awaits the completion of ongoing phase III trials. There is particular interest in these drugs with regard to treatment of elderly patients and development of combinations with toxicity profiles that are more favorable than those of doxorubicin-based regimens. Mitoxantrone is “apparentée” product from antracendione family.

In the antibiotic family, we include mitomycin which has a renal limiting toxicity. Among the **alkylating agents**, the main product is cyclophosphamide.
Three antimetabolites are used: Methotrexate and Fluoro-Uracil (5FU). Capecitabine, belonging to the subfamily of 5-FU prodrugs, which have acceptable oral bioavailability and produce results somewhat similar to those of active but inconvenient prolonged 5-FU infusion schedules. Capecitabine induced a 20% objective response rate in 162 heavily pretreated patients; a 29% response rate was documented in 42 of these patients, who had experienced rapid progression with both anthracyclines and taxanes.

Gemcitabine is the last antimetabolite showed good single agent activity as both first and second line treatment in advanced breast cancer. One of the most exciting aspects of this drug is its modest toxicity profile. This makes it particularly suitable for use as palliative therapy in elderly patients and in those with poor performance status.

**Microtubules inhibitors**: the discovery of the taxanes paclitaxel (Taxol) and docetaxel (Taxotere) has been the most encouraging chemotherapy development of the late 1980s and early 1990s that led to improvement of overall survival.

Docetaxel is generally given in a restricted range of doses as a 1-hour infusion because of its linear pharmacokinetics. Docetaxel is administered every 3 weeks. There is a significant response rate –relationship: the response rate in patients receiving 60mg/m², 75 mg/m² and 100 mg/m² in a recent study (ref. ??) was respectively 22.1, 23.3, 36 % and the time to progression 13.7, 13.9, 18.6 weeks. But an increase in hematologic and non-hematologic toxicity was noted with increasing dose.

The administration schedule of paclitaxel could be every 3 weeks as a 3-hour infusion or a weekly administration schedule with a relative lack of severe hematologic and non hematologic toxicity. Weekly administration of paclitaxel improves the response rate and decreases the hematologic toxicity compared with 3 weeks schedule, but increased neurotoxicity and therapeutic costs.

Vinorelbine, an antitubulin agent, it does have a favorable toxicity profile and significant antitumor activity, with response rate ranging from 34% to 41%. It could be an A number of new administration schedules besides the classic administration is weekly IV perfusion but it is available in an oral formulation.
Combination Chemotherapy
The principle of non-overlapping mechanisms of resistance and toxicities has been the basis for applying combination chemotherapy. Although combination chemotherapy has been widely enhanced, the validity of this concept has not been confirmed in breast cancer. In several randomized trials comparing combination chemotherapy to single agent therapy, response rates are higher in the combination arm, and times to first progression are longer. However, overall survival has only been minimally improved at best. An overview including 106 randomized trials that focused on five major chemotherapy strategies is summarized in table 10.2.

The main findings from this overview concerning chemotherapy are summarized as follow: response rate is increased by polychemotherapy, compared with monochemotherapy; polychemotherapy with anthracyclines, compared with polychemotherapy without anthracyclines; polychemotherapy other than combination therapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) compared with CMF regimens; more intensive chemotherapy regimens compared with less intensive chemotherapy regimens; and chemoendocrine therapy compared with chemotherapy alone.

In general, higher response rates were accompanied by definite increases in the occurrence of World Health Organization grade 3-4 toxicities. With only two comparisons was a clinically modest but statistically significant survival benefit found: (1) polychemotherapy versus single-agent chemotherapy and (2) cytotoxic agents delivered at higher doses or for longer periods versus less intensive cytotoxic regimens. Thus, polychemotherapy reduced the risk of death by 18% and, more intensive chemotherapy by 10%, translating in each case into a 5% to 6% absolute survival benefit at 2 years. In spite of the fact that combined cytotoxic therapies are more efficient if response rate is the major criteria, monotherapy cytotoxic therapy can be discussed if overall survival is the main criteria.

The important points gleaned from the overview are that (1) short inadequate-dose chemotherapy regimens should be avoided; (2) CMF or anthracycline-based or taxane (alone or in combination) regimens are reasonable treatment options for many metastatic patients, and ways of identifying those patients most likely to benefit from anthracyclines are needed; (3) chemotherapy and endocrine therapy should not be routinely combined; and (4) careful attention must be paid to treatment side effects and their impact on quality of life, given the narrow therapeutic index of cytotoxic agents and their modest impact on survival.
An important question is to know is whether to use a combined therapy versus single chemotherapy agent. Randomized comparisons of combination therapy with the same agents used in a sequential therapy do not show any difference in overall survival. But combined therapy improves the response rate and the time to progression and is often preferred for patients with excellent performans status and who have a symptomatic metastatic disease.

It seems now that there is no place for the stem-cell supported high-dose chemotherapy the highly toxic and costly strategy, with its as yet undefined impact on survival, remains difficult to justify outside the context of a prospective randomized clinical trial.

<table>
<thead>
<tr>
<th>Strategy Under Study</th>
<th>No. of Patients</th>
<th>Response</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Trials</td>
<td>Total</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PCT versus single-agent therapy</td>
<td>15</td>
<td>2442</td>
<td>1.79</td>
</tr>
<tr>
<td>PCT with A versus PCT without A</td>
<td>30</td>
<td>5241</td>
<td>1.30</td>
</tr>
<tr>
<td>Other PCT versus CMF therapy</td>
<td>17</td>
<td>3041</td>
<td>1.22</td>
</tr>
<tr>
<td>More intensive CT versus less intensive CT</td>
<td>19</td>
<td>3193</td>
<td>1.67</td>
</tr>
<tr>
<td>CT+ HT versus CT alone</td>
<td>25</td>
<td>3606</td>
<td>1.56</td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
<td>17523</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: A, anthracycline; CI, confidence interval; CMF, cyclophosphamide, methotrexate, and Fluorouracil chemotherapy; HT, hormonal therapy; PCT, polychemotherapy.

Table 10.3. Overview of Metastatic Breast Cancer Treatment, 1975-1997: Chemotherapy

Guidelines for selection of the sequence of chemotherapeutic agents is shown in (Fig. 10.2.)
**First-line chemotherapy**

- **<12 mo since prior adjuvant CTX**
  - Different CTX than used in adjuvant (see Progress on first line or second line, below)
  - AC, CMF, or single-agent taxane (paclitaxel, docetaxel)

- **>12 mo since prior adjuvant CTX**
  - No prior CTX or ensure adequate cardiac function if considering doxorubicin and previously treated

**Progress on first line**

- **First-line nontaxane**
  - Taxane
  - AC (see above) or CMF

- **First-line taxane**
  - erb-b2 overexpressed candidate for paclitaxel

**Progress on second line**

- Vinorelbine
- Capecitabine
- Leucovorin / infusional 5FU
- Liposomal doxorubicin
- Etoposide (VP16)

- Trastuzumab with paclitaxel (do not give with doxorubicin)

---

**Figure 10.2.** Decision Algorithm for Patients with Metastatic Breast Cancer

**Targeted therapy**

HER-2/neu, a new member of the group 1 growth factor receptor family, is amplified and/or overexpressed in 20% to 30% of patients with breast cancer. Overexpression of this oncogene product is associated with increased rates of tumor growth, enhanced rates of metastasis, shorter disease-free survival, and overall survival.

As a single agent, trastuzumab produces complete and partial remission in 13% to 20% of patients with metastatic breast cancer. In association with chemotherapy, trastuzumab enhances the response rate of the combination compared with chemotherapy alone and result in prolonged time to progression and increases 1-year survival rates. Trastuzumab is well tolerated, low-grade fever, chills, fatigue, and constitutional symptoms occur primarily with the first infusion, and serious
adverse effects are infrequent. In association with anthracycline chemotherapy, an increased incidence of subclinical and clinical cardiac toxicity has been observed.

There is compelling evidence to consider the use of trastuzumab in the initial management of women with HER-2/neu positive, hormone refractory metastatic breast cancer, however, there are a multitude of unanswered questions about the use of trastuzumab Herceptin in clinical practice. Cardiac toxicity It is unknown how long trastuzumab Herceptin should be administered and whether it should be continued with second-line chemotherapy after disease progression.

Recently two others targeted therapies are proposed alone or in association with chemotherapy. A murine anti VEGF antibody bemacizumab given as monotherapy demonstrated a modest activity in pretreated patients. It can be associated with chemotherapy (capecitabin or taxanes) and with hormonal treatement.

Lapatinib a tyrosine kinase inhibitor for patients with positive expression of HER 2 is proposed if failure of trastuzumab The main Side effects : fatigue nausea, cutaneous eruptions, diarrheas, skin dryness Acnée.

Toxicity of those treatments are not to be neglected en citer quelques unes … Actually, their cost very high (for a benefit which is not obvious regarding the overall survival) is an important limiting factor of their use.

**Bisphosphonates in the treatment of Bone Metastasis**

Bone is the most common site of metastasis in breast cancer. Bone metastases are also the most common cause of morbidity, including serious and sometimes catastrophic complications such as pathologic fractures, hypercalcemia of malignancy, and spinal cord compression. Approximately 20% of patients who develop bone metastases have only bone metastases for protracted periods.

Bisphosphonates are a large family of hypophosphate analogs that inhibit osteoclast activity by interfering with osteoclast binding to the osteoid surface, recruitment of osteoclast precursors, and secretion of osteoclast-activating factors by tumor cells.

Treatment with bisphosphonate in women with lytic lesions has become a standard of practice. It has an important effect on the frequency of bone-related complications such as pain, the need for palliative radiation and hypercalcemia. But biphosphonates have some side effects : risk of renal insuffisiancy and jaw osteonecrosis need a renal follow-up ans stomatis check-up before starting the treatment.
LOCAL TREATMENT

We can ask to Omar Omar to write several lines about hepatic surgery. Have you colleagues to write something about orthopedic and for thoracic and neurological treatment.
Chapter 11

Hormonal treatment of breast cancer
The breast is a tubulo-alveolar gland. The secretory units of the breast are the alveoli. These units are so responsive to hormone modulations that promote growth or regression of the breast tissue. It is well established that development and location of the normal breast are regulated by hormonal factors, and local cell-cell interactions. The endocrine steroids, peptides, and other molecules produced by the glandular tissue of the ovaries, pituitary, endocrine pancreas, thyroid, and adrenal cortex are the best defined of these factors.

On a more local levels of control, additional hormone-like substances are also synthesized by mammary tissue e.g. paracrine hormones, and juxtacrine factors. These juxtacrine growth factors are growth regulatory molecules that modulate adjacent cells by contracting their receptors. A third class of local factors is known as the autocrine or intracrine hormones. These are molecules that are synthesized by one cell and act back on the same cell type through surface or intracellular receptors.

A central organizing principle of endocrine hormone action in the breast has emerged. Systemic hormones regulate local production of growth factors. The actions of hormone-induced growth factors, and the complex interactions of the multiple cell surface signaling pathways with other hormone-induced gene products regulate both normal and abnormal glandular function and development (Fig. 13.1.).

The postpubertal breast may be mature, but it is inactive. A proliferative phase occurs during pregnancy. This is followed by a lactating phase after labor, and then regression takes place. An involutional or atrophic phase occurs after stopping lactation and when menopause occurs. Minor physical changes also occur in some women breasts before and during the menstrual cycle. All these changes and phases are controlled by a complex network of hormone and growth factor action.

Stage-by-stage action of these regulatory factors on mammary gland growth and development is illustrated in fig. 13.2.
### Endocrine Hormones

- **Ovarian sex steroids**: estrogen, progestin, androgen
- **Other steroids**: retinoids, vitamin D (?)
- **Other ovarian hormones**: inhibins and activins
- **Pituitary hormones**: oxytocin, prolactin, growth hormone (and tissue-derived IGFs)
- **Thyroid hormones**: T3, T4
- **Adenocortical hormones**: glucocorticoids, adrenal androgens
- **Pancreatic hormones**: insulin
- **Placental hormones**: placental lactogen, placental growth hormone, human chorionic gonadotropin

### Cell Adhesion-related Proteins

- E-cadherin
- Integins
- Nonintegrin cell substrate adhesion molecules
  - (67K laminin receptor, I-CAM-1, E-selectin, V-CAM-1, CD44)
- Focal adhesion kinase (FAK)
- c-Src
- b-Catenin

### Autocrine and Paracrine Hormones and Bioactive Milk Protein

- EGF (notch) family members;
- FGF family members
- TGF-B family members; IGF family members
- VEGF family members, Wnt family members
- CSF-1 and other cytokines
- Lactoferrin lactalbumin and whey acidic protein prolactin

### Signal Transduction and Transcriptional Control pathways

- MAP kinase pathways
- JAK – STAT pathways
- SMAD pathways
- Lipid metabolism pathways: PLCγ, PLD, PKC, P13K
- G-protein –cAMP pathways
- Steroid and thyroid hormone receptors
- Coactivators and corepressors of steroid receptors

### Cell Cycle Regulation

- Fos/Jun family – mediated transcription
- Myc/Max family – mediated transcription
- TCF family – mediated transcription
- Cyclin-dependent kinases, inhibitors, and cyclins
- E2F- Rb family – mediated transcription

### Milk products

- Milk proteins
- Lipids
- Growth factors
- Vitamins

### Cell Death and Tissue Remodeling

- Bcl family caspases
- UPA, TPA, plasmin systems
- Matrix metalloproteases / TIMPs
- Cathepsin D, B, and L; others?
- Matriptase?

