Accelerated partial breast irradiation with 3D-conformal and image-guided intensity modulated radiotherapy with low-risk invasive breast cancer after breast conserving surgery

Phd thesis

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Introduction

The complex oncological treatment of breast cancer has undergone through significant changes in the past decades. Today, the previous disease-centered approach has been replaced by a patient-centered approach that takes utmost account of the cancer's biological behaviour and the process of metastasizing. In recent decades, breast-conserving surgeries (BCS) and a 3-5-week whole breast radiation therapy (WBRT) aimed to kill any microscopic tumour cells that may remain in the breast have become universally accepted. Several prospective, randomized studies and their meta-analysis have also demonstrated that radiation therapy of the remaining breast reduces the rate of ipsilateral breast tumour recurrence by a third to a quarter, thereby also improves overall survival by preventing so-called secondary dissemination. Based on these results, the previously widely used removal of the whole breast (radical mastectomy) was replaced by BCS and WBRT. However, WBRT with conventional fractionation (1.8-2 Gy/day) lasted for 5-7 weeks, which was quite difficult for patients even in developed Western countries, including attending daily treatments, absenteeism, several weeks of hospital stay and absence from family. This is why many patients have refused BCS and opted for radical surgery to avoid long-term adjuvant treatment, or worse, in many cases, patients missed radiation therapy after BCS. In the 1990s, the rate of WBRT rejection following BCS in the United States was nearly 20%, and it has been demonstrated to have resulted in higher local recurrence rate and presumably a lower chance of survival for these patients. Researchers saw the solution in shortening the treatments, which can be achieved by increasing the daily dose of delivered fraction. However, the danger of increasing the daily fraction is, on the one hand, that it may increase normal tissue damage without achieving a significantly better cancer-destroying effect. However, another important determinant of normal tissue damage, in addition to the fraction dose, is the volume of irradiated tissue. At the turn of the 1980s and 1990s, for the reasons detailed above, the possibility of accelerated partial breast irradiation (APERT) of the tumour bed and its immediate area arose in several international and national working groups, shortening the overall treatment time to approximately 5-7 days. However, in the first such studies, launched in the UK at Guy's and Christie hospitals, the annual rates of local tumour recurrence were very high at 25-37%. In comparison, the recurrence rate after WBRT was 1- 2%/year at this time. This

very large difference is explained by the fact that at that time accurate patient selection criteria (patient selection protocols), uniform target volume definitions and quality assurance criteria were not yet available. The first APERT studies with appropriate patient selection and quality assurance were performed with interstitial brachytherapy, and the results of these studies have already come close to the 1% annual local recurrence rate of WBRT. Since the early 2000s, thanks to the development of radiotherapy devices, the spread of 3D-conformal and imaging-guided, intensity-modulated radiation therapy techniques has made it possible to use APERT in a non-invasive manner. From 2006, we launched a sequential phase II clinical trial at the National Institute of Oncology, performing APERT at first with 3D-CRT, and from 2014 with IG-IMRT. I chose APERT as the topic of my dissertation because, due to rapidly evolving diagnostics, a significant proportion of breast tumours are discovered at an early stage, so physicians may consider this radiation therapy technique at an increasing number of patients as an alternative to WBRT. Given that it is a low-risk group of cancer patients with good prognosis and long expected survival, in addition to the safety of treatments, it is very important to minimize the rate of late side effects and to provide patients with an acceptable quality of life and cosmetic results. In my dissertation, I describe the introduction of 3D-CRT and IG-IMRT methods in Hungary, the definition of the CTV-PTV safety zone required for the application of IG, and I report on the clinical results of the first 104 patients, the side effects of the treatments and the cosmetic results.

