Local treatment of ipsilateral breast recurrences: a comparative analysis of alternative therapeutic options

PhD thesis

Viktor Smanykó, MD

Doctoral School of Pathological Sciences
Semmelweis University

Supervisor: Csaba Polgár, MD, D.Sc.

Official reviewers: Szabolcs Bellyei, MD, Ph.D.
Attila Marcell Szász, MD, Ph.D.

Head of the Complex Examination Committee: Janina Kulka, MD, D.Sc.

Members of the Complex Examination Committee: Nóra Bittner, MD, Ph.D.
Róbert Farkas, MD, Ph.D.

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1. Introduction

In 2020, female breast tumor exceeded lung cancer as the leading cause of worldwide malignancy incidence, with an estimated 2.3 million new discovered patients, representing 11.7% of all cancer cases. Among women, it is the fifth leading cause of cancer mortality globally with 685 000 deaths.

Nowadays, the standard of care for early-stage breast cancer is breast-conserving surgery (BCS) followed by postoperative whole breast irradiation (WBI) to destroy any microscopic tumor cells that may remain in the breast. In spite of appropriate local treatment, the rate of ipsilateral breast tumor recurrence (IBTR) has been reported to be within the range of 6 to 8% in 10 years, and 10 to 15% in 20 years. Several treatment-, tumor-, and patient-related factors correlate with a higher risk of IBTR, e.g. the omission of adjuvant RT, histological grade, age of the patient, magnitude of the surgical margin, multifocal or multicentric tumors, perilymphatic or vascular invasion, and extensive in-situ component. IBTR is associated with an increased risk of distant metastases and breast cancer death.

Reappearance of malignancy in the ipsilateral breast could be due to recurrence of residual disease or a new primary tumor. Although new primary malignancies have a better prognosis than true recurrences, they do not in themselves affect the type of salvage treatment.

In the cases of IBTR, salvage mastectomy (sMT) is historically considered as the gold standard treatment. According to the literature, the rate of the second ipsilateral breast tumor recurrence (2^{nd}IBTR) is nearly 10% after sMT (range: 0-22%). However, in spite of the favorable recurrence rate, it should be considered that patients undergoing sMT may suffer from reduced self-esteem and impaired body self-image, also may develop physical and emotional distress, which impair quality of life.

Therefore, a large proportion of patients would prefer a second breast-conserving surgery (2^{nd}BCS), resulting in a better cosmetic result and quality of life. But unfortunately, the rate of 2^{nd}IBTR after repeated BCS – without re-irradiation of the remaining breast – has been reported to be as high as 28% (range: 7-50%). Theoretically, re-irradiation after 2^{nd}BCS may reduce the possibility of a third ipsilateral breast tumor, but unfortunately a

second course of irradiation to the whole remaining breast with an adequate dose is considered inappropriate due to the high risk of severe late side effects.

Accelerated partial breast irradiation (APBI) performed with multicatheter interstitial brachytherapy (MIBT) has been successfully used as postoperative RT after BCS in a defined group of patients with low-risk primary breast cancer. In the conventional approach the percutaneous catheters are inserted a few weeks after surgery, when the complete pathological report of the resected tissue is available. An alternative technique is the intraoperative catheter implantation, which allows for direct visualization of the excision cavity, consequently more accurate placement of the catheters, and which is intended to avoid the need for a second invasive procedure.

Introduced in the late 1970s, the concept of the second breast-conserving therapy (2^{nd}BCT) consists of a repeated surgical procedure (lumpectomy or wide excision) with external beam or brachytherapy (BT) re-irradiation limited only to the tumor bed of the recurrent cancer.

Although 2^{nd}BCT has an abundant literature, the oncological efficacy of the treatment has never been directly compared with the gold standard sMT.

2. Objectives

The objectives of the dissertation are:

1. To present the technique of intraoperative catheter implantation and perioperative breast brachytherapy, and analyze the dosimetric results of the method.