---

**Figure 11.1** Hierarchy of modulators of breast development

cAMP, cyclic adenosine monophosphate; CSF, colony-stimulating factor; EGF, epidermal growth factor; FGF, fibroblast growth factor; GF, growth factor; IGF, insulinlike growth factor; JAK-STAT, Janus kinase-signal transducers and inactivators of transcription; MAP, mitogen-activated protein; P13K, phosphatidylinositol 3’-kinase; PKC, protein kinase C; PLC-γ, phospholipase Cγ, PLD, phospholipase D; TGF-β, transforming growth factor β; TIMP, tissue inhibitor metalloprotease; TPA, tissue plasminogen activator; UPA, urinary-type plasminogen activator; VEGF, vascular endothelial growth factor, Wnt, wingless
### Epithelial Rudiment

(+) Transplacental material
hormones of pregnancy
(±) Unknown local factors
(-) Transplacental hCG
(-) Transplacental inhibin
(-) Fetal testosterone

### Ductal Penetration and Branding into Fat Pad during Puberty

(+) Growth hormone
(+) Estrogen and progesterone
(+) Prolactin, insulin
(+) Glucocorticoids
(±) Other growth factors

### Lobuloalveolar Differentiation of Pregnancy

(+) Prolactin
(+) Estrogen
(+) Progesterone
(+) Placental lactogen
(+) Placental growth hormone

### Lactation

(+) Oxytocin

### Involution

(-) Multihormonal

---

**Figure 13.2.** Stage-by-stage action of regulatory factors on mammary epithelium.

CSF, colony-stimulating factor; EGF, epidermal growth factor; FGF, fibroblast growth factor; FIL, feedback inhibitor of lactation; hCG, human chorionic gonadotropin; HGF, hepatocytes growth factor; IGF, insulinlike growth factor; TGF, transforming growth factor
**HORMONAL THERAPY**

An ovarian link that controls the growth of some breast cancers has been known for almost a century. The discovery of steroid receptors in the mid-1970s, however, has provided the rationale for a more selective application of endocrine treatment. Commonly, endocrine manipulations need a delay of 7 to 8 weeks before exerting their beneficial effects. So, all rapidly growing lesions are better treated with other forms of therapy.

**I. Physiological and Biological Background**

The hormonal environment of the breast is largely dependent on that part of the endocrine involving the hypothalamus, the pituitary gland and the ovaries (Fig. 13.3).

![Figure 13.3.](image)

Overview of the neuroendocrine control of breast development and function with relationship to gonadotropic hormones of the anterior pituitary and ovary.

Estrogen is the major stimulus for the growth of hormone-dependent breast cancer, and most forms of endocrine therapy are directed toward inhibiting, ablating, or interfering with estrogen activity. The ovary is the principal site of estrogen synthesis, but it is also synthesized by the adrenal gland, adipose tissue, and even by mammary tumors themselves.

After menopause, estrogens are essentially secreted by the adrenals. They are biosynthesized from cholesterol with a series of enzymatic steps including cleavage, hydroxylation, and aromatization. Ductal
Hormonal treatment

growth is promoted by estrogen in the presence of growth hormone, while tubular development is promoted by prolactin and progesterone. The roles of cortisol, thyroxin, and insulin are permissive rather than regulatory.

Estrogens act by diffusing through the cell membrane to the interior of the cell, whether estrogens bind to ER in the cytoplasm or in the nucleus, the estrogen-ER complex then binds tightly to the hormone response element of target genes, and promotes the binding of a second complex to form a dimer.

When ER is activated by estrogen, the complex assumes a conformation that promotes specific gene transcription. Growth stimulation by estrogen is accompanied by an increase in growth stimulatory transforming growth factor alpha (TGFβ) production, whereas growth inhibition of hormone responsive breast cancer cell lines by an antiestrogen is paralleled by increased secretion of growth inhibition, TGFβ.

II. Hormone and Growth Factor Receptors

The genomic pathway of estrogen activation involves interaction of estrogen with a nuclear receptors protein that retains estrogen in target cell nuclei. The estrogen receptor (ER) α protein consists of 595 amino acids, and is, like the recently discovered 485-amino acids ERβ, a ligand regulated transcription factor. Both receptors, expressed in different amounts in different tissues, can be activated with different affinities by steroids and non-steroidal compounds. Both ER isoforms possess six (A-F) similar functional dominations, each responsible for different functions like hormone-binding, hormone response elements, transcription activation functions (AFs) and initiation of gene transcription (Fig. 13.4).

When activated by hormone binding, the ER undergoes transformation which enables it to bind specific DNA sequences, termed estrogen responsive elements found in the vicinity of target genes. Subsequently, recruitment of co-activators and general transcription factors results in the formation of an active transcriptional complex and enhancement of target gene transcription.

During recent years we have seen a paradigm shift in our understanding of estrogen action. This is mainly due to the discovery of the second ER, ERβ which is the encoded by a separate gene from that ERα. Many organs express both ERPsubtypes, but different cell-types within each organ may express different ERs indicating that ERα and ERβ have distinct functions in some instances.

![Figure 13.4](image_url) Schematic diagram of estrogen receptor α functional domains.

The ER contains 595 amino acids (aa) with the functional domains labeled A through F and a central DNA-binding domain (DBD) and hormone-binding domain (HBD). The regions important for dimerization (Dimer) and transactivation functions (AF-1, AF-2α, AF-2) are shown. Region A/B is
important for hormone-independent ER transcription; region C is the DBD; region D is the hinge domain; region E is the HBD responsible for hormone-dependent transcription; region F is important for modulation of ER activity.

ERβ is expressed in partially different tissues from ERα, notably prostate, ovary, lung, kidney, gastrointestinal tract and especially colon, as well as in tissues where ERβ is also found, e.g. breast, central nervous system, testis. ERβ predominates in the uterus and liver. It has clearly been shown that the benefit from endocrine therapy is directly proportional to the amount of ER present in the tumor.

1. Hormone Receptor Analysis

The ER has recently originally been determined with cytosol measurements and more recently immunohistochemically (IHC) or with cytosol measurements. The advantages of the cytosol measurements via a ligand binding assay, include the generation of numerical results across the whole of the likely concentration range, good reproducibility, full technical and clinical validation, inclusion of measures of receptor functionality and existing quality assurance schemes. Disadvantages include a relative large amount of tissue required, the necessary care over handling, storage, assay and data processing, the labor intensive nature of the assay, and the lack of information about the nature of the tissue being homogenized. As improved anti-ER antibodies became available, IHC assay replaced the ligand binding assay (LBA). However, there were again advantages and disadvantages. Advantages of IHC include the fact that routine, fixed, material could be used, archival material could be assayed retrospectively, only small quantities of tissue are needed, receptor content could be related to morphology and there was a measure of cellularity, internal positive control was often provided by the normal epithelial tissue in the section. The disadvantages included the subjectivity, the lack of quantitation, the absence of any indication of functionality of the receptor, the lack of standardization of staining, the absence of an appropriate quality assurance schemes are now existing. Several IHC scoring of receptor have been proposed (and the lack of clinical validation. An 8-point scoring system from 0-5 points according to the proportion of stained nuclei, score combining the intensity of staining and proportion of stained nuclei like Allred score...proportion of nuclei staining and 0-3 for the intensity of staining, with corresponding clinical recommendations according to the final score has been proposed by Harvey and colleagues. It was concluded by these authors that IHC was probably the more clinical useful score. In another study by Gordts and colleagues with 299 breast cancer cases IHC was used in a semi quantitative method and scored between 0 and 300 (the H-score). In this study concordant results between LBA and IHC were observed in 230 out of 299 cases (77%) while 69 patients had discordant results (kappa=0.537). Thus for both LBA and IHC assay, the use of a single cut-off should be avoided and activity quantified, or stratified into categories.

2. Definition of Cutoffs for Receptors Status

Like most biological phenomena, endocrine responsiveness is a continuous variable dependent on levels of ER and, to a lesser extent, PR. This consideration has been lost with the increasing use of the semi-quantitative IHC. Establishing a threshold or lower range in which the likelihood of response is very low or nil is still important, however. In the past, cutoff points as high as 20 fmol/mg of protein were used to define ER negativity, perhaps with the notion of giving patients with the remaining “ER+” tumors the highest probability of responding. Because evidence indicates that tumors with even a small amount of measurable protein, 3 to 10 fmol/mg, have response rates in the 20% to 30% range, classifying them as negative has two deleterious consequences. First, patients may be denied a trial of hormone therapy, from which they have a good chance of benefiting; second, such classification can lead to the clinically erroneous impression that a substantial number of patients with ER- tumors benefit from hormone therapy. To avoid these pitfalls, stringently low cut points should be adopted. For example, evidence suggests that setting a cutoff for ER negativity of 3 fmol or less of ER protein per milligram of cytosol
protein by ligand assay and 1% of positively stained cells by IHC analysis best separates patients who do not derive benefit from endocrine treatment from those who do. When stringently low cut points are adopted, special attention to quality control is crucial to avoid variability and false-positive results.

3. Factors Influencing the Level of Steroid Receptors
Numerous clinical and physiologic factors must be considered when assessing the significance of a steroid receptor level. These include race, sex, age, menopausal status, day of cycle for premenopausal women, pregnancy and lactation, organ site, tumor cellularity and histologic differentiation, and history of drug therapy.

Relative to histopathology, it may be generally concluded that the presence of both estrogen and progesterone receptors implies retention of the regulatory mechanisms operating in normal breast epithelium. Thus, a loss of receptor may be taken with other neoplastic features as a mean for identifying patients at increased risk of tumor recurrence.

Several studies have not found a correlation between steroid receptor status and either the size or location of the tumor in the breast, the axillary node status, or the clinical stage of the disease.

The endocrine status of the patient influences the incidence and the concentration of steroid receptors in breast tumors i.e. being lower in premenopausal women than in postmenopausal ones. Clearly, patient age influences the level of receptors, higher concentrations are exhibited by tumors from elderly patients.

In general, the levels of specific steroid receptors in specimens of metastatic breast cancer are similar to those observed in primary tumors. However few studies suggest that there may be a progressive loss of receptor levels as the disease progresses.

The influence of therapies using cytotoxic drugs or antihormones was also studied. Allegra et al. suggested that intervening hormone therapy selectively eliminates estrogen receptor containing cells, but chemotherapy apparently has no or little effect. Also, as it is known that among criteria used to select therapy for breast cancer patients is the site of metastases, no correlation was generally found between the presence of steroid receptors and the organ site of metastatic lesions

4. Clinical Significance
ER and PR can be used as both predictive and prognostic factors. A predictive factor indicates the likelihood of a response (or no response) to a particular treatment – in the cases of ER and PR, to hormone therapy.

A prognostic factor is indicative of the inherent biological aggressiveness of a tumor, reflecting the natural history of the disease after local therapy. An example is nodal status. Prognostic factors are therefore most accurately assessed in systemically untreated patients, although in reality, most studies of prognostic factors contain a mixture of treated and untreated patients. Prognostic and predictive factors are not mutually exclusive – a given factor can be both prognostic and predictive, as in the case of ER and PR.

It has been demonstrated conclusively that the presence of estrogen receptors provides a molecular basis for the distinction between tumors that are responsive to hormone manipulation and those that are not. Analysis of approximately 8000 breast cancer specimens over a 10-year period has indicated that 60% to 65% of primary lesions and 45% to 55% of metastatic tumors exhibit more than 10 fmol/mg cytosol protein binding of estrogen receptors. Also, 53% of estrogen receptor positive tumors were responsive to hormone therapy. Furthermore, when the collective results from the NIH Consensus Development
Conference (1990) were summarized, the spectrum of response ranged from less than 6% when estrogen receptor levels were below 10 fmol/mg to more than 80% objective remissions when tumors contained more than 200 fmol/mg cytosol protein.

The prognostic value of estrogen receptor analysis in primary lesions was supported by several studies. Most of these studies indicated clearly that estrogen receptor status is useful in predicting the course of the disease as patients with breast cancer containing free estrogen receptors exhibited longer disease free survival than those whose tumors did not contain estrogen receptors.

An overview of trials of women with early-stage breast cancer who were randomized to adjuvant tamoxifen therapy versus no adjuvant tamoxifen therapy provides the best data for examining the relationship of ER and PR status to benefit from adjuvant hormone therapy. This meta-analysis involved more than 37,000 women in 55 trials; in general, follow-up is at least 10 years. The results clearly and unequivocally demonstrate that women with ER+ tumor derive significant benefit from 5 years of tamoxifen treatment in terms of reduction in odds of recurrence and death, whereas those with ER- tumors do not.

The simultaneous determination of the progesterone with the estrogen receptors is reported to increase the accuracy of selecting the patients who are most likely to respond to hormone therapy.

The relationship between estrogen receptor exhibition and response to chemotherapy, is remains no more controversial. Some Several studies suggest exhibit that a correlation exists between lack of receptors and response to chemotherapy. Others have reached different conclusions with opposite results, and even some of these authors were unable to demonstrate any relationship between receptor status of the tumor and patients response to chemotherapy.

So, in conclusion, it is recommended that both estrogen and progesterin receptors should be analyzed in all tumor specimens from patients with breast cancer. Laboratories should comply with criteria assigned by quality assurance programs. Receptor profiles may be useful and used as a predictive indicator of an endocrine-responsive tumor, and as a prognostic index of a patient’s clinical course.

**Therapeutic Modalities**

In 1896, Beatson’s historic observations on breast cancer regression after oophorectomy provide the first insight into the estrogen-dependent nature of breast cancer. Further surgical research followed for almost a century with considerable vigor. Initially, researchers focused on procedures that removed other endocrine organs besides the ovaries e.g. resection of adrenal glands and pituitary. Starting in 1960s, ablative surgery began to be replaced by pharmacologic approaches, and currently, most patients are managed with medical rather than surgical forms of endocrine therapy.

**Breast cancer endocrine therapies that target sex hormone receptors may be recently classified as follows:**

1. **Tamoxifen and Selective Estrogen Receptor Modulators (SERMs)**

Tamoxifen has been the preferred hormonal treatment for breast cancer for the last 30 years. The decline in breast cancer mortality in western countries is considered to be in part because of tamoxifen. It is a nonsteroidal triphenylethylene that was first synthesized in 1966, initially as an oral contraceptive but activity in metastatic breast cancer was first described in the early 1970s. The dazzling favorable experience with the drug in the metastatic setting led to its use as an adjuvant therapy. Initially, tamoxifen was believed to be an antiestrogen in breast tissue through competitive inhibition of estrogen, binding to ER. With increasing experience, clinicians observed effects on several other organs. So, it is associated
with the development of endometrial cancer and venous thrombosis as a result of its estrogenic effects on endometrium and the coagulation system. It is also associated with beneficial effects on bone mineral density and blood lipid profile through the same estrogenic effect on bone and the cardiovascular system. Furthermore, the mixed agonist/antagonist actions of tamoxifen explain several well-described clinical syndromes associated with treatment with the drug including tamoxifen-induced flare reactions, and tumor regression after withdrawal of tamoxifen therapy.

