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

PhD thesis

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List of Abbreviations

2ndBCS: second breast-conserving surgery

2ndBCT: second breast-conserving therapy

2ndIBTR: second ipsilateral breast tumor recurrence

ACROP: Advisory Committee for Radiation Oncology Practice

APBI: accelerated partial breast irradiation

BCS: breast-conserving surgery

BCT: breast-conserving therapy

BT: brachytherapy

CI: coverage index

COIN: conformal index

CT: computer tomography

CTV: clinical target volume

CVS: cavity visibility score

DCIS: ductal carcinoma in situ

DEGRO: Deutsche Gesellschaft für Radioonkologie

DHI: dose homogeneity index

DNA: deoxyribonucleic acid

DNR: dose nonuniformity ratio

EBRT: external beam radiotherapy

EIC: extensive in-situ component

ER: estrogen receptor

ESTRO: European Society for Radiotherapy and Oncology

ETT-TUKEB: Egészségügyi Tudományos Tanács - Tudományos és Kutatásetikai Bizottság (Medical Research Council - Committee on Scientific and Research Ethics)

GBq: gigabecquerel

GEC-ESTRO: Groupe Européen de Curiethérapie – European Society for Radiotherapy and Oncology

Gy: gray

HDR: high-dose-rate

HIPO: hybrid inverse planning optimization

HR: high-risk

IBTR: ipsilateral breast tumor recurrence

IGRT: image-guided radiotherapy

IMRT intensity-modulated radiotherapy

IR: intermediate-risk

LDR: low-dose-rate

LINAC: linear accelerator

LR: low-risk

MIBT: multicatheter interstitial brachytherapy

MRI: magnetic resonance imaging

OAR: organ at risk

PD: prescribed dose

PDR: pulsed-dose-rate

PLI: perilymphatic invasion

PR: progesterone receptor

PTV: planning target volume

RR: relative risk

RT: radiotherapy

SLNB: sentinel lymph node biopsy

sMT: salvage mastectomy

WBI: whole breast irradiation

1. Introduction

1.1. General 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 first leading cause of cancer mortality globally with 685 000 deaths [1]. According to the National Cancer Registry, in 2019 a total of 8244 new cases were reported, while 2174 patients died of breast cancer in Hungary [2].

From both pathological and clinical points of view, breast cancer is not a specific disease, but a group of malignant lesions of the breast. Several classifications of breast cancer have been developed, attempting to identify the predictive and prognostic features of each category. The most commonly used classification relates to immunohistochemical characteristics (estrogen receptor, progesterone receptor, Her-2 receptor, Ki-67 status), histological grade, TNM, and the staging system based on it [3]. Hereditary gene mutation is present in approximately 5-10% of breast cancer cases, while 90-95% of occurrences are sporadic. In the etiology of sporadic breast cancers, long-term estrogen effects caused by early first menstruation, late menopause, hormonal contraception, and old age hormone replacement play key roles. High-fat diets, alcohol consumption, and smoking can also increase the risk of breast cancer. However, there is also evidence of a protective effect of early childbearing, breastfeeding, and physical activity [4].

Although the incidence of breast cancer is increasing, breast cancer mortality in developed countries has been on a downward trend in recent years. This is due to the introduction of mammography screening and increasingly effective local and systemic oncological treatments. Mammography screening for women aged between 45 and 65 has been centrally organized and funded in Hungary since 2001. The affected population receives invitations to participate biannually. Unfortunately, the 40-45% participation rate is below the desired target of 70-80%.

The complex therapy of breast cancers is an excellent example of multidisciplinary treatments involving surgery, radiation and clinical oncology. With an increasing incidence rate of early-stage breast cancer, the management has been continuously developing from mutilating mastectomy, which was the benchmark until

the 1980s, to the breast-conserving radio-surgical multidisciplinary approach. Nowadays, the standard of care for early-stage breast cancer is breast-conserving surgery (BCS) followed by postoperative radiotherapy (RT) to destroy any microscopic tumor cells that may remain in the breast [5-7]. A meta-analysis of several prospective, randomized studies has demonstrated that RT of the residual breast reduces the rate of ipsilateral breast tumor recurrence (IBTR) by three quarters, and also reduced the risk of breast cancer death (absolute reduction 3.8% at 15-year) by preventing secondary dissemination [8]. Based on these results from the 1980s, BCS and whole breast irradiation (WBI) consisting of 25 daily fractions (2 Gy/day, 5 fractions/week, total dose of 50 Gy) became a generally accepted treatment for early-stage invasive breast cancer.