Objectives

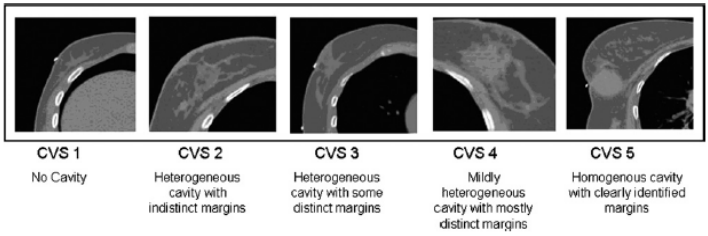
The objectives of the dissertation are:

- introducing APERT with 3D-CRT and IG-IMRT in a prospective, sequential, phase II study into clinical practice.
- evaluating the effectiveness of treatments with 7-year clinical results.
- analysis of early and late side effects as well as cosmetic outcomes.
- dosimetric comparison and evaluation of APERT with 3D-KRT and IG-IMRT.
- determining the size of the CTV-PTV safety zone (SZ) required during imaging-guided APERT in different directions.

Methods and materials

As a new procedure, we performed the first partial accelerated breast irradiation with 3D-CRT at the Department of Radiation Therapy of the National Institute of Oncology in December 2006. By 2011, 44 patients were enrolled in our study. In 2011, at the National Institute of Oncology, imaging-guided intensity-modulated radiation therapy became available, so from July 2011 to March 2014, 60 patients were enrolled in the phase II sequential study and partial accelerated breast irradiations were performed with IG-IMRT. Our study was carried out with the permission of the local institutional ethics committee and the ETT TUKEB, and it was registered on the ClinicalTrials.gov website with number NCT02003560. All subjects included in the study were informed verbally and in writing and gave their written consent to the investigation. Prior to their enrolment in the study, a CT scan of the operated breast was performed to decide whether the tumour bed can be determined. For the objective evaluation of this, the so-called “cavity visibility score” (CVS) was used to classify postoperative tumour bed visibility on a 5-point scale. Patients with low visibility scores (CVS 1-3) were not included in the study (Figure 1).

Figure 1. CVS scores and cavity visibility on CT slices



CT slices from patients used for radiation therapy planning were made with 5-mm-slices in supine position using a reproducible, armrest-equipped table setup. Radiation therapy of patients treated with 3D-CRT was performed after X-ray simulation, during which the isocenter of the irradiation was marked on the patient's skin. With the help of these markings, fast and accurate patient adjustment was possible on the accelerator, and any minor deviations were corrected by moving the control table based on the electronic field control images. The total dose delivered to PTV in all patients was 9 x 4.1 Gy (total dose: 36.9 Gy). Treatment was performed with 3-6-field, isocentric, non-coplanar, wedged photon beams. In patients treated with IG-IMRT, the lateral and longitudinal wall-mounted lasers were aimed at the tattooed reference skin points prior to treatment. During radiation planning, we determine the so-called reference point in the patient based on these markings. Based on the radiation plan, according to the LAT, LONG and VERT differences between the reference point and the irradiation center (isocenter), the table was adjusted so that the lasers pointed to the isocenter. The patient's determined isocenter was marked with 3 spherical radiopaque skin markers, and before each fraction, the table (with the patient on it) was rotated 180 degrees, and serial images were taken of the target volume with a rail-track-mounted kilovoltage CT in the treatment room. Subsequently, automatic image registration was performed on the plan and verification CT images based on soft tissue and bone anatomy using image fusion software, then patient alignment error was determined in three directions (LAT, LONG, VERT) and correction was performed by automatically moving the treatment table. After the automatic image registration, a visual check was also performed each time to check the spatial adjustment of the two image sequences. Automatic image registration was performed on the plan and verification CT images based on soft tissue

and bone anatomy using image fusion software, then patient alignment error was determined in three directions and correction was performed by automatically moving the treatment table. During patient follow-up, acute adverse reactions were recorded and classified according to the RTOG/EORTC system between the 7th and 14th days after the end of radiation therapy. Evaluation of the cosmetic result was performed by both the patients and the examining physician before the start of and 3, 6 and 12 months after the radiation therapy, and then annually. Cosmetic results were also documented with digital photographs and graded on a 4-point scale (excellent, good, adequate, bad) based on Harvard criteria. Late adverse events (fibrosis and dermal side effects) were also evaluated according to the RTOG/EORTC classification system every 3 months for the first 2 years and then every six months. To assess fat necrosis, we used the classification system previously developed by our working group. Curves of different survival parameters (LRFS, DFS, OS, MFS) were calculated using the Kaplan-Meier method.