So, although tamoxifen is the well established therapy to consider in all stages of breast cancer, the above mentioned side effects have led researchers to investigate new agents that retain favorable estrogenic properties in specific tissues and display antiestrogen activity on the endometrium. Such research has generated the concept of selective estrogen receptor modulators (SERMs) that mediate either estrogen agonist or estrogen antagonist effect in different tissues.

Ideally these drugs are antiestrogenic in the breast and retain beneficial effects on bone mineralization and blood lipid profile but do not exhibit adverse estrogenic effects on the endometrium. So, drugs such as tamoxifen that exhibit a mixed agonist/antagonist profile has been designated as SERMs. In 1998, however, a new SERM “raloxifene” was approved in the USA for treatment of osteoporosis. An early evaluation of raloxifene activity in tamoxifen-resistant breast cancer was disappointing, and little further clinical research directed toward metastatic breast cancer has been performed. Consequently, it is difficult now to know where to place raloxifene in the treatment of breast cancer.

A third-generation SERM, currently designated SERM3 have recently entered clinical trials. Preliminary results from phase I studies have been reported, and it appears safe and well-tolerated. Results from phase II and phase III trials should be available soon. However, none of the new SERMs, including idoxifene, droloxifene, and toremifene (Farestone®), has been found to have activity in tamoxifen-refractory patients.

2. Pure Antiestrogens
Two steroidal antiestrogens have been developed that have pure antiestrogen activity in all tissues; ICI 164,384 and the more potent ICI 182,780 (Faslodex®). Faslodex is not orally bioavailable and must be given intramuscularly on monthly basis. An initial phase II clinical trial in metastatic breast cancer reported promising results in tamoxifen-refractory population with a response rate of 37%. Menopausal side effects did not appear to be increased by therapy. Two large prospective randomized trials are underway comparing Faslodex to anastrozole in tamoxifen-refractory patients, and to tamoxifen in patients who have never received tamoxifen or not received the drug for at least one year.

Another pure antiestrogen, EM800 is also under trial. It is orally active and structurally related to raloxifene.

3. Estrogen Deprivation Therapy for Premenopausal Women
In subsequent clinical experience throughout the twentieth century, it has been demonstrated that oophorectomy results in objective responses in ~30% of unselected premenopausal patients with metastatic disease.

In the 1980s, LHRH-As were introduced providing an alternative to oophorectomy. Acting on the pituitary LHRH-A treatment first stimulates FSH and LH secretion and then profoundly suppresses the pituitary-ovarian axis, with a fall in estrogen to menopausal levels. Results from prospective randomized
trials have demonstrated that response rates to LHRH-A are comparable to those observed with oophorectomy.

More recently, a meta-analysis of four trials addressing the value of LHRH-A and tamoxifen combination in premenopausal women suggests that this combination is more effective than single-agent LHRH-A with more response rates and a modest improvement in progression-free and overall survival.

The LHRH-A Goserelin has also been used as a component of adjuvant therapy in early breast cancer. It appears to provide added benefit to cytotoxic chemotherapy, and has the advantage over ovarian ablation of being given for a period of time with return to normal hormonal status by stopping the use of the agent. Moreover, in more recently randomized comparisons of adjuvant chemotherapy and adjuvant ovarian ablation using either radiation, surgery or an LHRH agonist, with or without tamoxifen, results have failed to show any advantage for chemotherapy. However, in 3 of these six trials, the chemotherapy (IV CMF) was clearly suboptimal. Firm conclusions about this important question await further follow up, more events in some of these trials, and a meta-analysis of all of the studies.

4. Estrogen Deprivation Therapy for Postmenopausal Women

The therapeutic benefits of reducing estrogen levels by ovarian ablation or LHRH-A therapy are restricted to patients with functioning ovaries. As ovarian function declines, the relative proportion of estrogens synthesized in extragonadal sites increases, and eventually nonovarian estrogen predominate in the circulation. Peripheral tissue depend on the aromatization of androgenic precursors of adrenal origin (testosterone and androstenedione) to generate estradiol and estrone. Aromatase, the enzyme responsible for this conversion, is present in adipose tissue, liver, muscle and brain. Aromatase activity has also been identified in the epithelial and stromal components of the breast. Therefore, local synthesis of estrogens may contribute to breast cancer growth in postmenopausal women.

Aromatase inhibitors have different mechanism of action than antiestrogens and have been used primarily in the postmenopausal population. The first aromatase inhibitor to become commercially available was aminoglutethimide. Aminoglutethimide has demonstrated activity in the metastatic breast cancer setting (response rates of 20% to 40%) when compared to established second-line therapy with megestrol acetate. It produces effects on glucocorticoid production and is now used infrequently in the clinical setting due to side effects.

The new generation steroidal (exemestane, formestane) and non-steroidal (anastrozole, letrozole) aromatase inhibitors (AIs) act on peripheral and tumor aromatase and do not suppress adrenal function like aminoglutethimide. The most frequent side effects is nausea, and the risk of thromboembolic events is substantially lower than tamoxifen. By irreversibly (exemestane, formestane) or reversibly (anastrozole, letrozole) inhibiting peripheral and tumor aromatase, these drugs effectively reduce levels of circulating estrogens, thereby removing a growth stimulus for hormone sensitive tumors.

The efficacy and safety of many of these agents is already established in the treatment of postmenopausal patients with metastatic hormone sensitive tumors. Anastrozole (Arimidex®), letrozole (Femara®) and exemestane (Aromasin®) thus far have shown the most promise. However, it is unknown at this time if any drug is superior to the others. Fadrozole is being less potent and less specific, and formestane is less convenient and equivalent to tamoxifen and megace.

Equivalence to tamoxifen in terms of response rate, and superiority in terms of time to disease progression have recently been demonstrated for anastrozole in the first line treatment of metastatic breast cancer in two combined randomized trials of identical design. However, follow up is relatively short. In another study comparing letrozole to tamoxifen as front line therapy in 907 patients, the drug was significantly superior to tamoxifen as measured by overall response rate, time to progression and time to
treatment failure. In the adjuvant setting, recent evidence from clinical trials including the ATAC trial indicate that improvement in disease-free survival does not translate into improved survival. Upfront use of aromatase inhibitors could be recommended only in women who have contraindications to the use of tamoxifen.

So, given the tolerability and efficacy of these agents in the metastatic setting, they are likely to play an increasingly prominent role in adjuvant therapy. However, their routine use in the adjuvant setting cannot be recommended outside clinical trials.

The success of AIs therapy in postmenopausal women has raised the issue of whether this approach might be successful in premenopausal women. Unfortunately, inhibition of ovarian aromatase activity is associated with polycystic ovaries and androgens excess caused by activation of the pituitary-ovarian axis. Thus AIs therapy is contraindicated in premenopausal women. However, consideration is being given to treating premenopausal women who have advanced breast cancer with combinations of LHRH analogues and AIs. However, until more information becomes available, premenopausal patients resistant to tamoxifen and LHRH-A should be treated with megestrol acetate. The alternate is to offer oophorectomy followed by an AI.

5. Endocrine Therapy Using Sex Steroids

Progestins
The semisynthetic progestins: medroxyprogesterone acetate and megestrol acetate are the two most active agents of this class of hormones available for treating breast cancer patients. The mechanism of action of the progestins is not well understood. However, in vitro studies suggest direct antiproliferative effects on human breast cancer cell lines. They may also exert direct antiestrogenic action by increasing the oxidative activity of 17 beta-hydroxy-steroid dehydrogenase, thereby facilitating the conversion of estradiol to esterone. Progestins may exert additional antiestrogenic effects by suppressing estrogen receptor levels. They also may cause estrogen deprivation indirectly through suppression of pituitary ACTH secretion, resulting in reduced production of adrenal androgen precursors.

The most frequently used dose of medroxyprogesterone acetate is 1000 mg/d given orally or intramuscularly for the first month followed by 500 mg/d once or twice each week. The therapeutic dose of megestrol acetate in common use is 160 mg/day in divided oral doses.

General side effects of progestins include facies lunaris, increased sweating, fine tremors, leg cramps, weight gain, fluid retention, hypertension, skin rash, hypercalcemia, worsening of diabetes mellitus, and hypertrichosis.

Androgens
Androgens, including testosterone, fluoxymesterone, and the less virilizing testolactone, are associated with response rates in the range of 20%. Major side effects include virilization and jaundice. Androgens are rarely used to treat metastatic breast cancer. If considered, fluoxymesterone (Haltestin) 10 mg orally twice a day is as effective and nontoxic as any other.

6. Combination Endocrine Therapy Versus Sequential Single-agent Therapy
Tamoxifen has been used in combination with androgens, estrogens and progestins. The general conclusion from such studies is that the addition of these sex steroids adds toxicity to tamoxifen therapy without any clear gain in clinical outcomes e.g. time to disease progression and overall survival. So, combining sex steroids with tamoxifen is not recommended. On the other hand, combining antiestrogen and estrogen deprivation in premenopausal women continues to intrigue investigators. The modest improvement in response rate, progression-free survival, and overall survival associated with the
combination of LHRH-A plus tamoxifen versus LHRH-A alone contrast with studies in postmenopausal
women in whom the combination of tamoxifen and estrogen deprivation with aminoglutethimide is no
more active than tamoxifen alone. However, the potential of combining an aromatase inhibitor
(anastrozole) and tamoxifen against using each agent alone in the adjuvant setting is now being examined
in the ATAC trial. Currently, there are no data on the combination of an AI with tamoxifen in the
metastatic setting. Therefore, tamoxifen and AIs should be used in sequence and not in combination until
the efficacy and toxicity of the combination have been fully examined.

Guidelines for endocrinal therapy

I. Hormonal Treatment for Metastatic Breast Cancer

An overall therapeutics strategy for treating patients with metastatic breast cancer is based on many
factors including age, disease-free interval, hormone receptor status, and extent of disease. For women
with limited and non-life threatening disease, elderly, or have estrogen-receptors-positive tumors,
hormonal therapy is the initial treatment of choice. The following algorithm describes the preferred
sequence of current hormonal options (Fig. 13.5).

It is likely that this algorithm will become outdated in the future in view of the pending clinical trials that
will mature in the coming few years (Table 13.1).

II. Adjuvant Endocrine Therapy For Early Breast Cancer

The role of tamoxifen and other endocrine therapies in the management of patients with early breast
cancer are clearly emphasized and explained in the overview analysis of the EBCTCG, NIH consensus
and St. Galen recommendations reviewed in other part of this book.

It is important to recognize that adjuvant endocrine manipulations which is mostly 5 years of tamoxifen
should be given for anyone with a tumor that is estrogen or progesterone receptor-positive, and that
patients with tumors lacking both will not benefit by endocrine therapy. Also, for patients with node
negative cancers less than 1 cm in diameter regardless of histologic grade, or tumors 1 to 2 cm in diameter
of low grade, evidence of a benefit exceeding the detriments of hormonal therapy is lacking.

Future thoughts and new role of endocrinal therapy

Classically, “endocrine therapy” for breast cancer has implied interference with the signal transduction
pathway mediated by the estrogen receptor. Disruption of other signal transduction pathways has been
recently tried with promise for toxic-benefit ratios that are better than classic endocrine therapies.

Retinoic acid and its derivatives interact with a family of receptors with similar structural motifs as those
of estrogen and progesterone receptors. It was suggested that one of the retinoic acid receptor agonist
(ATA) might reverse tamoxifen resistance. A new class of retinoids, designated rexinoids (Targetretin®)
has been well tolerated in phase I trials and it is being examined in phase II trials both as a single agent
and in combination with tamoxifen.

Because resistance to endocrine therapy in ER positive tumors may be associated with overexpression of
erß2, trials of the combination of antibody targeting erß2 (Trastuzumab) with endocrine therapy are
appealing.
### Table 11.1: Ongoing Endocrine Therapy Trials

<table>
<thead>
<tr>
<th>Class of agent</th>
<th>Agents in trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non steroidal AI vs. Progestin</td>
<td>Femara vs. Megace</td>
</tr>
<tr>
<td>Steroidal AI vs. Progestin</td>
<td>Exemestane vs. Megace</td>
</tr>
<tr>
<td>Non steroidal AI vs. Same</td>
<td>Femara vs. Arimidex</td>
</tr>
<tr>
<td>Non steroidal AI vs. Tamoxifen</td>
<td>Femara vs. Tamoxifen</td>
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<tr>
<td></td>
<td>Arimidex vs. Tamoxifen</td>
</tr>
<tr>
<td>Pure antiestrogen vs. non steroidal AI</td>
<td>Faslodex vs. Arimidex</td>
</tr>
<tr>
<td>Pure antiestrogen vs. Tamoxifen</td>
<td>Faslodex vs. Tamoxifen</td>
</tr>
</tbody>
</table>
Metastatic breast cancer
Hormone responsive disease

First line hormonal therapy
(Anti-estrogen and/or ovarian ablation - chemical, surgical, or postradiation in premenopausal women)

Response
No response (Chemotherapy)

Disease progression

Second line hormonal therapy
(ovarian ablation after anti-estrogen; anti-estrogen after ovarian ablation in premenopausal women)
Or Aromatase inhibitors in postmenopausal women

Response
No response (Chemotherapy)

Disease progression

Third line hormonal therapy
(Progestins in both pre- and postmenopausal women)

Response
No response (Chemotherapy)

Disease progression

Fourth line hormonal therapy
(Androgen or Estrogen)

Figure 11.5.
Chapter 12
Prognostic and predictive factors
The prediction of the clinical course of a primary breast tumor is very difficult. Some patients are cured by local therapy, and survive for many years. Other patients experienced early recurrence of the disease and died shortly after. It would obviously be useful to be able to identify individual patients who have a high or low risk of relapse in order to plan the appropriate management of the patient’s breast cancer. Patients with a low probability of recurrence could be spared the potential toxicity associated with therapy, while patients, whose tumors are most likely to recur could be given the option of aggressive adjuvant therapy.

Collaboration between clinicians, pathologists and biologists is essential in order to select each patient’s treatment, according to prognostic factors.

