Constraints and Common Techniques in Postmastectomy Radiotherapy

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ABSTRACT: Over the past 50 years breast cancer has become a major health problem affecting as many as one in eight women during their lifetime. Mastectomy is one of the main options in the treatment of breast cancer patients in an aim to avoid metastases of the disease. Yet, a successful operation does not eliminate the risks of local recurrence. Postmastectomy radiotherapy can significantly reduce these risks. This study intends to review and evaluate the challenges and complications which are sometimes associated with postmastectomy radiotherapy.

Clinical and dosimetric trials were carried out using various techniques to optimize the treatments by maximizing the dose to the tumor and minimizing it to the healthy tissues at proximity. No one technique studied fulfilled these requirements. This is basically because the heterogeneity of the breast cancer means that the response to therapy and a systematic approach to treatment cannot be derived and treatment regions must be determined on a patient-by-patient basis. The accuracy of dose distributions is crucial to the quality of treatment planning and consequently to the doses delivered to patients undergoing radiation therapy. The successful radiation therapy depends on the stage of cancer.

KEYWORDS: Breast cancer, Postmastectomy radiotherapy, IMRT, PMRT

INTRODUCTION

Breast cancer was recognized by the Ancient Egyptians as long ago as 1600 BC [Bonney 1996]. Mastectomy is one of the main options in the treatment of breast cancer patients in an aim to treat and avoid metastases of the disease. Unfortunately, even after a successful operation, an appreciable risk of local recurrence (e.g., in the chest wall or lymph nodes) can remain unless some reliable method of investigation, such as axillary clearance, has found no evidence of nodal involvement. If axillary investigation reveals nodal involvement (or if the axilla has not been adequately investigated) or if the tumor stage is T3/T4, other treatment modalities are mandatory [EBCTCG 2005].

Advances in diagnosis and treatment in oncology combined with technical advances in radiotherapy have resulted in qualitative and quantitative changes in the use of radiation to treat breast cancer. Over the past 5 decades, there have been more than 50 randomized prospective clinical trials that have evaluated the benefits of radiation after mastectomy for patients with breast cancer [Thomas et al 2002, De Steene et al 2004]. The rationale for the use of post-mastectomy radiotherapy (PMRT) is to decrease locoregional recurrence and improve overall patient survival. Locoregional recurrence occurs mostly in the first five years after initial treatment and can be in the form of local or nodal metastases in the body. It depends on many factors including pathological characteristics such as tumor size, nodal involvement, etc, and on the type of surgery. In patients who develop a locoregional recurrence, the chest wall is the most common site, which represents 70% of all locoregional failures. The mastectomy scar on the chest wall is the most common site of chest wall involvement. The supraclavicular / infraclavicular nodes are the next most common site (10-20%), with the axilla and internal mammary nodes being the least common (5 - 10%) [Rudoltz 1998, Strom 2005].

Indication of PMRT

There are several reasons or end points that might justify the use of
postmastectomy radiotherapy (PMRT) for patients with invasive breast cancer. These include a reduction in the risk of locoregional failure (LRF), with its potential physical and psychological morbidity, as well as a reduction in the risks of distant relapse and death. There are a number of conditions that must be met in order for an individual patient to achieve a survival benefit from postmastectomy radiation. Pathologically close or positive surgical margins, tumor size of 5cm or greater and/or involvement of the chest wall or skin, vascular invasion and greater than three lymph nodes positive for metastatic disease are determinant factors for indication of PMRT. PMRT is also indicated for patients with persistent disease in the local-regional area after mastectomy and those without distant metastasis. Radiation must be effective in eradicating the persistent disease in the local-regional area and must not cause a life-threatening injury [Zimmerman 2005, Buchholz 2005, Huang 2006, Truong 2004, Højris 2000]. The role of PMRT for stages I and II A is a subject of research. Studies showed that there are no significant effects in the 10-year rates of locoregional recurrence rates, and is thus not recommended. [Luise 2007, Mcguire 2007] Another controversial question regarding indication for postmastectomy irradiation is whether or not radiotherapy is indicated in patients with 1–3 positive nodes. In two different surveys in North America and Europe, the percentage of centers that would use postmastectomy radiotherapy in patients with 1-3 positive lymph nodes ranged between 40-63% and 35-85% in North America and Europe respectively [Ceilley 2005, Jagsi 2006]. The accuracy of transfer of digital and non digital data between planning and treatment units and the operator accuracy also affect the accuracy of irradiation. [Probst 2006, Beavis 2006].

