Original Articles

In-vivo Dosimetry Systems for routine Cancer patient Dose verification

Fibromyalgia among Iraqi Breast Cancer patients

Concurrent chemo-radiotherapy in advanced nasopharyngeal cancer

Germinal testicular tumour metastatic exclusively to the spleen
New

javior
vinflunine

The 1st and only registered chemotherapy after failure of a platinum-containing regimen in advanced or metastatic TCCU

Pierre Fabre Oncology Middle East - Riad El Solh - P.O.Box 11 - 2131 Beirut - Lebanon   Fax : 00 961 1 98 98 42

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AMAAC Introduction
The Arab Medical Association Against Cancer (AMAAC) is a medical body that was established in 2001 as part of the Arab Medical Association where its main office is located in Cairo - Egypt, and it is also a continuation of the Arab Council Against Cancer that was founded in 1995. The Executive Committee of (AMAAC) is represented by two members who are named officially by the Oncology Society of each Arab Country.

The Arab Medical Association Against Cancer aims at strengthening relationships between members in different Arab Countries to raise the level of cooperation in the field of oncology on both scientific and practical aspects. Exchanging information and researches between members through Regional and Arab Conferences and Publications. Holding Public Awareness Campaigns in the field of oncology that are organized by Arab Countries. Participating in scientific activities with International Oncology Societies. Finally, encouraging researchers and doctors to meet and exchange experiences together with finding training opportunities in the field of oncology inside and outside the Arab World.

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Evaluation of the accuracy and efficiency of the in-vivo dosimetry systems for routine cancer patient dose verification

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Key words: In vivo dosimetry, Uncertainty in experimental measurements, Calibration, TLD dosimetry, Semi-conductor (diode) dosimetry.

ISSN: 2070-254X

Abstract

In external beam radiotherapy quality assurance is carried out on the individual components of the treatment chain. The patient simulating device, planning system and linear accelerators are tested regularly according to set protocols developed by national and international organizations. Even though these individual systems are tested errors that can be made in the transfer between systems. The best quality assurance for the system is at the end of the treatment planning chain. In-vivo dosimetry measures the dose to the target volume through indirect measures at the end of the treatment planning chain and is therefore the most likely method for picking up errors which might occur earlier in the chain. In vivo dosimetry, using diodes or thermoluminescent dosimeters (TLDs) is performed in many radiotherapy departments to verify the dose delivered during treatment. The limitation of this technique is that dose can only be in system readout difficulty and type of readout (TLD system and diode) as the patient dose is directly measured. Several authors have investigated the measurements was 1.3%, with a standard deviation of 2.6%. Results were normally distributed around a mean as -0.39 and 0.34 respectively. After the evaluation of in vivo dosimetry brain case as an example, the mean doses for both eyes were 1.8%, with a standard deviation of 2.7%. These results are similar to studies conducted with diodes and TLD’s. From these results we can conclude that the diode is superior to TLD, since the diode measurements can be obtained on line and allows an immediate check. Other advantages of diodes include high sensitivity, good spatial resolution, and small size, simplicity of used.

Introduction

Based on the steepness of dose-response relationships, both for local tumor control and for normal tissue complications, an accuracy requirement of 3.5% or one standard deviation (1SD) in dose delivery in radiotherapy daily clinical practice has been formulated. However, systematic errors in dose delivery for an individual patient can arise, due to: (i) incorrect linac calibration, machine output and field flatness, use of beam modification devices, (ii) incorrect treatment planning system (TPS) calculations, and/or (iii) incorrect patient setup and internal organ motion. Therefore, several international organizations recommend performing in vivo dose measurements.

Currently, the most diffused in vivo dosimetry method is based on the use of two diodes positioned at the beam central axis entrance and exit, respectively, on patient skin surface. Thus the patient midpoint dose, dmax, along the beam axis can be determined by a simple relationship and readings of calibrated diodes. However, this method requires: (i) periodic diode recalibrations; (ii) accurate positioning of the detectors on the patient for every gantry angle; (iii) corrections for temperature, angle of beam incidence and beam energy. Moreover, this method has some limitations when a patient presents asymmetric inhomogeneities along the beam central axis. Experimental and clinical evidence shows that small changes in the dose of 7% to 15% can reduce local tumor control significantly.

So the International Commission on Radiological Units and Measurements (ICRU) recommends that the dose delivered to a tumor be within 5.0% of the prescribed dose. Each of the many steps in the treatment planning and execution will contribute to the overall uncertainty in the dose delivered. Therefore, some organizations (AAPM 3, 4, ICRU 1-3) recommend that in vivo dosimetry (i.e. assess the dose directly in the patient) should be made. In vivo treatment verification includes geometrical and dosimetrical verification. The geometry, i.e. the patient anatomy and tumor location, can be obtained by using a simulator, CT or MRI. Usually the CT and/or MRI data (image fusion) are used to design the 3D treatment plan with a computer treatment planning system. However, due to setup errors and internal organ motion, the planned high dose volume may not agree with the target very well.

Researchers have been working on this, and a new real-time tracking system was introduced. The dosimetric treatment verification is also very important. Each step can contribute to the final dose uncertainty, for example, geometry errors mentioned above, errors introduced by transferring treatment data from the treatment planning system or simulator to the accelerator, errors of beam setting, etc. The final accuracy of the dose delivered can only be checked directly by means of in vivo dosimetry. The most commonly used detector types for in vivo dosimetry are diodes and TLD. In vivo dosimetry is applied to assess the delivered dose to critical organs or in complex geometries where the dose is hard to predict from the treatment. In vivo dosimetry can also be used to monitor the dose delivered in special treatment techniques like Total Skin Irradiation (TSI).
and Total Body Irradiation (TBI). Additionally, in vivo dosimetry is strongly recommended. The role of in vivo dosimetry in radiation therapy is two-fold:

1. Verify the calculations of the TPS at interfaces, i.e. close to the skin.
2. Evaluate the target dose in order to verify the treatment delivery process.

Materials and Methods

Current in-vivo dosimetry techniques are investigated to find the technique that would best suit diodes dosimetry in comparison with TLD system for external beams. These investigated techniques include entrance dose, as well as, entrance and exit dose combined techniques. The diode can be placed at the exit point. Theoretically exit measurements can check all of the parameters mentioned above for entrance measurements, plus changes in patient thickness, contour errors and problems with CT data transfer or CT miscalibration (inhomogeneities in tissue). However, there are some reasons for avoiding the exit position measurements; there are much better more direct methods than in vivo diode measurements to provide quality assurance checks for CT and treatment planning system. These quality assurance methods should be applied long before an in vivo diode measurement is made.

Test included Absolute dose:

1. Beam entrance.
2. Dose per pulse dependence.
3. Field size dependence.
4. SSD dependence.
5. Energy dependence.
6. Temperature dependence.
7. Directional dependence.
8. Sensitivity as a function of dose per pulse.

A. Diode dosimetry step

1. Determine the dose at the d_max on the central axis using a calibrated ion chamber. For convenience the phantom is usually a plastic phantom. For this work solid water phantom (PTW sided window 30cm³) was used. Usually the reference setup is a Gantry of 270 degree, SSD of 100 cm, field size of 10x10 cm² (1.00x Gy / MU at d_max).
2. With the same setup, tape the diode on the top of the phantom and also on the central axis of the beam. The internal build-up in the diode should be sufficient to absorb electron contamination, and provide electron equilibrium. Diodes should be positioned with the flat surface on the phantom and the build-up side facing the beam. Measure the diode reading for the same irradiation as in step (1).
3. The calibration factor can be obtained by finding the ratio of the readings from the ion chamber and the diode. This is done automatically by the IVD software. The Diode System used in current study is SunNuclear Model N-type.
4. Using this ratio, the diode has been calibrated to read the dose at d_max. (1.00 Gy / MU at d_max).
5. The calibration factor is verified on a regular basis, because radiation damage affects the diode sensitivity. For p-type diodes, a re-calibration will be necessary after about one Gy. Re-calibration has to be performed much more frequently for n-type diodes due to their faster decrease in sensitivity. Besides a calibration factor, determined under reference conditions, correction factors have to be applied for accurate dosimetry. They originate from the variation in sensitivity of the diode with dose per pulse, the photon energy spectrum, the temperature, and from directional effects.

B. TLD dosimetry step

A total of 40 thermoluminescent dosimeters (TLD) divided into 2 batches (one of 20 and other of 20 TLDs) were used. The thermoluminescent dosimeters are LiF:Mg,Ti (TLD 700) in the form of extruded square ribbons (about 3.1x3.1x0.9 mm³) manufactured by Harshaw. Thermoluminescent readouts were performed using a Harshaw model 6600 C automatic TLD reader with a linear heating rate of 8 C/s. Nitrogen gas was used. Readouts were taken within 25 s and temperature between 50 C and 250 C. An oven and a furnace were used for annealing procedures of the LiF:Mg,Ti. The annealing procedure used consists of two subsequent annealings: 1 h at 400 C and 2 h at 100°C. The irradiations were carried out using a Co-60 unit (MSD model Theratronics T780E) with polymethylmethacrylate serving as buildup material (5 mm thick). The reference standard system consists of a cylindrical ionization chamber (Farmer type) model TN30013 (0.6 cm³) and an electrometer model UNIDOS E T10008 both from PTW-Freiburg. The International Atomic Energy Agency code of practice was followed in the determination of absorbed dose to water. All TLDs of the 2 batches were annealed and irradiated to same dose. After readout, the procedure was repeated 3 times. A sensitivity factor was determined for each TLD. The intrinsic precision of each batch was evaluated calculating the pooled standard deviations. Supralinearity of response with dose of LiF:Mg,Ti after 1 Gy was investigated by determining the variation of TLD response with doses between 0.25 Gy and 3.5 Gy.

Results

A. Results and Discussion for Diode

The reproducibility of the sensitivity of the Diodes detector, that is, the change in reading for irradiation to known doses, was measured. The sensitivity was investigated for a range of simulated treatment fraction deliveries from 2-10 Gy/fraction, including simulated breaks for gantry motion between beams. Diodes were irradiated at 1.5cm depth in a 30x30x30cm³ water slab phantom with a standard Field size 10x10 cm² and 6MV photon beam at 100cm SSD. Six field treatment fractions of 2-10 Gy/fraction were simulated by irradiating a diode up to the fraction dose in six equal increments (to simulate irradiation from each beam). The fraction sizes simulated are given as shown in Figure1, showing response of the diode with respect to Monitor unit, and in Figure2 showing response of the diode with respect to field size and is compared to the ionization chamber and Treatment Planning System (TPS) outputs.

![Response of The Diode with respect to Monitor Unit](image-url)
Fig 2: Response of the Diodes with respect to field size in compared with ionization chamber and TPS output.

Diodes correction factor of one type of photo diode (6MV – diode) for 6 MV photon beam as function of Field size for open and different standard wedge angle as shown in Figure (3);

Fig 3: Correction factor of 6MV – diode of as a function of the field size, FS for Open field and different Wedge Angles, for entrance measurements. All data in this figure are for SSD 100 cm and ratio to ionization as standard (for standard Field size 10 X10 cm²). (Max Sq. field size for W 60 is 15 cm).

As illustrated in Figure (3), the correction factor (CF) of this diode doesn’t change much when the field size changes. From this figure, one can see that CF increases with wedge angle. This is because dose per pulse decreases with increase of wedge angle, due to the beam hardening also contributed to this effect. The field size effects are more significant than QED diode. The field size dependences for open, 15 degree and 30 degree wedged fields are almost the same, but those for 45 degree and 60 degree wedged fields are larger, up to 6%. Diodes correction factors of the 6MV IsoRad photo diode as function of SSDs for open and different standard wedge fields is shown in shown in Figure4. Also diodes correction factors dependence on the SSDs of the same type of photo diode with energy of 15MV photon beam is shown in Figure5.

Fig 4: Diode correction factors as a function of the SSD for entrance measurements. All data in this figure are for field size 10x10 cm² (6MV photon).

Fig 5: Diode correction factors as a function of the SSD for entrance measurements; (15MV photon). All data in this figure are for field size 10x10cm².

The DCF for a wedged field is generally larger than that for corresponding open field, since dose per pulse becomes lower for a wedged field. When the SSD decreases, the number of contamination electrons and scattered low energy photons from head are able to reach the sensitive part of the diode detector so the DCF ratio of ion chamber and diode reading decreases.

B. Results and Discussion for TLD

TLDs are not linear in their glow curve output as the dose increases. The dose is generally Supralinear till a saturation point is reached after which the dose tapers off as all traps are full and are therefore less likely to accept electrons (saturation region).

The useful range of the TLDs is therefore an important factor when measuring dose. TLDs suffer from fade which means that after irradiation they lose electrons in the trapped regions through random processes over time. The fading of TLD is small (5-10% per year for LiF) when used in the in-vivo dosimetry. TLDs have a similar constancy to Diodes on a measurement to measurement basis with typically 1σ being 2% for radiotherapy applications. TLDs have excellent water equivalence and are less susceptible to low energy radiation than other dosimeters in the 30 to 100 keV range. They also do not require cables for measurement which makes them ideal for mail based studies. TLDs have no dose rate or temperature dependence.

Before we use TLD batches measurements for fading has to be done (after eliminating low level signals). 5 sets of Chips (each set contains around 6 chips) wrapped into plastic foil and kept on the bolus material at 1cm depth were used under standard conditions, SSD: 100 cm; FS: 10 x 10 sqcm; Applied dose: 1 Gy and at 1 cm depth. Each set of detectors was read in different time after their exposure. Dosimeter responses versus Time delay (t) are plotted as in Figure7. Responses are in cGy.

Fig 7: Measurements for Fading (After Eliminating Low Level Signals).

