EVIDENCE FOR THE USE OF INNOVATIVE RADIATION TECHNIQUES FOR BREAST CANCER

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1 BENEFIT OF BREAST RADIOTHERAPY

Curative treatment for breast cancer consists of surgery, radiotherapy and systemic treatments such as chemotherapy, antihormonal therapy and targeted agents. The local treatment options are breast conserving treatment, consisting of breast sparing surgery followed by radiotherapy, and mastectomy with or without radiotherapy. Radiotherapy is used to eradicate occult microscopic disease in the breast, the chest wall and the draining regional nodal areas and has shown to decrease local recurrence rates and to improve survival with an absolute gain in breast cancer mortality of 8,1% at 20 years[1]. Those improved outcomes compare favourably to systemic chemotherapy as studied by the same group and methodology (6,5% absolute 10 y gain for anthracyclines, with an additional 2,8% gain at 8 years for taxane delivery)[2]. Hormonal treatment is associated with a 10,6% 15 year gain in breast cancer mortality[3].
The randomized studies from the 1970 -1980s usually delivered the radiation dose locally (breast or chest wall) and to the regional nodes[1]. The concept of stopping metastases at their source was understood[4].
In 2015, 3 major studies were published and demonstrated the additional value of nodal directed radiation, in addition to breast and post-mastectomy chest wall fields: the randomized trials EORTC 22922 trial[5] and NCIC MA 20[6] demonstrated a significant gain in metastases-free survival and breast cancer mortality, while a Danish population based cohort study demonstrated an improved overall survival with internal mammary irradiation[7]. The recent AMAROS study[8] suggests that after a positive sentinel node procedure, additional surgical clearance can sometimes safely be replaced by nodal irradiation.
Breast cancer is nowadays a highly curable disease that affects a large proportion of the Belgian population. High quality treatment should therefore not only focus on disease eradication but also on the quality of life of the long-term survivors. The introduction of innovative radiotherapy technology allows not only to improve the dose delivery to the target volumes, but also to better spare the normal tissues adjacent to the target volumes. For breast cancer patients this means that doses to the heart, lungs, oesophagus, thyroid and contralateral breast can be decreased substantially. The aim of the present paper is to describe how these new radiotherapy techniques can have an effect on normal tissue complication probabilities.

2 SIDE EFFECTS

Acute skin toxicity and impaired long-term cosmesis are well-known side effects of breast radiotherapy. In the acute phase dermatitis, moist desquamation, oedema and pain have been described[9]. Late breast toxicities include suboptimal cosmesis, breast shrinkage, telangiectasia, induration (fibrosis), oedema and pigmentation[10]. Both acute breast toxicity (in particular moist desquamation) and breast cosmesis have an impact on quality of life[9,11].

Pericarditis is the typical acute manifestation of radiation injury to the heart, while coronary artery disease, cardiomyopathy and valvular disease are possible late complications[12]. In the past, the heart was thought to be relatively radioresistant to the effects of radiation and damaged only by doses of ≥ 30 Gy. More recent data from several independent sources have provided substantial evidence that the mean heart dose of ≤ 20 Gy and even ≤ 5 Gy can increase the risk[13]. Darby et al. investigated the occurrence of major coronary events in 2168 women who underwent radiotherapy for breast cancer between 1958 and 2001[14]. They found that the rates of major coronary events increased linearly with the mean dose to the heart by 7.4% per Gray, with no apparent threshold. The increase started within the first 5 years after radiotherapy and continued into the third decade after radiotherapy.

Breast radiotherapy is also associated with an increased risk of radiation-induced pneumonitis, lung fibrosis and secondary lung cancer[15-17]. A prospective cohort study of more than 500,000 women in the US SEER cancer database showed a lung cancer mortality ratio in irradiated women, ipsilateral (irradiated side) versus contralateral (non-irradiated side), of 1.30[18]. This ratio increases with time since diagnosis of breast cancer, with no significant excess during the first 10 years. More than 20 years after diagnosis, the mortality ratio, ipsilateral versus contralateral, peaks to 3.87. The risk of developing a secondary lung cancer increases linearly per Gy extra lung dose[19,20]. For smokers the excess risk is significantly higher than for non-smokers[19].