BCS is not a uniform surgical procedure, its extent ranges from tumorectomy (meaning that the tumor is excised with minimal surgical margin), through wide local excision (lumpectomy, meaning that the tumor is excised with a 1 cm clear parenchyma without the skin and fascia), to quadrantectomy (meaning that the tumor is excised with a margin of 2 cm, along with the skin above the tumor and the pectoral fascia).

WBI generally consists of an opposed tangential field arrangement, using computer tomography (CT)-based 3-dimensional treatment planning, and is performed with a linear accelerator (LINAC). During treatment, patients are in supine position, with their head turned contralaterally, arms raised above their head, and fixed in a patient fixation device (breast board).

The site of the resected cancer is referred to as a tumor bed. During surgery, the margins of the tumor bed (walls of the excision cavity) are marked with 4-6 radiopaque titanium clips. In a study, Bartelink et al. showed that 10-16 gray (Gy) additional (boost) irradiation delivered only to the tumor bed after a 50 Gy of WBI further reduces the risk of local recurrence. After a median follow up of 17.2 years of 5318 randomized patients, the 16 Gy boost reduced the 20-year cumulative incidence of IBTR by 4.4%, but demonstrated no difference in overall survival [9].

In spite of adequate local treatment, the rate of IBTR (true recurrence or second primary tumor) has been reported to be within the range of 6 to 8% in 10 years, and 10 to 15% in 20 years [7, 8, 10]. However, the published incidences do vary significantly between series due to differences in extent of surgery, patient selection, and usage of adjuvant systematic treatment and RT.

1.2. Risk factors for local recurrence in the breast

Several treatment-, tumor-, and patient-related factors are correlated with a higher risk of IBTR.

Omission of adjuvant RT after BCS of the residual breast increases the rate of IBTR by 75% [6, 8].

It is controversial whether histological grade is also a risk factor for IBTR. Some researcher report that the risk of IBTR increases with an increasing grade. For example, in the study of Sinn et al., the 5-year recurrence-free survival rates of grade I and grade II carcinomas were very similar (97% and 95%), but for grade III tumors the figure was 86% ($p<0.001$) [11]. While others have found no such association [12], higher histologic grade predicted an increased incidence of distant metastasis (15% in grade I vs. 29% in grade III tumors at 10 years ($p=0.002$) [13].

Age is one of the most confirmed risk factors for IBTR after breast-conserving therapy (BCT). In the EORTC Boost vs No Boost Trial, the cumulative incidence of IBTR at 20 years was 34%, 14%, and 11%, in patients 40 years or younger, 41 to 50 years old, and 50 years or older, respectively ($p<0.001$) [14]. According to Elkhuizen et al., in terms of the probability of IBTR, patients <45 years old had a relative risk (RR) of 4.09, while patients 45–65 years old had a RR of 2.41 compared to patients >65 years old ($p=0.001$ and $p=0.044$) [15]. Nixon et al. reported that the group of patients younger than 35 years is a significant predictor of IBTR compared with patients 35 to 65 years old (36% vs. 24% at 5 years, $p=0.002$, RR: 1.71) [16].

Several studies have reported a significantly increased rate of IBTR in patients with positive surgical margins compared to those with negative surgical margins. Although it is commonly accepted that a positive margin is defined by the presence of tumor cells immediately at the resection edge, the definitions of negative or close margins vary between the studies. In the study of Schnitt et al., a positive margin was defined as a tumor being present at the inked margin of resection, a close margin as a tumor within 1 mm, and a negative margin as no tumor within 1 mm of the inked edge. The 5-year IBTR rates among patients with negative, close, and positive margins were 0%, 4%, and 21%, respectively (p-value not reported) [17]. In the study of Gage et al., using the same surgical margin classifications the 5-year rate of IBTR was 3% for negative and 2% for close margin patients ($p=0.87$), vs. 16% for patients with positive margins ($p<0.001$) [18].