**Prognostic factors may be classified in three categories**

- Variables, which predict distant relapse and survival, the most accurately.
- Risk factors for local recurrence, essentially following breast conservative treatment,
- Predictive factors of response to a particular adjuvant systemic therapy.

The diagnosis of breast carcinomas is now done at an earlier clinical stage than in the past. The treatment approach has changed and conducted to adapt the therapy to the particular clinical stage of each patient, taking into consideration the factors, which affect prognosis (mastectomy or conservative treatment, adjuvant chemotherapy and/or hormonal treatment,...). At the same time, in the past decades, more knowledge of natural history in the development of breast tumors has led to the description of numerous biological factors involved in tumorogenesis. Their potential interest for prognostic assessment was researched with the development of many new biological tests, which may have confused the clinician who had to choose the most useful.

Traditional (well-established) prognostic factors including clinical, pathological factors, hormonal receptor and her2 status is usually the only information routinely used in international clinical trials and recommended since 1990 by the National Institute of Health (NIH) consensus conference (1991) and integrated in some models of prediction, useful in indicating an adjuvant treatment and its choice, retained or proposed models in different consensus conferences (Nottingham, saint Gallen, saint Paul) or on line (http:, adjuvant online). Its estimation is more than ever considered as a hot subject, with the extension of therapeutic possibilities related to the development of new targeted treatment and especially due to the presence on the market of kits obtained thanks to the development of microarray techniques that guarantee a more accurate prediction. The problems are multiple, related to
the methodology, the commercial part and finally related to the modifications of tumor characteristics induced by the screening, not yet included in the prediction molecules. Our purpose is to give a practical view of prognostic factors in breast cancers.

**Definition of a useful prognostic factor**

A prognostic factor may be defined as a factor able to give information on the clinical outcome of each patient.

**Multistep research had to be carried out before being able to recognize a prognostic variable.**

1. The factor must have a clinical or biological significance, and be related to tumor progression and/or metastases potential.
2. It must be easily identified for all patients. The method of detection must be accurate, reproducible, and widely applicable.
3. It must have a significant prognostic value demonstrated on a large and representative series of patients (particularly with homogeneous treatment protocols, and with a sufficient follow-up period). It must also be shown to be independent from other well-established prognostic factors by using appropriate statistical analysis, such as multivariate analysis (Cox model). New statistical techniques are being studied in order to better define the prognosis (neural network analysis).
4. After the first description of an independent prognostic value for survival of a new factor, this relationship must be found in a second set of patients. After this, the prognostic value must be confirmed in prospective studies before being used by the clinician.
5. Some biological factors have a prognostic value for survival, but are also predictive of response to treatment. So, the prognostic value of a factor may change with the type of adjuvant treatment, which must be taken into account in the analysis.
6. This factor must be easily used by the clinician in order to be integrated in the treatment protocol and must have clinical interest.

The relation between feasibility, cost and additional prognostic information must be analyzed. The definition of an additional prognostic factor thereby requires close cooperation between clinicians, pathologists, biologists and statisticians. Numerous biological factors with prognostic implication were recently described with univariate statistical analysis, but very few have independent prognostic significance demonstrated using multivariate statistical analysis including all well-defined clinical or pathological prognostic factors. Rare prospective studies are now available. For these reasons, complementary work needs to be done to clarify the value of these biological factors. Many reviews have noted the weak statistical quality of the prognostic studies and of the meta-analysis allocated to them, that conducted to publication of recommendations, under
the term of REMARK (JNIC 2005) concerning the methodology rules, which should be followed for the evaluation of new prognostic factors. But these rules apply only to unique factors. With the development of the microarray techniques which can simultaneously analyze thousands of different genes, new statistical methodology problems are updated, some major and not yet resolved (Koscielny 2008) and recommendations have started to be edited for them (duval 2008).

**Prognostic factors of survival**

**Well-Established (Traditional) Prognostic Factors**

**A- Clinical factors**

The TNM staging records the size of the tumor (T), the axillary clinical involvement (N) and the presence of distant metastasis (M). Tumors with distant metastasis (M+) at diagnosis, have a worse prognosis with a 5-year survival rate lower than 20%.

For non-metastatic tumors (M0), the degree of evolution of the tumor is classified in three groups: PEV0 (stable tumor), PEV1 (rapidly growing tumor), PEV2 and 3 (inflammatory cancer). Survival is higher for PEV0 than PEV1 and lower for PEV2-3 group.

The fixation of the tumor to deepest structure is a factor of bad prognosis with a 5-year survival rate of 40% compared to 70% in its absence (p < 0.01). Skin fixation is also a poor clinical factor.

The size of the tumor (T) is found to be an important prognostic parameter in many studies. The 5-year survival rate is about 45% for operable cases with tumor size between 5 and 7 cm, while it is more than 80% when the size is less than 2 cm (p < 0.01).

The clinical axillary node status (N) allows us to distinguish cancer with metastatic fixed nodes (N2) with a disease-free survival rate less than 40%, while it is nearly 80% when nodes are not palpable (N0) and intermediate when palpable (N1). However, clinical axillary status is not correlated with histologic involvement as 40% of palpable nodes are not metastatic and 40% of metastatic nodes are not palpable. So, in multivariate analysis, the prognostic value of clinical node status was found to be less important than histologic node involvement.

A young age at diagnosis (< 35 years) was usually described as a factor of poor prognosis. However, it could be linked to the higher percentage of node involvement for these patients. In the other age ranges, no prognostic value was found.

No prognostic value was associated with menopausal status or localization of a tumor in the breast.
**B. Pathological factors**

1. **The anatomic size**
   Tumor size reflects the natural history of the cancer. When tumor size increases, the rate of metastases increases. The size can be evaluated by clinical examination, radiologic imaging and by pathologic analysis; the anatomical size has been the reference. For the radiologic imaging, the size determined by ultrasound has a better correlation to the anatomical one. The MRI, thanks to contrast taking, brings an excellent, more sensitive, evaluation, but disturbed by taking non specific contrast of benign lesions or of normal breast according to the time during the cycle.

   The anatomic size is measured on the surgical specimen and represents the largest diameter of the tumor including the fine satellite spicules. The 5-year disease free survival rate is less than 60% in tumors larger than 25 mm, while it is more than 75% in smaller tumors ($p < 0.01$). Although the size is well correlated with the number of involved lymph nodes, the independent prognostic value of the size remains in multivariate analysis.

   A second evaluated measure is the complete size of tumor extension, incorporating the in-situ and the infiltrating components, size without prognostic value but it gives important information to the surgeon to select the type of surgery, conservative or mastectomy.

   With regards multifocal tumors; such neoplasms proved to generally represent a clonal proliferation of a single tumor. The diameter of the largest focus determines the real tumor size, but this is currently debated, some have proposed to use the summation of the sizes or the surfaces of each nodule, identifies (andea 2002, Coombs 2005). Multifocal tumors have a higher propensity for dissemination than unifocal tumors of the same dimension.

2. **Histologic type**
   According to the WHO classification, ductal and lobular carcinomas represent the majority of invasive carcinomas (85%). For a long time, most undifferentiated carcinomas were described as having a poorer prognosis than differentiated forms. Among rare kinds of carcinomas, pure mucinous, tubular, and papillary carcinomas have a very favorable prognosis with a greater than 95% 5-year survival. The typical medullary carcinoma, defined by five histologic criteria, represents only 1/3 of carcinomas with inflammatory stroma and had a particularly good prognosis with a 92% 10-year survival.

   On the other hand, d'autres formes sont particulièrement agressives. The metaplastic carcinoma et plus particulièrement ses variantes à cellules fusiformes ou à différenciation cartilagineuse ou osseuse, bien qu'elles s'accompagnent d'un taux relativement faible d'envahissement ganglionnaire métastatique. On peut également citer la forme micropapillaire infiltrante, récemment décrite qui comporte souvent des emboles extensifs et un envahissement ganglionnaire important et fréquent.
3. Histologic grade
Numerous methods of grading were described including nuclear characteristics and differentiation. The histoprognostic grading of Scarff, Bloom and Richardson (SBR) described in 1957 is most often used. It is a combination of three scores, i.e. degree of differentiation, degree of nuclear size variation (anisonucleosis) and mitotic activity. The initial description was more clearly defined by Contesso and its use extended to each form of invasive carcinoma except medullary carcinoma. More recently, Elston and Ellis have proposed l’adoption de critères précis pour chacun de ces paramètres afin d’améliorer la reproductibilité du grade. Ainsi le compte mitotique s’effectue sur 10 grands champs consécutifs et sa valeur est adaptée à la surface du champ microscopique (EE). Good histopathologic technique, especially fixation, and training pathologists in grading are required for precise evaluation and good reproducibility (65-80%) of the grading.

One recent modification was (modified SBR) to include only anisonucleosis and mitosis in a two parameters classification (Le Doussal) as mitotic score was found to be the most important factor of discrimination. Celle ci à l’intérêt de distinguer au sein du groupe des carcinomas de grade II, ceux à potentiel plus agressif.

Le Grade étant un des facteurs pronostiques les plus puissants, différentes analyses génomiques ont essayé d’identifier les gènes qui lui sont associés. Une signature génomique a été publiée et aujourd’hui commercialisée, constituée pour majorité de gènes liés à la prolifération. Si l’équivalence pronostique n’est pas encore prouvée, elle s’oppose au grade SBR dont le but est de disposer d’un outil simple et universel, évaluable à partir de n’importe quelle tumeur, même de façon rétrospective et quelle qu’en soit sa taille, alors que le grade génomique requiert un fragment congelé, ce qui en limite considérablement sa portée.

4. Node involvement
The number of involved axillary lymph nodes is the strongest predictor of clinical outcome in nearly all prognostic studies. Nodal disease appears physiologically to be a confirmation of the metastatic potential of the tumor.

The presence of nodal metastases is found in 40% of cases. The 10-year disease free survival rate of N+ cases was lower (45% for cases with more than 3N+ and 55% for cases with 1 to 3 N+) than N- cases (70%) (p = 0.01).

A precise analysis of lymph-node involvement requires a complete removal of axillary lymph nodes by the surgeon (at least 7), a methodical gross dissection and macroscopic serial slicing of each lymph node. En l’absence de métastase ganglionnaire, le nombre de ganglions prélevés est un élément pronostique, plus celui-ci est élevé, meilleur est le pronostic. En cas d’identification de métastases, le pronostic est d’autant plus mauvais que le nombre de ganglions métastatiques est élevé.
The presence of micrometastases is also linked to a higher risk of relapse, for ductal but not lobular type. Different works have proven that immunohistochemical staining could improve the detection of micrometerstases, but this is cost effective and time consuming for a complete axillary dissection. Capsular invasion and rupture is related to the number of lymph nodes involved and has no prognostic value by itself, as a histiocyte reaction.

**Sentinel Node Biopsy (SLN)**
Even though it is not yet considered as a validated technique, it is today applied in first intention by most of the working teams. To guarantee its credibility, it is necessary to adopt a particular technique of histological analysis requiring multiple cut section levels and immunohisto-chemical staining. This latter, guarantees more frequent detection of metastasis, especially the small size ones, less than 2mm.

The risk of invasion by tumor cells of the remaining part of the axillary lymph nodes increases with the increase in number of metastatic sentinel nodes and the size of detected metastasis. However, even in case of presence of minimal lymphatic metastasis <0,02 mm (pN0i+), the risk of invasion of other lymph nodes reaches or exceeds 10%. Different trials are taking place to evaluate the therapeutic importance of complementary axillary dissection in case of sentinel node metastasis.

Many automated instruments for sentinel lymph node analysis are now available on the market. The principle is based on the combined detection of the genetic material after amplification of some cytokeratin and mucin genes. It allows in nearly 30 min a study of the sentinel node, which should be chewed up. Their sensitivity is however limited to metastasis having a size of more than 0.2 mm and doesn't allow the quantification of the metastatic invasion, classified as pN0 mol+.

5. **The so called molecular classification:**
Emerged from the microarray studies, this classification recognizes 5 main types that will be associated with different prognosis, bad for the “basal-like” and Her2 types, intermediate for the luminal B and “normal-like” types and good for the luminal A types.

Their prognostic value appears limited, due to the limited number of studied patients and the heterogeneity of the analyzed population regarding the treatment and follow up. There is also a strong correlation existing between this classification and the classic factors, the luminal A type was classified as grade SBR 1, RE and RP+ while the basal forms are of grades SBR III, RE and RP negative. But the presence of different histological precursors according to the classes and also the presence of different metastatic sites, directed the way of thinking towards the possibility of the presence of different diseases, this will encourage the identification of the class type for each lesion.
6 Other histologic features
The presence of endolymphatic invasion was shown as a poor prognosis factor. The problème de la faible reproductibilité de son identification, l’incidence des cas rapportés variant de 1 à plus de 40% selon les études, est aujourd’hui résolu grâce au développement d’anticorps spécifiques des cellules endothéliales lymphatiques. Ce paramètre prend une importance de plus en plus grande en raison de la diminution de la taille des tumeurs et de l’incidence des métastases ganglionnaires induit par le dépistage.
The absence of clastosis and the presence of necrosis were described as poor prognostic factors but are also difficult to analyze routinely. The lymphocyte infiltrate is without prognostic value.

6. Hormonal receptors
Estrogen and progesterone receptors have been used since the late 1970’s to predict the outcome of breast cancer patients. But the presence of these receptors is also correlated with response to endocrine therapy. So the value of hormonal receptors as prognostic factors of survival is more difficult to determine because they are also predictive of response to treatment. Their value for prognostic assessment will be analyzed first in this chapter.
- Estrogen receptor (ER)
Estrogens exert their action on target cells by diffusing through the cell membrane and binding to their specific receptor. ERs are located close to the nucleus.

Oestradiol itself is thought to regulate the number of ERs in normal breast and in tumor. Thus, higher levels of ER are seen in the first half of the menstrual cycle than in the second half, and this cyclical variation is lost in breast cancer. About 70% of carcinomas are ER positive.