TLD chips were wrapped into plastic foils and kept on the bolus material of size 1.5x30x30 cm³. SSD: 10x10 cm²; SSD: 100 cm; Depth: 1cm; 1cm bolus material
was kept on the chips. Sufficient thickness (11 cm) of bolus material and PMMA sheets were kept under the chips for backscatter. Different doses of Co\textsuperscript{60} beam were delivered on the chips at 1 cm depth and SSD: 100 cm. The TLD response with dose was plotted versus the dose for each batch. Uncorrected response against the applied dose is plotted as in Figure 8. The batch of 20 TLDs was found to have an intrinsic precision of 1.5%. The other batch of 20 TLDs was found to have an intrinsic precision of 1.6%. The thermoluminescent dosimetric system allows individual dose measurements with an expected overall uncertainty lower than 3%. This overall uncertainty is less than 5%, the action level recommended by ICRU\textsuperscript{39}.

Conclusion

TLDs and diodes are used with entrance dose or exit dose measurements to verify the entire planning process to delivery. There are obvious errors associated with exit dose measurement such as detector placement on the exit surface. Measurement error is also harder to trace back to the source of the problem when making exit dose measurements. Entrance dose is far easier to predict. For these reasons entrance dose has been the favorite choice for institutions measuring IVD system\textsuperscript{31}. Although the TLDs response presents a good reproducibility, (1.6 ± 0.7) %, on average, the uncertainty in experimental measurements and in the dose values obtained by the planning system achieves about 10%. The TLDs calibration was based on mathematical formulas developed in the AAPM Report 51.

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</table>

\textsuperscript{a} TPS based plan: Planned for 6MV beam: Standard Head phantom; Parallel Opposed Lateral Skull Fields; Open and 15 wedge beams for both Rt and Lt lateral fields, dose of 180 cGy/fraction is delivered to normalization point in 28 fractions. All dose values are in cGy.

The results of in vivo entrance dose measurements are presented in table 2 and showed a mean percentage deviation of measured dose from expected dose of 99% with a standard deviation of 2.6%. The comparison between the standard deviation of the mean percentage deviation of measured dose from expected dose (2.6%) and the estimated overall uncertainty of individual dose measurements (3%) indicates that small discrepancy between the measured and expected mean value (±1%) was due to limitations of the dosimetric system. In this pilot study no discrepancies larger than 5% between the expected dose and measured dose were detected. These data are argument with different published data\textsuperscript{7}.

Table 1: The Comparison of the measurements and percentage variation between measured dose by the Diodes, TLD, ionization chamber and calculated dose for standard field size by TPS (Eclipse Version 10.0).

<table>
<thead>
<tr>
<th>Mu</th>
<th>Diode</th>
<th>TLD</th>
<th>Ionization Chamber</th>
<th>TPS</th>
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</thead>
<tbody>
<tr>
<td>100</td>
<td>99.3</td>
<td>99.47</td>
<td>100</td>
<td>100</td>
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<tr>
<td>200</td>
<td>198.6</td>
<td>198.93</td>
<td>200</td>
<td>100</td>
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<tr>
<td>300</td>
<td>297.0</td>
<td>298.00</td>
<td>300</td>
<td>300</td>
</tr>
</tbody>
</table>

- Mean variation between measured dose with diode and TPS was found to be 0.7 % (SD 0.36)
- Mean variation between measured dose with TLD and TPS was found to be 0.53 % (SD 0.32)

Table 2: Comparison between vivo dosimetry for head phantom for different detectors like TLD, Ionization chamber (IC) and Diode system all data are compared with data for planning system.

- Mean variation between measured dose with diode and TPS was found to be 0.7 % (SD 0.36)
- Mean variation between measured dose with TLD and TPS was found to be 0.53 % (SD 0.32)

A formula proposed by (Mayles et al)\textsuperscript{7} was applied to correct for the photon beam of Supralinearity on the TLD response curve. Figure 8 show a linear region up to about 1 Gy, from which the TLD response becomes supralinear as in Figure 9, consistent with the literature \textsuperscript{7,8}. The linear is to the experimental data corrected by the formula proposed by (Mayles et al)\textsuperscript{7} showed a correlation equal to 1, showing its applicability in clinical practice.

For TLD dosimetry to be accurate, quality assurance of the system should be performed periodically. TLD accuracy depends on the annealing process. The annealing process involves heating in order to remove all trapped electrons in the crystal, so that it is primed for receiving radiation again. During annealing, the linearity of the heating and cooling, as well as heating and cooling time periods affect the sensitivity of the TLD. The TLD should therefore be annealed in the same way every time. The reader heating linearity and time should be kept constant, as should the gain on the Photomultiplier tube (PMT).

Fig 8: Linearity for TLD patches as function in different doses.

Fig 9: Supralinearity correction for TLD patches as function in different doses in cGy.

\[ y = 9E^{-10}x^2 - 3E^{-05}x + 1.0132 \]

\[ R^2 = 0.9894 \]
The diode is superior to TLD, since the diode measurements can be obtained on line and allows an immediate check. Other advantages of diodes include high sensitivity, good spatial resolution, small size, simple instrumentation, no bias voltage, ruggedness, and independence from changes in air pressure. The sensitivity relative to the ionization volume is high for a semi-conductor, about 15,000 times higher than for an air ionization chamber.

The average energy required to produce an e-hole pair in silicon is only 3.5eV compared with 34eV in air. The sensitive volume can thus be small, and hence the diode detector has high spatial resolution. However, there are many factors that can affect the response of the diode to radiation, and diodes are different from one to another, even from the same batch, same model and same manufacturer. So the commissioning or characterization of every diode individually is necessary for accurate dosimetry.

Radiation damage induces recombination centers in the crystal lattice resulting in a greater chance of recombination of charges thereby reducing the resulting current. Sensitivity therefore is reduced with dose. At higher dose rates recombination centre become “occupied” this means that there is less recombination and that more current flow an over-response will therefore become apparent with high instantaneous dose rate. This effect is more pronounced in n-type diodes than in p-type diodes.

Diodes have a proven track record for giving in-vivo dose with a low intrinsic error. IVD measurement error for diodes and TLDs is similar to diodes that have an intrinsic error of 2.0% and TLD about 4.9%. Another factor influencing choice of dosimeter is man-hours per readout. TLDs require the greatest amount of time per readout, while Diodes require shorter times, as preparation of these detectors consists of placing detector on the patient and pressing a button once the initial calibration of the relevant factors has been made.

Acknowledgments

All the authors thank the anonymous reviewers for their helpful comments on the original manuscript. This study was supported by grants from Al-Hosain Hospital, Faculty of Medicine, Al Azhar University and Tanta University.

References

The importance of radiation optimization using CT-planning for supraclavicular irradiation in breast cancer patients

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Key words: Breast cancer, CT planning, Supraclavicular volume irradiation.

ISSN: 2070-254X

Abstract

Introduction: For breast cancer patients, routine prescription of the dose to supraclavicular (SC) region at depth of 2.5-3 cm may underdose these regions due to differences in the depth of SC and axillary lymph nodes (AXLI-III).

Aim: to determine whether radiation optimization using CT-planning should be used for SC irradiation for breast cancer or routine prescription of the dose to 2.5-3cm achieves adequate coverage for SC and AXLI-III lymph nodes for all patients.

Methods: Ten breast cancer patients with post mastectomy radiation that included a SC field were selected. The planning target volume (PTV) of the chest wall, SC region, AXLI-III, contra-lateral breast (CB), heart and both lungs were contoured. Three plans were generated for each patient by prescribing the dose at 2.5cm, 3cm and 5cm depth for anterior SC field. The three plans were compared and analyzed statistically. A correlation was tested between the depth of the SC and of AXLI-III lymph nodes, their minimum dose, D95%, dose inhomogeneity & body maximum dose.

Results: Significant improvement in different target volumes coverage when the dose is prescribed to 3 or 5cm compared with 2.5cm. There is a significant positive relationship between the depth of SC and AXLI-III lymph nodes. A correlation was found between depth of different target volumes and its min dose, D95, dose inhomogeneity & body maximum dose.

Conclusion: CT simulation and generation of optimized treatment plan for each patient should be the standard way for radiation treatments of SC and AXLI-III lymph nodes in breast cancer patients.

I declare that there is no conflict of interest with any financial organization regarding the material in this manuscript

Introduction

Breast cancer is the most common malignancy among women. Breast-radical or conservative surgery followed by radiotherapy is a major choice for breast cancer treatment. Post mastectomy radiotherapy routinely includes two tangential fields to irradiate the chest wall. If AXLI-III lymph nodes are positive, SC region is irradiated using a direct anterior 6 MV photon field. The dose of 50Gy in 25 fractions is commonly prescribed to the center of PTV for tangential fields and to 2.5-3 cm depth for anterior SC field. The anatomical locations of the SC and AXLI-III beds vary according to patient’s position and body built; they are deeper for those who are thicker or heavier. Because of the more lateral position of AXLI/II lymph nodes, they have a much deeper location. Prescription of dose to a standard depth of 2.5-3 cm does not take into account the fore mentioned difference and so the dose may not properly cover the target nodal areas in all patients.

The variation in lymph nodes depth needs CT simulation to accurately define the target volumes and normal tissues based on anatomical features of individual patient. CT customized radiation treatment planning is also needed to evaluate the dose distribution and to improve the target coverage, dose homogeneity and conformity within SC and AXLI-III beds. If they are not properly covered when the dose is prescribed to 2.5-3cm, the plan can be modified by using a posterior axillary boost field or by prescribing the dose to a deeper depth which can vary depending on the dose distribution in the target volumes and the dose to adjacent critical structures and the maximum body dose.

Aim

To determine whether radiation optimization using CT-planning should be used for SC irradiation for breast cancer or routine prescription of the dose at 2.5-3 cm achieves adequate coverage for SC and AXLI-III lymph nodes for all patients.

Material and methods

CT simulation was performed for ten post-mastectomy breast cancer patients with the patient supine in breast board with the ipsilateral arm above the head. The CT data were transferred to Precise Elekta treatment planning system at the Clinical Oncology and Nuclear Medicine department, Alexandria University Hospital, from January 2011 to March 2012.

The PTV of the chest wall and SC region were contoured according to the breast...
cancer atlas for radiation therapy planning consensus definitions of the Radiation Therapy Oncology Group (RTOG) \( ^{14} \). Organs at risk (OARs) including contralateral breast, heart and both lungs were also contoured. The maximum depth of AXLI-III and SC region was measured vertically from the skin surface as Bentel et al. did in their work.

3DCRT plans were generated using Precise Elekta treatment planning system. Optimized plans were carried out using medial & lateral wedged tangential photon fields and anterior SC field. The matching between the tangential and SC fields was adjusted. SC field extended superiorly to thyroid cartilage, inferiorly to clavicular head, mediially to trachea, posterolaterally to anterior scalene muscle and posteromedially to carotid artery. To optimize coverage of the target volumes, to reduce the dose to the lung and heart and to avoid CB irradiation; beam angles, wedge angles, and beam weighting were adjusted. For tangential fields, gantry angles ranged from 30° to 319° & 120° to 146° for the medial fields and the lateral fields respectively. Collimator and couch rotation of 8°-30° & 6°-28° respectively was done. Wedge angles of 10°, 15° & 35° were used as needed. For SC field, gantry angle of 341°-353° with 1°-2° collimation rotation and 90° couch rotation were used. Multi-leaf collimator (MLC) was used to shield ipsilateral humeral head. A tissue equivalent bolus of 1-1.5 cm thickness was used in tangential and supraclavicular fields to improve target coverage in build up region.

A dose of 50 Gy in 25 fractions was prescribed to the center of the PTV for tangential fields and to 2.5, 3 and 5cm depth for anterior SC field. Different dose prescription points of SC field generated three plans for each patient. For each plan, the added dose plan function was used to check the dose coverage of the tangential and SC fields. The target coverage, dose inhomogeneity, hot spot of different target volumes and maximum body dose of the three plans were compared. Target coverage was compared using minimum dose & D95% of PTV, SC and axillary level I-III lymph nodes. Hot spot was compared using maximum dose, and Dmin of the target volumes. Dose homogeneity was calculated as the ratio of Dsys/Dsys.

This study had approval of Institutional Review Board as a retrospective one in which confidentially of records was considered.

Statistical Analysis

DVPs for the three plans were listed and analyzed statistically using Wilcoxon signed Rank test of SPSS (version 18). A P value of less than 0.05 was taken as statistically significant. A correlation was tested between the depth of the SC and the depth of AXLI-III. The differences between the depth of SC and the depth of each axillary lymph node level (I-III) were calculated and correlated to each other. A correlation was tested between the maximum depth of different target volumes and their min dose, Dsys, dose inhomogeneity and body maximum dose.

Results

Figure 1 shows an example of the contours of SC and AXLI-III nodal beds. The maximum depth of SC lymph nodes ranged from 4.5 cm to 8 cm (mean, 6cm). The depth of AXLI-III lymph nodes ranged from 5.5cm to 9.5cm, 4cm to 10cm and 4 to 9.5cm (mean, 7cm, 6cm & 6cm) respectively.

SC coverage was adequate when the dose prescribed to 2.5cm depth for one patient, to 3cm for 5 patients and to 5cm for 4 patients. AXLI coverage was adequate when the dose prescribed to 2.5cm depth for 5 patients, to 3cm for 3 patients and to 5cm for 2 patients. AXLI II & AXLI III coverage was adequate when the dose was prescribed to 3cm for 6 patients and to 5cm for 4 patients.

Table I shows the comparison of DVPs of SC and AXLI-LIII lymph nodes irradiated by three different dose prescription methods. The comparison was based on target coverage, hot spot and dose inhomogeneity within the target and the body maximum dose. There is a statistically significant increase in most DVPs for different target volumes when the dose is prescribed to a point deeper than 2.5cm (3cm & 5cm).

The hot spot within different target volumes was evaluated by maximum point dose and Dsys. The average of the maximum dose within SC, AXLI I, AXLI II and AXLI III when the dose prescribed to 3cm was 111%, 105.5%, 104% and 107.5%. It increased to 122%, 107.5%, 108% and 115% respectively when the dose was prescribed to 5cm depth. The average of Dsys of different target volumes was 107%, 102%, 102% and 104% when the dose prescribed to 3cm and 118%, 104%, 105% and 112% when the dose prescribed to 5cm; removing the bolus reduced the hot spot (for 5cm depth).

