PH.D THESIS

MULTISEGMENTED CONFORMAL BREAST IRRADIATION

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Introduction

The treatment strategy for malignant breast cancer has changed dramatically in the last 20 years. Today the standard of care in terms of radiotherapy for the adjuvant treatment is [a total dose of] 50 Gy for the whole breast followed by 10-16 Gy boost [to the tumour bed]. The breast has traditionally been irradiated using two tangential fields (medial and lateral). The introduction of CT-based three-dimensional conformal (3D-CRT) treatment planning allowed treatment to be optimized through the use of individualised target volumes and beam directions. Despite this, breast radiotherapy remains a challenge due the concave target volume and the close proximity of organs at risk (e.g. lung, heart). With the help of the introduction of intensity-modulated radiotherapy (IMRT) it has become possible to adapt the dose-intensity within the irradiation field. However, this technology requires individual patient quality assurance and therefore the clinical implementation of IMRT needs adequate preparation and planning. This may be why it has not been widely introduced into daily clinical practice, despite its dosimetric advantages.

In the last decade several clinical studies have been initiated in early stage breast cancer, investigating the equivalence between accelerated partial breast irradiation (APBI) and whole-breast irradiation (WBI). Based on the recently completed and currently ongoing studies we are still lacking adequate long-term follow-up to provide the clinical evidence supporting the APBI approach. Therefore the area of whole vs. partial and external vs. interstitial breast irradiation needs to be carefully explored and investigated, especially with reference to the linear-quadratic model, to illustrate and predict several aspects regarding the different treatments.

Aims

My primary goal was to create a treatment technique which incorporates the advantages of both 3D-CRT and IMRT: short planning and treatment time without the need for individual patient QA and better PTV coverage and homogeneity with a reduction of the radiation burden for the organs at risk. The investigation aimed to assess the effect of the novel approach on treatment positioning and verification and on the neccesity of an additional machine QA procedure.

My additional goal was to compare the APBI and WBI approaches based on physical dose- and volume-distribution through an appropriately modified LQ-model.

The scientific achievements were measured through the SWOT (Strengths, Weaknesses, Opportunities, and Threats) analysis, to assess the difficulty and efficacy of the implementation into daily clinical practice.

Therefore I proposed to answer the following questions:

1. Is it possible to create a treatment approach that combines the advantages of the 3D-CRT and the IMRT?
2. What kind of additional measurements are needed for the safe introduction of the novel treatment technique?
3. Is it possible to introduce individual adaptation for treatment planning to reduce the effect of different breast shape and sizes?
4. What is the effect of the novel technique on the risk of secondary radiation-induced cancer?

5. How large are the systematic and random errors in treatmemt positioning? What is the (minimal) safety margin for the clinical target volume? Is our approach safe?
6. Is it possible to compare the APBI and the WBI approaches? If yes under what conditions?
7. What are the predictions for the clinical implementation of the different achievements from the SWOT analysis?

Patients and methods

Between January 2005 and February 2007 436 women from the University of Pecs Oncotherapy Department with breast cancer were treated with multisegmented conformal irradiation (MS-CRT). To generate the MS-CRT plan first a 3D-CRT plan was produced, then an optimized low-weight sub-field was added to the tangential fields. The 3D-CRT and MS-CRT plans were compared dosimetrically (target volume coverage, homogeneity, and the possible reduction of radiation burden on organs at risk and normal tissue) and, on top of this, the risk of secondary radiation-induced cancer was estimated based on published data. Comparison with other published techniques was performed based on patient population size, target volume range and the efficacy of the optimisation approach.

In a pilot study we compared the standard verification procedure (ST) and the ST extended by using an infrared reflective-based ExacTrac (ET) system. We investigated treatment position accuracy, derived the corresponding systematic (SE) and random errors (RE), and calculated the sufficient safety margin (SM).