- Progesterone receptor (PR)
Estrogens regulate progesterone receptors. The presence of the PR is generally coupled to functional growth regulated by estrogens. About 50% of carcinomas are PR positive. For the 2 receptors, the distribution is: 46% ER+ PR+, 23% ER-PR-, 25% ER+ PR-, 6% ER-PR+.
Expression of ER and PR can change from primary tumor to metastasis. Loss of expression is noted in 20% of metastatic tumor cells that were positive in the initial primary tumor. Disease progression is associated with hormone profile change with less favorable outcome.

- Measurement of hormonal receptors
Currently a variety of methods are able to characterize ER and PR in breast cancers. In routine practice, immunohistochemistry is the gold standard. Other techniques are the biochemical assays which characterize the protein product, using ligand-binding assay or receptor antibody assay done in clinical laboratories and more recently the molecular assay, still in development, which analyses the transcription level. They are carried out on tumor homogenates and usually require freezing of the tumor specimen.
The immunohistochemical technique, initially applied to frozen tissue, could now be performed on paraffin-embedded tissue and on fine-needle aspirate. With paraffin-embedded tissue, a good fixation (in formalin, for example) and heating retrieval incubation
(microwave, ...) are needed. For imprints or aspirates, cells are fixed and slides are conserved at –20 °C.

The comparison between the biochemical, molecular and immunohistochemical assays shows an excellent correlation between these techniques. Each has relative merits. The biochemical assays were used first and have been the accepted standard for ER and PR quantification. The molecular assay can assess other genes of prognostic value. Biochemical and molecular techniques are quantitative and accurate techniques but are carried out on a tissue sample homogenate with no information on the nature of the sample and need a relatively large amount of tumor for radio legend assay.

The immunohistochemical technique provides semi quantitative evaluation and is expressed in different ways but gives information about the cell types expressing receptor (malignant vs. benign or normal breast) and can be done on small biopsy specimens, even on individual tumoral cells and is able to evaluate tumoral heterogeneity of the expression. The quality and reproducibility of the analysis has greatly improved with the development of the antigen retrieval technique and more sensitive revelation’s system, the commercialization of entirely automatized devices which control every steps of the process and the extent of European quality assurance program and guidelines for the immunochemistry.

Biological and immunohistochemical techniques provide complementary information regarding receptor content. The second one is simpler, less expensive, could also be applied on paraffin-embedded tissue or cytological samples, and provides concordant information with biochemical assay. Some of the molecular assays seem very correlated with the immunohistochemistry and might be pronostic for relapse (bavre 2008). However, their interest seems more in looking for resistance or sensitivity marker s for treatment more than for prognostic analysis, these techniques being restricted by the quantity of evaluated cells.

- **Hormonal receptor and prognosis**

The value of hormonal receptors as prognostic indicators remains controversial. Many of the initial studies included women treated with various therapies. It is, therefore, difficult to separate the prognostic value from the predicting response to therapy.

In the studies restricted to women without adjuvant therapy, the presence of ER gives an advantage (but does not reach significance) in some studies or does not show any prognostic value at all.

A correlation was demonstrated between ER and PR positivity and low tumor differentiation, low histoprognostic grade and low proliferative index. The presence of PR also has favorable predictive value in patients with node-negative breast cancers treated without adjuvant therapy, but does not achieve statistical significance.

The prognostic utility of both ER and PR has been reported to be strongest in pre-menopausal women. However, the relative importance of ER and PR is still controversial. The PR level is more sensitive than ER levels for predicting recurrence stage II tumors. The difference of prognosis linked to PR became insignificant with time.

Overall, all this data supports the fact that PR and ER positivity correlated with better survival. However, this advantage may be less than 10% over a long period of observation and disappears in multivariate analysis including tumor differentiation, grade, and proliferative rate.
7. c-erbB-2

C-erbB-2 (or HER2 neu) gene located on chromosome 17, codes for a transmembrane glycoprotein, which has homology with the epidermal growth factor receptor (EGF-R). In normal cells, only one copy of the gene is expressed. In breast carcinomas, a c-erbB-2 gene amplification with an elevated number of copies of the gene has been seen in 10% to 25% of the cases. High levels of c-erbB-2 protein or mRNA are linked to gene amplification but could be observed without it following transcriptional disorders. Different methods, immunohistochemistry on fixed and embedded tumors, is situ hibridation (FISH, CISH, SISH), RT-PCR, CGH array, can detect an amplification. In routine practice, immunohistochemistry is generally realized in first intention, using a score from 0 to 3+ which combine intensity of the cytoplasm membrane staining and percentage of invasive stained cells. Intermediate score 2+ corresponds to tumors with an uncertain her2 status which requires additional study. Similarly, FISH with a number of her2 copies between 4 to 6 or with a ratio between number of copies of her2 and chromosome 17 centromere from 1.8 to 2.2 require additional study.

In 1987, Slamon demonstrated that amplification of the c-erbB-2 gene is associated with shorter survival. There is a strong association between c-erbB-2 amplification/overexpression and other established poor prognostic factors: ER-, PR-, involved axillary lymph nodes (N+), poor histoprognostic grade, inflammatory carcinomas, high mitotic activity, DNA aneuploidy. c-erbB-2 amplification/overexpression is a poor prognostic factor usually found in women with axillary lymph-node involvement. For node-negative patients, the prognostic utility of c-erbB-2 was not demonstrated and contradictory results were published.

c-erbB-2 evaluation is essential to the selection of treatment, her2 amplified tumor could benefit from antiher2 treatment. Positive Her2 tumors seem to be more sensitive to chemotherapy and specially anthracyclin based regime.

MULTIVARIATE ANALYSIS OF THE TRADITIONAL PROGNOSTIC FACTORS

Many of the previous factors described are interrelated at different degrees. Only a multivariate analysis (like Cox model) allows us to determine the relative importance of each factor.

I. Non Operable Carcinomas (Table 14.1.)

1. Inflammatory carcinomas

In a series of 103 cases, treated at the Institut Gustave-Roussy with primary irradiation, followed in certain cases by mastectomy and/or by radiation castration, the histologic grade evaluated on drill biopsies is the only important predictor for disease-free survival. The kind of inflammation (localized or diffuse) is at the limit of significance. Age, clinical tumor size, tumor fixation, clinical node status, and histologic type were not significant.

2. Non inflammatory carcinomas

In a series of 289 cases, comprising 141 with rapid clinical growth and 148 either with tumor size >7 cm or skin fixation, treated at the Institut Gustave-Roussy by primary irradiation,
followed in some cases by mastectomy and/or by radiation castration, the clinical node status (N) and the histoprognostic grade were the only statistically independent predictive factors for disease-free survival. Clinical size is at the limit of significance, but age, rapid clinical growth (PEV1), histologic type, and skin fixation were not significant.

II. Operable carcinomas (T1-T3, <7 cm, N0 - 1) (Table 14.2.)

In the experience of the Institut Gustave-Roussy, 612 patients were treated between 1967 and 1974, by mastectomy, radiotherapy and radiation castration for pre- and peri-menopausal node positive patients but without chemotherapy. Among the criteria evaluated: age, clinical size, clinical node status, histologic type, histoprognostic grade and node involvement, the multivariate analysis showed two independent prognostic factors for poor 10-year disease-free survival: the presence of histologically involved lymph nodes (N+) (p = 0.00001) and a high histoprognostic grade (p = 0.0001). Clinical tumor size showed a strong trend, but does not reach significance (p = 0.08) (Table 14.2.). When axillary invasion and grade are used together, the relative risk of relapse is significantly different between patients with grade I - N+ 3 or grade II - N- tumors with 72% 10-year disease free survival and patients with grade II - N+ > 10 or grade III - N+ > 4 tumors with 27% survival (p = 10-3) (Table 14.3).

In studies including hormonal receptor status, the only independent factors for disease-free and overall survival are histologic grade, lymph node status and tumor size. A more detailed analysis showed that the most significant prognostic factors are the number of lymph nodes involved and the histologic grade. The presence of estrogen receptor is without prognostic value while the progesterone receptor is found a prognostic factor for metastasis-free survival at 2 and 5-year but lost its significance at 10 years. The prognostic value of hormonal receptor seems more important in series of patients, which did not include histologic grade. This could be partly due to the correlation between ER and PR negativity and high histologic grade. In addition, the prognostic value of hormonal receptor varies with time.

Node-negative carcinomas (Table 14.4)

A series of 1322 patients with node-negative tumors treated by surgery without adjuvant chemotherapy had a metastasis-free survival rate of 72% at 10 years. After multivariate analysis including hormonal receptors, the most important factors of good prognosis were a low SBR grade (p = 10-6) and small tumor size, whether considered from a clinical (p = 10-6) or a pathological (p= 10-3) point of view (Table 14.4).

Other studies including a high number of cases show that the tumor size, the nuclear grade and to a lesser extent, the histologic type are important prognostic factors. The 5-year disease-free survival rate is lower in ER- tumors but only by 8-9%. This leads us to conclude that hormonal status alone was not a sufficiently important prognostic factor to select patients who need adjuvant chemotherapy.

In this group of patients, 30% will relapse in the 10 first years and traditional prognostic factors were not sufficient to predict those with a higher risk. For these reasons, the research for new prognostic factors was essentially focused on this population of patients.

These previous prognostic factors are well-established and remain widely used to select patient protocol. However, the need for other predictive factors and progress in breast cancer
biology has led to the description of new prognostic factors, which have to be compared with the traditional ones.

**New Prognostic Factors**

Numerous biological factors allow a better understanding of tumor growth, cancer invasion, and tumorogenesis. They could be classified into markers of proliferation, oncogenes or markers of metastatic potential. Some of them are not confirmed as prognostic factors of survival; others are closely related to traditional prognostic factors. For these reasons, only the most important biological factors which could become additional prognostic factors and which would be useful for the clinician will be described below.

**Circulating tumor cells**

The technological breaking through of the molecular biology and the techniques of reduction, have allowed the creation of instrument detecting the tumor cells in the general circulation. The detection of these cells is done either by size, the epithelial cells being larger than the elements present in the blood or by antigenic affinity by using some cytokeratins and / or mucines which are only expressed on cells of epithelial origin. The number of detected elements is few; they are essentially detected during the metastatic phase. The presence of epithelial elements in the circulation of control group formed by healthy persons supports the use of a threshold value (cut off value) in case of techniques which doesn’t perform morphologic analysis. Their presence or absence before starting the treatment and their modification during the treatment will represent independent prognostic elements (Cristofanilli).

**Micro array**

The automated instruments, simultaneously analyzing thousands of genes, have been used to study breast cancers, first, classifying them by homology of expression (unsupervised analysis) which has allowed the identification of the so called molecular classes then for prognostic reasons, classifying them by the differential of expression from different groups of patients, one that have recurrences and the other who doesn’t have (supervised analysis). Different genomic fingerprints have thus been described, based on radically different concepts. So, some are only correlated to prognosis (Amsterdam), others to the genomic grade, but also to the repair (wound signature) to the tumor stem cells, to the stroma reaction … etc. They are all different; these different fingerprints have only one gene in common between them. Many methodological difficulties was raised, from one hand, the gene selection, the constituents (koscienly), from the other hand, taking in consideration the tumor diversity, their analysis being done on a fragment which is not always representative of the lesions diversity. Finally, most of the genes incorporated in each of these signatures are related to the proliferation.

But are the results obtained by these DNA chips (or microprocessors?) superior to the simple evaluation of the proliferation where the low cost and the simplicity of their performance cannot compared to these sophisticated genomic tools? From the other hand, is the mARN analysis more important than that of the protein, being the final step of the procedure?
Finally, can we really determine a group of genes having a valid prognostic value for all patients and during all the phases of carcinogenesis?

**Proliferation**

The cellular division being one of the most controlled events of the cellular machinery, the observed proliferation in the tumors requires escaping from the whole group of these controls which also requires multiple genetic anomalies.

Mitotic activity was the first factor of poor prognosis described. This criterion is included in histoprognostic grade or nuclear grade.

Other techniques were used to estimate proliferation. Firstly, the labeling index is determined after in vitro incorporation of tritiated thymidine in proliferative cells. This autoradiographic method is difficult to perform, because it is time consuming and can only be applied on fresh tissue. For these reasons, the labeling index (LI) is rarely used routinely, although several studies confirm the independent poor prognostic value of a high LI in non operable as well as in operable node negative tumors.

The evaluation of DNA content per cell and the percentage of cells in the S phase of the cell cycle using a mathematical model by flow cytometry have been widely studied. However there value was inconstant according to the studies.

Immunohistochemistry on fixed and embedded tissue is the favored method of proliferation evaluation. The antibody Ki 67 recognizes a nuclear antigen, expressed in cells into GI, S, G2 and M phases of the cell cycle, and not into GO. The percentage of proliferating cells is calculated as the ratio of cells with nuclear staining by the total number of cells. Different thresholds are used, according to the purpose, low (about 10%) for prognostic value, higher (25%) for predictive response to chemotherapy.

A high proportion of Ki 67 positivity correlates with poor tumor grade and absence of ER. It indicates poor prognosis, but its independent prognostic value is debatable.

Ki 67 staining is correlated with the labeling index and to S phase fraction. Ki 67 may provide an alternative approach for measuring proliferation.

**Problem related to screening**

**II. Other Markers**

Proliferating cell nuclear antigen (PCNA) is a nuclear protein. Its level was shown to be correlated with DNA synthesis. PCNA staining could be measured by immunohistochemistry. The results concerning its prognostic value are very “divergent”.

DNA polymerase-alpha appears earlier in G1 than Ki 67 and is a marker of the kinetics of the tumor. Its increase might be a poor prognostic factor.

The incorporation of bromodeoxyuridine (BrdU) allows analysis not only of the S phase fraction but also the potential doubling time of the tumor. The value of the potential doubling time has yet to be confirmed.

**III. Oncogenes and anti-oncogenes**

Human cancers result from the accumulation of somatic DNA cell alterations. Genetic changes such as amplification, mutation, translocation, and deletion lead to phenotypic
changes produced by protein overexpression, loss of activity, or altered activity and give characteristics of cancer.

2. **p53 tumor suppressor gene**

p53’s function is to regulate the passage through the cell cycle, DNA repair and to program cell death. Normal or wild-type p53 is expressed in low levels in all normal cells helping to co-ordinate a complex system of response to any DNA damage and protect cells from DNA alterations that could lead to neoplasm.