The average of dose inhomogeneity within SC, AXLI I-III was comparable for the three prescription points except for inhomogeneity within AXLI II which was significantly lower when the dose prescribed to 3cm than to 2.5cm (table 1).

The average of body max dose was 118% (range 108%-126%) for 2.5cm prescription point, 121% (range, 113%-131%) for 3cm and 132% (range, 122%-148%) for 5cm prescription point.

As shown in figure 3, there is a significant positive linear relationship between the depth of SC and the depth of level II & III lymph nodes (R=0.77 and 0.96).

The differences between the depth of SC and the depth of AXLI-I-III nodes were calculated, its average was 0.75cm, 0.2cm & 0.05 cm respectively. The AXLI I, II and III were deeper than the SC in 7, 4 and 2 patients respectively; however these differences were not statistically significant (P=0.12, 0.887 & 0.915). The differences in the minimum dose and Dsys between that of SC lymph nodes and that of AXLI, AXLI II & AXLI III were calculated SC min dose was 5% higher than that of AXLI and 4% and 2.5% lower than that of AXLI II and AXLI III. SC Dsys was lower than that of AXLI I-III lymph nodes by 1.5, 2.3 and 1.1 respectively. However these differences in min and Dsys were not significant (P=0.859, 0.168, 0.257, 0.476, 0.308 & 0.528).

To find how the variation in depth of different target volumes affects the dose distribution and so the depth of prescription point, a correlation was done between the depth of different target volumes and its min dose, Dsys, dose inhomogeneity and body max dose.

As shown in figure 4 there is a negative correlation between the depth of SC, AXLI, LII & LIII and Dsys of each (R= -0.80, -0.57, -0.85 & -0.78) (R2= 0.65, 0.33, 0.72 & 0.61), however this correlation is not significant between depth of AX LI and Dsys (P=0.005, 0.08, 0.002, 0.007 respectively). Also there is a significant negative correlation between the depth of SC, AX II & III and min
dose of each ($R= -0.65,-0.908, & -0.91$) ($R^2= 0.42, 0.82 & 0.83$) ($P=0.04, <0.001 & <0.001$). (Figure 5)

There was a positive correlation between the depth of SC, AXLI, LII and dose inhomogeneity within corresponding target ($R=0.77, 0.54 & 0.70$) ($R^2=0.59, 0.30 & 0.49$), however this correlation was not significant for AXLI ($P=0.009, 0.104, 0.02$).

There was a week positive correlation between the depth of SC, AX LI & LIII and body max dose ($R=0.60, 0.49 & 0.61$) ($R^2= 0.36, 0.24 & 0.37$), however this correlation was not significant ($P=0.06, 0.159 & 0.06$ respectively).

Fig 1: (a) Axial CT from CT simulation showing the supraclavicular nodes outlined in red and AX LIII nodes in blue (b) Axial CT showing AXLI outlined in yellow & LII nodes in green. 95% isodose line displayed in blue covers SC and LI-III lymph nodes.

Fig 2: Dose volume histograms in % for SC lymph nodes in red, AX LI in yellow, AX LII in green and AX LIII lymph nodes in blue for a typical case of supraclavicular irradiation for breast cancer. It shows that 95% of their volumes covered by ≥ 95 % of the dose.
Table 1: Comparison of target volume DVPs irradiated by three different dose prescription points (2.5cm, 3cm & 5cm) in postoperative supraclavicular radiation therapy for breast cancer. P values for the difference between plans are also shown.

<table>
<thead>
<tr>
<th>DVPs</th>
<th>2.5 cm</th>
<th>3cm</th>
<th>5cm</th>
<th>P (2.5, 3cm)</th>
<th>P (2.5, 5cm)</th>
<th>P (3, 5cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC</td>
<td>Min</td>
<td>81 (75-89)</td>
<td>85.5 (78-94)</td>
<td>92 (79-107)</td>
<td>0.008</td>
<td>0.005</td>
</tr>
<tr>
<td>Max</td>
<td>107 (101-111)</td>
<td>111 (103-119)</td>
<td>122 (104-138)</td>
<td>0.012</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>D_{sys}</td>
<td>88 (80-95)</td>
<td>92 (85-98)</td>
<td>100.5 (83-122)</td>
<td>0.007</td>
<td>0.007</td>
<td>0.011</td>
</tr>
<tr>
<td>D_{sys}</td>
<td>104 (100-108)</td>
<td>107 (100-112)</td>
<td>118 (101-132)</td>
<td>0.016</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Dose inhomogeneity</td>
<td>1.18</td>
<td>1.17</td>
<td>1.18</td>
<td>0.859</td>
<td>0.878</td>
<td>0.445</td>
</tr>
<tr>
<td>AXI</td>
<td>Min</td>
<td>77 (20-97)</td>
<td>79.5 (21-98)</td>
<td>82 (20-101)</td>
<td>0.011</td>
<td>0.011</td>
</tr>
<tr>
<td>Max</td>
<td>103 (94-110)</td>
<td>105.5 (96-114)</td>
<td>107.5 (95-126)</td>
<td>0.006</td>
<td>0.007</td>
<td>0.232</td>
</tr>
<tr>
<td>D_{sys}</td>
<td>90 (73-99)</td>
<td>92 (80-100)</td>
<td>94 (80-108)</td>
<td>0.017</td>
<td>0.008</td>
<td>0.050</td>
</tr>
<tr>
<td>D_{sys}</td>
<td>101(90-108)</td>
<td>102(92-110)</td>
<td>104(92-119)</td>
<td>0.453</td>
<td>0.070</td>
<td>0.453</td>
</tr>
<tr>
<td>Dose inhomogeneity</td>
<td>1.13</td>
<td>1.12</td>
<td>1.11</td>
<td>0.285</td>
<td>0.139</td>
<td>0.445</td>
</tr>
<tr>
<td>AXII</td>
<td>Min</td>
<td>85.5 (69-96)</td>
<td>88 (74-97)</td>
<td>92.5 (74-101)</td>
<td>0.007</td>
<td>0.008</td>
</tr>
<tr>
<td>Max</td>
<td>102 (93-110)</td>
<td>104 (93-111)</td>
<td>108 (94-124)</td>
<td>0.011</td>
<td>0.008</td>
<td>0.082</td>
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<tr>
<td>D_{sys}</td>
<td>90.5 (75-99)</td>
<td>94 (80-99)</td>
<td>95 (79-108)</td>
<td>0.011</td>
<td>0.008</td>
<td>0.232</td>
</tr>
<tr>
<td>D_{sys}</td>
<td>101 (90-110)</td>
<td>102 (90-110)</td>
<td>105 (90-119)</td>
<td>0.070</td>
<td>0.453</td>
<td>0.289</td>
</tr>
<tr>
<td>Dose inhomogeneity</td>
<td>1.13</td>
<td>1.09</td>
<td>1.1</td>
<td>0.038</td>
<td>0.203</td>
<td>0.959</td>
</tr>
<tr>
<td>AXIII</td>
<td>Min</td>
<td>84 (69-91)</td>
<td>87 (71-96)</td>
<td>92 (71-104)</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>Max</td>
<td>105 (100-114)</td>
<td>107.5 (101-120)</td>
<td>115 (102-123)</td>
<td>0.075</td>
<td>0.005</td>
<td>0.009</td>
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<tr>
<td>D_{sys}</td>
<td>89 (75-97)</td>
<td>92 (78-98)</td>
<td>96 (78-108)</td>
<td>0.073</td>
<td>0.008</td>
<td>0.017</td>
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<tr>
<td>D_{sys}</td>
<td>102 (95-110)</td>
<td>104 (95-112)</td>
<td>112 (97-119)</td>
<td>0.070</td>
<td>0.002</td>
<td>0.008</td>
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<tr>
<td>Dose inhomogeneity</td>
<td>1.17</td>
<td>1.14</td>
<td>1.17</td>
<td>0.241</td>
<td>0.878</td>
<td>0.169</td>
</tr>
</tbody>
</table>

Fig 3: The graph shows that the depth of AXII & III is significantly correlated with the depth of SC nodal region.

Fig 4: The relationship of the maximum depth of SC and AXII & AXIII to its D_{sys}. This graph shows that D_{sys} is significantly correlated with the depth of the supraclavicular (SC), the axillary level II, and level III nodal region.
Discussion

For breast cancer patients; radiotherapy after radical mastectomy is a common treatment strategy. Although in most of the departments CT optimization is the standard technique for all patients, however in some departments in developing countries some patients are treated using routine prescription of the dose of SC volume to 2.5cm.

In this study, irradiation of SC fields with prescription of radiation dose to depths of 2.5 cm-3cm leads to suboptimal coverage of SC and AXL I-III, and dose inhomogeneity in a group of patients (40 %). In this group, prescription of the dose to 5cm with addition of a bolus leads to adequate coverage however; it results in an increase in the hot spots within the target volumes, dose inhomogeneity in AXLIII lymph nodes and an increase in the body maximum dose. These findings are in accordance with Liengsawangwong et al1. Our findings agree with Cavey et al who showed that using 6MV photons with routine prescription to the depth of 3 and 5 cm produced significant inadequate target coverage and dose heterogeneity. Liengsawangwong et al' overcame suboptimal coverage and hot spots by using a combination of 6MV and 18MV AP approach and individualized calculation point. Cavey et al overcame these by using AP/PA fields. In current work, we overcame these by changing the point of dose prescription of SC region to 2.5cm in 10%, 3cm in 50% and 5cm depth in 40% of the patients without using a bolus.

Comparing SC D95% with AXL-I-III, the average of SC D95% was less than that of AXL-I-III by 1.5%, 2.3% and 1.1% respectively. However these differences in D95% were not significant (P=0.779, 0.497 & 0.944). D95% of AXL-I was lower than SC in 20% of the patients by a maximum of 16% in this patient SC was shallower by 2.5cm. AXL-I D95% was higher than SC in 70% of the patients by a max of 15%, in this patient SC was deeper by 1.5cm. D95% of AXL-II was comparable in 10% of the patients. We found also that D95% of AXL-I was lower than that of SC in 40% of the patients by a maximum of 14%, in this patient SC was shallower by 3cm. D95% of AXL-II was higher compared to SC in 60% of the patients by a max of 15%, in this patient the SC and AXLIII was at same depth. D95% to AXLIII was lower than SC in 30% of the patients by a maximum of 9% in this patient the SC was shallower by 1cm. D95% of AXLIII was higher in 50% of the patients with max of 11% in this patient the SC and AXLIII was at same depth. In 20% of the patients there was no difference, in these patients SC was deeper by 1cm.

Bentel et al4 found the AX dose was 90% of the dose delivered in the SC in 90% of the patients. In these patients the difference in depth ranged from 2.4 to 4.8 cm (median, 3.0 cm). In the patient with the largest depth difference (5cm), the AX dose was 80% of the SC dose. They considered using higher beam energy and/or opposed SC and axillary fields to achieve adequate coverage for axillary lymph nodes.4

Several investigators measured the depth of the LN vertically from the surface of the skin and attributed the difference in the coverage of different target volume among patients to large variations in location and depth of the SC and AX nodes among different patients with different arm positions. 7–11

Liengsawangwong et al1 found that the mean maximum depth of SC and AXL-I-III nodal beds was 3.2 cm (range, 1.4–6.7 cm) and 3.1 cm (range, 1.7–5.8 cm) respectively. Bentel et al4 confirmed the variation in depth of SC and AX lymph nodes, in their study, the maximum depth of SC lymph nodes ranged from 2.4 to 9.5 cm (median, 4.3 cm). The depth was less than 3 cm in 4 patients (8%), 3–6 cm in 39 patients (80%) and greater than 6 cm in 6 patients (12%). The depth of the axillary lymph nodes ranged from 1.4 to 8 cm (median, 4.3 cm). The depth was less than 3 cm in 8 patients (16%), 3–6 cm in 32 patients (65%), and greater than 6 cm in 9 patients (18%). Wang et al12 found that the mean maximum depth of the treatment target of the Level II axilla was 5.7 cm (range, 4.7–7.1
and greater than 6 cm in 50%, 40% & 40% of the patients respectively. As some investigators showed the anatomical correlations between depth of SC and other nodal chains, the current study found a positive relationship between the depth of the SC and the depth of the Level I-III lymph nodes (R=0.49, 0.77 & 0.96) (R²=0.24, 0.60 & 0.93) respectively. The depth of the AXL I and III was 6cm in 20%, 30% & 20% of the patients, less than 6 cm in 30%, 30% & 40% of the patients and greater than 6 cm in 50%, 40% & 40% of the patients respectively.

As some investigators showed the anatomical correlations between depth of SC nodes and other nodal chains, the current study found a positive relationship between the depth of the SC and the depth of the Level I-III lymph nodes (P= 0.009 & <0.0001) but it was not significant between depth of AXI and depth of SC region. (P=0.147). On the other hand, Bentel et al. found no relationship between the depth of the SC and AX lymph nodes and Liengsawangwong et al. found a significant correlation between body mass index and the depth of SC and LIII (p value <0.0001).

The differences in figures of the SC and AXI-III lymph nodes compared to other investigators might be related to either position variation or variation of the direction of measurement from the skin whether vertical or with an angle. Bentel et al. found that SC depth measured at a 15° angle ranged from 2.4 to 8.6 cm (median, 4.8 cm) compared to 2.4 – 9.5 cm (median, 4.3 cm) when measured vertically. The AX node depth measured at a 15° angle ranged from 1.4 to 9.5 cm (median, 5.2 cm) compared to 1.4 to 8 cm (median,4.3 cm) when measured vertically.

We found a significant linear relationship between maximum depth of the SC and AX nodes in the SC region and min dose, D95%, and inhomogeneity within target volumes. Wang et al. found a significant correlation between V105% and the maximum depth of the target (p < 0.0001).