CTV-PTV safety zone

The dimensions of the CTV-PTV safety zone (SZ) in different directions were determined based on the Herk formula, which takes into account the systematic (Σ) and random (σ) error of patient setup for a given patient population (108). The use of a safety zone calculated from the formula ensures that in 90% of the patients, the PTV receives 95% of the specified dose. A systematic error is any error that occurs during each treatment fraction, i.e. its effect is repetitive. Random errors occur to varying degrees in different fractions, their effect is smaller than systematic errors. The size of the CTV-PTV safety zone is the sum of systematic and random errors:

$$\mathbf{BZ = 2{,}5 \times \Sigma + 0{,}7 \times \sigma.}$$

Results

Dosimetric comparison of 3D-CRT and IG-IMRT APERT

In terms of target volume coverage, the mean dose of PTVeval for both techniques were 36.9 Gy. There were no significant differences between the two techniques in either PTVeval, CTV $V_{95\%}$ or CTV $V_{90\%}$. Regarding the organs to be protected, examining the ipsilateral breast, better results were obtained with the IG-IMRT technique than with 3D-CRT. The $V_{100\%}$ values of the ipsilateral breast were 7.2% and 10.3% with IG-IMRT and 3D-CRT, while the $V_{50\%}$ values were 35.3% and 44.1%, respectively. In the same volume, D_{max} was 103.9% for 3D-CRT and 104.6% for IG-IMRT – the difference was not significant. The contralateral breast was better protected with 3D-CRT, V_{10} and V_5 were 0%, while with IG-IMRT, the same parameters were 8.1% and 0.3%, respectively. Significantly better results were obtained with non-coplanar 3D-CRT in the radiation burden of the ipsilateral lung. Compared to 3D-CRT, V_{10} and MLD values for IG-IMRT were significantly higher for the ipsilateral lung: 10% vs. 34%; and 4.7% vs. 8.5%, respectively ($p<0.01$ for both). However, IMRT plans are no longer inferior to the 3D-CRT technique for higher doses. The $V_{5\%}$ of the contralateral lung was significantly lower with the 3D-CRT technique (0%) than in IMRT plans (8%; $p<0.001$). With the 3D-CRT technique, the maximum dose of the contralateral lung and breast was on average 0.3 and 0.5 Gy, respectively, while with the intensity-modulated technique, mean values between 3 and 4 Gy were obtained for both volumes. Regarding the heart, a significantly lower load was noted with the 3D-CRT technique: in the case of left side breast tumours, cardiac V_5 and V_{15} values were 1.5% and 0.1%, respectively, while with IMRT, they were 22.6% and 2.9%. The same difference was noted in right side tumours, with V_5 and V_{15} at 0% and 0% with 3D-CRT, and 16.8% and 0.7% with IMRT, respectively. The contralateral lung and breast received low doses in both techniques. Detectable results and differences are present only in 5% of the prescribed dose, higher loads were not received by any contralateral organ. Overall, 3D-CRT can be used to perform treatments at a lower integral dose and to better protect the organs at risk with the exception of the ipsilateral breast. With static IMRT, we were able to achieve a more homogeneous dose distribution with excellent conformity, however, the radiation burdens of the organs at risk proved to be higher. However, the dose restrictions we set were always followed.

The average tumor size was 12 mm (range: 5-30mm). The average PTV_EVAL volume was 152.6 cm^3 (range: 42.0-460.7 cm^3), the average PTV/whole breast rate was 0.17 (range: 0,05-0,40) volt. The 95% dose coverage of CTV and PTVEVAL (V95CTV and V95PTV_EVAL) averaged 99.9% (range: 96-100%) and 99.6% (range: 95-100%), respectively. The 90% dose coverage of CTV and PTVEVAL (V90CTV and V90PTV_EVAL) averaged 100% (range: 99.9-100%) and 99.9% (range: 99.3-100%), respectively. The dose covering at least 90% of PTVEVAL (D90) averaged 98.6% of the prescribed dose. The Dmax of the treated breast was 104.8% (range: 99.2–117%). The mean MHD and V5 hearts were 3.8% (range: 0.5–15.3%) and 17.4% (range: 0–48.3%) on the left and 1.5% (range: 0–4.6%) and 6.45% (range 0-34.6%) for right breast irradiation. For the mean ipsilateral lung, the MLD and V10 lungs were 8.5% (range: 1.5–19%) and 26.6% (range: 2–58%), while for the contralateral lung, 1.5% (range: 0, 3–6.2%) and 10.5% (range: 0–30.5%), respectively.