2. To evaluate the 5-year clinical efficacy of second breast-conserving surgery with re-irradiation using perioperative high-dose-rate (HDR) multicatheter interstitial brachytherapy (MIBT), compared to standard salvage mastectomy (sMT).

3. To analyze the late side effects and cosmetic results after second breast-conserving therapy (2^{nd}BCT).

3. Methods

We identified 195 patients who had an IBTR following a prior breast-conserving therapy (BCT) between 1999 and 2016. For the treatment of the first breast cancer, all women underwent BCS (wide local excision or lumpectomy) and either sentinel lymph node biopsy or axillary block dissection. Adjuvant RT consisted of 46 to 50 Gy WBI.
After detailed information and discussion about the treatment methods available, 39 patients who refused sMT underwent 2ndBCS (wide re-excision) and perioperative HDR MIBT. The other 156 women were treated with standard sMT.
Patients were treated with 2ndBCT when all of the following inclusion criteria were met:
- unicentric, parenchymal tumor recurrence, without regional or distant metastasis,
- size of the tumor was ≤ 3 cm based on clinical, mammographic, breast ultrasound or breast MRI examination,
- recurrence at least 2 cm distance from the skin surface,
- favorable expected tumor bed / breast volume ratio after repeated BCS,
- and the patient's strong preference for 2ndBCT.

Exclusion criteria were the multicentric or multifocal IBTR.

During re-operation, the walls of the excision cavity were marked with 6 radiopaque titanium clips. With an open surgical wound, depending on the volume of the cavity an average of 8 metal guide needles in 1 to 3 planes were inserted in the tumor bed freehand, without template guidance, spaced 10-15 mm apart and forming equilateral triangles, according to the rules of the Paris system dosimetric method. Afterward, the guide needles were replaced with flexible hollow plastic catheters and secured with fixation buttons on both side of the skin. At the end of the implantation, the wound was closed with sutures. After histological confirmation of the lesion and measurement of the microscopic surgical margins (on approximately the third or fourth postoperative day), CT-based computerized treatment planning was performed of the implanted breast. As a target volume, the tumor bed extended by an additional margin (20 mm minus the intact surgical margins given in the six main directions) was contoured by excluding a 5 mm rim of subcutaneous tissue beneath the skin surface and the pectoral muscle.
During treatment planning, active source positions and dwell times within the catheters were determined to obtain a conformal dose distribution and achieve the best dose

homogeneity, target coverage and the lowest possible dose to organs at risk (heart, ribs, lung, skin, ipsilateral non-target breast, and contralateral breast).

Patients were treated with a microSelectron® or a Flexitron® HDR remote afterloading unit using an Iridium-192 isotope source with 370 GBq initial activity (Elekta Brachytherapy, Veenendaal, The Netherlands). A total dose of 22 Gy was delivered to the target volume, in 5 fractions of 4.4 Gy, with a twice-a-day fractionation, provided at least 6 hours apart and over 3 consecutive days. Following the last fraction, the catheters were removed, and after a few hours of observation the patients were discharged home.

The following dose-volume parameters were used for quantitative evaluation of plans: $V_{PTV,}$ V100, V150, and V200, D90 and D100, D_{mean} (non-target breast), $D_1(x)$ and $D_{0.1}(x)$ (x = heart, ribs, ipsilateral lung, skin, contralateral breast).

The following parameters were calculated for quantitative analysis of dose distributions regarding dose homogeneity and conformality: Dose nonuniformity ratio (DNR), Dose homogeneity index (DHI), Conformal index (COIN), Coverage index (CI).

After analyzing patient data, we found that the distribution was equal between the two treatment arms in the patients related parameters, such as age, menopausal status, and mean time to recurrence.

Although the mean size of the IBTR was significantly larger in the sMT group than in the 2^{nd}BCT group (25 mm vs. 16 mm, p=0.0005), no other significant difference was found in the pathological characteristics of the recurrent tumors between the two groups (e.g., margin status, histologic type and grade, receptor status).

As systematic treatment, most of the patients had chemo- or hormonal therapy in both treatment groups (90% and 87%, p=0.18).