**Conclusion**

As the depth of nodal beds varies from patient to patient; the routine use of 2.5- 3 cm depth for irradiation of SC region and axillary lymph nodes is not optimal. CT simulation and generation of optimized treatment plan for each patient should be the standard way for radiation treatments of supraclavicular and axillary lymph nodes in breast cancer patients.

**References**

Radiation doses to heart and contralateral breast: A comparison of different left chest wall irradiation techniques

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Key words: Chest wall radiotherapy techniques, Heart and contralateral breast sparing.

ISSN: 2070-254X

Abstract

Introduction: Reduction of heart and contra-lateral breast (CB) doses is considered an important factor when selecting radiotherapy technique in left sided breast cancer patients.

Aim: To compare radiation doses received by heart and CB using three different left chest wall irradiation techniques aiming to achieve optimum technique with good target coverage and sparing of heart and CB among patients with left breast cancer treated by modified radical mastectomy according to size of CB & PTV.

Methods: CT simulation was performed for ten left sided breast cancer patients. Three techniques using different shielding (multileaf collimator (MLCs), asymmetric half-beam technique (HBB) and lead custom block) of the lungs, heart and CB were generated for tangential fields. The dose volume parameters (DVPs) of the three plans were analyzed statistically. A correlation was tested between the differences in DVPs of the plans and the volume of PTV and CB to find out which technique shows the best DVPs according to size of CB & PTV.

Results: Lead custom block shows the best heart & CB sparing. The significant correlation between the differences of the DVPs of the plans and volume of PTV and CB shows that the volume of PTV and CB help in the selection of optimum technique.

Conclusion: Volume of PTV and CB are the predictors for selection of the optimum technique. Lead custom block is the best shielding method specially in patients with small PTV and CB while MLCs could be used in patient with large CB.

I declare that there is no conflict of interest with any financial organization regarding the material in this manuscript.

Introduction

Breast cancer is one of the most common malignancies in women and is the most common cause of death among women aged between 40 and 50 years.1-2 The most common treatment modalities are either breast conserving surgery followed by adjuvant breast irradiation or mastectomy followed by adjuvant radiotherapy of the chest wall for the patients with locally advanced disease at diagnosis.3,4

Adjuvant radiotherapy of the chest wall is commonly achieved with tangential beams5-6, although adjuvant radiotherapy of the chest wall improves local control and survival in breast cancer patients after mastectomy, it is associated with a significantly increased risk of developing ipsilateral second lung cancer and cardiac morbidity and mortality in patients treated on the left side.4-7 This is because tangential beams include part of the anterior thoracic cavity, so they are affecting the organs at risk (OARs) in particular lung and heart.1 In addition, CB dose is an issue of concern in radiotherapy field. As it is exposed to leakage and scattered radiation which is influenced by wedges, blocks and the use of half beam.8,9 This might lead to significant doses of radiation to CB with an increase in CB cancer rate in patients who had radical mastectomy under the age of 45 and received a total dose of 46–54 Gy.1,7,9,10

Different radiotherapy techniques such as electrons and external photon beams using half-beam with asymmetric collimator jaw, cerrebond, lead custom block, or MLCs for shaping the target volume deliver different levels of scatter doses to heart, lungs and CB.8,10 Hence they may induce different risks of secondary cancers, pulmonary complications or cardiomyopathy, therefore, a reduction of the dose to CB, lungs and heart is considered an important factor when selecting a treatment technique.3,8,9

So every effort should be made to apply recent technical advances in the delivery of radiation therapy and to minimize the dose to heart, lungs and CB. In practice, minimizing the dose to the ipsilateral lung and heart has higher priority than minimizing the dose to the CB. Then if minimizing the dose to CB is prioritized, other treatment techniques may be considered.6,12

Aim

To compare radiation doses received by heart and CB using three different left chest wall irradiation techniques aiming to achieve optimum technique with good target coverage and sparing of heart and CB among patients with left breast cancer treated by modified radical mastectomy according to size of CB & PTV.
Methods

Ten left sided breast cancer patients who had modified radical mastectomy aged 40-63 years treated from January 2011 to March 2012 in the Clinical Oncology and Nuclear Medicine department, Alexandria University Hospital were included in this study.

CT simulation was performed in the supine position on breast board with the arms positioned above the head. The CT data were transferred to treatment planning system (Precise Elekta) where all required structures were contoured. The planning target volume (PTV) definition for the chest wall was done according to the breast cancer atlas for radiation therapy planning consensus definitions of the Radiation Therapy Oncology Group (RTOG). Supraclavicular nodes and axilla Level I-III nodes were also contoured. CB, heart and both lungs were also contoured.

All CT scans were planned, calculated with a 6 MV photon beam on a Precise Elekta linear accelerator. Optimized plans were carried out using medial & lateral wedged tangential photon fields and anterior supraclavicular field (SC). To optimize coverage of the PTV, and to reduce the dose to the lungs, heart and to avoid CB irradiation beam angles, wedge angles, and beam weighting were chosen. Gantry angles ranged from 300° to 319° for the medial fields and ranged from 120° to 146° for the lateral fields. Collimator and couch rotation of 8°-30° & 6°-28° were done. Wedge angles of 10°, 15° & 35° were used in tangential fields. For SC field, gantry angle of 341°-353° with 10°-20° collimation rotation and 90° couch rotation was used. A bolus of 1-1.5cm thickness was used in tangential and SC fields to improve the target coverage in build up region.

Then for the tangential photon fields for each patient three isocentric radiation techniques were generated using different methods for shaping the PTV and shielding of the lungs, heart and CB; a) multileaf collimator (MLCs) (Figure 1 a), b) asymmetric half-beam technique using asymmetric collimator jaw (HBB); the centre of the field is not at the centre of PTV but at the periphery of the PTV at the lung side and one jaw is used to create the field size; the other jaw is closed (Figure 1 b), and c) lead custom block. (Figure 1. c).

SC field extended superiorly to thyroid cartilage, inferiorly to clavicular head, medially to trachea, posterolaterally to anterior scalene muscle and posteromedially to carotid artery. The matching between tangential and SC field was adjusted using the couch and collimator rotation of the tangential fields and gantry rotation of SC field.

The dose of 50 Gy in 25 fractions was prescribed to the isocenter which is placed at the center of the PTV for tangential field and at 3-5cm depth for SC field. For each plan the added dose plan function was used to check the dose coverage of the tangential and SC fields.

Isodose distributions and DVHs for these techniques were generated and compared. The plans evaluation depends on the coverage of different target volumes and the sparing of the heart and CB. The coverage of target volumes was evaluated using the dose to 95% of the PTV, supraclavicular area, axilla Level I-III nodes (D20g), the sparing of the heart was assessed using the volume of the heart that receives 2.5 Gy, 5 Gy, 10 Gy, 20 Gy and 30 Gy (V2.5 Gy, V5 Gy, V10 Gy, V20 Gy, & V30 Gy), and the dose to 5% & 30% of heart volume (D5% & D30%). The dose to CB was assessed using maximum point dose to breast tissues. This study had approval of Institutional Review Board as a retrospective one in which confidentially of records was considered.

Statistical Analysis

The DVFs for the three plans for each patient were compared and analyzed statistically using excel sheet and Wilcoxon signed Rank test of SPSS (version18). A P value of less than 0.05 was taken as statistically significant. Then the differences and the percentage of the reduction in the most important DVFs between the plans were calculated. Then a correlation was tested between these differences and the volume of PTV and CB to find out if any of them affect the DVFs differences. Also to find out which technique show the best DVFs among patients according to size of CB & PTV.

Fig 1: Beam eye view for medial tangential field comparing shielding of heart (pink) & CB (green) from radiation using MLCs (A), (B) asymmetric collimator jaw and (c) a block.
Results

A. Dose distribution
By reviewing the DVPs of the three treatment plans of all patients, the followings were the results as regards the dose distribution of the target volumes and OARs including heart and CB (table 1 & figure 2 & 3).

As regard radiation dose to target volumes
For all patients the coverage of different target volumes was adequate and comparable for all plans (p values >0.05).

As regard radiation dose to organs at risk (OARs)
Table 1 shows the min and max average of DVPs among the three plans, & Table 2 summarises the differences in heart and CB DVPs among the plans that were statistically significant.

Fig 2: Isodose distributions of adding tangential and SC fields for chest wall irradiation in axial, coronal & sagittal plane. It also shows that chest wall and supraclavicular area are well covered by 95% of the dose (pink shadow).

Fig 3: Dose volume histogram parameters in % for heart in pink, & CB in blue comparing shielding using MLCs, asymmetric jaw and custom lead block (triangle curve).

Table 1: Comparison of the average of DVPs for target volumes, heart and CB for different plans. The dose is in % and the volume is in cc

<table>
<thead>
<tr>
<th>DVPs</th>
<th>Plan 1</th>
<th>Plan 2</th>
<th>Plan 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D_{5 Gy}</td>
<td>94</td>
<td>94.5</td>
<td>87</td>
</tr>
<tr>
<td>D_{30Gy}</td>
<td>11</td>
<td>15.5</td>
<td>8</td>
</tr>
<tr>
<td>V_{2Gy}</td>
<td>54</td>
<td>52</td>
<td>53</td>
</tr>
<tr>
<td>V_{5Gy}</td>
<td>28</td>
<td>27.5</td>
<td>21</td>
</tr>
<tr>
<td>V_{10Gy}</td>
<td>23</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>V_{20Gy}</td>
<td>19</td>
<td>19</td>
<td>13.5</td>
</tr>
<tr>
<td>V_{30Gy}</td>
<td>16</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>CB Max dose</td>
<td>14</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>PTV D_{95%}</td>
<td>95</td>
<td>95</td>
<td>93</td>
</tr>
<tr>
<td>SC D_{95%}</td>
<td>98</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>AXL I D_{95%}</td>
<td>93</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>AXL II D_{95%}</td>
<td>94</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>AXL III D_{95%}</td>
<td>95</td>
<td>93</td>
<td>95</td>
</tr>
</tbody>
</table>

Table 2: The differences in DVPs between the plans for heart and CB that were statistically significant.

<table>
<thead>
<tr>
<th>Heart DVPs</th>
<th>CB</th>
</tr>
</thead>
<tbody>
<tr>
<td>D_{30Gy}</td>
<td>V_{5Gy}</td>
</tr>
<tr>
<td>V_{10Gy}</td>
<td>V_{20Gy}</td>
</tr>
<tr>
<td>V_{30Gy}</td>
<td>Max dose</td>
</tr>
<tr>
<td>Differences 1 &amp; 3 P value</td>
<td>0.045</td>
</tr>
<tr>
<td>Differences 2 &amp; 3 P value</td>
<td>0.007</td>
</tr>
</tbody>
</table>

B. Correlation results
Table 3 summarises the correlation between the differences in heart & CB DVPs of the three plans from one side and the volume of the CB (ranges from 425-1156 cc (average 805cc) and volume of PTV (ranges from 257 to 1288cc (average 646cc) from other side. Table 4 shows how heart & CB DVPs differ among the plans according to the volume of CB and PTV. (+) sign indicates that the corresponding plan shows the best DVPs among the plans for the patients according to the volume of PTV and CB.

From both table we concluded that:

Comparing sparing of heart using MLCs and HBB, we found that; with smaller volume of CB, there is no difference to use MLCs (plan 1) or asymmetric HBB (plan 2) for shaping the tangential fields and sparing heart and CB (as the differences in DVPs decrease with the decrease in CB volume). On the other hand for large CB, MLCs is preferred for shaping the PTV and to spare heart and CB (this is because plan 1 shows better results than plan 2 (table 1) and as the
differences in DVPs between the plans increase with the increase in the size of CB). Regarding volume of PTV, MLCs shows best heart sparing for small PTV (the differences between two plans increase with the decrease in the size of PTV).

Comparing sparing of heart using lead block (plan 3) with using either HBB (plan 2) or MLCs (plan 1); we found that; lead block (plan 3) shows the best heart sparing when the volume of CB and PTV is small (as the differences between the plans increase with the decrease in the volume of CB & PTV). So block is the best method for shaping the tangential fields for small CB and PTV.

For small PTV and CB lead custom block should be used to reduce heart DVPs.

So for small PTV and CB lead custom block should be used to reduce heart DVPs.

So lead custom block is the best shielding method for patients with small PTV and CB as it shows the best heart and CB sparing.

Table 3: The correlation between the differences in heart and CB DVPs of the plans and the volumes of PTV and CB.

<table>
<thead>
<tr>
<th>Differences</th>
<th>Heart DVPs</th>
<th>CB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 &amp; 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CB (r)</td>
<td>-0.59</td>
<td>0.71</td>
</tr>
<tr>
<td>P value</td>
<td>0.07</td>
<td>0.022</td>
</tr>
<tr>
<td>PTV (r)</td>
<td>-0.49</td>
<td>-0.42</td>
</tr>
<tr>
<td>P value</td>
<td>0.149</td>
<td>0.228</td>
</tr>
<tr>
<td>Differences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 &amp; 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CB (r)</td>
<td>-0.68</td>
<td>-0.3</td>
</tr>
<tr>
<td>P value</td>
<td>0.029</td>
<td>0.39</td>
</tr>
<tr>
<td>PTV (r)</td>
<td>0.62</td>
<td>-0.41</td>
</tr>
<tr>
<td>P value</td>
<td>0.05</td>
<td>0.237</td>
</tr>
<tr>
<td>Differences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 &amp; 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CB (r)</td>
<td>-0.71</td>
<td>-0.64</td>
</tr>
<tr>
<td>P value</td>
<td>0.02</td>
<td>0.04</td>
</tr>
<tr>
<td>PTV (r)</td>
<td>0.68</td>
<td>-0.64</td>
</tr>
<tr>
<td>P value</td>
<td>0.03</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Table 4: Summary table showing the differences in heart DVPs between the plans and the volume of CB and PTV. (+) indicates that the corresponding plan shows the best DVPs among the plans.

