Conservative surgery with preservation of fertility in gynecologic malignancy

Denis Querleu

Abstract

Gynecological malignancies may affect women in their reproductive age. As a consequence, loss of fertility is a concern for those women who have not fulfilled their desire for maternity. On the other hand, it has been recognized for years that subsequent pregnancy does not adversely affect the outcome of patients managed for cancer, and that the majority of drugs currently used for the treatment of gynaecological malignancies do not impair ovarian function. On the contrary, the dose of pelvic radiation therapy required to control pelvic malignant conditions definitively inhibits the reproductive and hormonal function of the ovaries, and impairs the ability of the uterus to maintain a viable pregnancy.

As a consequence, preservation of fertility in the management of gynaecologic malignancies requires the maintenance of at least the uterus and one ovary without radiation therapy, if possible without inducing pelvic adhesions impairing fertility, although the latter can be overcome using assisted reproductive technologies. Conservative surgery is defined as surgery with complete staging and preservation of at least the uterine corpus and at least part of one ovary.

Department of Surgery, Claudius Regaud Cancer Center, Toulouse, France
Querleu.Denis@claudius regaud.fr

Carcinoma of the uterine cervix

surgeons that are not at ease with radical vaginal procedures. The laparoscopic variant, that mimics the abdominal operation, has also been described [12-13]. In addition, less than radical surgery, involving simple trachelectomy, may be accepted in selected cases of early cervical cancer with negative nodes [14], although this cannot be accepted as a standard.

Oncological outcome

A case-control study comparing conservative versus radical management has provided evidence of the safety of the concept [15]. Central as well as lateropelvic or distant metastases have been described [16-17]. An ovarian recurrence has been reported [18].

The most recent information about long term oncological results has been orally presented in 2006 by the author [19]. A combination of databases of 7 major centers in Canada, Germany, United States, and France totalled 532 patients. Incidentally, duration of surgery was 232 minutes and hospital stay averaged 4.7 days in this large collaborative series. 1% and 1.4% intraoperative and 5.6% and 15.3% postoperative complications were secondary to lymph node dissection and trachelectomy, respectively. 32 patients had some adjuvant therapy impairing fertility as a result of positive nodes or margins. In the remaining 500 patients, 18 recurrences were observed, 7 of them were central recurrences. Six patients died of disease. No influence of pathologic subtype was found, that means that adenocarcinoma is an acceptable indication. LVSI and tumor diameter were strongly related to the risk of recurrence. Tumor diameter is available in 189 patients. Two patients out of 22 presenting with tumors larger than 2 centimeters recurred, compared to 4 out of 167 in patients with tumors less than 2 centimeters ($p<.001$). Information on peritumoral lymph vascular space invasion (LVSI) is avaible in 403 patients. A significant proportion (11 out of 99, 11%) of patients with LVSI recurred, compared to 4 out of 304 patients without LVSI ($p<.001$).

This large series provides a clear information available for a safe selection of patients : only patients with node negative, less than 2 centimeters squamous cell or adenocarcinoma of the uterine cervix, without LVSI. Others pathologic subtypes are excluded. Patients with polypoid tumors larger than 2 centimeters with a narrow implantation base on the cervix, far from the endocervical canal may be accepted. The presence of LVSI is a strong argument against the indication.

Obstetrical outcome

Although Dargent's operation is reserved to young women with a real desire of childbearing, some patients do not really desire pregnancy. Preserving at least the option of future childbearing may be the only goal of the operation. Infertility related to the reduction of cervical function does exist but is becoming less frequent as a result of a trend towards strict selection of patients allowing to preserve a 10 mm endocervix [20]. Patients presenting with evidence of impaired fertility may be included as long as the infertility factor is curable. Assisted reproductive techniques including in vitro fertilization, intrauterine insemination, and ovarian stimulation have been be used after radical trachelectomy [21].

Pregnancies occur in approximately half of patients. There is a definite risk of premature birth or late abortion that is only partially prevented by permanent isthmic cerclage and additional cervical closure during pregnancy. Early reports by the Lyon team and others [21] found an average 17% of second trimester loss. This can be overcome only by maintaining 10 mm of endocervix [20, 22].