Challenges in breast cancer irradiation: Irradiation, whether of the postmastectomy chest wall or in the setting of breast conserving surgery or reconstruction, is complex, because of the large, curved target volume and its proximity to heart and lung. A number of challenges or issues should be considered as relevant to breast cancer radiotherapy. Within treatment planning, these include patient positioning, immobilization or localization, proximal-organ (heart lung or contralateral breast) irradiation, target motion or correction, dose homogeneity, especially in regions with inhomogeneities as the thoracic region, and cosmic effects. The accuracy of transfer of digital and non digital data between planning and treatment units and the operator accuracy also affect the accuracy of irradiation. [Probst 2006, Beavis 2006].

TARGET MOTION: TARGET motion can be divided into two categories: intrafractional motion which occurs during irradiation as a result of respiration, cardiac pulsation and gastro-intestinal systems and, interfractional motion which refers to the change or displacement during the course of treatment as a result in variation of target size and patients’ position and weight. Motion of the treated volume during the course of treatment presents a big challenge in breast cancer irradiation. In a previous paper [Sulieman 2006], we showed that intrafractional variation ranged from 0.85 mm for the inferior central margin (ICM) to 2.1 mm for the central breast distance (CBD),...
while interfractional variations ranged from 3.2 mm to 6.25 mm for CBD and ICM respectively. Different techniques were suggested for actively and effectively adjusting these movements in order to optimize the treatment. These include breath holding control, respiratory gating techniques, electronic portal imaging, active breath control and real time tumor tracking. [Sulieman 2006].

TISSUE INHOMOGENEITIES: The thoracic region is a heterogeneous medium composed of dense bone, water-equivalent soft tissues and lung tissues. A major concern in chest wall irradiation is the penetration of electrons into the lung. Since the lung has a physical density of only about 0.3, after penetrating the chest wall, the remaining portion of the depth-dose curve can penetrate three times deeper in lung than in unit density tissue.

INCREASED NUMBER OF PATIENTS AND TIME: The number of cancer patients who need radiation therapy is increasing every day. It is estimated that over a million breast cancers are diagnosed yearly worldwide. [Bonney 1996, Parkin 1997] The time required for treatment plays an important role in the efficiency and quality of the service provided to patients. Any delay in treatment may negatively affect the patient especially if the cancer is of an aggressive type.

Complications

Although the beneficial effect of postoperative radiotherapy for breast cancer is well documented, this treatment may be related to a number of complications that may affect patient quality of life and possibly survival. Among significant long-term irradiation sequelae, which occur in over 3-6 months are:

CARDIAC DAMAGE: Case reports of heart injuries resulting from postmastectomy radiotherapy were published as early as the 1950s [Pearson 1957, Höjris 2000]. The gain in overall survival is increased mortality by cardiac injury. Ischemic heart diseases caused by irradiation of the cardiac chambers and coronary vessels are amongst the major causes of mortality in postmastectomy irradiation. This is specially the case when inclusion of internal mammary nodes that lie in close proximity of the heart is necessary [Krueger 2004]. Cardiac damage is more associated with the irradiation of the vascular system than of the heart itself [Dewar 2006]. It is believed that the increase in the risk of myocardial infarction is associated with factors other than radiation, including: age, ethnicity, advanced stage, non-rural residence, more than one comorbid condition, a hormone receptor-negative tumor, and other cardiac risk factors [Doyle 2007].

LUNG DAMAGE: The lung is one of the important dose limiting organs for radiation therapy of tumors in the thoracic region. Pulmonary complications are divided into early effects (radiation pneumonitis) and late effects (lung fibrosis). Clinically, these conditions are usually diagnosed from chest x-rays in symptomatic and asymptomatic patients [Skoczylas 2006]. Both are confined to radiation portals: antero-lateral peripheral lung after chest wall irradiation or lung apex after irradiation of supraclavicular area. [Senkus-Konefka 2006]. The early phase of radiation induced lung injury, radiation pneumonitis, usually becomes manifested by cough, fever and dyspnea 1-6 months after treatment. The probability and severity of radiation induced lung damage depend mainly on the radiation dose, fractionation schedule and the amount of irradiated lung volume. However, the exact tolerance dose of the normal lung tissue is not fully known in humans. An early study showed that dose effect relation for early changes in perfusion and ventilation showed an almost linear increase of the reduction in local function as a function of dose. This suggests that early local pulmonary changes can occur at fairly low dose levels.
with progressive dysfunction for doses up to 50-80 Gy [Pehr 2001, Theuws 1998]. The risks of cardiac and pulmonary toxicities are highly technique-dependent, so appropriate estimates of these risks could aid in clinical decision-making for selection of the treatment field arrangements. Other factors such as age, sequential chemotherapy hormonal therapy and smoking and eating habits have been reported to influence pulmonary complications post irradiation.