<table>
<thead>
<tr>
<th>Plans</th>
<th>CB</th>
<th>PTV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>small</td>
<td>large</td>
</tr>
<tr>
<td>MLCs</td>
<td>=</td>
<td>+(heart)</td>
</tr>
<tr>
<td>1/2 BB</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>blocks</td>
<td>+(heart)</td>
<td>=</td>
</tr>
<tr>
<td>1/2 BB</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>blocks</td>
<td>+(heart)</td>
<td>+(heart) &amp; CB</td>
</tr>
</tbody>
</table>

Discussion
Breast is one of the difficult sites in treatment planning, where inhomogeneity could be higher because of the shape and size of the breast.

The choice of technique for chest wall irradiation in post-mastectomy breast cancer patients depends on patient geometry (chest wall (CW) thickness, curvature, separation, length of mastectomy scar, and breast volume), adequate target coverage and normal tissue tolerance.

Current study compared radiation doses received by heart and CB using three different left chest wall irradiation techniques.

Using MLCs or lead custom block for shaping the tangential fields showed the lowest dose to CB. On the other hand using asymmetric HBB showed the highest dose to CB. These results are against the results done by Tercilla et al8 & Charmayne et al11 & Kelly et al14 who found that the asymmetric HBB technique gives significantly lower dose than the cerrobend HBB. They attributed this to the difference between the cerrobend block transmission and the collimator transmission. Kelly also found that the use of physical wedges, cerrobend blocks or compensators increases the scatter dose to the opposite breast; therefore, protection to the CB is necessary when 3DCRT plus cerrobend is used. Our results against their work because in the current study, a piece of block was only used to cover part of lung, heart and CB present in the field, on the other hand they use the block to shield the whole length of the field (HBB) not only a part of the field as we did so the scatter was more than in our work.

On the other hand, the results of current study are in accordance with those reported by Edgardo et al1 who found that the dose to CB was reduced by 60% when a 2.5 cm lead shield was used. Because they use it as in the current study to shield part of the tangential field. They concluded that as the use of lead shield reduced the dose to OARs and therefore the risk of radiation-induced cancer, thus a 3DCRT plan with lead blocks should be used. Our results also agree with Muller-Runkel et al13 work that used lead shield for covering and protecting CB.

This study also showed that using lead custom block for shaping the tangential fields is considered the best technique for sparing heart. These results agree with the work done by Tercilla et al8 who recommended non use of HBB as it increases the dose to the OARs.

Also our results are in accordance with David et al18 who achieved lower doses to lung, heart and CB by using conformal lead blocks to shield both tangential beams compared with standard tangents.

The current study also correlated the differences in heart and CB DVPs between the plans with the volumes of the PTV and CB to find if any of both volumes affect these differences and the results of the plans and so the selection of a suitable chest wall irradiation technique (table 4). Both the volumes of PTV and CB are considered as the predictors for the selection of the optimum technique for chest wall irradiation; for patients with large CB, MLCs is preferred for shaping the target volume to spare the heart. For patients with small PTV and CB lead custom block is the best shielding method as it shows the best heart and CB sparing.
Some authors correlated the choice of technique with patient geometry (chest wall [CW] thickness, CW curvature, length of mastectomy scar, chest wall separation and breast volume), adequate target coverage and normal tissue tolerance. 3,11 Bhatnagar et al17 have studied the effect of breast size on scatter dose to CB. They found that the contribution to CB dose is strongly dependent on primary breast size of the patient.

Prabhakar et al12 correlate the breast dose heterogeneity with different breast parameters such as chest wall separation and breast volume. They found that the increase in dose inhomogeneity was correlated with increasing the target volume. Neal et al16 also correlated large-breasted women with heterogeneous dose distributions. Das et al18 correlated larger chest wall separation with the hot spot presence and he solved this by using energy higher than 6 MV.

Moody et al19 found a correlation between breast size and dose inhomogeneity which may account for the marked changes in breast appearance reported in women with large breasts.

Based on the results of this study, we recommend that lead custom block should be used in 3DCRT of the chest wall as a shielding method for heart and CB, as it provides the best sparing. We also determined that the volume of PTV and CB are the predictors for the selection of the optimum technique for chest wall irradiation. Lead custom block should be used instead of asymmetric half beam techniques and MLCs in patients with small PTV & CB volume for the best heart and CB sparing. However the limited number of the patients included in our study does not allow for determining the cutoff value for the volume of PTV & CB that could be used for optimal technique selection. So this work should be continuing in future on large patient group.

Conclusion

The volume of PTV and CB are the predictors for the selection of the optimum technique for left side chest wall irradiation. Lead custom block is the best shielding method for 3DCRT of the chest wall as it provides the best heart and CB sparing specially in patients with small PTV and CB and MLCs could be used in patient with large CB.

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The role of Docetaxel, Cisplatinum And 5-Fluorouracil induction chemotherapy followed by concurrent chemo-radiotherapy in locally advanced nasopharyngeal cancer

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Key words: Neoadjuvant TPF in Nasopharyngeal Carcinoma.

ISSN: 2070-254X

Abstract

Purpose: To evaluate Docetaxel based induction chemotherapy preceding concurrent chemoradiation in locally advanced nasopharyngeal carcinoma (LANC) determining its feasibility, efficacy (response rate and its impact on progression free survival and overall survival) and associated toxicities.

Patients and Methods: Retrospective review of LANC patients (T1,N1-3 and T2-T4,any N disease) treated with induction chemotherapy consisting of docetaxel , cisplatin , and 5-fluorouracil (TPF) followed by concurrent chemoradiation with weekly cisplatin. Response rate was correlated with overall survival (OS) and progression free survival (PFS).

Results: The study population included 48 patients. Six patients (12.5%) achieved complete response (CR) after induction chemotherapy. Patients were assessed 6-8 weeks after concurrent chemoradiation and 41 patients (85.4%) were found to have CR to all treatments. On multiple regression analysis the response achieved after completion of all treatments was significantly associated with tumor stage (P<0.001), nodal stage (P= 0.002) and treatment breaks (P<0.001). The 4year OS and PFS rates were 94.9% and 84.7%, respectively. The median OS and PFS intervals were not reached. Grade 3 mucositis developed in 25 patients (52.1%) while 3 patients (6.1%) suffered from Grade 4 mucositis during chemoradiation. There were no treatment related deaths.

Conclusion: This retrospective study confirmed the feasibility and tolerability of TPF induction chemotherapy followed by concurrent chemoradiation in LANC. Phase III trials are needed to further prove the benefit of this approach. (The international phase III trial entitled Groupe Oncologie Radiotherpie Tete et Cou (GORTEC) will answer the benefit of this approach).

Introduction

Nasopharyngeal carcinoma (NPC) has been characterized by a dissimilar epidemiology, etiology, and clinical course compared with other head and neck squamous cell carcinomas due to its notorious predilection for distant metastases. Southern China and Southeast Asia have the highest incidence, while it is an uncommon tumor in the Western countries, with an annual incidence of less than 1 per 105 in whites.1 4

Chemoradiation has been established as the standard treatment of locally advanced NPC based on the results of randomized trials and a recent meta analysis which demonstrate a clear benefit of chemotherapy and radiotherapy in comparison to radiotherapy alone.5-11 Initially a meta analysis of two phase III studies showed 5.4% improvement in a disease specific survival rate with the use of induction chemotherapy but failed to show an improvement in the overall survival (OS).7 Moreover, another meta analysis of 8 trials evaluating the role of chemotherapy as an adjunct to radiotherapy found a significant benefit for both OS (6% at 5 years)and progression free survival (PFS) (10% at 5 years).9 However, the paramount method of incorporation of chemotherapy to chemoradiotherapy is still indeterminate. The Intergroup-0099 was the first randomized trial to compare concurrent chemoradiotherapy (cisplatin 100 mg/m2 every 21 days) for three cycles followed by adjuvant cisplatin and 5-fluorouracil with radiotherapy (RT) alone. The chemoradiation arm resulted in a clear and statistically significant improvement of OS, disease-free-survival (DFS), locoregional failure rate and time to distant metastases. However, low compliance was reported in the chemoradiation arm, with only 55% undergoing adjuvant treatment and a particularly poor survival observed in the RT alone arm. Moreover, the incidence of locoregional and distant metastases were found to be very high.8 Thus, to overcome these problems, induction chemotherapy has been an attractive strategy for many researchers. Several phases II studies have shown that this strategy might obtain good results on a limited but poor prognostic population.12-17

In the last five years, taxanes have been employed in several phase II and III clinical trials in patients with squamous cell carcinoma of the head and neck, showing a good activity and manageable toxicity profile.18 On the basis of encouraging results with TPF induction chemotherapy in advanced NPC, this study was performed to determine the feasibility and safety of induction chemotherapy with TPF followed by concurrent chemoradiation (CCRT) for locoregionally advanced NPC. The primary endpoint was the objective response rate, and the secondary endpoints included PFS and OS.
Patients and Methods

We retrospectively reviewed charts of locally advanced nasopharyngeal carcinoma (LANC) patients treated between January 2007 and December 2011. The study protocol was approved by the ethical committee in our institute. Forty eight patients with (LANC) (T1, N1-3 and T2-T4, any N disease) who received induction TPF chemotherapy followed by cisplatin based concurrent chemoradiation were selected. All patients signed informed consent. Baseline imaging included computed tomography (CT) and/or Magnetic Resonance Imaging (MRI) and patients were staged according to American Joint Committee on Cancer Stage Classification System 6th Edition.

Patients were treated with 3 cycles of induction TPF (docetaxel 75 mg/m² and cisplatin 75 mg/m² on day 1, and continuous infusion of 5-fluorouracil 750 mg/m²/day for five consecutive days) repeated every 21 days. During radiation treatment, cisplatin was administered either as 40 mg/m² weekly or 100 mg/m² every 3 weeks. Patients were evaluated by complete physical and laboratory investigations including complete blood count and serum chemistries before each cycle of induction chemotherapy. At the end of induction chemotherapy, the response was assessed with imaging (CT or MRI) and clinical examination.

Some patients received 3-dimensional conformal radiotherapy (3DCRT). A total dose of 70 Gy was administered in daily fractions of 2 Gy per fraction, 5 days a week for the primary tumor and involved lymph nodes (Pre-chemotherapy volumes). The rest of nasopharynx, the oropharynx, posterior two thirds of the anterior maxillary sinuses and non involved upper neck nodes received 60 Gy. The lower non involved neck nodes received 54 Gy. Intensity modulated radiation therapy (IMRT) using simultaneous integrated boost (SIB) was also used in treating patients. Three planning target volumes (PTVs) were created: PTV 70 Gy to the primary tumor and involved nodes, PTV 60 Gy to rest of nasopharynx, the oropharynx, posterior two thirds of the anterior maxillary sinuses and to non involved upper neck nodes and finally PTV54 Gy to lower non involved neck nodes. Patient care before, during and after radiotherapy includes maintaining good oral hygiene, dental care, adequate nutritional support and analgesia. Patients were assessed weekly during radiotherapy and toxicity was recorded. Toxicity was graded according to version 3.0 of the National Cancer Institute-Common Toxicity Criteria (NCI-CTC).29 Patients were evaluated by physical examination and complete blood count weekly and by serum chemistries every 3 weeks until the end of chemoradiotherapy. Post treatment baseline imaging was done by CT and/or MRI at 6-8 weeks after completion of the therapy. Tumor response was assessed according to response evaluation criteria in solid tumors (RECIST).20 Late radiation toxicity was assessed according to the “RTOG/European Organisation for Research and Treatment of Cancer Late Radiation Morbidity Scoring Schema”.21 Each patient was assessed at 3, 6, and 12 months during the first year, then every 6 months for 5 years, and then annually.

Statistical Analysis

The primary endpoint was the response rate, and secondary endpoints were the median PFS and OS.

Survivals were calculated using the Kaplan Meier analysis. Overall Survival (OS) was measured from the first day of diagnosis until death or the last clinical visit. Progression Free Survival (PFS) was defined as the time from the first day of diagnosis until the date of loco-regional failure or distant failure. Analyses were performed by SPSS 13.0 package program.

Results

From January 2007 to December 2011, 48 patients received induction chemotherapy (DCF) followed by radiation treatment and concomitant cisplatin. The median age was 46 (range 18–68) years and median follow up was 39 (range 14–58) months for all patients. Table 1 summarizes the baseline patients and disease characteristics.