Preoperative workup and selection of patients

Selection of patients is crucial to ensure oncological safety and prevent second trimester abortions and

premature deliveries. Specific preoperative workup is made of MRI and cone biopsy. MRI allows to precisely assess the maximum diameter of the tumor, selecting with a few exceptions patients with tumors less or equal to 2 centimeters. Localization of the upper limit of the tumor is another essential information, that helps to predict the requirements for endocervical resection and estimate the length of remaining endocervix.
A majority of patients are referred after diagnostic cone biopsy. Careful review of the report and whenever necessary review of slides is mandatory. Special attention is given to the identification of lymph-vascular space invasion. The adverse prognosis attached to the presence of LVSI is important enough to advise preoperative cone biopsy in all cases, although repeat multiple biopsies may help to rule out this prognostic factor, that is considered by many authors as a contra-indication to conservative surgery and an indication for adjuvant external radiation therapy.

Another issue is the required upper margin. As much of the endocervix should be retained in order to avoid impairing fertility, and to improve the obstetrical outcome. On the other side, a 8 mm clear pathologic margin is theoretically required for squamous cell cancer, as observed in vulvar cancers [23]. There is obviously a trade-off between fertility preservation and oncological safety that also affects patient selection : location of the upper endocervical limit of the tumor must be compatible with the dual requirement of sufficient clear margin and sufficient remaining endocervix.

Finally, aggressive pathologic subtypes such as neuroendocrine carcinomas are absolute contra-indication. Overall, after a careful selection process, up to 40% of patients presenting with cervical cancer under the age of 40 might still be candidate to conservative management [24].

Other fertility preserving options

Neoadjuvant chemotherapy followed by simple conization has been proposed [25-27]. Although investigational, the option is the only one available for patients with tumors larger than 2 centimeters.

Epithelial ovarian cancer (EOC)

Conservative treatment of at least a part of one ovary and the uterus in order to preserve fertility in young patients can be proposed in selected patients with EOC. However, the results and limits of such treatment remain unclear. Only three studies involving a large number of patients have been published on the results of conservative management of EOC [28-30]. The largest and the only one to include a centralized pathologic review of the ovarian tumor by the same pathologist is the French study [30]. 34 patients of this study fulfilled all inclusion criteria. Thirty had stage IA disease (G1 n=13; G2 n=14 and G3 n=3); 3 stage IC and 1 stage IIA. Ten patients received postoperative chemotherapy. Eleven patients recurred : ten patients had invasive disease and one had borderline recurrence. Among the 10 patients with invasive recurrence, initial stage and grade were: stage IA G1 n=1; stage IA G2 n=4; stage IA G3 n=1 and stage $\geq$ IC n=4. Overall, all patients with stage > IA recurred. Ten pregnancies were observed in 9 patients. The conclusion is that conservative management is safe in stage IA grade 1 patients, can be discussed in stage IA grade 2 and in selected small volume stage IA grade 3 patients, but that stages IC and over must be excluded. Comprehensive staging including peritoneal cytology, peritoneal biopsies, omentectomy, systematic bilateral pelvic and aortic lymph node dissection, and dilatation and curettage, is mandatory to correctly stage candidate patients and exclude occult advanced stage disease. Pathological examination by a pathologist experienced in ovarian malignancy is mandatory.

As far as the affected ovary is concerned, unilateral salpingo-oophorectomy is advised as a standard. Technique is straightforward, although the need for an oncologically safe removal, without any rupture or morcellation and consequent contamination of the peritoneal cavity or abdominal wall must be stressed. In this regard, laparoscopic technique or small transverse incisions may adversely affect the outcome if they lead to faulty technique and contamination of the abdominal wall. On the other hand, laparoscopic surgery is adapted to the reassessment of apparent stage I diagnosed during primary surgery [31]. Laparoscopic surgery by an experienced surgeon allows careful examination of the contralateral ovary, is an adapted tool to rule out peritoneal growth, and has been found to be a safe technique to perform advanced staging operation such as omentectomy and pelvic/aortic lymph node dissection [32].