SECOND MALIGNANCIES: Radiation-induced cancers are an uncommon but feared late complication of radiation therapy. Carcinogenic risk seems to be highest for tissues receiving low doses (≤6 Gy). However, there seems to be a tissue-specific dose–response effect for radio-carcinogenesis, with radiation-induced sarcomas developing in tissues receiving higher doses (30–60 Gy) and carcinomas developing in tissues receiving much lower doses. Both the integral dose to normal tissue and its dose distribution therefore influence this risk [Ruben 2008]. The data on the incidence of second malignancies in breast cancer survivors are contradictory. 10 and 15-year cumulative incidences of all second tumors in women receiving radiotherapy for breast cancer are in the range of 16-19%, with a similar proportion of contralateral breast cancer and other tumors. Among the latter, as in the general population, the most common are skin, endometrial, colorectal and pancreatic cancers. However, some tumors seem to occur with relatively higher frequency. These include ovarian, uterine and lung cancers, leukemia, malignant melanomas and sarcomas. A proportion of these cases may be a result of misclassification of metastatic disease. Some of these malignancies may be related to interaction between radiation and genetic factors. Indeed, in some series, the use of radiotherapy was related to an overall increase in the risk of second tumors whereas others demonstrated no effect. For example, breast cancer radiotherapy increases the risk of leukemia and lymphomas, but not of thyroid cancer. The increased risk is observed predominantly in women diagnosed with breast cancer at a young age. [Senkus-Konefka 2006]

OTHER SEVERE LONG-TERM SIDE EFFECTS, including lymphedema, brachial plexopathy, rib fractures, chronic pain, axillary vein thrombosis, bone necrosis, are relatively rare. These complications resulted from large daily doses combined with hot spots from overlapping fields experienced in Co-60 treatments [Huang 2006, Højris 2000, Senkus-Konefka 2006, Johansson 2002, Hinrichs 2004].

COMMON SHORT-TERM SIDE EFFECTS OF PMRT, including fatigue and skin erythema, are generally tolerable and not dose limiting [Senkus-Konefka 2006]. The radio-therapeutic doses received by the patient are limited by the tolerance of the normal tissues. Radiation is an unusual toxic agent, because the time of expression of cellular injury can be very variable from one tissue and tumor to another. Moreover, different patients given a standardized treatment can exhibit a range of normal tissue reactions. Thus, there is both dose dependence and variability in individual radio-sensitivity. However, it is impossible to predict the late effect in normal tissues from the acute reactions. Radiotherapy practice has changed over the years with the recognition of the importance of fraction size, number of fractions, total dose, and overall time for both tumor and normal tissue reactions. A clear distinction was found between the response of early reacting tissues, which are not much influenced by the size of the dose per fraction, and late reacting tissues for which the fraction size is crucial. In addition, it was recognized that shorter schedules are more damaging to tumors and early reacting tissues, but these do not increase
the damage in critical late reacting tissues. In general, there was a move toward more and smaller fractions to spare late reactions and to smaller fields in more clearly defined risk groups. The success of RT has thereby led to longer patient survival [Johansson 2002]. The risks and benefits of postmastectomy radiation treatment for breast cancer patients was one of the most comprehensively studied topics in all of oncology. Indeed, some of the very first randomized trials in the history of medicine investigated the role of radiation after radical mastectomy. Fortunately, radiation is a highly effective treatment modality for breast cancer. Multiple studies have indicated that radiation reduces the relative risk of local-regional recurrence by 65%-75% [Truong 2004, Luise 2007, Overgaard 2007, Dewar 2006, Hehr 2004, Overgaard 1997, Overgaard 1999, Ragaz 1997, Ragaz 2005]. Comprehensive meta-analyses of patients in randomized trials of radiation therapy for operable breast cancer have failed to resolve a fundamental question: whether the reduction of locoregional recurrence associated with postoperative radiation therapy is reflected in improved overall survival. In general, these meta-analyses have concluded that postoperative radiation therapy was not statistically significantly associated with increased overall survival at 10 years. Moreover, they have shown that any reduction in breast cancer mortality was offset by mortality from late side effects of radiation therapy, including heart disease and lung damage. This conclusion has profoundly affected multidisciplinary management of operable breast cancer.