In the study of Freedman et al., margins of excision were classified as negative if tumor cells were more than 2 mm, or close if tumor cells were less than 2 mm from the inked edge. Patients with a negative surgical margin have a low risk of IBTR (7% at 10 years), however patients with a close or positive margin have identical risk (12% and 14%) (p=0.04) [19]. In the study of Pittinger et al., the margin status was given as negative if it was more than 3 mm, and close if it was 3 mm or less. The 3-year rates of IBTR were 3%, 3%, and 25%, of the negative, close, and positive margin groups, respectively (p-value not reported) [20]. Differences in definitions of margin assessment make it difficult to determine the extent of the increased risk associated with margin involvement. But irrespective of the method and the definition used, the status of the surgical margin does provide an indication of the risk of IBTR.

In the case of multifocality, there are at least two invasive or in situ tumor foci in the same quadrant, separated by intact breast tissue. In multicentricity, the tumors are located in different quadrants in the breast. Even when the identified multiple foci are completely resected, patients with multiple tumors are at an increased risk of IBTR after BCS. The higher the number of multiple foci, the greater the chance of IBTR [21]. Nowadays, by choosing the right oncoplastic methods and precise localization techniques, if the size of the breast allows, multifocal and, less frequently, multicentric tumors can be removed with a sufficiently intact margin. An important prerequisite is a perfect preoperative diagnosis, of which breast magnetic resonance imaging (MRI) is a desirable part. If these conditions are met, the higher IBTR rate can be reduced to an acceptable level. Nevertheless, BCS in multifocal or multicentric breast tumors should not be considered as a routine procedure [22-24].

Invasion of cancer cells into blood and/or lymphatic vessels has been shown to be associated with an increased hazard of IBTR. In the study of Clemente and coworkers, the probability of developing IBTR at 7 years was 5% for perilymphatic invasion (PLI)-negative patients and 38% for PLI-positive patients (p=0.0001) [25]. According to the study of Voogd et al., the 10-year actuarial rates of IBTR after BCT was 15% for patients with vascular invasion and 8% for those without vascular invasion (p=0.003) [26].

In the EORTC Boost vs. No Boost Trial, the cumulative incidence of IBTR at 20 years was 18% and 9% for tumors with and without ductal carcinoma in situ (DCIS) (p<0.001) [14]. Sinn et al. also found that the proportion between the in-situ component

and the invasive carcinoma was significantly related to the presence of IBTR. Patients with an extensive in-situ component (EIC) had a 5-year recurrence-free survival of 85% vs. 95% in patients with a small or no in-situ component ($p< 0.001$) [11].

The presence or absence of estrogen or progesterone receptors, the total tumor size, and the axillary lymph node status was not significantly related with IBTR [11, 27].

1.3. True recurrence or new primary tumor

Re-appearance of malignancy in the ipsilateral breast could be due to recurrence of residual disease or a new primary tumor. According to the literature addressing this question, true recurrences are cases consistent with re-growth of malignant cells not removed by surgery and not eradicated by adjuvant RT. However, new primary tumors are new malignancies arising from residual breast tissue, and the incidence is the same as in the contralateral breast.

With increasing time interval, an increasing percentage of IBTR is located elsewhere from the tumor bed in the breast. This difference confirms the hypothesis that early recurrences are caused by cell repopulation due to persistent tumor cells, whereas late recurrences are more probably attributable to a new primary tumor origination. The majority of recurrences after 10 years could be considered as new primary tumors [28-31]. About 90% of the IBTR are invasive cancers, and 10% are non-invasive cancers [32]. Subsequent literature suggests that new primary malignancies have a better prognosis than true recurrences, especially for overall and metastatic-free survival [30, 31, 33].

Although both types of neoplasm should be considered, they do not in themselves affect the type of salvage treatment.

1.4. Prognostic impact of ipsilateral breast tumor recurrence

IBTR is associated with an increased risk of distant metastases and breast cancer death after BCS and postoperative RT [34, 35]. The estimated magnitude of the increased hazard of distant metastases is two to five times higher, and the increased mortality is in the range of two to four times [34-36]. The risk decreases with increasing time from treatment of IBTR [36].