However, some reports of pregnancy after chemotherapy for advanced ovarian cancer are available in the literature [33]. Anecdotically, pregnancies have been reported in patients previous managed by normothermic or hyperthermic intraperitoneal chemotherapy [34].

Germ cell tumors of the ovary [35]

Germ cell tumors are rare, but prefentially occur in adolescent or young females. As they are usually curable with fertility preservation at all stages of disease including stage III, fertility preservation is a mainstay of surgical management. This also holds in the setting of residual masses after chemotherapy, that may be benign. Preoperative diagnosis is essential, and involves a routine performance of specific markers in all young women that present with a pelvic mass. Elevated alpha-fetoprotein for the diagnostic of yolk sac tumors and human chorionic gonadotrophin for

the diagnosis of choriocarcinoma are diagnostic of an ovarian germ cell tumor. Ca-125, lactate deshydrogenase, placental alkaline phosphatase are less sensitive and less specific. Diagnostic of malignant transformation of mature teratomas is more difficult, and based on size and squamous cell carcinoma marker of apparently benign dermoid cysts. Diagnostic of non secreting dysgerminomas and immature teratomas is only obtained at final pathology. Thus, conservative management is advisable in young patients even in the case of advanced disease with peritoneal implants. Frozen section is not reliable enough to decide a hasty radical surgery. Unilateral salpingo-oophorectomy is safe, but is too radical if the tumor is benign. Cystectomy may thus be acceptable [36].
Most patients, but those with stage I dysgerminomas or low grade immature teratomas, will received platinum and etoposide based chemotherapy, with or without bleomycin. Fertility is not impaired after chemotherapy for germ cell tumor of the ovary[37].

Borderline ovarian tumors

As the majority of borderline ovarian tumors (BOT) is observed in patients of reproductive age, fertility is a major issue in young female patients presenting with suspicious adnexal masses. It must be stressed that BOT are not precursors of ovarian cancer, and recurrence as a malignant tumor is observed in only 2% of cases [38-39]. BOT are almost invariably controlled by surgical management, and the use of chemotherapy is limited to the unfrequent occurrence of invasive peritoneal implants. Recurrence is possible, but can still be controlled by repeat surgery [40-41]. Prognosis is excellent, with 97-98% long term survival in early stages, 92% in advanced stage serous BOT. Advanced stage mucinous BOT carry a worse prognosis, but the difficulties of differential diagnosis with invasive adenocarcinoma might account for the apparent difference in prognosis.

In general, definitive pathology by an experienced pathologist is required for the diagnosis of BOT, in order to rule out invasive disease, and identify micropapillary serous BOT that carry a worse prognosis and are classified by some authors as “low-grade carcinomas” rather than BOT. When a doubt persists at the time of surgery and frozen section, conservative management then referral to an oncological team including experienced surgeons and pathologists is advised.

The mainstay of management of BOT in young female patients is conservative surgery. Total hysterectomy and bilateral salpingo-oophorectomy is no longer advocated in young patients, whatever the stage. Unilateral salpingo-oophorectomy is standard. Cystectomy only is accepted when the tumor is bilateral or develops on a remaining ovary. When a BOT is diagnosed after cystectomy of an apparent benign ovarian cyst, complementary salpingo-oophorectomy is indicated only in multifocal or large tumors, and/or when complete removal has not been clearly obtained. Conservative surgical management of advanced stage BOT is acceptable after extensive discussion and informed consent of a patient eagerly desiring children [42].

Surgical staging is based on careful macroscopic examination of the contralateral ovary and peritoneum. Biopsy of the contralateral ovary is not advised as it may induce adhesions without improving the detection of implants compared to visual examination of the ovary. Removal and pathological examination of any extraovarian growth is mandatory to com pletely manage the disease and detect invasive implants. Node dissection is not standard. Omentectomy, and appendectomy in mucinous tumors, is part of surgical staging and management. However, the low yield of restaging surgery in incompletely staged patients does not justify routine reoperation for the only purpose of random biopsies [43].