Based on the location and histological type relationship of the first and second tumor, approximately four-fifths of the IBTR can be considered to be true recurrences, and a quarter as second primary tumor, in both groups.

During follow-up, patients were controlled every 3 months in the first 2 years after salvage treatment, then every 6 months in the first 5 years, and every year thereafter.

The cosmetic results were assessed by the Harvard criteria. Skin side effects and fibrosis were scored by the RTOG/EORTC (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer) late radiation

morbidity scoring system. To assess fat necrosis, we used the classification system previously developed by our working group.

The primary oncological endpoint of this study was the 5-year cumulative incidence of a 2nd IBTR. Secondary oncological endpoints were the 5-year overall survival, the 5-year cumulative incidence of regional relapse, the 5-year cumulative incidence of distant metastasis, the 5-year cumulative incidence of disease-free survival and the 5-year cumulative incidence of specific survival.

The actuarial rates of specific events and survivals were calculated using the Kaplan-Meier method. Survival curves were compared using the log-rank (Mantel-Cox) test. The statistical significance was considered at $p < 0.05$.

4. Results

4.1. Dosimetric evaluation of perioperative multicatheter interstitial brachytherapy with intraoperative catheter implantation technique

At the 2nd BCS with an open surgical cavity, a median of 8 (range: 4-24) flexible hollow plastic catheters in 1 to 3 planes were placed in the tumor bed.

The mean volume of the PTV was 58 cm^3 (range: 21-130 cm^3).
Dose-volume parameters for the PTV are presented in the Table 1.
Based on this data, with the technique of intraoperative catheter implantation we were able to keep the dose exposure of the organs at risk at a sufficiently low level, with a conformal dose distribution, appropriate dose homogeneity and target coverage.
These dosimetric data are comparable with our previous results of ABPI for primary breast cancer, executed by the postoperative catheter implantation technique.

Table 1. Dose-volume parameters and quality indices for perioperative multicatheter interstitial brachytherapy. Reference dose: 5x4.4 Gy. Values refer to 1 fraction.

Dosimetric characteristic	Mean	Range
Mean volume of treated breast (cm^3)	831.7	407.8–1858.9
PTV / treated breast ratio	0.07	0.02–0.16
V100 (%)	85.8	71.2–94.7
V150 (%)	41.0	29.3–59.3
V200 (%)	18.7	11.3–45.0
D90 (%)	93.0	70.6–105.6
D100 (%)	56.2	18.3–78.3
DNR	0.4	0.24–0.53
DHI	0.59	0.46–0.75
COIN	0.51	0.17–0.96
CI	0.86	0.71–0.94
D_{mean} (non-target breast) (Gy)	1.45	1.08–1.84
D_1 (heart)* (Gy)	1.12	0.41–2.26
$D_{0.1}$ (heart)* (Gy)	1.30	0.55–2.49
D_1 (ribs) (Gy)	2.93	1.39–6.34
$D_{0.1}$ (ribs) (Gy)	3.58	1.65–9.33
D_1 (ipsilateral lung) (Gy)	2.11	0.91–3.75
$D_{0.1}$ (ipsilateral lung) (Gy)	2.39	1.13–4.04
D_1 (skin) (Gy)	2.72	1.14–7.15
$D_{0.1}$ (skin) (Gy)	3.16	1.31–4.68
D_1 (contralateral breast) (Gy)	0.08	0–0.13
$D_{0.1}$ (contralateral breast) (Gy)	0.13	0.02–0.25

V100, V150, V200: volume of planning target volume (PTV) received x% of the reference dose, D90, D100: the minimum dose delivered to 90 and 100% of PTV, DNR: dose nonuniformity ratio, DHI: dose homogeneity index, CI: coverage index, COIN: conformal index. Gy: gray, D_{mean} (non-target breast): the mean dose of non-target breast, D_1 (x) and $D_{0.1}$ (x): the minimal dose of the most exposed 1 and 0.1 cm^3 of 'x' organ at risk, *: only in left-sided tumors.