Mutation in the p53 gene results in the synthesis of a mutated p53 protein, which has a prolonged half-time. The accumulation of p53 protein could be visualized in the nucleus by immunohistochemistry and is an indirect indication of the mutation, although there are exceptions, such as gene mutation with no protein synthesis or accumulation of the normal protein.

p53 accumulation is detectable in 36% to 46% of breast cancers. It is linked to negative hormonal receptor status, to high grade tumors, to high S phase fraction, and to c-erbB-2 positivity. p53 positivity is an independent factor of poor prognosis for overall and disease-free survival. For node-negative tumors, overexpression is a poor prognostic factor, which is not always found to be statistically independent when histologic grade is included in the analysis. Its role has yet to be confirmed.

**IV. Tumor invasion markers**

1. **Angiogenesis**

Tumor growth requires the formation of new vessels. Angiogenesis permits a tumor to spread by giving a channel to tumor cells. The number of vessels, stained by immunohistochemistry is correlated to node involvement. Some authors evaluate VEGF or VEGFR receptors by immunohistochemistry and biochemical techniques in the tumor or in the serum. Several studies confirm the poor prognostic value of a high number of microvessels for disease-free and overall survival particularly for node-negative patients. However, there is no consensus on the method of counting microvessels and more work is necessary to determine the place of this promising factor.

**PREDICTIVE FACTOR OF LOCAL RECURRENCE**

Recent progress in diagnosis has increased the incidence of small tumors, which may be treated by tumorectomy followed by radiotherapy. However, recurrent tumor in the remaining breast was found in 10-15% of the patients. Essentially, pathological findings influenced recurrence: the quality of the surgical excision and the presence of an extensive in situ component.

One factor is the presence of an extensive ductal in situ component (EIC). A tumor is defined as EIC+ when intraductal carcinoma is present both in the invasive tumor (comprising at least 25% of the tumor area) and in the surrounding normal breast tissue. The likelihood of finding residual foci of carcinoma is 70% in EIC+ cases and 28% in EIC- cases when a mastectomy was carried out following tumorectomy. In most studies, the extensive in situ component (EIC+) is the most important factor of relapse in multivariate analysis. Five-year breast relapse rate is significantly higher for patients treated by tumorectomy and radiotherapy with EIC+ carcinomas (24%) than for those with EIC- tumors (6%) (p =
0.0001). However, when surgical margins is associated, EIC+ tumors with a complete resection have a similar rate of relapse than EIC- tumors. The adequacy of the surgical margins appears to be the main other important pathological factor of relapse. The 10-year local relapse rate was 9% when the resection was complete and 24% when it was incomplete. The adequacy of the surgical margins could be estimated by gross examination or by histologic examination but the quality of the analysis is better at microscopic level by inking the borders of the tumorectomy. Smitt proposed a classification of the margins as positive (invasive or in situ carcinoma on the inked specimen margins), close (2 mm), negative (>2 mm free margins). In this study, the re-excision of the margins for patients with close or positive margins increased the 10-year local control (97% vs. 84% without re-excision). The adequacy of the resection was also a factor of better survival. The young age of the patient, lymphatic invasion and high histoprognostic grade seem to a lesser extent predictive of local failures.

**Predictive Factors of Response to Treatment**

Prognostic factors of survival may help to select patients eligible for adjuvant chemotherapy. Some of them are also useful indicators for selection of patients who are likely to respond to a particular form of therapy. For these reasons, the relative importance of prognostic factors of survival described in former series of patients treated exclusively with surgery and radiotherapy may change with addition of adjuvant chemotherapy. Predictive Factors help to determine the probability of response to a particular drug class. There are numerous proteins and genes involved in breast cancer growth, proliferation and metastasis. Exploration of their role in predictive response to various therapies may help draw the tumor profile and plan appropriate treatment for them.

**I. Response to Hormonal Treatment**

**Standard methods**

Oestradiol is one of the most important tumor growth factors. Numerous studies on patients with metastatic disease demonstrated a tumor rate of response dependent on the steroid receptor status of the tumor (10% ER-, 50% ER+, 75% ER+ PR+ tumors). The same correlation was also demonstrated when steroid receptor status was determined by immunohistochemistry (Table 14.6).

pS2 protein is induced by estrogen. pS2 must be shown to be more of a predictive factor of response to hormonal treatment than a prognostic factor for survival. pS2 protein may indicate a functional estrogen regulatory system. In ER+ PR+ tumors, pS2 may identify patients, who have an intact ER pathway. pS2 protein identifies an ER+ PR+ subgroup of patients who were more likely to respond to hormonal treatment.

**New techniques**

**Micro arrays (oncotype)**

**II. Response to Chemotherapy**

**Histologic type lobular vs others**

Grade and mitotic count

P53

Molecular classification

Micro arrays
Her2 patients
Several biological factors were studied in metastatic, locally advanced tumors or large breast tumor treated by pre-operative CT.
In a series of 89 patients with large breast tumors (>3 cm) treated at the Institut Gustave-Roussy with neoadjuvant chemotherapy in order to reduce the tumor size and to begin systemic treatment earlier, the predictive factors of clinical tumor regression were analysed (Table 14.6). The high mitosis rate is linked to better clinical response. A high S phase fraction was correlated with a clinical response 75%. The initial overexpression of c-erbB-2, or the accumulation of p53 determined by immunohistochemistry was not predictive of response to treatment. This data does not confirm the hypothesis of a role of c-erbB-2 in chemoresistance determined in series treated by adjuvant chemotherapy. Preclinical and some clinical data suggest that tumors with p53 mutation may be particularly sensitive to taxanes and relatively resistant to anthracyclines.

In literature, proliferative activity evaluated by flow cytometry (S-phase fraction) or by labeling index was always associated with a higher rate of objective clinical response (>50%). DNA aneuploidy and/or high histologic grade were not found to be predictive of higher clinical response.

The expression of multidrug resistance (MDR) phenotype is associated with chemoresistance. The initial expression of P-glycoprotein, which is encoded by MDR gene, is related to a worse response to preoperative chemotherapy but the series of patients is small.

Topoisomerase II alpha (topo 2α) gene detection is associated with resistance to doxorubicin treatment. It is also usually associated with HER-2/Neu gene amplification. Simultaneous detection of topo 2α and HER-2/Neu can be done by PCR.

Taxol (Taxane) has an anti angiogenic effect. It causes tumor necrosis, microtubulin-associated protein level may predict sensitivity to taxanes.

Mib-1 proliferation marker is decreased after neoadjuvant chemotherapy. It could be estimated to evaluate the degree of neoadjuvant effectiveness. P27 tumor suppressor gene involved in control of G1-S transition may predict response to chemotherapy. HER-2 overexpression may denote sensitivity to anthracyclines and anthracycline dose intensity and less responsiveness to CMF. However, only strongly positive HER-2 overexpression (+++ is considered, while lack of HER-2 overexpression have similar results with low and standard doses. Breast International Group Herceptin Adjuvant (HERA) still questions whether HER-2 3+ should receive 1 or 2 years of trastuzumab or not, irrespective of adjuvant chemotherapy regimen given.

Thymidylate synthase and dihydropyridine dehydrogenase levels may predict response to fluoropyrimidines. So far, they have been tested in colorectal cancer.

CONCLUSION
The ultimate goal of the research of prognostic factors is to better tailor the treatment of the patient to the clinical, pathological and biological characteristics of the tumor.

For the clinician, the main questions are how useful are these prognostic factors for daily routine practice and how to interpret them. The interrelation between the biological factors in breast cancers is important and complicates the determination of the relative value of each
factor. For these reasons, multivariate statistical analysis only allows one to determine independent prognostic factors. The relative value of the new biological parameters had to be compared to the well defined prognostic factors.

The prognostic value of factors determined in a series of patients receiving no adjuvant therapy may be modified when hormonal treatment or chemotherapy are given, if this factor is predictive of response to treatment.

The cost of measuring a factor as well as the reproduction of the measure must be taken into account. The value of well-established prognostic factors determined after good histopathologic technique has been confirmed by a large number of studies and remains the most important.

For operable breast tumors, the axillary involvement, the histoprognostic grade and the size of the tumor remain the most important prognostic factors. The value of S-phase fraction, angiogenesis and p53 overexpression has to be confirmed by prospective studies (Table 14.7).

For patients who have conservative treatment, the main factors of local breast relapse are: the presence of an extensive intraductal component and the involvement of the margins of the tumorectomy (Table 14.7).

However, these prognostic factors may be modified with the use of new therapy. The response to hormonal treatment is well correlated with the presence of hormonal receptors. The response to chemotherapy is associated with high proliferation, but other predictive factors remain to be studied (c-erbB-2, MDR, ..) (Table 14.7).

Research will not tend towards a multiplicity of factors of prognostic assessment but to a precise determination of the most useful and reproducible factors using precise statistical methodology and to better treatment decisions individualized for each patient. The relative value of well-established prognostic factors may be modified in the future with the use of biological parameters as predictors of response to treatment and even as targets for new treatments (immunotoxins, angiogenesis inhibitors...).

| Table 14.1. Disease-free survival of 398 inoperable carcinomas treated at the Institut Gustave-Roussy |
|-------------------------------------------------------|---------------------------------------------------|
| Criteria                                              | Inflammatory (n= 109) | Non inflammatory (n= 289) |
|                                                      | p value              | p value               |
| Age                                                  | NS                   | NS                    |
| PEVO/1                                                | -                    | NS                    |
| PEV2/3                                                | 0.09                 | -                     |
| Tumor fixation                                       | NS                   | NS                    |
| Clinical size                                        | NS                   | 0.07                  |
| Clinical nodes                                       | NS                   | 10^-4                 |
| Histologic type                                       | NS                   | NS                    |
| SBR grade                                            | 0.001                | 0.03                  |

*IGR (Contesso 1987)*

<table>
<thead>
<tr>
<th>Table 14.2. Disease-free survival at 10 years of 612 operable carcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated at the Institut Gustave-Roussy</td>
</tr>
</tbody>
</table>
Criteria       | P value
---------------|---------
N+             | $10^{-5}$
SBR grade      | $10^{-4}$
Clinical size  | 0.08
Age            | NS
Clinical nodes | NS
Anatomic size  | NS
Histologic type| NS

Table 14.3. Disease-free survival rate at 10 years for operable breast carcinomas

<table>
<thead>
<tr>
<th>Histologic Grade</th>
<th>N-</th>
<th>N+ 1-3</th>
<th>N+ 4-10</th>
<th>N+ &gt;10</th>
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<tr>
<td>I</td>
<td>72%</td>
<td>72%</td>
<td>63%</td>
<td>51%</td>
</tr>
<tr>
<td>II</td>
<td>72%</td>
<td>63%</td>
<td>51%</td>
<td>27%</td>
</tr>
<tr>
<td>III</td>
<td>63%</td>
<td>51%</td>
<td>27%</td>
<td>27%</td>
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</table>

IGR (Contesso 1987)

Table 14.4. Metastasis-free survival rate at 10 years for 1322 N- carcinomas

<table>
<thead>
<tr>
<th>Clinical size</th>
<th>SBR grade</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 cm</td>
<td>97% (78)*</td>
<td>80% (93)</td>
<td>78% (32)</td>
<td></td>
</tr>
<tr>
<td>1 - 3 cm</td>
<td>89% (228)</td>
<td>70% (432)</td>
<td>57% (183)</td>
<td></td>
</tr>
<tr>
<td>&gt; 3 cm</td>
<td>80% (50)</td>
<td>57% (130)</td>
<td>53% (96)</td>
<td></td>
</tr>
</tbody>
</table>

IGR

Table 14.5. Multivariate Analysis of the Prognostic Value of S Phase Fraction

<table>
<thead>
<tr>
<th>Study year</th>
<th>N</th>
<th>Follow-up (years)</th>
<th>N histo</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>DFS</td>
<td>OS</td>
</tr>
<tr>
<td>Kallionemi 1988*</td>
<td>297</td>
<td>6</td>
<td>N+/-</td>
<td>-</td>
</tr>
<tr>
<td>Stal 1989*</td>
<td>472</td>
<td>7</td>
<td>N+/-</td>
<td>0.05</td>
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<tr>
<td>Toikkanen 1989</td>
<td>351</td>
<td>25</td>
<td>N+/-</td>
<td>-</td>
</tr>
<tr>
<td>Gnant 1992</td>
<td>241</td>
<td>10</td>
<td>N+/-</td>
<td>NS</td>
</tr>
<tr>
<td>O’Reilly 1992</td>
<td>169</td>
<td>8</td>
<td>N+/-</td>
<td>NS</td>
</tr>
<tr>
<td>Fisher 1991</td>
<td>398</td>
<td>10</td>
<td>N+/-</td>
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<td>NS</td>
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<td>4</td>
<td>N-</td>
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<tr>
<td>Bosari 1992</td>
<td>147</td>
<td>4</td>
<td>N-</td>
<td>0.0001</td>
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*No histologic grade included in the multivariate analysis
Table 14.6. Predictive factors of response to CT for 89 large carcinomas (>3 cm)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>N</th>
<th>Clinical regression</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TNM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>45</td>
<td>59%</td>
<td>NS</td>
</tr>
<tr>
<td>T3</td>
<td>36</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>8</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td><strong>Rapid growth</strong>**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEV0</td>
<td>61</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>PEV1</td>
<td>28</td>
<td>67%</td>
<td>P=0.02</td>
</tr>
<tr>
<td><strong>Menopausal status</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>42</td>
<td>64%</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>47</td>
<td>51%</td>
<td>P=0.03</td>
</tr>
<tr>
<td><strong>Histologic type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ductal carcinoma</td>
<td>83</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td>Lobular carcinoma</td>
<td>5</td>
<td>39%</td>
<td>NS</td>
</tr>
<tr>
<td>In situ ductal carcinoma</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Histoprognostic grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>44</td>
<td>52%</td>
<td>NS</td>
</tr>
<tr>
<td>III</td>
<td>38</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td><strong>Mitosis (SBR)</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>26</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>47%</td>
<td>0.02</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>Not evaluated</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fibrosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4</td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>52</td>
<td>61%</td>
<td>&lt; 0.03</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td><strong>Necrosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>60</td>
<td>52%</td>
<td></td>
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<tr>
<td>1</td>
<td>10</td>
<td>72%</td>
<td>&lt; 0.03</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>67%</td>
<td></td>
</tr>
</tbody>
</table>