Recurrence rate is definitely higher after conservative surgery : 7 % of patients experience recurrence, most frequently on the contralateral ovary, after unilateral salpingo-oophorectomy. Recurrences on the affected ovary are observed in patients managed by cystectomy only, accounting for an overall recurrence rate of 23 % [41]. Repeat fertility preserving surgery is acceptable [39]. Fertility-inducing methods, including ovarian stimulation, have been shown not to impair the outcome [44]. However, most authors advise limitation of the number of stimulation cycles.

Sex cord stromal tumors

Sex cord stromal tumors may occasionally carry a malignant evolution The majority of unilateral sex cord stromal tumors can be managed conservatively in patients of reproductive age, as the survival for patients who underwent unilateral salpingo-oophorectomy is similar to patients who were managed by hysterectomy [45]. Standard staging is similar to BOT. The need for lymph node dissection is not clearly established, as the yield of lymph node dissection is quite low at the time of primary management, while late node recurrences account for a significant proportion of long-term recurrences [46]. However, radical surgery and chemotherapy are indicated in advanced stage disease.

Uterine sarcomas

It is widely accepted that uterine sarcomas requires upfront surgical management including total hysterectomy. In addition, low grade endometrial stromal sarcomas are hormone dependent, that means that bilateral oophorectomy is an essential feature of surgical management. Even though carcinosarcomas are managed as adenocarcinomas, they are assimilated to grade 3 adenocarcinomas, and therefore cannot be managed conservatively.

Exceptions to the rule are few. Low grade uterine sarcomas found after myomectomy in young patients have been managed conservatively after extensive imaging and counseling [47]. Mullerian adenosarcomas presenting as polyps may also be managed conservatively under the same restrictions.

On the other hand, preferential management of vaginal and cervical rhabmyosarcomas in children is definitely conservative, based on chemotherapy completed by surgery or radiation therapy only in those girls who do not achieve complete remission [48].

Conclusion

Preservation or intentional sacrifice of fertiliy is an essential part of counselling at the time of management of primary gynaecologic malignancy in a potentially fertile patient. Upfront radical surgery is not acceptable without informed consent and full exploration of the possibilities of fertility preserving policies. Gynecologic surgeons and gynecologic oncologists must be aware of all the available techniques. They also must be aware that upfront hysterectomy and/or bilateral salpingo-oophorectomy is faulty in adolescent or young female patients who could be safely managed using conservative techniques. Careful preoperative workup of any uterine or ovarian mass is the best prevention of unexpected findings and difficult decisions at the time of surgery. In the case of unexpected suspicious ovarian tumors in young patients, comprehensive staging, and conclusion of the operation awaiting the results of definitive pathology is standard. The limitations of frozen section as a diagnostic test between BOT and invasive ovarian tumors must be known [49].

On the other hand, conservative management seems reasonable only in patients currently or potentially desiring pregnancy. The minimal additional risk of recurrence involved by the conservation of uterus and ovary is not acceptable when pregnancy is not at stake.

Patients managed with fertility preservation deserve active follow up. Special consideration must be given to the need of annual ultrasound examination of retained ovaries (BOT or ovarian cancer patients), or Pap smears and MRI in radical trachelectomy patients. Patients with a stable partner should be advised to attempt pregnancy, considering the cumulative risk of recurrence with time. Any infertility factor must be corrected using available techniques, including ovarian stimulation which is not contraindicated even after BOT. Exceptions to the general rule are high risk conditions, including advanced germ cell tumors that may need additional chemotherapy, knowing that the confounding effect of pregnancy on the levels of markers is a follow up issue.

It is not clear whether radical surgery is indicated after completion of the desire of pregnancy. It is reasonable to advise total hysterectomy and contralateral oophorectomy in the case of invasive ovarian cancer. In other conditions, such as BOT or conservatively managed cervical cancers, the final decision will be taken with the patient, taking into consideration the risk and curability of recurrence, the accuracy of follow-upin the detection of recurrences, and psychological considerations.

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