4.2. Comparing the 5-year oncological outcome of second breast-conversing therapy to salvage mastectomy

No significant difference was found regarding the total follow-up time (up to 189 months) neither in second ipsilateral breast tumor recurrence-free survival (p=0.22) nor in regional recurrence-free survival (p=0.77), neither in distant metastasis-free survival (p=0.24) nor in disease-free survival (p=0.13), neither in cancer-specific survival (p=0.32) nor in overall survival (p=0.15), after 2ndBCT or sMT.
No significant difference was found regarding the 5-year median follow-up times either.

At a median follow-up of 59 months, a 2ndIBTR detected in 4 women (10.2%) in the 2ndBCT group, and at a median follow-up of 56 months in 28 patients (17.9%) in the sMT group. The 5-year actuarial rate of 2ndIBTR was 6% after 2ndBCT vs. 18% after sMT (p=0.16) (Figure 1.).
Ipsilateral axillary lymph node metastasis detected in 2 patients (5.1%) in the 2ndBCT group, and in 11 women (7.1%) in the sMT group. The 5-year probability of regional recurrence-free survival was 94% after 2ndBCT vs. 95% after sMT (p=0.62) (Figure 2.).
The 5-year probability of distant metastasis-free survival was 76% vs. 74% in the 2ndBCT and the sMT group (p=0.41) (Figure 3.).
The 5-year probability of disease-free survival was 69% after 2ndBCT vs. 65% after sMT (p=0.20) (Figure 4.).
The 5-year probability of cancer-specific survival was 85% vs. 78% (p=0.51), respectively (Figure 5.).
And the 5-year probability of overall survival was 81% vs. 66% (p=0.12), in the same order (Figure 6.).

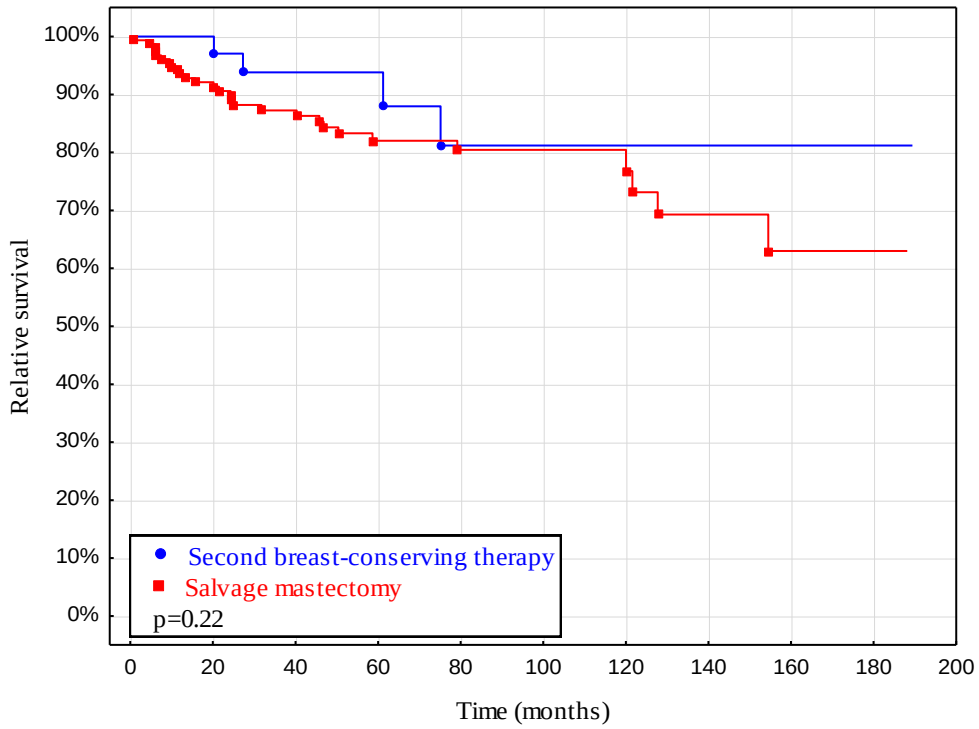

Figure 1: Second ipsilateral breast tumor recurrence-free survival after second breast-conserving therapy or salvage mastectomy.