We created a specific additional QA procedure for the machines to ensure adequate measurement and safety of delivery low monitor units (MU) within the MS-CRT delivery. Our threshold was a maximum of 2% error for each individual measurement, and 1% for the average error.

For the investigation of interstitial and external APBI versus external WBI we documented the inhomogeneity of the radiotherapy. This inhomegenity was incorporated into the LQ-model through an introduction of a dose-modification factor (DMF), in the following way:

$$\boldsymbol{BED_{DMF} = n \cdot d \cdot DMF \cdot \left(1 + \frac{d \cdot DMF}{\alpha/\beta}\right)}$$

BED is the biological equivalent dose, DMF is the dose modification factor, n is the number of fractions, d is the dose of each fraction and α/β ratio is the corresponding clinical factor for the outcome (tumour control, acute and late toxicity). The DMF range for external therapy is considered to be between 80-110% (based on the ICRU 50) and 20-200% for the interstitial brachytherapy.

For each achievement a SWOT analysis was performed with the following conventions for the different aspects:

- External aspect: related to the patients
- Internal aspects: effect on the internal workflow
- Positive
- Negative

Based on the evaluation matrix, a prediction was made on the efficacy and difficulty of introducing the technique into daily clinical practice.

Results

In the comparison of MS-CRT and 3D-CRT all three volumetric parameters (PTV<D95%, PTVD95-107% and PTV>D107%) and the maximum dose of the PTV (PTVDMAX) showed a beneficial effect for all 436 patients with MS-CRT compared to 3D-CRT. Statistical analysis (two-sided t-test) showed this difference to be statistically significant (p<0,001). Even though the PTV size varied in our patient population (279-3028 cm^3) the standard deviations of the PTV parameters were low for MS-CRT, which confirms the reproducibility of the adaptation of the technique for the individual patient. The mean doses to organs at risk did not show statistically significant differences, however the normal tissue maximum doses were significantly lower for MS-CRT (p<0,001). The planning required, on average, 15-20 minutes for the MS-CRT. The additional sub-segments required, on average, 7.6 MU (SD: 4.0), which is 4.2% increase in total MU compared to 3D-CRT. The estimated risk of secondary radiation-induced cancer was increased from 1% (3D-CRT) to 1.016-1.032% using MS-CRT.

Comparison of 3D-CRT and MS-CRT results based on treatment planning of 436 patients / Mean (SD)

	3D-CRT	MS-CRT	Significant?
$PTV_{95\text{-}107\%}$	82.8 (6.7)	90.9 (3.0)	Yes
$PTV_{<95\%}$	11.4 (3.4)	8.8 (2.8)	Yes
$PTV_{>107\,\%}$	5.9 (3.2)	0.3 (0.8)	Yes
PTV_{MAX}	56.6 (1.1)	54.3 (0.5)	Yes
ipsil. lung	10.5 (2.6)	10.4 (2.5)	**No**
contral. lung	0.4 (0.4)	0.4 (0.2)	**No**
contral. breast	0.8 (0.4)	0.8 (0.3)	**No**
heart (left tumour)	4.8 (1.7)	4.8 (1.7)	**No**

heart (right tumour)	1.4 (0.3)	1.4 (0.3)	**No**
normal tissue max	54.9 (1.5)	53.3 (0.8)	Yes
Total MU	**191.1 (6.2)**	**198.7 (7.7)**	

The MS-CRT treatments took 10 minutes on average, where the irradiation was performed first from the main segment followed by the sub-field for both tangential beams.

In four cases we performed an extensive pilot study through daily treatment verification. Two patients were positioned by the standard approach, meanwhile for the other two cases we extended it with the ET system. The calculated three-dimensional (cranio-caudal (CC), ventro-dorsal (VD), medio-lateral (ML)) errors were transferred to the SE, RE and the derived SM.