### Table 1: Patients and Disease Characteristics at Baseline (N=48)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age , years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Range</td>
<td>46</td>
<td>18-68</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36</td>
<td>75%</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Pathological Subtype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non keratinizing</td>
<td>13</td>
<td>27.1%</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>30</td>
<td>62.5%</td>
</tr>
<tr>
<td>Basaloid</td>
<td>5</td>
<td>10.4%</td>
</tr>
<tr>
<td><strong>T stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>4</td>
<td>8.3%</td>
</tr>
<tr>
<td>T2</td>
<td>17</td>
<td>35.4%</td>
</tr>
<tr>
<td>T3</td>
<td>19</td>
<td>39.6%</td>
</tr>
<tr>
<td>T4a,b</td>
<td>8</td>
<td>16.7%</td>
</tr>
<tr>
<td><strong>N stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>18</td>
<td>37.5%</td>
</tr>
<tr>
<td>N1</td>
<td>25</td>
<td>52.1%</td>
</tr>
<tr>
<td>N2</td>
<td>5</td>
<td>10.4%</td>
</tr>
<tr>
<td><strong>Stage group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>13</td>
<td>27.1%</td>
</tr>
<tr>
<td>III</td>
<td>27</td>
<td>56.3%</td>
</tr>
<tr>
<td>IVA,B</td>
<td>8</td>
<td>16.7%</td>
</tr>
</tbody>
</table>

Forty three patients (89.6%) received all 3 cycles of induction chemotherapy. While five patients received only 2 cycles of induction chemotherapy due to development of grade 3 nausea and vomiting in 3 patients and febrile neutropenia in two patients. Fourteen patients (29.2%) received standard 3 weekly concomitant cisplatin (100 mg/m²) treatment. Five patients of them (35.7%) completed 3 cycles of 3 weekly cisplatin with 25% dose reduction in 2 patients due to grade 3 mucositis, dermatitis and neutropenia, while seven patients (50%) tolerated 2 cycles and only two patients (14.3%) had 1 cycle. The other 34 patients (70.8%) received concomitant cisplatin (40 mg/m²) on weekly basis. Of these patients, two patients (5.9%) received 3 weeks of weekly cisplatin, four patients (11.8%) had 4 weeks, 12 patients (35%) had 5 weeks, and 16 patients (47.1%) had 6 weeks. A 20% dose reduction of the dose of cisplatin was necessary to continue the 6 cycles in 5 patients due to development of grade 3 side effects. Table 2 summarizes the Chemotherapy Delivery.
Table 2: Chemotherapy Delivery

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant</td>
<td></td>
</tr>
<tr>
<td>2 cycles</td>
<td>5 (10.4%)</td>
</tr>
<tr>
<td>3 cycles</td>
<td>43 (89.6%)</td>
</tr>
<tr>
<td>Concurrent</td>
<td></td>
</tr>
<tr>
<td>3Weekly cisplatin 100mg/m2</td>
<td>14 (29.2%)</td>
</tr>
<tr>
<td>Weekly cisplatin 40mg/m2</td>
<td>34 (70.8%)</td>
</tr>
</tbody>
</table>

Patients were assessed after induction chemotherapy by physical examination and imaging with CT or MRI. Six patients (12.5%) achieved complete response while 37 patients (77.1%) developed partial response and 5 patients (10.4%) had stable disease.

As regards to radiation technique 17 patients (35.4%) received radiotherapy using IMRT with simultaneous integrated boost, while 31 patients (64.6%) were treated using 3-D conformal radiotherapy (3D-CRT). Radiation therapy dose delivered ranged from 66 to 70 Gy.

All patients were assessed 6-8 weeks after definitive concurrent chemoradiation with radiologic imaging (CT and/or MRI). 41 patients (85.4%) achieved CR and 7 patients (14.6%) had PR after completion of all treatments. On multiple linear regression analysis the response achieved at the end of definitive concurrent chemoradiation was found to significantly associated with Tumor stage (P<0.001), Nodal stage (P= 0.002), and treatment breaks (P<0.001). Table 3 illustrates the association between different clinicopathological factors and response.

Table 3. Association between Response and other Clinicopathological Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Patients no CR</th>
<th>PR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31 (64.5%)</td>
<td>5 (10.4%)</td>
<td>0.889</td>
</tr>
<tr>
<td>Female</td>
<td>10 (20.8%)</td>
<td>2 (4.1%)</td>
<td></td>
</tr>
<tr>
<td>Pathological subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non keratinizing</td>
<td>13 (27%)</td>
<td>4 (8.3%)</td>
<td>0.133</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>24 (50%)</td>
<td>2 (4.1%)</td>
<td></td>
</tr>
<tr>
<td>Basaloid</td>
<td>4 (8.3%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Baseline T stage</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T1</td>
<td>4 (8.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>17 (35.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>19 (39.5%)</td>
<td>2 (4.1%)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>8 (16.6%)</td>
<td>5 (10.4%)</td>
<td></td>
</tr>
<tr>
<td>Baseline N stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>18 (37.5%)</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>N2</td>
<td>22 (45.8%)</td>
<td>5 (10.4%)</td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>1 (2%)</td>
<td>2 (4.1%)</td>
<td></td>
</tr>
<tr>
<td>Radiation Technique</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3DCRT</td>
<td>26 (54.1%)</td>
<td>3 (6%)</td>
<td>0.412</td>
</tr>
<tr>
<td>IMRT</td>
<td>15 (31.2%)</td>
<td>4 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Concurrent Chemoradiation Break</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 7 Days</td>
<td>38 (79.1%)</td>
<td>3 (6%)</td>
<td></td>
</tr>
<tr>
<td>&gt;7 Days</td>
<td>2 (4.1%)</td>
<td>5 (10.4%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

At a median follow up time of 29 months, there were nine relapsed patients. Two patients had local relapse only, four patients had distant metastases and three patients had both local and distant metastases. The three patients who had both local and distant relapse died due to their disease. The 4 year OS and PFS rates were 85% and 74.2%, respectively (Fig. 1, 2). The median PFS and OS intervals were not reached.
Induction chemotherapy was well tolerated with only five patients (10%) received only 2 induction cycles because of grade 3 toxicities: two (4%) of them developed grade 3 neutropenia while three (6%) of them had G3 nausea and vomiting.

The most frequent acute toxicity encountered during chemoradiation was mucositis as 25 patients (52.1%) developed Grade 3 while only 3 patients (6.1%) suffered from Grade 4 mucositis which necessitated hospitalization and discontinuation of treatment for 7-10 days.

Before the concurrent chemoradiation patients were advised to have gastestomy tube inserted under ultrasound guidance for maintaining proper feeding during the radiation. Ten patients (20%) did not agree to have the procedure done upfront but four of them accepted the procedure when they developed grade 3 mucositis, dysphagia and weight loss by the end of the third week of concurrent chemoradiation. Consequently, ten patients (20%) developed grade 3 weight loss (10-19.9 Kg) while two patients (4.1%) had grade 4 weight loss (>20 kg) during the concurrent chemoradiation phase (Table 4). Interestingly, it was noticed that the two patients who developed grade 4 and eight of the patients who had grade3 weight loss were initially those patients who refused the insertion of gastestomy upfront prior the concurrent chemoradiation phase. Moreover, grade 3 anemia, neutropenia and thrombocytopenia were encountered in 2%, 6%, and 4%, respectively. No treatment related deaths occurred.

Table 4: Treatment related grade 3&4 acute toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Induction chemotherapy No. of patients (%)</th>
<th>Chemoradiation No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Mucositis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>3 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Discussion

The incidence of locoregional or distant metastasis for locoregionally advanced NPC remains in the order of more than 40%, despite concomitant chemoradiotherapy. These disappointing results might be explained by the poor patient tolerance of adjuvant chemotherapy after chemoradiation due to side effects. Moreover, in patients who were able to tolerate adjuvant chemotherapy, penetration of chemotherapeutic drugs into the tumor tissue might be very limited due to the disruption of native blood vessels after the radiation treatment. Moreover, the dose of concomitant chemotherapy used during radiation could not be sufficient for the control of systemic disease. More interestingly, the high objective response rate usually observed and the good tolerance in treatment-naïve patients is in favor of induction chemotherapy compared to adjuvant chemotherapy. Consequently, the role of neoadjuvant chemotherapy followed by concurrent chemo-radiotherapy (CCRT) is a matter of outstanding interest.23,24

In this retrospective study, we explored the role of induction chemotherapy with TPF in locally advanced NPC. Our patient median age was 46 (range 18–68) years. 56% and 17% of patients had stage III and stage IV A,B respectively. Similarly, in Ekenel et al study the median age was 49 (range 18–68) years and 63% and 13% of patients had stage III and IV respectively.11 Moreover, the use of induction TPF resulted in 89.6% objective response as 12.5% of patients achieved complete response while 77.1% attained partial response, respectively. After CCRT, the objective response rate was 100% (CR in 85.4% and PR in 14.6%). These results compare favorably with previous reports on induction chemotherapy. In the study by Bae et al the objective response rate was 97% after induction chemotherapy (CR in 15.2% and PR in 81.8%) and 97% (CR in 69.7% and PR in 27%) after CCRT.14 Similarly, Ekenel et al reported that the objective responses were 87% with 12% CR after induction and 100% with 95% CR after chemoradiotherapy, respectively, in all patients.17

As regards to survival data, The 4 year OS and PFS rates were 85% and 74.2%, respectively. The median PFS and OS intervals were not reached. When survival data were reviewed, comparable survival rates have been published in the literature. Bae et al. treated 32 locally advanced NPC patients with docetaxel, cisplatin and infusional 5 FU followed by chemoradiotherapy. Three year PFS and OS rates were 75% and 86% respectively.18 Also, in a Hellenic Cooperative Oncology Group Study, the cisplatin, epirubicin and paclitaxel combination chemotherapy was given to 47 patients. The one year survival rate was 93.5% and the 2 year PFS rate was 62%.25 Ekenel et al reported that the use of induction chemotherapy resulted in 94.9% and 84.7% of 3 year OS and PFS rates, respectively.11 Additionally, Hiu et al. showed a clear OS benefit with this induction strategy. In the induction chemotherapy arm the 3 year PFS and OS rates were 88.2% and 94.1%, respectively.26 More recently, Kong L et al. reported the results of phase II trial on induction TPF followed by chemoradiotherapy using weekly cisplatin. The overall response rate three months after RT was 90.2% and the 1-year overall survival was 100%.27

As regards to treatment related toxicities, induction chemotherapy was well tolerated. Five patients (10%) received only 2 induction cycles because of Grade 3 toxicities, two (4%) of them developed Grade 3 neutropenia while three (6%) of them had Grade 3 nausea and vomiting. In general the acute toxicity was mild and reversible in most cases. The increase in acute toxicity during induction chemotherapy was mainly associated with neutropenia, which was uncomplicated and manageable. The most frequent acute toxicity encountered during chemoradiation was mucositis as 25 patients (52.1%) developed Grade 3 while 3 patients (6.1%) suffered from Grade 4 mucositis which necessitated hospitalization and discontinuation of treatment for 7–10 days. Moreover, ten patients (20%) developed Grade 3 weight loss (10–19.9 Kg) while two patients (4.1%) had Grade 4 weight loss >20 Kg during the concurrent chemoradiation phase. Similarly, Bae et al reported that febrile neutropenia (9.1%), and nausea (9.1%) were the most severe toxicities (Grade 3–4) during induction chemotherapy, and mucositis (39.4%), fatigue (15.2%), and nausea (9.1%) were the most common toxicities (Grade 3–4) during chemoradiation. Moreover, the RT was interrupted in 12 patients (36%); of these 12 patients, 11 had Grade 3 or 4 mucositis and 1 patient had disease progression. However, the chemoradiation was continued and completed in these patients after 1 week of rest.26 Additionally, Ekenel et al reported that TC induction chemotherapy followed by CCRT was very well tolerated with a 10% rate of Grade 3/4 hematologic toxicity. There were no treatment related deaths.26 Moreover, Kong L et al reported that the rate of Grade 3/4 myelosuppression during TPF induction was 55.9% and the corresponding rate during concomitant chemotherapy and RT was 11.9%.27 An Egyptian study enrolled thirty-six patients who were treated with three cycles of induction paclitaxel and cisplatin, followed by CCRT using cisplatin. The main toxicity encountered was Grade 3/4 neutropenia which was observed in 25% of patients.26 Induction chemotherapy has evolving role in the management of locally advanced NPC. With manageable toxicities and no treatment related deaths.

Conclusion: This retrospective study confirmed the feasibility and tolerability of the TPF induction chemotherapy followed by cisplatin based concurrent chemoradiation in the management of locally advanced NPC. The international phase III trial entitled Groupe Oncologique Radiotherapie Tete et Cou (GORTEC III) will answer the benefit of this practice in near future.

References

Fibromyalgia Syndrome among Iraqi Female Patients with Breast Cancer

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Key words: Fibromyalgia syndrome, Breast cancer, Solid tumors.

ISSN: 2070-254X

Abstract

Objective: To assess the prevalence of fibromyalgia syndrome (FMS) among Iraqi Female patients with Breast Cancer (BCA).

Patients and Methods: One hundred Iraqi Breast Cancer Female patients and 100 healthy controls were included in this study. Full history was taken and complete clinical examination was done for all patients. Disease characteristics [age, sex, onset of diagnosis of BCA, body mass index (BMI), waist circumference, social history and drug history] were documented. Laboratory analysis included complete blood count, erythrocyte sedimentation rate (ESR), C - reactive protein (CRP), and thyroid function tests. Individuals in both groups were assessed for FMS and the American College of Rheumatology 1990 criteria for fibromyalgia was applied for both groups.

Results: FMS was present in 3 (3%) breast cancer patients compared to 7 (7%) individuals of the control group (P<0.194). We found that onset of diagnosis of BCA was significant associate with FMS (P<0.046).

Conclusion: Prevalence of FMS was 3% among Iraqi Female patients with BCA.

Introduction

Fibromyalgia syndrome (FMS) is a chronic non-inflammatory and non-autoimmune painful musculoskeletal disorder composed of core features that are always present (wide spread pain and characteristic tender points present on physical examination). (1)

The prevalence of FMS ranges from 0.66% to 10.5%, women are 10 times more commonly affected than men, and usual age of presentation is 20-50 years but has been diagnosed in children, adolescents and older people. (2)

Previous studies have reported elevated levels of a nerve chemical signal (substance P) and nerve growth factor in the spinal fluid of fibromyalgia patients. Levels of the brain chemical serotonin are also relatively low in patients with fibromyalgia. Studies of pain in fibromyalgia have suggested that the central nervous system may be somehow supersensitive. Scientists noted a diffuse disturbance of pain perception in patients with fibromyalgia and impaired non-rapid eye movement or non-REM sleep phase (which likely, at least in part, explains the common feature of waking up fatigued and unrefreshed in these patients). In addition, the onset of fibromyalgia has been associated with psychological distress, trauma, and infection. (3-5)

Breast cancer (BCA) is a malignant neoplasm originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk. (6) Breast cancer is by far the most common cancer diagnosed in women worldwide. (7) The incidence varies greatly around the world: it is lowest in less-developed countries and greatest in the more-developed countries. (8) Breast cancer comprises 10.4% of all cancer incidences among women. It is about 100 times more common in women than in men. (9)

Prevalence of FMS in BCA patients has been reported to be increased in 2 other studies. (10,11) Because cancer is a serious health problem that affects the patients’ quality of life and due to limited available data about prevalence of FMS in patients with BCA and to the best of our knowledge there was no previous study conducted in Iraq assessed FMS in patients with BCA so we evaluated prevalence of FMS among Iraqi patients with BCA.