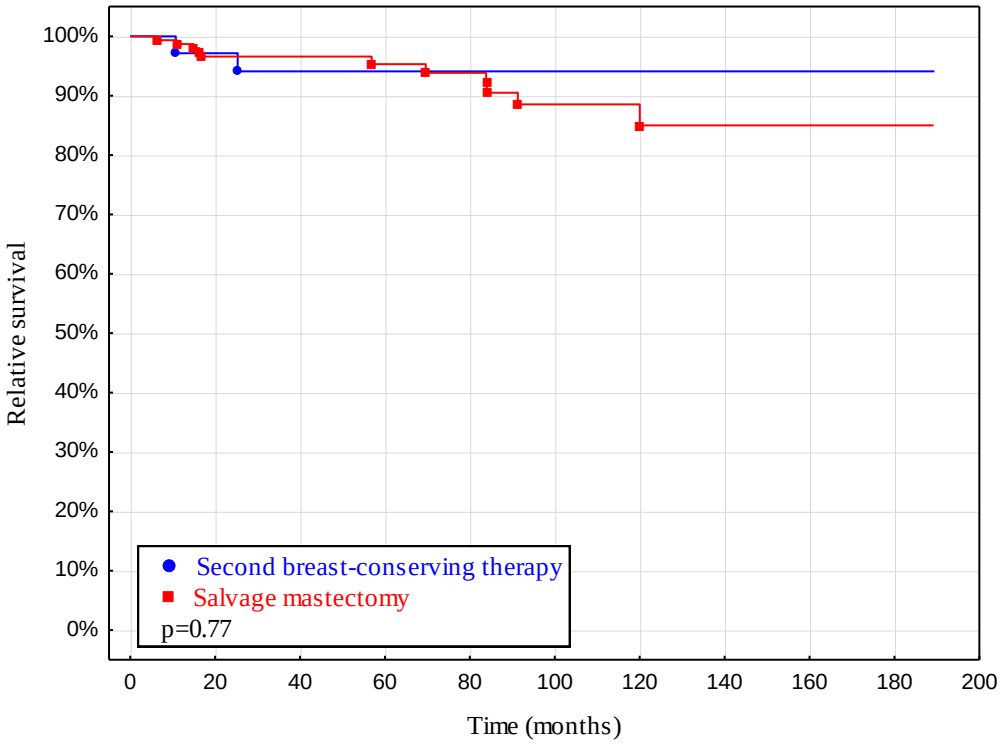

Figure 2: Regional recurrence-free survival after second breast-conserving therapy or salvage mastectomy.