The systematic (SE) and random error (RE) and the derived safety margin (SM) in mm

	Standard positioning (CC, VD, ML)	**Standard with ET positioning (CC, VD, ML)**	**Standard with ET positioning IR-based**
SE	$(-2.9; 1.9; 1.5)$	$(-0.7; 0; 0)$	2.1
RE	$(3.6; 4.6; 4.8)$	$(1.4; 1.7; 2.1)$	0.9
SM	$(9.8; 8.0; 7.1)$	$(2.7; 1.2; 1.5)$	5.7

The markers did not cause difficulty for the patients (tolerability is good), however the entire treatment time increased by 2 min (20%) for each treatment session, due the time of the placement of the 5 markers. The positioning with ET reduced the (possible) safety margin by 6.6-7.1 mm, and almost eliminated the systematic error.

At the time of the introduction of the MS-CRT technique, we performed introductory measurements for the low MU fields for dose-MU

linearity at each photon energy. The 6 MV photon energy showed less than 2% error for each individual measurement (starting with 1 MU), and the average measurement error was less than 1% from 2 MU. The same conditions for 18 MV resulted in acceptable stability from 2 MU for individual measurements (with 2% thresholds) and for the average (with maximum 1% error). This confirms that regardless of the photon energy (6MV or 18MV) using larger than or equal to 2 MU fields is feasible. Based on the initial measurements the institutional machine quality assurance protocol was extended to have specific measurements on the low MU with adequate frequency.

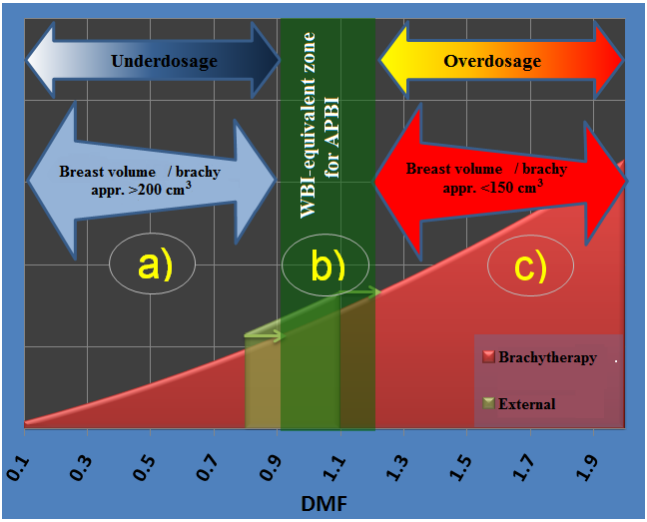
The calculation based on the LQ-model at 25x2 Gy and 10x3.75 Gy fractionation for BED tumour (BED10Gy) showed advantages of the „regular" 25x2 Gy approach for the each volumetric dose-inhomogeneity (i.e. that found in external WBI and that found in external APBI). The comparison related to the late toxicity (BED3Gy) resulted in similar ranges for the two approaches. DMF was introduced into the LQ-model to correct for the wide range of inhomogeneity (20-200%) in the breast volume. Single value-based comparison was performed (shown in the table below) and further graphical representations were produced for tumour/acute toxicity (BED10Gy) and for late toxicity (BED3Gy).

The result of the DMF corrected LQ-model calculation

	external WBI	**external APBI**	**brachy APBI**
DMF range (%)	90-110%	90-110%	20-200%
Dose per fraction	2 Gy	3.75 Gy	3.75 Gy
Nr. of fractions	25	10	10
BED10Gy	46.4-67.1 Gy	39.0-58.3 Gy	3.9-131.3 Gy

BED3Gy	61.3-95.3 Gy	60.0-98.0 Gy	4.2-262.5 Gy

The breast tissue (and its volume) can be projected into a function-effect line to represent the dose-distribution from interstitial brachytherapy.. The following illustration reflects the general representation of external WBI and brachy APBI:



Comparison of external WBI and brachy APBI for tumour control and acute toxicity (BED10Gy)

For individual brachytherapy the breast volume can be divided into three main categories based on BED: a) relative large and underdosed, b) adequately dosed and c) a small and overdosed volume. The effect of the b) and c) category will vigorously contribute to the late toxicity, since those part of the tissue represents a very high BED value (> 200Gy).