3 TECHNIQUES TO REDUCE TOXICITY

3.1 IMRT/VMAT/HELICAL TOMOTHERAPY

Intensity modulated radiation therapy or IMRT is a technique in which the beams are subdivided in smaller beams of varying intensities to precisely irradiate the tumour. In breast radiotherapy the most common form of IMRT is based on 2 opposing beams, usually referred to as 'field-in-field IMRT'. For more complex targets, multiple beams are used, often referred to as 'full IMRT'. An alternative for full IMRT is VMAT (Volumetric Modulated Arc Therapy) or Helical Tomotherapy (HT).
Field-in-field IMRT allows to compensate for the complex 3D shape of the breast leading to an increased dose homogeneity in the breast and a decrease of the areas receiving excessive dose (hot spots) compared to 3D conformal radiotherapy (3D CRT). Several studies have demonstrated that IMRT therefore reduces the incidence of acute dermatitis, oedema, and hyperpigmentation. Less skin telangiectasia and improved cosmesis were also demonstrated[9,10,21].
Dosimetric studies confirm that full IMRT, VMAT and HT also provide excellent target coverage, improved dose homogeneity and conformity in the target volumes and reduced high doses to organs at risk (OAR) compared to 3D CRT[22-24]. However, in the same time these techniques often give low doses to larger volumes of normal tissues such as the contralateral breast, the lungs and the heart.[25-27]. Nevertheless, the risk to benefit ratio seems to be in favour of these techniques as opposed to 3D CRT in complex target volumes, such as funnel chest, tumour in the inner quadrant when internal mammary chain and tumour bed boost are indicated, large breast size, bilateral breast irradiation, patients with implants or unfavourable cardiac anatomy[24-26,28,29].

3.2 HYPOFRACTIONATION

Hypofractionation, in which a larger dose of radiation is delivered with each treatment, thereby reducing the total number of treatment days and the total dose, has been evaluated in several trials comparing 13 to 16 daily treatments to conventionally fractionated radiation, consisting of 25 daily treatments. Three large and recent randomised trials with 10-year follow up results are available[30,31]. With long-term follow-up, these studies have found equivalent rates of local/locoregional control and survival with similar or improved toxicity and cosmetic outcomes in favour of the hypo fractionated schedule.

In START-A moderate or marked breast induration, telangiectasia and breast oedema were significantly less common in the 39 Gy regimen patients group than in the 50 Gy regimen group. Moderate or marked normal tissue effects did not differ significantly between 41.6 Gy and 50 Gy (1).
In START-B moderate or marked breast shrinkage, telangiectasia and breast oedema were significantly lower with 40 Gy than with 50 Gy respectively 26,2% vs 31,2% (p:0.015), 4,2% vs 5,8% (p: 0.032) and 5,1% vs 9% (p:0.001) (1). In the Canadian study, at 10 years no significant differences in global cosmetic outcome were observed between the groups at any time.

3.3 RESPIRATION RELATED TECHNIQUES

Breathing-adapted radiation techniques can be engaged to take advantage of the respiratory motion by irradiating only in deep inspiration. In this respiratory phase, the heart moves inferiorly and posteriorly, enlarging the distance between the breast target volume and the heart. Studies examining the dosimetrical benefit of breathing-adapted radiation techniques for breast cancer patients have shown a clear reduction in cardiac doses[28,32]. A variety of strategies exist to perform breathing-adapted radiotherapy. For breast cancer patients, deep inspiration breath-hold (DIBH) techniques, free breathing respiratory-gated techniques or DIBH respiratory-gated techniques are used.