A greatly contested topic is whether the IBTR by itself can cause dissemination of tumor cells, leading to distant metastases, or if it is only a marker for a more aggressive disease.

According to a hypothesis of Halsted [37], breast cancer is a localized disease initially, spreading sequentially, firstly to the lymph nodes, then later to the blood vessels causing distant metastases through hematogenous dissemination. This means that effective treatment must recognize this orderly, coherent spread of the disease.

An alternative hypothesis by Fisher [38] is that breast tumor is a systemic disease from the beginning. Nodal involvement is not an orderly, contiguous extension, but rather an indicator of distant disease. Local treatment may influence the risk of IBTR, but local control is not important for survival. An IBTR is undoubtedly associated with a worse survival rate, but it is simply an indicator of poor prognosis. Although Fisher's hypothesis is more generally accepted, it is questionable for several reasons. For example, early treatment of screening-detected breast cancers has led to a lower mortality [39], and postoperative RT can improve overall survival (the "One-to-Four Rule") [8].

According to the Spectrum Hypothesis of Hellman – an intermediate concept between the Halsted's and Fisher's hypotheses – breast cancer is a heterogeneous disease, ranging from one that remains local, through to one that is systemic when first discoverable [40]. Persistent cancer, locally or regionally, can be the origin of distant metastases, therefore – in contrast to the Fisher's theory – locoregional therapy is important. As a consequence, for patients with non-systemic tumor at primary operation, loco-regional treatment (surgery and postoperative RT) appears to be of significant role to improve survival results. In patients in whom microscopic metastases are present at the time of the primary surgery, residual disease leading to IBTR has less prognostic significance.

1.5 Surgical-only management of ipsilateral breast tumor recurrence without radiotherapy

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%) [33, 41-55]. 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 [56, 57].

Therefore, after detailed discussion and information, 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. A conservative approach may be considered after a careful assessment of surgical feasibility, which should take into account the dimension of the IBTR, its focality, and the size of the breast in order to achieve a cosmetically acceptable result. 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%) [33, 41-48, 58-61].

A comparison of the results of these two treatment methods has been published previously, and is now summarized in Table 1. [62].

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.

Table 1. Results of second breast-conserving surgery (2ndBCS) without radiotherapy versus salvage mastectomy (sMT) (Smanykó V, 2019 [62]).

Author	Median FUP (months)	No. of patients		2ndIBTR (%)		5-year 2ndIBTR (%)		5-year OS (%)	
		2ndBCS	sMT	2ndBCS	sMT	2ndBCS	sMT	2ndBCS	sMT
Salvadori B [41]	73	57	133	14%	3%	19%	4%	85%	70%
Fodor J [42]	165	32	32	28%	16%	NR	NR	81%*	81%*
Dalberg K [43]	72	14	65	50%	18%	33%	12%	NR	NR
Voogd AC [33]	52	20	229	40%	22%	NR	NR	NR	NR
Alpert TE [44]	165	30	116	7%	7%	NR	NR	58%*	66%*
Komoike Y [45]	43	30	11	30%	0%	37% †	0%†	90% †	91% †
Abner AL [46]	39	16	123	31%	6%	NR	NR	NR	79%
van der Sangen MJC [47]	NR	8	89	50%	11%	NR	NR	NR	NR
Kurtz JM [48]	35	34	36	9%	3%	22%	4%	NR	NR
Doyle T [49]	44	-	112	-	3%	-	NR	-	86%
Beard HR [50]	55	-	59	-	12%	-	NR	-	NR
Botteri E [51]	60	-	121	-	15%	-	NR	-	73%
Lindford AJ [52]	66	-	60	-	10%	-	NR	-	93%
Tanabe M [53]	55	-	118	-	9%	-	9%	-	NR
Recht A [54]	32	-	65	-	8%	-	37%	-	NR

Table 1. Results of second breast-conserving surgery (2ndBCS) without radiotherapy versus salvage mastectomy (sMT) (continued) (Smanykó V, 2019 [62]).