*1 + 2 vs. 3  p= 0.005
**PEV1= rapid clinical evolution (subjective clinical growth in 6 months) Denoix 1970
### Table 14.7. Relative Importance of Prognostic Factors In Breast Carcinomas

<table>
<thead>
<tr>
<th>Factors</th>
<th>Poor survival</th>
<th>Increase of local recurrence</th>
<th>Good response to Hormonal therapy</th>
<th>Chemo-therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size (High)</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pathological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph-node involvement</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Histoprognostic grade (high)</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>(+)</td>
</tr>
<tr>
<td>Anatomic size (high)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Extensive intraductal component (EIC+)*</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>(++)</td>
</tr>
<tr>
<td>Involvement of margins*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Biological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormonal receptor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA aneuploidy</td>
<td>+/-</td>
<td>(+)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>S-phase fraction (high)</td>
<td>++</td>
<td>(-)</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>c-erbB-2</td>
<td>++/-</td>
<td>(-)</td>
<td>(-)</td>
<td></td>
</tr>
<tr>
<td>p53</td>
<td>++</td>
<td></td>
<td>(-)</td>
<td></td>
</tr>
<tr>
<td>Angiogenesis (high)</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

( ) data have to be confirmed;
* conservative treatment
An update of prognostic factors in Breast cancer

Immunologic and Genetic Markers

- **Mib-1** proliferation marker is useful in subtyping of diploid tumors. It is superior to SPF.
- **CD10**: a cell surface neutral endopeptidase is negative in normal stromal cells. But in some breast cancer cases, CD10 is expressed, facilitating cancer cell invasion. This is associated with aggressive behavior.
- **p63** is a member of p53 gene family. It is involved in mammary gland development (myoepithelial cells).
- **Syndecan (CD138)** is a cell surface heparin sulphate proteoglycan. It is involved in cell proliferation, migration, and cell matrix interaction. It is expressed frequently in breast cancer and is associated with tumor aggressiveness and poor prognosis.
- **Kit protein**: Kit proto-oncogene encodes transmembrane tyrosine kinase growth factor receptors and is essential for cell differentiation. Its protein expression is lost in aberrant formation of tumor.
- **Apoptotic markers**: Bax is a pro-apoptotic tumor suppression gene. p53 is a direct transcriptional activator of Bax, aberration in the normal programmed cell death mechanisms is critical in the proliferation of breast cancer. Bcl-2, Bcl-x and Bax are significantly expressed in low grade ER/PR +ve tumors. This apoptotic pathway is in equilibrium in good prognostic group.
• **Metallothionein isoform3 (MT-3)** is a matrix component. Its regulation is aberrant in breast cancer and its overexpression is associated with poor progression.

**Chromosomal Changes**
- Numeric aberration of chromosome 1 and 7 indicate abnormal DNA and aggressive tumor.
- LOH 3p14 correlates with aggressive biology.
- Mismatched repair gene: inactivation of DNA repair in breast tissue could lead to tumor pathogenesis.

**Methodologies**
- **Tissue microarray DNA technology**: is a new method, which allows detection of mutated, deleted or amplified status of up to 1000 genes simultaneously. This forms a library of individual tumor profiles associated with sensitivity and resistance to specific cytotoxic treatment. Individual tumor samples can be tested for optimal regimen on the basis of their DNA fingerprint. It could be performed on tumor sample from paraffin blocks. One gene in question could be correlated with the status of numerous other genes that could affect its function.
- **Comparative Genomic Hybridization**: the genetic profile of two tissue samples could allow the study of tumor development progression or regression.
- **Automated Cellular Imaging System** can assist the quantitation of immunohistochemistry; it is a sensitive and rapid system with objective findings.
Chapter 13

Persistent Pain in Breast Cancer
Although breast cancer is basically non-painful, and that is why it is malignant, pain usually arise from its complications, whether due to spread of the disease to painful sites, or due to its therapy. Advances in the researches in the field of pain, gave the possibility to understand management of chronic pain and to do measures to prevent the occurrence of some preventable forms, but by any means, a good control of pain must be our target in patient management.

In breast cancer, persistent pain as a symptom occurs approximately in half of patients. Not all patients’ present difficulty in their management and only about 9% of them has pain of difficult therapeutic or diagnostic problems.

In the mean time, the stress associated with the disease may lead to psychological disturbances, which will share in the exaggeration and initiation of pain problems. The fear of disfigurement, therapeutic failure, and uncontrolled pain will drive some of patients into anger, anxiety and depression, creating a vicious circle that has to be broken to get a good control of the painful condition.

The affinity of this type of cancer to disseminate will need a good and thorough patient assessment to get grasp of the presented clinical stage and to make a good plan for patient management. Moreover, one has to understand how therapeutic measures can inevitably produce a painful syndrome, such as post-mastectomy pain, post-irradiation neuralgia, and some forms of aseptic bone necrosis from corticosteroid therapy. Some other forms of pain may be produced by a non-malignant associated condition as disc lesions or diabetic neuropathy, or back pain from prolonged phases of bed rest and inactivity.

**Breast Cancer Pain**

Three broad categories of pain mechanisms may be posited: ongoing nociceptive, neuropathic processes, and psychological influences.

**Nociceptive Pain**

This term is applied when pain is perceived to be corresponding with tissue damage associated with an identifiable somatic or visceral lesion. This type includes:

A. Somatic pain that originates from somatic structures and is typically well localized, sharp, aching throbbing or pressure like.
B. Visceral pain that originates from viscera and is often diffuse, gnawing, cramping, aching, sharp or throbbing.
**Neuropathic Pain**

It is believed to be sustained by a site of aberrant somatosensory processing in the peripheral or central nervous system, most strongly suggested when there is a sensory affection in the form of hypoesthesia, dysesthesia, or allodynia, sometimes with loss of sensation and burning form of pain.

**Pathogenesis of Pain Syndromes**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Causes</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Postmastectomy pain</td>
<td>Surgical differentiation</td>
<td>19%</td>
</tr>
<tr>
<td>2. Intercostal Neuralgia</td>
<td>Herpes Zoster, Rib metastasis</td>
<td>7%, 5%</td>
</tr>
<tr>
<td>3. Heavy painful arm</td>
<td>Irradiation fibrosis, Axillary recurrence</td>
<td>19%, 7%</td>
</tr>
<tr>
<td>4. Low back pain</td>
<td>L1 metastasis, L4, 5 sacroiliac metastasis</td>
<td>5%, 7%</td>
</tr>
<tr>
<td>5. Joint pain</td>
<td>Hip, femur, Shoulder &amp; humorous</td>
<td>7%, 5%</td>
</tr>
<tr>
<td>6. Upper abdominal pain</td>
<td>Liver metastasis</td>
<td>12%</td>
</tr>
<tr>
<td>7. Neuralgias</td>
<td>Sciatic &amp; ulnar neuralgia</td>
<td>7%</td>
</tr>
</tbody>
</table>

**Acute Pain Syndromes**

Acute pain in breast cancer is usually related to patient’s management, and can be prevented. Acute pain hospital service should be available to prevent the occurrence of these forms. Pain is usually simple, cause-related, and has a short duration. Acute pain syndromes associated with breast cancer are:

- Pain associated with diagnostic interventions e.g. Myelography, Percutaneous biopsy.
- Postoperative pain.
- Pain associated with chemotherapy infusion techniques as intravenous infusion pain due to venous spasm, chemical phlebitis or extravasation.
- Pain associated with chemotherapy toxicity e.g. mucositis, corticosteroid induced perineal discomfort.
• Pain associated with hormonal therapy as hormone-induced pain flare in breast cancer.
• Pain associated with immunotherapy e.g. interferon-induced acute pain.
• Pain associated with radiotherapy e.g. early onset brachial plexopathy, subacute radiation myelopathy, incident pains associated with positioning and mucositis.
• Pain associated with infection due to altered immunity e.g. acute herpetic neuralgia.
• Pain associated with analgesic techniques e.g. injection pain, opioid headache, spinal opioid hyperalgesia syndrome, epidural injection pain.

**Breast Cancer related chronic pain syndromes**

**A. Tumor Related Pain Syndromes**

**1. Bone pain**

Metastatic tumor in breast cancer can be presented by a variety of bone pain symptoms. It is a form of ongoing nociceptive pain, increases significantly with mobility, and is relieved in the majority of patients by rest and with the use of steroidal or non steroidal anti-inflammatory drugs, but in some patients more invasive techniques are mandatory to control such pain as vertebroplasty or bone fixation. Syndromes related to bone metastasis are:

I. Generalized or multifocal-metastases and marrow expansion

II. Vertebral syndromes

- C7-T1 syndrome: pain referred to the interscapular region.
- T12-L1 syndrome: pain referred to the ipsilateral iliac crest or the sacroiliac joint.
- Sacral syndrome: radiates to buttocks, perineum and posterior aspect of the thigh.
- Atlantoaxial destruction and odontoid fractures: radiates over the posterior aspect of the skull to the vertex and exacerbates by flexion of the neck.

III. Back pain: should be viewed as potential indicator of epidural compression.

IV. Pain syndromes of the bony pelvis and hip: cause pain with ambulation.

**2. Headache and facial pain**

- Intracerebral tumor metastasis with manifestation of increased intracranial tension and will respond to dehydrating measures (steroids, diuretics and positioning) in addition to analgesics.
- Leptomeningeal metastases.
- Skull base metastases.
3. **Tumor involvement of the peripheral nervous system.**
   - Radiculopathy.
   - Cervical plexopathy.
   - Brachial plexopathy “early onset transient”.
   - Post herpetic neuralgia.

4. **Pain syndromes of the viscera**
   - E.g., liver metastases cause hepatic distention syndrome.

**B. Cancer Therapy Related Chronic Pain Syndromes**

1. **Post chemotherapy pain syndromes**
   - As chronic painful peripheral neuropathy, and avascular necrosis of femoral or humeral head.

2. **Chronic post surgical pain syndromes** e.g.
   - **Post mastectomy pain syndrome**
     - It affects 20% of women who undergo breast surgery, although it has been reported to occur after almost any surgical procedures on the breast but it is most common after procedures involving axillary dissection. Pain may begin immediately or as late as many months following surgery. The onset of pain later than 18 months following surgery is unusual and a careful evaluation to exclude recurrent chest wall disease is recommended. It is usually constricting or burning in character that is localized to the medial arm, axilla and anterior chest wall. On examination, there is often an area of sensory loss within the region of the pain and sometimes trigger points can be palpated in the axilla or chest wall. The patient may restrict movement of the arm, leading to frozen shoulder as a secondary complication. Its etiology is believed to be related to damage of the intercostobrachial nerve, a cutaneous sensory branch of T1, 2, 3. There is marked anatomic variation in the size and distribution of the intercostobrachial nerve and this may account for some of the variability in the distribution of pain observed in patients with this condition.

   - **Phantom breast after mastectomy**
     - Occurs in 15% of patients and appears to be related to the presence of preoperative pain, it tends to start in the region of the nipple and then spread to the entire breast. The character of the pain is variable and may be lancenating, continuous or intermittent.
• Heavy painful arm
  Edema of the upper limb after radical mastectomy is very common due to radical axillary evacuation of lymph nodes. Intermittent lymphangitis usually occurs due to lymph stasis, especially in diabetic patients with inflammatory signs and symptoms.

3. Chronic postradiation pain syndromes

Radiation-induced brachial plexopathy: “Progressive plexopathy of a delayed onset which can occur 6 months to 20 years after a course of radiotherapy that included the plexus in the radiation portal.

In the pain clinic, National Cancer Institute Cairo University, the pain syndromes associated with breast cancer was found to have the following distribution:

Management of Breast Cancer Pain

We have to take into consideration the meaning of pain to the patient. It usually carries the mind of patient to failure of treatment, which in approximately 50% of patients; it is due to treatment success, as in post-mastectomy pain, irradiation fibrosis, herpes zoster, sciatic and ulnar neuralgia. They usually appear 6 months after treatment, which logically means in the patient’s opinion failure of treatment. Detailed explanation to the patients about the condition will dramatically affect their sufferings.

A second important point to be considered is that the presence of pain for a prolonged period will affect the function of the nervous system in a way that the threshold of pain will be lowered. Intolerable pain will be converted tolerable when supporting the exhausted or deranged perceptive system in such patients. This is the aim of medical treatment, rather with prescribing analgesics, which has a good controlling effect in all cases, and by itself can control 47% of cases.

I. Medical treatment

Prophylaxis

Preventing pain before operative interference, or what is called pre-emptive analgesia, is now regarded important. The tissue injury usually sets up a vascular, immunological, and sympathetic stimulation that will bring about a long list of inflammatory mediators in the form of peptides. The primary effect of these mediators is to stimulate the immune mechanisms and tissue repair. The effect of these mediators on nociceptors may cause stimulation of abnormal severe pain, which is difficult to control, and is manifested with hyperalgesia. It was found that preventing these effects on the sensory nerve is essential in preventing the
occurrence of post-surgical chronic pain syndromes. This can be done by using opioids, α2 agonists, GABA agonists, or local anesthetic infiltration to the site before inducing surgical trauma.

- Trial to preserve the intercostobrachial nerve as possible during surgery.
- Slow rate of infusion of chemotherapy
- Avoidance of extravasation of chemotherapy infusion.
- Early rehabilitation and physiotherapy and encouragement of active movements to avoid frozen shoulder

### Pain Control
Two main tools are available (non-invasive drug therapy and minimally invasive procedures aiming for pain control) and can be used separately or in combination to control such pain. Pharmacotherapy in the form of analgesics constitutes the most common form of pain control in breast, and other cancer pain. It does not need equipment and experience compared to invasive methods used for pain relief. The most common disadvantages, which one should work to minimize during drug treatments, are tolerance and side effects. These should be regarded with the start of treatment and not to permit its development. It needs also continuous monitoring to make the control of pain and side effects reasonably good. The advantages of drug therapy comprise its simplicity and availability for large number of population to be treated in the same time. However, interventional pain therapy in the form of minimally invasive procedures aiming for pain relief can play an important role in controlling pain in certain situations e.g. percutaneous neurodestructive procedures, neuroaxial drug delivery devices and vertebroplasty.