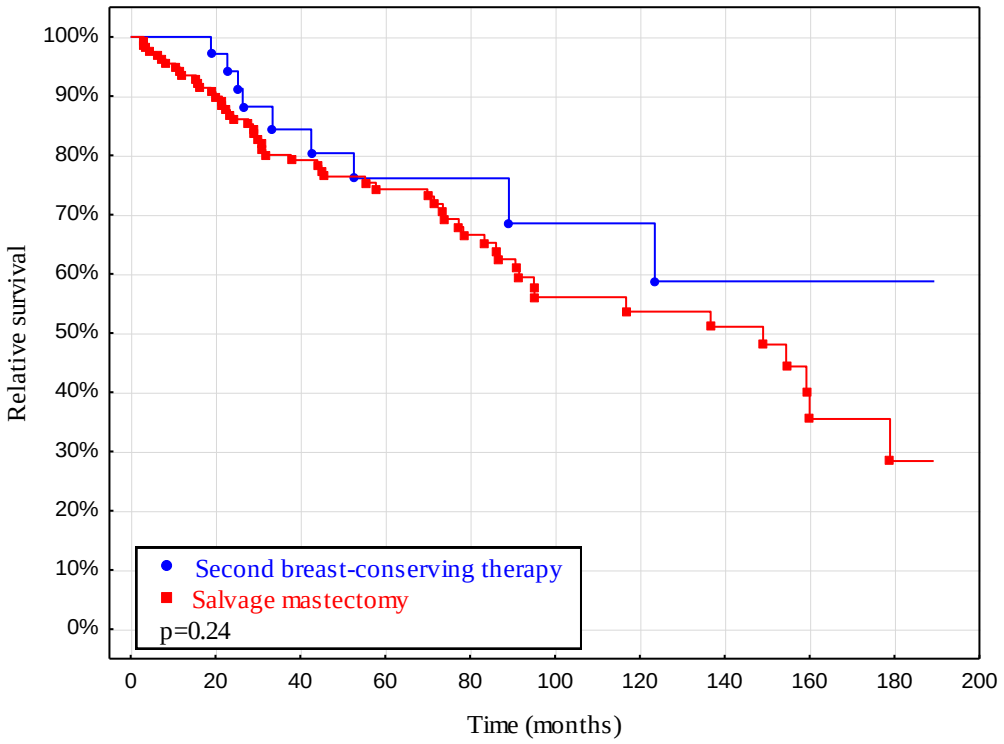

Figure 3: Distant metastasis-free survival after second breast-conserving therapy or salvage mastectomy.

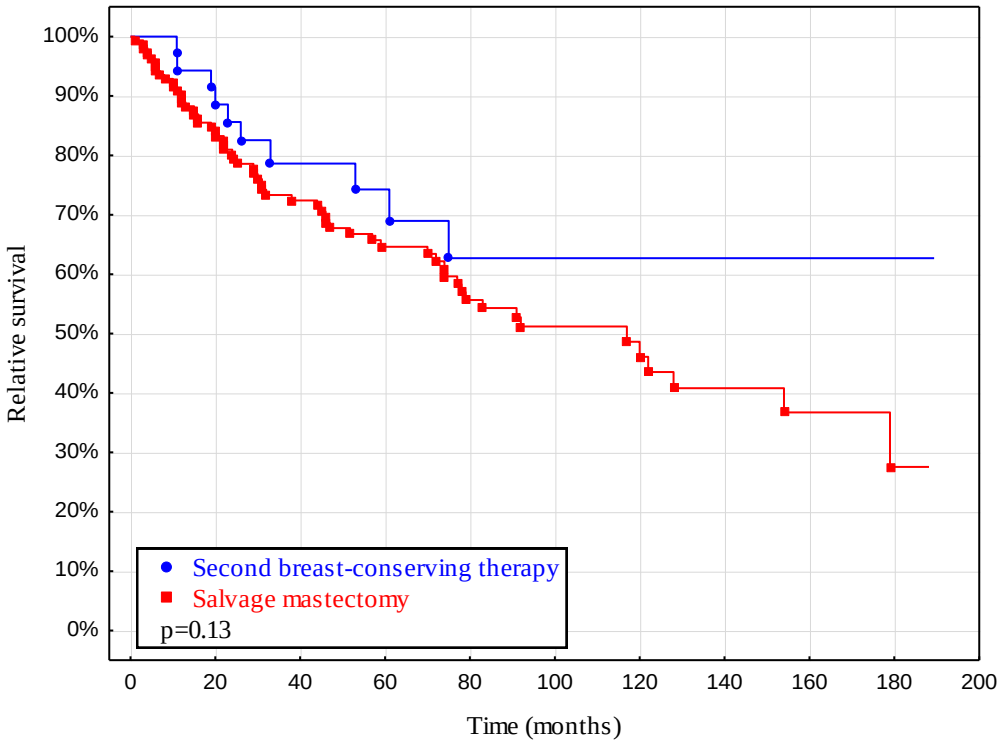

Figure 4: Disease-free survival after second breast-conserving therapy or salvage mastectomy.