Author	Median FUP (months)	No. of patients		2ndIBTR (%)		5-year 2ndIBTR (%)		5-year OS (%)	
		2ndBCS	sMT	2ndBCS	sMT	2ndBCS	sMT	2ndBCS	sMT
Osborne MP [55]	28	-	46	-	15%	-	45%	-	76%
Kurtz JM [58]	72	52	-	23%	-	21%	-	79%	-
Kurtz JM [59]	51	50	-	32%	-	38%	-	67%	-
Gentilini O [60]	81	161	-	29%	-	29%	-	84%	-
Ishitobi M [61]	40	78	-	22%	-	21%	-	NR	-
Present study	56	-	156	-	18%	-	18%	-	66%
Range for all patients	**28-165**	**582#**	**1571#**	**7-50%**	**0-22%**	**19-38%**	**4-45%**	**67-85%**	**66-93%**

FUP: follow-up period; 2ndBCS: second breast-conserving surgery; sMT: salvage mastectomy; 2ndIBTR: second ipsilateral breast tumor recurrence; OS: overall survival; NR: not reported; *****: 10-year actuarial rate; †: 3-year actuarial rate; #: total number of patients.

1.6. Accelerated partial breast irradiation (APBI)

WBI for 5-7 weeks has caused many difficulties for patients, even in developed countries (travel for daily treatments, absence from work, hospital stays of several weeks), which in many cases involved the omission of necessary irradiation. Clinicians have seen a solution in shortening the treatments, which can be achieved by increasing the daily dose of fraction. Therefore, during the 1980s and 1990s it was suggested that an accelerated partial breast irradiation (APBI) – giving irradiation only to the tumor bed and its immediately surrounding tissue – could be an appropriate compromise between WBI and complete abandonment of RT.

Postoperative WBI is based on the premise that microscopic tumor cells may remain anywhere in the remaining breast. A study found that tumor cells can be up to 4 cm from the main tumor mass [63]. However, later pathological studies, which excluded high-risk cases (EIC or invasive lobular cancers), found that microscopic tumor spread beyond 2 cm from the index tumor occurs only rarely in cases with unfavorable histology characteristic [64-66]. Vicini et al., in their pathological processing of 333 breast specimens, also found that if the tumors were removed by negative surgical margins, the range of maximum tumor spread was 90% within a distance of 10 mm, and 96% within 15 mm [67].

The clinical basis for partial breast irradiation was provided by early studies showing that in selected cases, the vast majority of IBTR after BCS and WBI should only be expected in the tumor bed or in its immediate vicinity. Based on these controlled clinical trials, more than two-thirds of IBTR develop from malignant cells remaining in the direct surrounding of the primary tumor bed [68-74]. The incidence of elsewhere recurrences was about 0-3.8%, which was independent of omission RT [72, 75]. This suggests that RT mainly affects microscopic tumor cells remaining around the tumor bed and reduces the risk of IBTR by destroying them. Given that WBI does not significantly reduce the rate of elsewhere recurrences, a notable proportion of these cases are not a true recurrence of the original breast cancer but a de novo second primary tumor.

Irradiation of the whole remained breast to the same homogenous dose therefore is not the optimal adjuvant treatment for all operated breast cancer patients, since adjacent vital organs being exposed to unnecessary ionizing radiation increases the risk of potentially serious side effects. From a dosimetrical point of view, it is evident that the

radiosensitive organ at risk (OAR) – such as the heart and ipsilateral lung – can be better protected when the target volume is significantly smaller than in WBI [76]. Because of its ability to focus an effective dose on a limited area by rapid fall-off of doses around sources, brachytherapy (BT) is a promising method to safely irradiate the tumor bed.

The idea of accelerated fractionation is to reduce the overall treatment time and to reduce the possibility of tumor cell regeneration, thus providing better tumor control. Chadwick and Leenhouts in 1981 developed the "molecular model", which has come to be widely known as the "linear-quadratic (LQ) model", and which can be used to obtain estimates of effectivity/toxicity after changes in dose per fraction and in total dose [77]. According to this model, the integrity of the double-stranded deoxyribonucleic acid (DNA) is essential for clonogenic survival. The LQ model with its α/β value describes the curvature of cell killing, both for normal tissue complications and tumor control in relation to RT dose. The linear term (α component) corresponds to lethal (DNA double-stranded break) and the quadratic term (β component) to sublethal damage. The α/β ratio is the dose where the linear and the quadratic component cause the same amount of cell killing. It can be concluded that cancer cells with low α/β ratio are more responsive to a larger fraction size [78]. According to the START-B study, the α/β-value of breast cancer is 3.5 - 4 Gy for loco-regional control and 3.8 - 4 Gy for late side effects (fibrosis, telangiectasia) [79]. Based on these data, due to the relatively low α/β values, moderate hypofractionation is safe in breast cancer. Given that the total treatment time has a minor effect on the severity of late normal tissue damage, if sufficient time is allowed for normal tissue to regenerate between fractions (minimum 6 hours), the total treatment time can be reduced to 3-5 days by twice-a-day fractionation.