Based on the inhomogeneity and the overdosed volume, there is a possibility to define a sub-volume and a DMF range where the risk of acute toxicity is reasonably low. However this risk increases significantly for late

toxicity. The clinical results are likely to confirm that this happens in a DMF range of 1.5-2.0.

Conclusions

1. The described MS-CRT technique combines the advantages of 3D-CRT and IMRT: PTV coverage could be improved from a mean of 82.8% to 90.9% while the doses to organs at risk were unchanged; planning and the treatment time remained low (15-20 mins and 5-10 mins respectively). [1,3]

2. The MS-CRT technique introduced low MU fields compared to 3D-CRT. This required an adequate adjustment of the existing machine QA. My pilot investigation confirmed the feasibility of the use of low MU fields: individual measurements error did not exceed 2%, and the average of the errors remained under 1%.

3. Based on the comparison between 3D-CRT and MS-CRT using the treatment data of 436 treated patients, the standard deviations of the PTV coverage parameters reduced by the factor of two. This means that even though the PTV size differed substantially in our patient population (279-3028 cm^3) the MS-CRT technique could be reproduced and adapted to individual patients effectively. Based on the comparison of our approach with other published technique, we concluded that with the best MU/dose ratio we achieve better or equal results. In summary our technique surpasses the criteria of effective individual adaptation. [1]

4. Based on the published literature it is known that the risk of secondary radiation-induced cancers is about 1% with 3D-CRT, which increases to 1.75% by using 2-3 times more MU during IMRT. For our patient population with MS-CRT the MU increment remained low - on average 4.2% - compared to 3D-CRT, therefore our estimation of the risk of secondary radiation-induced cancer is between 1.016-1.032%.[1,3]

5. In four cases we performed daily treatment verification: for two patients we used the standard approach and for a further two we extended it with the ExacTrac system. The resulting safety margins for the standard approach were 9.8/8.0/7.1 mm (for cranio-caudal/ventro-dorsal/medio-lateral direction). These were reduced to 2.7/1.2/1.5 mm while using ExacTrac. Therefore with both approaches our MS-CRT technique can be safely delivered.[4]

6. External WBI vs. brachy APBI comparison based on LQ-model is not possible without taking the factor of dose inhomogeneity into consideration. A dose-modification-factor (DMF) was included in our LQ-model-based investigation to represent the existing volumetric dose-distribution. The DMF correction highlighted the fact that the overdosed volume (>200%) might be tolerable for acute toxicity but that this results in extremely high (>200 Gy) BEDs for late toxicity. This calculation confirms the clinical experience [2].

7. Results of the SWOT analysis

a) The MS-CRT technique should only affect one part of the treatment preparation workflow. In all other ways the treatment chain did not suffer any substantial changes. Therefore its introduction into daily clinical practice should be feasible without any major planning.

b) Using the ExacTrac system to increase the accuracy of patient positioning might be difficult, since its introduction alters several steps within the workflow, especially treatment delivery. The benefit of its introduction is also dependant on patient consent and compliance, which also requires a learning curve. Even with experienced staff the treatment time was increased by approximately 20%, which might limit practical usage. Our investigation is limited due the small number of patients, therefore larger number of patients need to be investigated to have a final conclusion on the feasibility of daily ExacTrac positioning.

c) Based on the DMF corrected LQ-model and the SWOT analysis the brachytherapy APBI is lacking feasibility on economic, dosimetric, and toxicity aspects, thereby highlighting why, as a standard treatment, it is not well-established on the evidence-based level. Until a patient population is properly identified that will benefit specifically from APBI, external treatment modalities should be employed and investigated preferentially.

Publications	
Cut-off date:	2010 May
Cumulative impact factor:	**28,978 (IF:2008)**
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