The results of these meta-analyses were based on studies performed by older radiotherapy techniques, where the target volume was more extensive and were thus associated with an excess risk of cardiovascular and pulmonary toxicities [Spieler 2004, Gebski 2006]. Moreover these meta-analyses were not based on dosimetric analysis. The estimation of the radiation induced risks of today’s breast radiotherapy requires the development of reliable dose–response relationships, which, in turn, require detailed organs at risk OAR dosimetry of past regimens given to women for whom long-term follow-up data is available. For example, at present, few heart dosimetry data from breast cancer RT are available. Furthermore, it is unknown which quantitative measures of the heart dose or volume is most relevant to subsequent heart disease risk. Studies have used a variety of heart dose specifications, including the absorbed dose, biologically effective dose (BED), and the “cumulative radiation effect” (an estimate of the biologic radiation dose). Published data recording the percentage volume of the heart irradiated to various doses are limited. Such information might, however, be important in assessing radiation-related heart disease, because the percentage volume of the heart irradiated to a certain “threshold” dose might be a better predictor for cardiac death than, for instance, the mean heart dose or BED. Information is also needed concerning the effect of irradiating different cardiac structures, especially the coronary arteries. Coronary artery doses have been reported for several techniques, but only for left-sided irradiation; however, most studies have reported only the mean dose to the whole heart [Carolyn 2005].

In the past two decades, new equipment and techniques for radiation therapy have led to a better understanding of the dose – response relationships in the control of sub-clinical breast cancer. This substantially raises the possibility that a more effective dose to the target volume that avoids direct irradiation of the organs at risk could be associated with improved outcomes in patients treated with postoperative adjuvant radiation therapy.

The main techniques used for postmastectomy irradiation are:


**PHOTON IRRADIATION:** Photon beams from linear accelerators or from Cobalt-60 sources are widely used in postmastectomy radiotherapy. The different applications of photon beams include:

**Standard tangents:** this is one of the most common techniques used to treat the chest wall where the chest wall is treated by two opposed tangential fields. The internal mammary nodes (IMNs) are either treated with antero-posterior (AP) electron fields of high energy or mixed electron-photon beams or are not intentionally treated. Anterior or AP photon field are prescribed to the Supraclavicular fields (SCF) [Zimmerman 2005, Dewar 2006, Pierce 2002, Gez 2005].

**Cobalt fields** are also used in some radiotherapy departments. In this technique the medial CW and IMNs are treated by an anterior $^{60}$Co field and the SCF was treated with a $^{60}$Co beam as per standard tangents [Pierce 2002].

**Reverse Hockey Sticks:** This term refers to traditional opposed photon-only CW field in an inverted L fashion, with an abutted anterior field treating the medial CW, IMN and SC lymphatics [Pierce 2002, Sonnik 2007].

**Partially wide tangent fields (PWTFs):** This plan was generated with the explicit use of the 3D planning system to identify and treat the IMNs in the first three intercostal spaces. Medial and lateral coplanar photon tangents are used. The inferior medial CW (heart shadow) is treated with supplemental electrons (6 or 9 MeV). The SCF are treated as per standard tangents. Adequate blocking can be added to spare the contralateral breast, the heart and the lungs [Pierce 2002, Gez 2004, Thomsen 2008].

**ELECTRON IRRADIATION:** The use of electrons for chest wall radiation was criticized because of reports of pulmonary toxicity. Some earlier studies concluded that patients treated with electron-beam therapy to the chest wall had a higher incidence of pulmonary toxicity. However, the energy of electron beam used to treat those patients was 8 MeV or greater, which has more penetration to the underlying pulmonary tissue. In addition, the prescription point for radiation therapy was the subcutaneous tissue/chest wall junction in many of these studies [Zimmerman 2005].

**Anterior electron** Fields of energies ranging from 6 to 12 MeV are commonly used to treat the CW IMN’s and SCF. An additional posterior field is usually necessary for patients with large AP distance. An electron boost is sometimes recommended to account for the obliqueness of the peripherals [Rudoltz 1998, Højris 2000, Spierer 2004, Pierce 2002, Gez 2005, Gez 2004].

A technique for CW and IMN irradiation using oblique electron fields with gantry angles of 20–30$^\circ$ and with energies of 7.5, 9 and 10.5 MeV was reported to improve coverage of the PTV and minimize irradiation of OAR’s. Additional photon boost or mixed photon-electron beams to the IMN an SCF are usually used. [Kirova 2007].

**Electron Arc radiotherapy:** in which the irradiation is performed in 3 segments of 40$^\circ$ each with a customized secondary collimator for each segment is the modality of choice in several radiotherapy departments. Electron fields of energies 9, 12 and 16 MeV are used in the medial segment for the CW and IMN and 6 or 9 MeV are commonly used for the medial and lateral segments [Gaffney 2003, Gaffney 2001].