After a median follow-up of 90 months (range: 67–156), three (2.9%) local tumor recurrences occurred, all three in the 3D-KRT arm at 54, 88, and 126 months after radiotherapy. All three patients underwent complete removal of the remaining breast and are all currently alive. The mean time to ipsilateral breast tumor recurrence (IBTR) was 7.4 years (SD 1.3; range: 4.5–10.5). The 7-year IBTR rate was 1.1% (95% CI: +/- 2.1). Also, one patient (0.9%) had contralateral breast cancer at 24 months of follow-up, resulting in breast-conserving surgery and whole breast irradiation. Thus, the 7-year contralateral breast tumor rate was 1.0% [95% CI: +/- 1.9]). The 7-year regional relapse rate (RR) was 1.0% (95% CI: +/- 1.9). Overall, the 7-year locoregional relapse rate (LRR) was 2.0% (95% CI: +/- 2.8). During follow-up, two (1.9%) distant metastases (DM) and 7 (6.7%) second primary tumors were detected. The 7-year distant metastasis rate was 3.1% (95% CI: +% - 4.3). 6 (5.8%) patients died at follow-up, 1 of whom (0.9%) had breast cancer-related death due to multiple bone metastases. The 7-year overall survival (OS) was 94.8%. The early and late side effects as well as the cosmetic results are summarized in Table 1.

Figure 1. Early, and late side effects, cosmetic results with 3D-CRT and IG-IMRT

n=104	Grade 0	Grade 1	Grade 2	Grade 3-4
Early side effects				
Skin	48 (46.2%)	54 (51.9 %)	2 (1.9 %)	0 (0%)
Breast parenchyma	61 (58.7%)	43 (41.3%)	0 (0%)	0 (0%)
Pain	76 (73.1 %)	26 (25 %)	2 (1.9 %)	0 (0%)
Late side effects				
Skin	89 (85.6 %)	15 (14.4%)	0 (0%)	0 (0%)
Fibrosis	74 (71.2 %)	26 (25%)	3 (2.9 %)	1 (0.9%)
Fat necrosis	94 (90.4 %)	10 (9.6 %)	0 (0%)	0 (0%)
Pain	97 (93.3 %)	7 (6.7 %)	0 (0%)	0 (0%)
Cosmesis	**Excellent**	**Good**	**Fair**	**Poor**
Rated by physician	57 (54.8 %)	40 (38.5 %)	7 (6.7 %)	0 (0%)
Rated by patients	57 (54.8 %)	41 (39.5 %)	6 (5.7 %)	0 (0%)

As an early side effects G1 and G2 erythema was occurred in 54 (50.9%) and 2 (1.9%), G1 oedema in 43 (41.3%) and G1 and G2 pain in 26 (25%) and 2 (1.9%) patients. Grade 3-4 acute side effects were not observed. After a 6-year follow-up period, late side effects as G1 pigmentation were occurred in 15 (14.4%), G1, G2 and G3 fibrosis in 26 (25%), 3 (2.9%), 1 (0.9%) and G1 fat necrosis in 10 (9.6%) patients. G1 pain was observed in 8 (7.7%) patients. G2 or worst late side effects was not occurred with IMRT. The ratio of excellent and good cosmetic results was 93.3%, fair / poor results in 7 patients (6.7%), all of whom were in the 3D-KRT arm. Digital photo documentation of side effects and cosmetic results was also prepared.

IV.3. Verifying the CTV-PTV safety zone

The size of the CTV-PTV safety zone was calculated using the van Herk formula from the data of 1620 patient setup inaccuracies determined during CT verifications performed before 60 patients' 540 treatments. Based on our results, the size of the 1-cm CTV-PTV safety zone used in patients previously treated with 3D-CRT can be safely reduced to 5 mm using daily imaging guidance. According to our calculations, owing to image-guided therapy, PTV volume could be reduced by an average of 32% with IG- IMRT, and on average, 9% less of the ipsilateral breast's volume had to be irradiated than with 3D-CRT (without imaging guidance).