### A. Pharmacotherapy (analgesics)
We have to stick to the following rules during drug treatment otherwise, we will get easily side effects or failure of drug treatment. The rules are:

1. **Analgesics are prescribed by the clock**
   Do not permit the pain to appear to give the analgesic, as bouts of pain and pain relief will accelerate the development of tolerance. Drugs are given in the sufficient or full clinical dose and repeated according to their duration of action in order to keep the plasma level in a fairly constant level. So, the prescription of when required is now condemned.
2. Analgesics are given by a satisfactory route
The oral drugs constitute a good route, which is always satisfactory to the patient. However, it is not suitable for unconscious patients or patients with persistent nausea and vomiting. Oral drugs usually pass through a phase of liver metabolism before reaching their target, a fact which lowers drug availability and increases the effect of metabolites which should be counted in chronic drug administration. Transdermal route especially patches with long-term effects lasting for 72 hours is an ideal option for patients with persistent nausea and vomiting. The rectal route and Intramuscular route are always inferior as drug absorption is irregular. Intravenous route, by continuous infusion or by patient controlled analgesia PCA is the ideal, and usually needed to determine the effective daily dose in some cases. Subcutaneous route is also effective, and is regarded in some situations as good as the intravenous route. Also the transmucosal, nasal or sublingual routes are good options.

3. Analgesics are prescribed by a ladder
There is an agreement about the scheme of treatment by analgesics to go through a three ladder steps, and one should not jump any step in the ladder system.
Step I: A non steroidal anti-inflammatory drug NSAID is usually used, together with an adjuvant. We have to remember that the NSAIDs have a ceiling analgesic action and we must not exceed the clinical doses to get analgesia, as this will only result in production of side effects. The appearance of new selective COX II inhibitor drugs minimizes very much the incidence of occurrence and severity of side effects.
Step II: A weak opioid as codeine, dextropropoxyphene, oxycontine, tramadol; to be added to strengthen step 1.
Step III: You may replace the weak opioid with a strong opioid as morphine, oxymorphone, and fentanyl patches. The NSAIDs can potentiate opioid analgesia and reduce opioid consumption.

4. Always try to give adjuvants
Adjuvants are non analgesics, which have an analgesic effect in certain conditions as neuropathic pain. They were claimed also to potentiate morphine analgesia. The analgesic outcome is greatly enhanced by the use of adjuvants.

B. Adjuvant drugs
(i) Classical Adjuvants
These are drugs given to relief anxiety, to promote sleep and delay central exhaustion. This group includes:
1. The serotonergic antidepressants
A representative of this group is “Amitriptiline” or Tryptizol. Its action is to raise the central 5HT (Serotonin), which is important neurotransmitter acting with opioids in the analgesic body system.
It is important to recover the pain threshold, and to guard against tolerance to the administered opiates. It is important to remember that only serotonergic antidepressants are needed. The dose needed here is very small, ranging from 10 to 30 mg. daily.

2. The anticonvulsants
The representatives are “Carbamazepine” or Tegretol. They are essential if there is any element of neuralgic pain. Tegretol 200 mg tablets, initially twice daily are usually the starting dose, and it is gradually increased up to 2 tablets three times daily. It has a leucopenia effect, which necessitates periodical blood cell analysis. Other members are clonazepam and phenytoin and the new gabapenten.

3. Corticosteroids
They constitute one of the chemotherapeutic agents. They are particularly useful in cases of bone, brain, or liver metastatic pain. Their dramatic effect on pain necessitates their use in a loading dose, which can be adjusted afterwards.

4. Anxiolytic drug
Benzodiazepines are a favorable group of adjuvants to abolish anxiety and promote good sleep.

(ii) Non-Classical Adjuvants
This group includes;
1. Osmotic laxative
Lactulose may be needed to prevent constipation associated with opioid therapy. One has to note that the constipating effect is not related to the strength of the opioid, as constipation by dextropropoxyphene is more than that of morphine.
2. Anti-emetics
Are needed when there is nausea and/or vomiting. Dopamine antagonists are readily available and very suitable to use with opioids. It is useful to note that opioids can produce nausea only in ambulatory patients, and it is very responsive to treatment. Serotonin antagonists as ondansetron are used for persistent cases.

3. Antibiotics

ii. Interventional pain therapy
It is the use of minimally invasive procedures to control pain. Percutaneous neurodestructive procedures, implanting different devices for neuroaxial opioid delivery and vertebroplasty are the most common pain relief procedures used to control cancer pain. This type of therapy can offer excellent quality of pain relief.
for long duration without much impact on these patients especially when properly performed for selected patients, as most of these procedures can be performed percutaneously, under local anesthesia with radiological guidance and requires minimal hospital stay mostly for a couple of hours or days. So, in terminal cancer patients (life expectancy less than one year) it is recommended to interrupt or destroy the pain-transmitting pathway at a suitable target. This destruction should be attempted as early as possible to get benefit from the quality of pain relief with the possible reduction of analgesic medications and hence their side effects and burden on different organ functions which may be already impaired by cancer or its therapy.

As a rule, this line of pain therapy is indicated only in localized cancer pain except for hypophesectomy in case of generalized bony metastases or insertion of implantable systems for neuro-axial opioid delivery. Percutaneous vertebroplasty can be performed to alleviate pain originating from vertebral fractures due to tumors or their metastases. Bleeding tendency and local infection at the site of intervention are general contraindications, beside other contraindications specific for certain procedures and will be mentioned later within each procedure. The following are some examples of these interventions:

1. **Percutaneous Cervical Cordotomy**

   It is destruction of the lateral spinothalamic tract to interrupt pain transmission from the contralateral side of the body below the level of the lesion. It is performed percutaneously under local anesthesia and CT-guidance. At the level of C1-C2 as lesioning at that level is almost guaranteed to produce analgesia below C4 or C5 as pain fibers enter the cord through the dorsal horn and then may ascend several levels before crossing over and taking their final position in the spinothalamic tract at the anterolateral quadrant at the spinal cord.

   It is indicated in patients with unilateral cancer pain of somatic origin below the level of the shoulder. The success rate is more than 90% with excellent quality of pain relief, which lasts for more than one year and is associated with loss of pinprick sensation and temperature discrimination.

   The major risk of percutaneous cordotomy is respiratory decompensation and this risk increases with pre-existing severe pulmonary disease and bilateral lesions producing high levels of cervical analgesia, as the automatic respiratory fibers course through the reticulospinal tract, which is so adjacent or may mingle with fibers of the spinothalamic tract. Ipsilateral ataxia and motor weakness may occur in few cases but fortunately in a temporary manner.
2. **Posterior Rhizotomy (Sensory Nerve Root Destruction)**
Localized somatic cancer pain especially at the chest or trunk e.g. rib metastases can be alleviated by percutaneous posterior root destruction using subarachnoid neurolytic agents. 80-85% success rate can be obtained following the procedure. It may be followed by motor affection if anterior (motor) nerve roots are unintentionally destroyed. It is contraindicated in case of intraspinal tumor extension at the target level.

3. **Celiac Plexus Destruction**
85% success rate in alleviating upper abdominal visceral cancer pain originating from liver metastases. Celiac plexus is a prevertebral sympathetic plexus situated in the retroperitoneal space at the level of the first lumbar vertebra. It can be performed percutaneously, under L.A. and by the aid of biplanar fluoroscopy, using a total volume of 50 ml of 50% alcohol as a neurolytic agent injected bilaterally. Postural hypotension and diarrhea may follow this procedure but fortunately in a transient manner and respond well to symptomatic treatment. Therefore, in severely dehydrated patients, it is relatively contraindicated and preoperative adequate hydration is essential.

4. **Paravertebral Sympathectomies**
To alleviate sympathetic maintained pain in the upper extremities, especially following surgery or radiotherapy. Satellite or upper thoracic sympathectomy can be done percutaneously with 70-80% success rate by the aid of biplanar fluoroscopy or under CT guidance. Complications in the form of unintentional destruction of the nearby nerves and the occurrence of pneumothorax may rarely occur.

**Hypophyseotomy**
Pituitary destruction is indicated in generalized bony cancer pain not responding to pharmacotherapy e.g. metastatic breast cancer. It can be performed transnasally with good success rate but with some risk of mortality and morbidity (CSF leak, diabetes insipidus…). Hypothalamic pain suppressing response activated by elimination of hormonal feedback of the pituitary gland is the most accepted theory for the mechanism of action of such procedure.

**Local infiltration or intercostal block** in a rib metastasis, an epidural block in cases of vertebral metastasis with localized pains, and interpleural block which is particularly useful in pleural involvement, all can be applied using a mixture of local anesthetic and steroids. This proved successful in relieving such pain for one to four weeks and can be repeated.
Implantable Systems for CNS Drug Delivery Systems
The appearance of severe intolerable opioid side effects or tolerance in a patient who was opioid sensitive at the start of this treatment is a good indication to test for the effect of neuroaxial opioid before permanent implantation. Opioids are the main drugs used either alone or mixed with other medications (e.g. local anesthetics). Lesser dose, better analgesic response and fewer side effects are the main advantages of neuroaxial opioids, and implantation of these systems offer better stability and less infection.

Percutaneous vertebroplasty (PVP)
It is a minimally invasive therapeutic procedure that involves injection, under-radioscopic guide, of an acrylic polymer (mostly methyl methacrylate) into a vertebral body with pathologic compression in an effort to relieve pain and provide stability. As, it can achieve an immediate stabilization and pain resolution in 70-90% of the cases. It can be performed under local anesthesia ± sedation with a short hospital stay for one night or even as an outpatient procedure. Vertebroplasty may be performed in combination with radiation therapy or in conjunction with decompressive surgery.


similar to PI-3 kinase. Science 268: 1749.
Conservative versus radical Diagnosis and Treatment of Breast Cancer. Williams and Wilkins, Baltimore, 
London.
Eur J Cancer 36 (suppl 4) S 14-S 15
estrogen receptor and its selective modulators in gynecological and breast cancer. Eur J Cancer 36 (S1- 
S9).

Epidemiology, Risk factors Genetic predisposition Prevention

among BRCA2 mutation carriers: results from a combined analysis of 19 studies. Am J Hum Genet 81, 
342:564-71.
and life expectancy after prophylactic oophorectomy in women with BRCA1/2 mutations: a decision 
cancer in young women. J Natl Cancer Inst 86: 1403


a. Screening Diagnosis Imaging Staging, Pa-thology Prognostic


185. Berman CG. Recent advances in breast-specific imaging. Cancer Control 2007, 14 : 338-349


dynamic contrast-enhanced subtraction. MRI Radiology 191: 625

272. Gilles R; Mesurrolles B, Lesnik A, Rigaud C, Guinebretiere JM, Mas-selot JM, Contesso G and

Jakesz R (1992): DNA ploidy and other results of DNA flow cytometry as prognostic factors in operable

274. Good WF, Abrams GS, Catullo VJ, Chough DM, Ganott MA, Hakim CM, Gur D. Digital breast

275. Gohagan JK, Darby WP and Spitznagerel EL et al. (1986): Radiogenic breast cancer effects of

eighteen cases with implications for breast cancer screening. Histopathology 16: 119.

measurement of the estrogen receptor in invasive breast cancer tissue. Eur J Cancer 36 (suppl 4): S20-
S21.

JF, Blarney RW and Ellis IO (1995): A new immunohistochemical antibody for the assessment of estrogen
receptor status on routine formalin-fixed tissue samples. Hum Pathol 26: 291.

findings in 43 patients. Neurology 31: 530.

Steroid Biochen. 20: 51.


282. Guller U, Nitzsche EU, Schirp U, Viehl CT, Torhorst J, Moch H, Langer I, Marti WR, Oertli D,
Harder F, Zuber M. Selective axillary surgery in breast cancer patients based on positron emission

283. Gulsun M, Demirkazik FB, Ariyurek M. Evaluation of breast micro-calcifications according to
Breast Imaging Reporting and Data System criteria and Le Gal's classification. Eur J Radiol 2003, 47 : 227-
231.


294. Harvey JM, Calrk GM, Osborne CK, Allred DC (1999): Estrogen re-ceptor status by immunohistochemistry is superior to ligand-binding assay for predicting response to adjuvant therapy in breast cancer J Clin Oncol 17: 1474-1485


323. Kopans DB. Breast imaging and the symptomatic patient: enough with the "diagnostic" mammography. AJR Am J Roentgenol 2003, 181 : 1423-1424


370. Orel S. Who should have breast magnetic resonance imaging evalua-tion? J Clin Oncol 2008, 26 : 703-711


467. Tardivon A. [How to follow-up women with dense breasts by imag-ing?]. J Radiol 2008, 89 : 1204-1208


Valagussa P, Brambilla, C and Zambett M (1989): Salvage treat-ments in


Plast Reconstr Surg 2006; 117(2): 359- 365


550 Cothier- Savey I, Rimareix F, Belichard C Principes généraux de la chirurgie oncoplastique et de la reconstruction mammaire immédiate et diffé-rée Encyclopédies Médico chirurgicales , techniques chirurgicales : chirurgie plastique, reconstructrice et esthétique 45-664, 2002, 14p


571 Giuliano A. American College of surgeons Oncology Group. ACOZOG-Z0011. A randomized trial of axillary node dissection in women with clinical T1 or T2 N0 M0 breast cancer who have a positive sentinel node;2004. [available from:http://www.acosog.org/studies/organ_site/breast/index.jsp]


574 Grossman F. Uber die axillaren lymphdrusen:Inaugural dissertation. 1896, Berlin, Germany.


580. Halsted WS (1894/95): The results of operations for the cure of can-cer of the breast performed at the John Hopkins Hospital from June 1889 to July 1894, John Hopkins Hosp Bull. 4: 297.


626 Rainsbury R.M., Skin-sparing mastectomy British Journal of Surgery 2006; 93: 276–281


634 Sappey C. PH. Anatomie, physiologie, pathologie des Vaisseaux Lymphatiques Adrien Delahaye Librairie Editeur parvis 1874.


Greenspan EM (1966): Combination cytotoxic chemotherapy in ad-vanced disseminated breast carcinoma. J. Mt, Sinai Hospital.