Patients and Methods

A cross-sectional study was conducted on 100 patients with Breast Cancer who were randomly seen between December 2010 and April 2011 at the Breast Clinic of National Center for Early Detection of Cancer and Baghdad Teaching Hospital, Medical City, compared to 100 healthy individuals served as a control group who were randomly selected during the period of study; matched for age and sex of patient’s group.

The clinical assessment was performed using a comprehensive protocol. Full history was taken from all individuals including: age, sex, marital status, BCA stages, onset of BCA diagnosis and type of treatment. Complete clinical examination and the American college of rheumatology (ACR) 1990 criteria for fibromyalgia were applied for individuals in both groups. (12)
Patients with BCA were excluded from the study if they had conditions mimic FMS like: autoimmune disorders, neurological disorders, endocrine disorders, hepatitis C, other malignancies & osteomalacia.

BCA was diagnosed by the surgeon clinically and confirm histologically and the stage classified according to TNM classification of BCA.

Blood sample was obtained for measurement of erythrocyte sedimentation rate (ESR), C-reactive protein, packed cell volume (PCV), white blood cells count (WBC), blood urea, serum creatinine, total serum bilirubin, serum alkaline phosphatase, serum aminotransferase, hepatitis C virus antigens, and thyroid function tests (T3, T4, TSH). Body mass index (BMI) and waist circumference were measured. A signed consent was taken from individuals in both groups for admission in the study.

Statistical analysis was done by Statistical Package for Social Sciences version 18 (SPSS 18). Discrete variables presented as numbers and percentages. Continuous variables presented as mean and standard deviation (SD). To test the significance of difference between two variables; t test of two independent variables used if variables were normally distributed and Mann-Whitney test used if the distribution was not normally distributed. Chi square test for independence used to test the association between discrete variables. P value used was asymptotic and two sided for all tests. Findings with P value less than 0.05 considered significant.

Results

One hundred patients with BCA, 100 females and no males, their mean age (48.7 ± 9.7) years, and one 100 healthy females served as control group, their mean age was (48.4 ± 10.4) years were included in this study. The age and sex of patients and control showed no statistical differences (p-value = 0.839 and 1.000 respectively, Table 1).

Fibromyalgia syndrome (FMS) was present in 3 (3%) BCA patients, and absent in 97 (97%) of them, while it was present in 7 (7%) healthy individuals and absent in 93(93%) controls and (p-value = 0.194) which was statistically not significant in (Table 2).

In patients with BCA, the associated features as sleep disturbance was present in 60 (60%) and in control was present in 57 (57%) with P value (0.667), headache was present in 58 (58%) patients and 69 (69%) controls with P value (0.106), fatigue was present in 76 (76%) patients and 71 (71%) controls (P = 0.423), anxiety was present in 53 (53%) patients and 43 (43%) controls with P value (0.157), depression was present in 33 (33%) patients and 22 (22%) controls with P value (0.082), irritable bowel was present in 61 (61%) patients and 56 (56%) controls with P value (0.473), tender points was present in 57 (57%) patients and 63 (63%) controls (P = 0.386), the association between these associated features in patients and controls was statistically not significant, while numbness was present in 38 (38%) patients and in 52 (52%) controls with P value (0.047). The association was statistically significant as shown in table 3.

In Table 4, only onset of diagnosis of BCA is a significant associate with presence of fibromyalgia syndrome (FMS) in patients group. Increased age & waist circumference may be associated with increase prevalence of FMS but without reaching significant differences. Sex, body mass index (BMI), stages of BCA, family history of FMS, drug history, educational level and marital status are not predictors for prevalence of FMS in patients with BCA.

Table 1: Demographic characteristics of 100 patients with BCA and 100 controls.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Breast Cancer</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year), M ± SD</td>
<td>48.7 ± 9.7</td>
<td>48.4 ± 10.4</td>
<td>0.839</td>
</tr>
<tr>
<td>Sex Male, n(%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Female, n(%)</td>
<td>100 (100.0)</td>
<td>100 (100.0)</td>
<td></td>
</tr>
</tbody>
</table>

N; number, P; P value, %; percent, M; mean, SD; standard deviation.

Table 2: Distribution of FMS in 100 patients with breast cancer and 100 controls.

<table>
<thead>
<tr>
<th>Fibromyalgia Syndrome</th>
<th>Breast Cancer</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>3(3.0)</td>
<td>7(7.0)</td>
<td>0.194</td>
</tr>
<tr>
<td>Not</td>
<td>97(97.0)</td>
<td>93(93.0)</td>
<td></td>
</tr>
</tbody>
</table>

N; number, P; P value, %; percent.

Table 3: Distribution of fibromyalgia features in 100 BCA patients and 100 controls.

<table>
<thead>
<tr>
<th>Features</th>
<th>Breast Cancer</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep disturbance</td>
<td>60 (60%)</td>
<td>57 (57%)</td>
<td>0.667</td>
</tr>
<tr>
<td>Headache</td>
<td>58 (58%)</td>
<td>69 (69%)</td>
<td>0.106</td>
</tr>
<tr>
<td>Fatigue</td>
<td>76 (76%)</td>
<td>71 (71%)</td>
<td>0.423</td>
</tr>
<tr>
<td>Numbness</td>
<td>38 (38%)</td>
<td>52 (52%)</td>
<td>0.047*</td>
</tr>
<tr>
<td>Anxiety</td>
<td>53 (53%)</td>
<td>43 (43%)</td>
<td>0.157</td>
</tr>
<tr>
<td>Depression</td>
<td>33 (33%)</td>
<td>22 (22%)</td>
<td>0.082</td>
</tr>
<tr>
<td>Irritable bowel</td>
<td>61 (61%)</td>
<td>56 (56%)</td>
<td>0.473</td>
</tr>
<tr>
<td>Tender points</td>
<td>57 (57%)</td>
<td>63 (63%)</td>
<td>0.386</td>
</tr>
</tbody>
</table>

*p-value is significant, N; number, %; percent.

Table 4: Relationship between FMS and demographic and characteristic features of 100 patients with breast cancer.

<table>
<thead>
<tr>
<th>Variables</th>
<th>FMS</th>
<th>No FMS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year), M ± SD</td>
<td>54.7 ± 6.1</td>
<td>48.5 ± 9.7</td>
<td>48.7 ± 9.7</td>
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<td>Sex Male, n (%)</td>
<td>0 (0.0)</td>
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<td>Female, n (%)</td>
<td>3 (3.0)</td>
<td>97 (97.0)</td>
<td>100 (100.0)</td>
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<td>Onset of Diagnosis breast cancer (year), M ± SD</td>
<td>48.0 ± 20.8</td>
<td>24.3 ± 30.5</td>
<td>25.0 ± 30.5</td>
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<tr>
<td>Body Mass Index (kg/m²), M ± SD</td>
<td>30.5 ± 6.1</td>
<td>29.2 ± 5.1</td>
<td>29.2 ± 5.1</td>
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</table>
Waist circumference (cm), M ± SD

<p>| | | | |</p>
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<tr>
<td>109.3 ± 10.1</td>
<td>101.8 ± 13.7</td>
<td>102.0 ± 13.6</td>
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**Stage of breast cancer, n(%)**

<table>
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<th>Stage</th>
<th>0 (0.0)</th>
<th>6 (6.0)</th>
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<tr>
<td>Stage 1</td>
<td>2 (2.0)</td>
<td>47 (47.0)</td>
<td>49 (49.0)</td>
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<tr>
<td>Stage 2</td>
<td>1 (1.0)</td>
<td>38 (38.0)</td>
<td>39 (39.0)</td>
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<tr>
<td>Stage 3</td>
<td>0 (0.0)</td>
<td>6 (6.0)</td>
<td>6 (6.0)</td>
</tr>
</tbody>
</table>

Family history of FMS/MSK, n(%) 1 (1.0) 21 (21.0) 22 (22.0) 0.630

Drug History, n(%) 3 (3.0) 79 (79.0) 82 (82.0) 0.410

Educational Level, n(%) 0 (0.0) 18 (18.0) 18 (18.0) 0.410

Marital state, n(%) 0 (0.0) 12 (12.0) 12 (12.0) 0.340c

**Discussion**

The present study revealed no significant association between BCA and FMS which is in agreement with another study done by Dreyer. However, in contrast to Warner et al study, patients might have already symptoms of FMS before diagnosis of breast cancer.

To our knowledge, this is the first cross-sectional descriptive study investigating FMS in Iraqi female patients with BCA.

In this study, the prevalence rate of FMS among female Iraqi patients with breast cancer was 3% of the sample studied compared to 7% of healthy individuals, indicating non significant association between the two conditions. Possible explanation of not reaching the level of significance may be the small sample size.

In comparison to the prevalence of FMS in other malignant diseases, the prevalence of FMS in the present study was slightly lower than its prevalence in lung cancer patients (4.8%) and hospitalized cancer patients (solid and hematological malignancy) (10.7%).

Although Fibromyalgia syndrome was higher among healthy control group but it was not significant.

In this study, we found that onset of diagnosis of BCA was a significant associate with presence of fibromyalgia syndrome (FMS) among our patient however it was not highly significant.

Increased age and waist circumference may increase the prevalence of FMS but it was insignificant.

Sex, body mass index (BMI), stages of BCA, family history of FMS, drug history, educational level, and marital status were not significant associates with prevalence of FMS in patients with BCA.

Recently it has been found that post chemotherapy some patients developed features of arthralgia and myalgia of hands, feet, knees, and ankles. The small sample size might be a limitation of the study, however the strength of the study included all sample size were taken, being cross-sectional not case control, and it was not retrospective.

Because there is no specific treatment for FMS, the management of FMS is multifaceted program including education, stress management, and aerobic exercise to help the patients cope with their symptoms and improve their quality of life.

In conclusion, prevalence of FMS was 3% among Iraqi female patients with BCA. Large prospective studies may be needed to confirm these results.

**References**


Germinal testicular tumour metastatic exclusively to the spleen

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Key words: Germ cell tumor, Non seminomatous, Spleen metastases, splenectomy.

ISSN: 2070-254X

Abstract

Non seminomatous germ cell testicular cancer (NSGTC) often metastasizes to lung and lymph nodes. Spleen metastases are rare. We present an original case of a 27-year-old man with bilateral testicular ectopia history in childhood, presenting intra abdominal mixed non seminomatous germ cell cancer (embryonal carcinoma and Yolk sac tumor) with only spleen nodules in the pre chemotherapy abdominal CT scan. Metastases to spleen were confirmed by splenectomy at the end of chemotherapy; they had the same histology than the primitive tumor.

Background

Non seminomatous germ cell testicular cancer (NSGTC) often metastasizes to lung and lymph nodes. Spleen metastases are rare. We report here an original case of NSGTC metastasizing exclusively to spleen.

Observation

It is about a 27-year-old man with bilateral testicular ectopia history in childhood, suffering from abdominal pain with constipation. Physical examination finds a pelvic mass measuring 15 cm with no inguinal lymph nodes and empty scrotum. Ultrasound and magnetic resonance imaging were performed showing a heterogeneous pelvis mass above bladder, measuring 15 cm, developed on an ectopic testis. Human chorionic gonadotropine (HCG) and alfa-fetoprotein (AFP) serum levels were screened showing normal HCG and increased AFP at 90 ng / ml. The patient had undergone surgical excision of the pelvic mass. Histopathological study revealed an incomplete resection of a mixed non seminomatous germ cell tumor (embryonal carcinoma and Yolk sac tumor) developed on an ectopic testis associated to a vestigial uterus. Post operative chest and pelvis CT scan showed multiple poorly defined hypo dense spleen nodules with retro bladder remnant uterine mass (Figures 1 and 2). The spleen nodules were considered metastatic. Post operative AFP serum level remained high (10 ng/ ml). According to the 2002 TNM classification of testicular cancer and to the IGCCCG prognostic-based staging system for metastatic germ cell cancer (International Germ Cell Cancer Collaborative Group) [1], tumor was considered stage IIIC and belonged to the poor-prognosis group.

Consequently, four cycles of chemotherapy PEB (cisplatinum, Etoposide and bleomycin) were administered to the patient. At the end of chemotherapy, AFP serum level was normalized. Abdominal CT scan showed partial regression in spleen nodules and persistence of the remnant uterine mass. A splenectomy with excision of the remnant uterus was performed. The spleen histopathological study revealed multiple nodules containing the same testicular mixed germ cell tumor excised firstly (Figures 3 and 4). Because of the persistent viable tumor, VeIP-based adjuvant chemotherapy (vinblastine, Ifosfamide and cisplatinum) was proposed but denied by the patient. The patient is still alive with no evidence of disease after a follow-up of 6 years.

Discussion

Germ cells testicular cancer metastasize through lymphatic paths to reach para aortic lymph nodes than mediastinal and supra clavicle lymph nodes. Lymphatic spread of cancer cells precede usually blood dissemination, except for choriocarcinoma which is characterized by rapid cancer cells blood dissemination, responsible of lung, liver and cerebral metastases [2]. Germ cells cancer metastatic sites are represented, in decreasing order of frequency, by: retro peritoneal lymph nodes, lung, mediastinum, liver and rarely brain and bones. Other metastatic sites had been exceptionally described such as kidneys, gastro intestinal tract, spleen and pericardium.

Spleen metastases had been rarely reported in literature. In 1985, Husband et al had reported, in a retrospective series of 650 metastatic germ cells testicular cancers, 23 unusual metastatic sites. These sites included 2 cases of spleen metastases, which represent 0.3% of all patients and 8.6% of metastatic sites [3]. Later, three other cases were reported. In one of these cases, spleen metastases were diagnosed by PET scan while CT scan was negative [2, 4, 5].
In autopsy series, spleen metastases are not so rare like in clinical or radiological series. In an autopsy series of 1898 cases of solid cancers, Schön et al reported 57 spleen metastases which represent 3% of all cancers [6]. In this series, lung cancer, breast cancer and skin malignant melanoma represented the majority of autopsied cases and were the most spleen metastases associated cancers with rates of 24.6%, 15.8% and 12.3% respectively. Spleen was affected in 4 from the 9 cases of germ cells testicular cancers, representing 7% of all spleen metastases cases. All germ cells testicular cancers cases were partially or totally composed by choriocarcinoma; for spleen metastases, they were exclusively composed by choriocarcinoma cells [6].