**Electron rotation technique:** is designed for treating the whole CW, with electron energies between 4 and 10 MeV and a shortened electron applicator. IMNs are treated with mixed electron/photon beams. The starting and end points of irradiation are identical and the irradiated areas outside the target volume of rotational
electron field are masked with lead rubber [Hehr 2004].

**PHOTON ELECTRON MIX**: Using this technique the patient is usually placed in a tilted board. Medial and lateral photon tangents are used for the lateral CW and mixed photons and electrons with ratios (30%/70% or 20%/80%) are used for the medial CW and IMN [Pierce 2002]. A combined 3-field photon electron mix, [Thomsen 2008] the modified Kuske effect which employs a 4-field photon electron combination where a direct photon and an angled electron field covered the IMN region and two shallow tangents covered the chest wall but excluded the IMN were also investigated [Sonnik 2007].

The advantages of mixing as well as sequentially combining fixed electron and photon beams are:

1. Less severe acute and chronic skin reactions even with boost doses added to higher tumor risk areas.
2. Improved homogeneity through the chest wall thickness compared to the use of electrons alone.
3. Decreased lung, heart, mediastinal and spinal doses when compared with photons alone.
4. Fewer match line skin reactions.
5. No apparent compromise of loco-regional control rates. [Deigert 1995].

**PROTON IRRADIATION**: Proton beam therapy is characterized by remarkable depth-dose distributions that have a low to median entrance dose, followed by a unified high-dose region (Bragg peak region) in the tumor area, followed by a steep fall-off to zero-dose distal to the target. As a result, physical dose distributions with protons are both highly conformal and homogeneous. It must be emphasized that protons have biologic effects in tissue similar to those of the megavoltage photons used in conventional therapy. They are regarded as low linear energy transfer particles, unlike other non-conventional radiotherapy particles, such as neutrons or carbon ions. The unique dosimetric features of the Bragg peak of proton therapy make it an attractive treatment modality of three-dimensional conformal external beam radiotherapy. The target dose inhomogeneity encountered with mixing photon and electron beams is thus overcome by the use of proton beams.

Proton beam therapy, however, is more costly than conventional treatment, and any potential benefits must be assessed in the light of the associated costs to the health-care system. Yet is reasonable to assume that the expense of proton therapy per patient will decrease, as more facilities are built and greater numbers of patients treated [Limbergen 2006, Weber 2006].

**INTRAOPERATIVE RADIOTHERAPY IORT**: Intraoperative radiotherapy with electrons delivers a single fraction of 21 Gy directly to the tumor bed after wide excision or quadrantectomy, using a mobile linear accelerator in the operation theatre. It has a low inhomogeneity index, with high sparing of surrounding tissue [Limbergen 2006].

**BRACHYTHERAPY**: This is a form of accelerated partial breast irradiation APBI technique in which multi-catheter or single catheter (e.g. MammoSite balloon) high dose rate HDR or low dose rate LDR inserts are used to deliver high doses to the target and lower doses to the OARs. It is mainly used for patients with a low risk of multi-focal, multi-centric or lymphatic recurrences [Limbergen 2006].

**INTENSITY MODULATED RADIOTHERAPY (IMRT)** was explored as a technique to improve breast dose homogeneity by decreasing hot spots and dose to normal tissues thus reducing acute and late toxicities. IMRT removes the usual reliance on flat (or uniform intensity) radiation fields and, instead, replaces that simple paradigm with a variable intensity pattern that is usually determined with the aid of a computerized optimization algorithm. Complex dose distributions are
achieved using irregular fluence maps obtained through optimization processes. Despite significant improvements in dose inhomogeneity have been demonstrated in these studies, enthusiasm for widespread use of IMRT for breast cancer was tempered because the breast was successfully treated with other modalities for many years, resulting in excellent local control rates, low rates of pulmonary and cardiac complications, and excellent cosmesis in most patients [Krueger 2003, Xiong 1973, Bhatnagar 2006, McDonald 2008].

The optimal dose range — i.e., the range that offers the greatest chance of locoregional control of breast cancer at the lowest cost in locoregional morbidity — appears to be 40 – 60 Gy in 2-Gy fractions [Højris 2000]. These optimal biologically equivalent doses (BEDs) permit comparison of the total dose delivered in different fractionation schedules. It is now clear that the dose of postoperative radiation therapy in some trials was inadequate or excessive according to the current understanding of the dose – response relationships for minimal residual breast cancer [Dewar 2007].

CONCLUSIONS

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