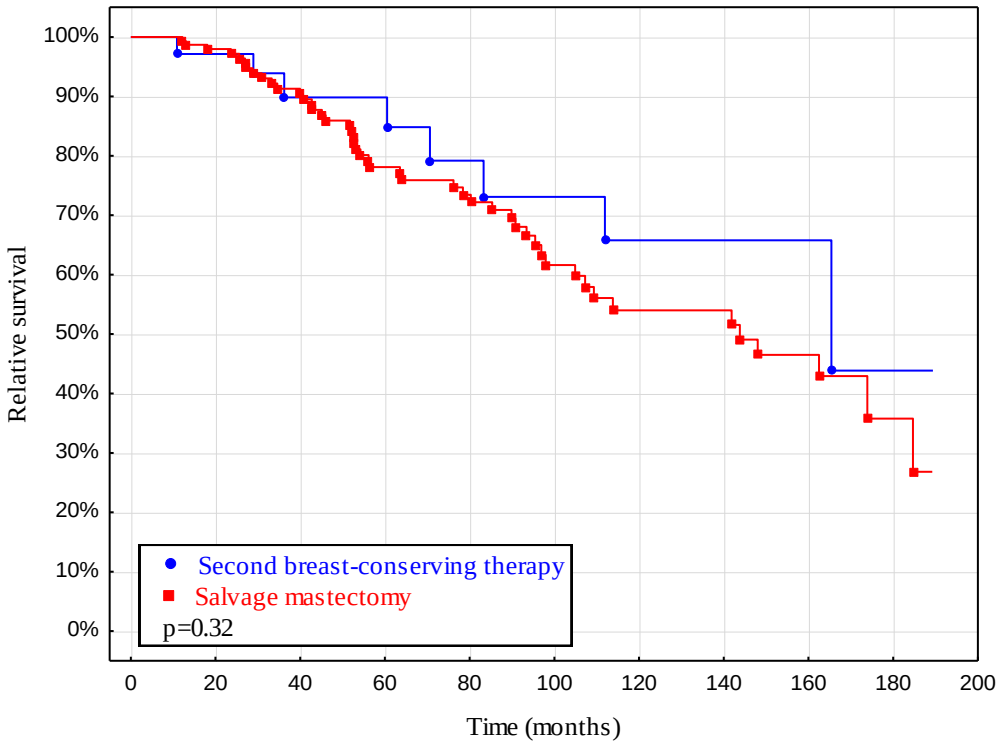

Figure 5: Cancer-specific survival after second breast-conserving therapy or salvage mastectomy.