Spleen metastases have usually lower density than the surrounding parenchyma in CT scan imaging; they can also take cystic density. A splenomegaly associated to poorly defined cystic lesions is suggestive of malignity [7].

In our article, we present an original observation of a germ cells testicular cancer with only spleen metastases, whereas, in previous reported cases, metastases affected other organs in addition to the spleen [2,3,4]. In our case, spleen metastases were in low density and poorly defined, which was very suggestive of malignity. Tumor was mixed, composed of embryonal carcinoma and Yolk sac tumor cells without choriocarcinoma; while literature spleen metastases cases were all composed, at least partially, by choriocarcinoma [6]. The presence of spleen metastases focuses on the importance of a complete staging before chemotherapy in order to assess all metastatic sites which would be surgically excised after chemotherapy completion.

Standard treatment of intermediate or poor prognosis metastatic non seminomatous germ cells tumors consists in 4 chemotherapy PEB cycles (cisplatinum, etoposide and bleomycine) followed by clinical, biological (AFP, HCG and LDH serum levels) and radiological evaluation by CT scan. After AFP and HCG normalization, all residual masses must be removed [1]. Residual masses concern generally lung and lymph nodes. After residual mass excision, additional chemotherapy should be performed if there are more than 10% of viable tumor cells [8].

To our knowledge, this is the second reported case, after Nguyen et al, where spleen metastases from germ cell tumor were histologically confirmed after splenectomy [2].

**Figures**

**Fig 1 and 2:** Axial section after intravenous contrast material injection in portal time showing many different measures low dense spleen nodules

**Fig 3:** Massive proliferation of atypical giant cells in the spleen parenchyma

**Conclusion**

The ascertainment of spleen lesions, even solitary, during germ cells testicular cancer staging, should be considered seriously. The rarity of spleen metastases in germ cells tumors may mislead physicians to the diagnosis of benign spleen lesions (spleen cysts). Surgical removal of all residual masses must be always performed, even in sites deemed unusual.

**Conflicts of interest:** no conflicts of interest
Fig 4: AFP positive immunostaining

References

### Activities

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<th>DATE</th>
<th>ACTIVITIES</th>
<th>LOCATION</th>
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<tbody>
<tr>
<td>February 4, 2013</td>
<td>Lung Cancer Symposium “International Cancer Day”</td>
<td>Sheraton Hotel, Dammam</td>
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<tr>
<td>February 6, 2013</td>
<td>Breast Cancer Symposium for Primary care physicians</td>
<td>Bisha</td>
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<tr>
<td>February 27 - 28, 2013</td>
<td>Updates on Multiple Myeloma Symposium</td>
<td>Sheraton Hotel, Dammam</td>
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<td>March 13, 2013</td>
<td>1 day Mini Symposium “Updates in Colorectal Cancer” (International Colorectal Cancer Month)</td>
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<td>Breast Cancer Symposium for Primary care physicians</td>
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<td>April 3 &amp; 4, 2013</td>
<td>ASCO – GFFCC Conference</td>
<td>King Fahd Medical City, Riyadh</td>
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<td>Breast Cancer Symposium for Primary care physicians</td>
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<td>April 25, 2013</td>
<td>Pharmacology Oncology Symposium</td>
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<td>May 8, 2013</td>
<td>Advanced Management of Breast Cancer</td>
<td>Plaza Conference Center, Aramco</td>
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<tr>
<td>September 15, 2013</td>
<td>Latest Improvement of Lymphoma Management (International Lymphoma Day)</td>
<td>Plaza Conference Center, Aramco</td>
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<td>October 2013</td>
<td>“5th Sharqiyyah Wardiyah” Breast Cancer Campaign</td>
<td>Eastern Province</td>
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<tr>
<td>November 20, 2013</td>
<td>Sick Children’s Day</td>
<td>Sunset Beach Resort</td>
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Fight Cancer on all fronts through all possible direct and indirect channels & by all means.
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News From The Arab World
## Cancer Awareness Calendar

<table>
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<tr>
<th>Month</th>
<th>Awareness Month(s)</th>
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<tr>
<td>JANUARY</td>
<td>Cervical Cancer Awareness Month</td>
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<td>FEBRUARY</td>
<td>Screening and Early Detection Awareness Month</td>
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<tr>
<td>MARCH</td>
<td>Colorectal Cancer Awareness Month</td>
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<td>APRIL</td>
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<td>MAY</td>
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<td>Pain Medicine and Palliative Care</td>
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<td>Prostate Cancer Awareness Month</td>
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<td>Leukemia and Lymphoma Awareness Month</td>
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<td>Smoking Cessation</td>
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<tr>
<td>DECEMBER</td>
<td>5 A Day Awareness Month</td>
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Objectives & Scope Of The PAJO

The Pan Arab Journal of Oncology (PAJO) is the official Journal of the Arab Medical Association Against Cancer (AMAAC). It is a quarterly publication targeting health professionals interested in the oncology field. It is a multidisciplinary peer-reviewed journal that publishes articles addressing medical oncology, malignant hematology, surgery, radiotherapy, pediatric oncology, geriatric oncology, basic research and the comprehensive management of patients with malignant diseases in addition to international oncology activities, congresses & news.

The journal will be addressed, as a first step, mainly to the professionals in the hematology & oncology field in the Middle East region and North Africa. The goal is to share local & regional research activities news and to be updated with international activities. We hope, with your support, to achieve our following objectives:
1. Promote and encourage research activities in the Arab World.
2. Disseminate & analyze epidemiological local, regional and international data.
3. Update health professionals with the most recent advances, news & developments in the field of oncology.
4. Improve the level of scientific publications arising from the Arab World.
5. Keep health professionals connected and exposed to the activities of different Arab cancer societies.
6. Share with our immigrant compatriots their activities & feedback in this field.
7. Involve all health professionals interested in the field of Oncology within the multidisciplinary scope of the Journal.
8. Encourage post graduates students to submit their research work.

Instructions For The Authors

1. Manuscript Categories

1.1. Clinical trials
The Editor-in-Chief and an Associate Editor generally review Reports from clinical trials. Selected manuscripts are also reviewed by at least two external peer reviewers. Comments offered by reviewers are returned to the author(s) for consideration. Manuscript acceptance is based on many factors, including the importance of the research to the field of oncology & the quality of the study. Authors should focus on accuracy, clarity, and brevity in their presentation, and should avoid lengthy introductions, repetition of data from tables and figures in the text, and unfocused discussions. Extended patient demographic data should be included in a table, not listed within the text. Reports from Clinical trials are limited to 3,000 words of body text, excluding the abstract, references, figures, and tables. They are limited to six total figures and tables. All abstracts are strictly limited to 250 words. Titles are to be descriptive, but succinct. Results of clinical studies should be supported by a clear description of the study design, conduct, and analysis methods used to obtain the results. Reports of phase II & III studies should include from the protocol a clear definition of the primary end point, the hypothesized value of the primary end point that justified the planned sample size, and a discussion of possible weaknesses, such as comparison to historical controls. Phase I studies will be well received if they have interesting clinical responses, unusual toxicity that pointed to mechanism of action of the agents, and important or novel correlative laboratory studies associated with the trials.

1.2. Review Articles
All reviews must be clinically oriented, ie, at least half the review must describe studies that detail human impact, marker effect on prognosis, or clinical trials. Review Articles should be prepared in accordance with the Journal’s Manuscript Preparation Guidelines, and will be reviewed in the same manner as Reports from Clinical Trials. Reviews are limited to 4,500 words of body text, excluding the abstract, references, figures, and tables. The editors also suggest a limit of 150 references.

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The Editor-in-Chief may solicit an Editorial to accompany an accepted manuscript. Authors who wish to submit unsolicited Comments and Controversies should contact the Editor-in-Chief, before submission to determine the appropriateness of the topic for publication in the Journal. Editorials should be no more than four to five pages in length.

1.4. Articles on Health Economics
Articles about health economics (cost of disease, cost-effectiveness of drugs, etc) are highly encouraged.

1.5. Case Reports / Correspondence / Special Articles
Correspondence (letters to the Editor) may be in response to a published article, or a short, free-standing piece expressing an opinion, describing a unique case, or reporting an observation that would not qualify as an Original Report. If the Correspondence is in response to a published article, the Editor-in-Chief may choose to invite the article’s authors to write a Correspondence reply. Correspondence should be no longer than three pages in length. Special Articles present reports, news from international, regional societies as well as news from our compatriots.
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3. Disclosures of Potential Conflicts of interest

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**Title Page**

The first page of the manuscript must contain the following information: (1) title of the report, as succinct as possible; (2) author list of no more than 20 names (first name, last name); (3) names of the authors’ institutions and an indication of each author’s affiliation; (4) acknowledgments of research support; (5) name, address, telephone and fax numbers, and e-mail address of the corresponding author; (6) running head of no more than 80 characters (including spaces); (7) list of where and when the study has been presented in part elsewhere, if applicable; and (8) disclaimers, if any.

**Abstract**

Abstracts are limited to 250 words and must appear after the title page. Abstracts must be formatted according to the following headings: (1) Purpose, (2) Patients and methods (or materials and methods, similar heading), (3) Results, and (4) Conclusion. Authors may use design instead of Patients and methods in abstracts of Review Articles. Comments and Controversies, Editorials and Correspondence do not require abstracts.

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The body of the manuscript should be written as concisely as possible and must not exceed the manuscript category word limits described herein. All pages of a submission should be numbered and double-spaced. Helvetica and Arial at 12pt size are the recommended fonts for all text (see Figures section for acceptable fonts for figures). The Journal adheres to the style guidelines set forth by the International Committee of Medical Journal Editors.

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Name of the medicinal product
Arimidex®: 1mg Tablets.

Qualitative and quantitative composition: Each ARIMIDEX tablet contains 1 mg of anastrozole. Pharmaceutical form: Film-coated, white, round, biconvex tablet with logo on one side and dosage strength on the other. Therapeutic indications: Adjunctive treatment of hormone receptor-positive early invasive breast cancer in postmenopausal women. Adjunctive treatment of hormone receptor-positive early invasive breast cancer in postmenopausal women who have received 5 to 3 years of adjuvant tamoxifen. Treatment of hormone receptor-positive advanced breast cancer in postmenopausal women. As there may be local variations in the approved label, please consult the local ARIMIDEX prescribing information before use. Mode of action and method of administration: Adults: Including the elderly, one 1 mg tablet daily once a day. Postmenopausal women with hormone receptor-positive early invasive breast cancer, the recommended duration of adjuvant endocrine treatment is 5 years. Postmenopausal women with hormone receptor-positive early invasive breast cancer, the recommended duration of adjuvant endocrine treatment is 2 years. Postmenopausal women with hormone receptor-positive advanced breast cancer, the recommended duration of adjuvant endocrine treatment is 2 years. Tamoxifen in combination with chemotherapy is generally recommended for use in women and adolescents due to insufficient data on safety and efficacy. A higher dose is recommended in patients with mild or moderate renal impairment. In patients with severe renal impairment, administration of Arimidex should be performed with caution. Hepatic impairment: No dose change is recommended in patients with mild hepatic disease. Cautions is advised in patients with moderate to severe hepatic impairment. As there may be local variations in the approved label, please consult the local ARIMIDEX prescribing information before use. Contraindications: Pregnancy or breastfeeding women. Patients with known hypersensitivity to anastrozole or any of the excipients. As there may be local variations in the approved label, please consult the local ARIMIDEX prescribing information before use. Interaction with other medicinal products and other forms of treatment: Anastrozole inhibits CYP 1A2, 2C9, 2C19, 2D6 and 3A4 in vitro. Clinical studies with corticosteroids and aspirin showed that anastrozole at a 1 mg dose did not significantly inhibit the metabolism of both drugs. No significant pharmacokinetic interactions with ranitidine have been observed. Anastrozole also inhibits CYP 2C19 and 2D6 in vivo. Clinical studies with nonsteroidal anti-inflammatory drugs showed that anastrozole at a 1 mg dose did not significantly inhibit the metabolism of these drugs. Combined administration with other drugs: Anastrozole is not expected to result in clinically significant medicinal product interactions mediated by CYP enzymes. The enzymes mediating metabolism of anastrozole have not been identified. Clinical data, a weak, non-specific inhibition of CYP enzymes, did not affect the plasma concentrations of anastrozole. The effect of potent CYP inhibitors is unknown. A review of the clinical safety database did not reveal evidence of clinically significant interactions in patients treated with Anastrozole who also received other common concomitant medicinal products. There were no clinically significant interactions with bisphosphonates. Co-administration of fatty acids or estrogen-containing therapies with Anastrozole should be avoided as this may diminish its pharmacological action. As there may be local variations in the approved label, please consult the local ARIMIDEX prescribing information before use.

Arimidex (anastrozole) side effects To date, it is estimated that local ARIMIDEX patient exposure equates to over 5.9 million patient-years. ARIMIDEX is generally well tolerated. The ARIMIDEX UK Summary of Product Characteristics (SmPC) data is the side effects of ARIMIDEX. The majority of information being derived from the ATAC trials. The most frequently reported adverse reactions (with a frequency of ≥10%) are: Headache, Hot flushes, Nausea, Rash, Arthralgia/arthralgias, Anorexia, Osteopenia, Anemia. As there may be local variations in the approved label, please consult the local ARIMIDEX prescribing information before use.

For Further Information please contact:AstraZeneca - UK Representative Office (Levant)PO Box 17788, Amman 11195 JordanTel 00962 6 5791 66www.astrazeneca.com

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