Figure 2. Systematic and random errors, the size of the CTV-PTV margin with image guidance calculated with the van-Herk formula

	LAT	Deviation LONG	VERT	LAT	Scattering (SD) LONG	VERT
Average error (range)	1,4 (0,4-2,8)	0,1 (0,2-2,8)	0,1 (0,1-2,8)	1,5 (0,4-2,5)	2,0 (0,5-2,6)	1,5 (0.,7-2,2)
Systematic error	1,6	1,5	2,0			
Random error	1,5	2,1	1,5			
PTV safety zone	**5,1 mm**	**5,0 mm**	**6,1 mm**			

Conclusions

- In the framework of a sequential, phase II clinical trial, we introduced accelerated, partial breast irradiation with three- dimensional conformal radiation therapy and imaging- guided, intensity-modulated external radiation therapy into Hungarian clinical practice.
- We demonstrated that its efficacy and safety are comparable to WBRT, and we developed dose-volume specification parameters and dose limits for use in radiation planning.
- Based on our results, APERT with 3D-CRT or IG-IMRT with appropriate technical parameters and quality assurance can be used as an alternative to WBRT and APERT with interstitial brachytherapy outside clinical trials.
- With daily image-guidance the CTV-PTV safety zone can be reduced to 5 mm thus, a significant reduction in the target volume can be achieved, which can lead to milder side effects.
- The advantage of the 3D-CRT technique is that it delivers small doses to small volumes and spares the organs at risk well thanks to its tangential field layout. Thanks to the high degree of conformality of IMRT, it minimizes the side effects expected in the ipsilateral breast, and significantly shorter treatment times can be achieved with it, however, it results in a higher load to some organs at risk.

List of publications

Publications related to the theses:

1. **Mészáros N**., Smanykó V., Major T., Stelczer G., Levente J., Zaka Z., Pukancsik D., Takácsi-Nagy Z., Polgár Cs.: Implementation of Stereotactic Accelerated Partial Breast Irradiation Using Cyber-Knife – Technical Considerations and Early Experiences of a Phase II Clinical Study. Pathol Oncol Res 2020 May 29. doi: 10.1007/s12253-020-00821-3. Online ahead of print**. IF: 2,826**
2. **Mészáros N**., Major T., Stelczer G., Zaka Z., MózsaE., Pukancsik D., Takácsi-Nagy Z., Fodor J., Polgár Cs.: Implementation of image-guided, intensity modulated accelerated partial breast irradiation – Three-year results of a phase II clinical study. Strahlenther Onkol Jan; 193 (1):70-79. 2017 **IF: 2,898**
3. Mózsa E., **Mészáros N**., Major T., Fröhlich G., Stelczer G., Sulyok Z., Fodor J., Polgár C.: Accelerated partial breast irradiation with external beam three-dimensional conformal radiotherapy. Five-year results of a prospective phase II clinical study.Strahlenther Onkol 190 (5):444-50 (2014). **IF: 2,914**
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Publications on the topic of the dissertation are an aggregate impact factor: 17,833

Other publications:

1. Smanykó V, **Mészáros N,** Újhelyi M, Fröhlich G, Stelczer G, Major T, Mátrai Z, Polgár C.: Second breast conserving surgery and interstitial radiotherapy for the treatment of breast tumor local recurrences. Five-year results. Orv Hetil. Mar;159(11):430-438. (2018) IF: **0,564.**
2. Smanyko V., **Meszaros N**., Újhelyi M, Fröhlich G, Stelczer G, Major T, Mátrai Z, Polgár C.: Second breast-conserving surgery and interstitial brachytherapy vs. salvage mastectomy for the treatment of local recurrences: 5-year results. Brachyterapy May - Jun;18(3):411-419. (2019) **IF: 2,030.**
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   Stelczer G, Tatai-Szabó D, Major T, **Mészáros N**, Polgár C, Pálvölgyi J, Pesznyák C.: Measurement of dose exposure of image guidance in external beam accelerated partial breast irradiation: Evaluation of different techniques and linear accelerators. Phys Med. 2019 Jul;63:70-78. **IF: 2.485**

The overall impact factor of the author of the dissertation: 33,072.