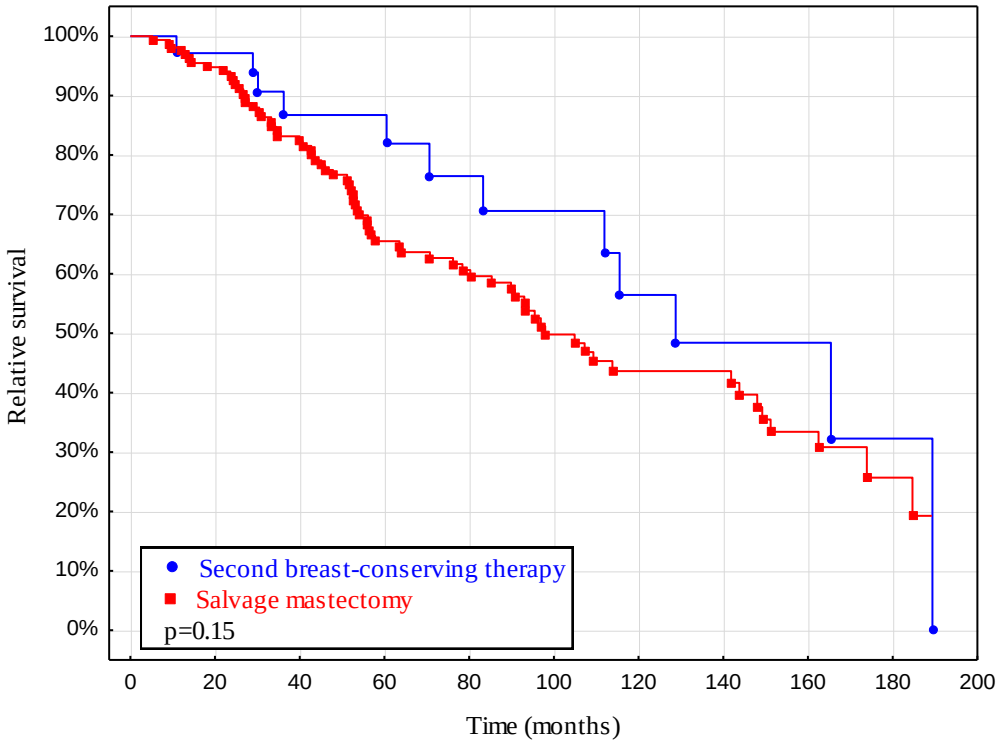

Figure 6: Overall survival after second breast-conserving therapy or salvage mastectomy.

4.3. Late side effects and cosmetic results after second breast-conserving therapy

After the 2ndBCT, cosmetic results were evaluated based on the Harvard criteria schema. Among these, 4 (10%), 23 (60%), 6 (15%), and 6 patients (15%) had excellent, good, fair, and poor cosmetic results, respectively. According to the RTOG/EORTC classification system, grade 2 and 3 late skin toxicity occurred in 11 (28%) and 3 patients (8%), and grade 2 and 3 fibrosis developed in 9 (23%) and 1 patient (2%), respectively. Asymptomatic fat necrosis was detected in 7 women (18%) and required no further surgical intervention.

5. Conclusions

1. In 1999, we implemented perioperative BT with intraoperative catheter implantation for the treatment of recurrent breast tumors. The evaluation of dosimetric and qualitative data are consistent with our previous results of ABPI for primary breast cancer, executed by postoperative catheter implantation technique, but the intraoperative method doesn't need a second invasive intervention for the patients. Since then, this approach has been routinely used in our clinical work.

2. This study was the first, which directly comparing 2ndBCT to sMT in patients who were treated at the same institute and during the same period. Based on the results, 2ndBCS with perioperative HDR MIBT results in equivalent, statistically non-inferior 5-year oncological outcomes for the management of IBTR, with regard to second local recurrence-free survival, regional recurrence-free survival, disease-free survival, distant metastasis-free survival, cancer-specific survival, and overall survival, compared to a standard sMT.

3. Second BCT is a safe treatment option with a low rate of late side-effects, yielding excellent or good cosmetic results in the majority of patients, with better patient satisfaction and quality of life, compared to the sMT.

6. Bibliography of the candidate's publications

List of publications on the topic of the dissertation:

English-language peer-reviewed publications:

1. Smanykó V, Mészáros N, Újhelyi M, Fröhlich G, Stelczer G, Major T, Mátrai Z, Polgár C. (2019) Second breast-conserving surgery and interstitial brachytherapy vs. salvage mastectomy for the treatment of local recurrences: 5-year results. Brachytherapy, 18: 411-419.
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   IF:0,564

The cumulative impact factor of publications on the topic of the dissertation: 10,43.

Peer-reviewed publications not closely related to the topic of the dissertation:

1. Kelemen P, Pukancsik D, Újhelyi M, Sávolt Á, Kovács E, Ivády G, Kenessey I, Kovács T, Stamatiou A, Smanykó V, Mátrai Z. (2019) Comparison of clinicopathologic, cosmetic and quality of life outcomes in 700 oncoplastic and conventional breast-conserving surgery cases: A single-centre retrospective study. Eur J Surg Oncol, 45: 118-124.
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6. Fröhlich G, Mészáros N, Smanykó V, Stelczer G, Herein A, Polgár C, Major T. (2021) Is stereotactic CyberKnife radiotherapy or multicatheter HDR brachytherapy the better option dosimetrically for accelerated partial breast irradiation? Brachytherapy, 20: 326-331.
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   IF:1,315

Cumulative impact factor of the author of the dissertation: 33,304.