3.4 PARTIAL BREAST IRRADIATION

Partial breast irradiation (PBI), in which only the part of the breast where the tumour was removed – and not the whole breast – is irradiated, offers the benefit of sparing healthy tissue because a considerably smaller breast volume is irradiated. Patient Reported Outcomes Measures (PROM) from the IMPORT-LOW trial using IMRT revealed significantly less change in breast appearance in the PBI group[33] and interstitial brachytherapy lead to fewer grade 2–3 late skin side-effects[34]. Intra-operative radiotherapy (IORT) reduces overall skin side effects in comparison to WBI, particularly erythema, dryness, hyper-pigmentation and pruritus[35]. In comparison to WBI, PBI with IMRT can greatly reduce the radiation dose to the heart due to the ability of limiting the extension of the posterior field border and thus removing the heart from the treatment fields. In a case of left-sided breast cancer that is not located in the vicinity of the heart, the breast tissue close to the heart that would be irradiated with WBI can be excluded from the target volume. Interstitial Brachytherapy is less effective in reducing the heart dose than PBI with IMRT, but the heart dose can be lowered in comparison to WBI depending on the tumour location.
In a meta-analysis of 8 randomized trials comparing PBI with WBI, a higher rate of local recurrences was observed in the PBI group[36]. However, some studies indicate that PBI with IMRT or multicatheter interstitial brachytherapy might be as effective as WBI in terms of controlling local recurrences if the technique is restricted to rigorously selected patients[33,34,37]. These trials have, however, a limited follow-up of maximum 5 years.

3.5 PRONE POSITION

The prone position for whole-breast irradiation was first described in literature for large-breasted patients, who are at a higher risk of developing skin toxicity. In prone position, the breast hangs down through an aperture and due to gravity the breast becomes narrower and skin folds disappear, resulting in better dose homogeneity, less overdosages and less dose to the skin. This translates in improved acute skin toxicity and breast cosmesis as shown in a randomized trial comparing prone and supine breast irradiation[38,39]. Long-term outcome data are not yet available for prone breast irradiation. The New York University School of Medicine reports excellent locoregional control after a very limited follow-up of 5 years in 404 patients[40].

In prone position, the breast falls away from the intrathoracic organs by gravity. This translates in a reduced radiation dose to the lungs in whole-breast irradiation. Evidence in literature is very consistent: prone is superior to supine position for sparing of lung tissue and this in all patients regardless of breast size or other anatomical features[38,41-43].

Prone position is also an effective means of reducing heart dose compared to supine position in about 85% of patients[43]. In the remaining 15%, mostly small breasted females, there is a risk of increased radiation dose to the heart in prone position[41,43]. The latter problem might be solved by using respiration related techniques, which are also feasible in prone position[44].

Drawbacks of prone breast irradiation are the uncomfortable and complicated positioning procedure which is sometimes difficult to reproduce.

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5 LIST OF ABBREVIATIONS/DEFINITIONS

DIBH = deep inspiration breath hold
Technique used to reduce heart dose. Radiation is delivered while the patient holds her breath for a limited amount of time. In deep inspiration, the distance between the heart and the breast is increased.

3D CRT = 3-dimensional conformal radiotherapy
In 3D CRT, the shape of the beams is conform with the shape of the target volume, based on CT-images of the patient.

HT = helical tomotherapy
Technique of rotational IMRT or arc therapy with a 360° freedom of possible beam angles. HT uses a 6-MV accelerator mounted on a ring gantry that rotates around the patient while the table advances slowly through the bore as in a CT scan.

IMRT = intensity modulated radiation therapy
Type of 3D CRT in which the beams are subdivided in smaller beams of varying intensities to precisely irradiate the tumour. In breast radiotherapy the most common form of IMRT is based on 2 opposing beams, usually referred to as 'field-in-field IMRT'. For more complex targets, multiple beams are used, often referred to as 'full IMRT'. An alternative for full IMRT is VMAT or HT.

IORT = intra-operative radiotherapy
technique which consists of treating the tumour bed in the operating room immediately after the breast-sparing procedure. Several technical solutions have been designed to achieve this goal. In Europe, a commonly used IORT technique is to treat the tumour bed with an intra-operative linear accelerator that produces high energy electrons

Multicatheter Interstitial Brachytherapy
In this approach multiple catheters are inserted through the tumour bed which are subsequently loaded with radio-active sources.

OAR = organs at risk

PBI = partial breast irradiation
a form of radiation delivered after breast conserving surgery limited to the part of the breast where the tumour was removed. Three main PBI techniques are used in clinical practice 1) ***IMRT****, 2)* ***Multicatheter Interstitial Brachytherapy****., 3)* ***IORT (****intra-operative radiotherapy)*

VMAT = volumetric modulated arc therapy
A form of rotational IMRT or arc therapy in which the gantry rotates around the patient, giving the advantage of 360° of possible beam angles.

WBI = whole-breast irradiation