Based on subsequent prospective clinical trials with appropriate patient selection and quality assurance, in selected cases APBI performed with multicatheter interstitial brachytherapy (MIBT) has been successfully used as postoperative RT after BCS since the 1990s [80, 84]. However, since the early 2000s the development of LINACs has made it possible to apply ABPI non-invasively as well; first only with 3D-conformal radiotherapy, and later with an intensity-modulated / image-guided radiotherapy (IMRT/IGRT) technique, which more closely approximated the accuracy of MIBT [85].

1.7. Intraoperative catheter implantation

In the conventional approach to MIBT, the percutaneous catheters are inserted a few weeks after breast surgery, when the complete pathological report of the resected tissue is available. There are two main surgical methods for managing the tumor bed after breast cancer excision. The determination of the tumor bed and thus the target volume is greatly influenced by the type of surgical technique. In open cavity surgery, after removal of the cancer the wound is closed only by skin and subcutaneous sutures, resulting in a fluid-filled cavity. In this situation, the cavity visibility score (CVS) developed by Smitt et al. is used to grade the visibility of the tumor bed after surgery on a 5-point scale [86]. Even with drains inserted to remove excess surgical fluid, a large seroma can develop, which can lead to post-operative complications. In a newer technique called closed cavity surgery (full thickness surgical closure), the cavity is closed by suturing the cavity walls together. This reduces the chance of post-operative infection and results in better cosmesis [87]. Closed cavity surgery does not result in large seromas, which makes it difficult to locate the tumor bed precisely.

An alternative approach to catheter implantation is the intraoperative technique. Compared to the postoperative method, the intraoperative technique allows for direct visualization of the excision cavity, and consequently more accurate placement of the catheters. In addition, this approach – which is intended to avoid the need for a second invasive procedure – does not increase the risk of postoperative complications and has no negative impact on the cosmetic outcome [88]. In this case, due to the preparation of the histological findings as early as possible, good cooperation with the pathologist is necessary to minimize the in-tissue time of the catheters.

1.8. Second breast-conserving therapy (2ndBCT)

Since many patients still have a good prognosis after an early-stage breast cancer, quality of life and patient satisfaction are becoming increasingly important. However, the above-mentioned studies have made it clear that the repeated local excision of IBTR leads to a favorable cosmetic outcome compared to sMT, but is not acceptable from an oncological point of view because of the high risk of further local recurrence, which is associated with poor prognosis. This has led to the need for a new, safer multidisciplinary

therapeutic option. Historically, repeated RT was contraindicated following WBI due to concerns about unacceptable side effects with a second course of irradiation, but more recently, with improved RT methods and the increasingly early detection of small volume IBTR, there has been growing interest in a second conservative treatment.

Introduced in the late 1970s, the concept of the 2ndBCT consists of a repeated surgical procedure (lumpectomy or wide excision) with external beam or BT re-irradiation limited to the tumor bed. After a previous WBI, only partial breast irradiation was a possible additional RT technique after repeated BCS, but even this could only be recommended with careful consideration. However, patients would rather accept the higher risk of local toxicity with re-irradiation to avoid sMT. Among the more widely available external beam radiotherapy (EBRT) methods, well-focused and limited depth of penetration electron irradiation – which is more protective of the surrounding tissue than photon irradiation – was introduced into clinical practice in the mid-1980s [89-90]. For the first time, Mullen et al. [90] published a study of repeated lumpectomy and external beam electron re-irradiation to the operative area in patients who had an IBTR after an initial breast cancer cured by BCS and WBI.

Despite its more limited availability, and due to its more favorable dosimetrical properties mentioned in the previous points – its ability to focus radiation only on a limited area with rapid fall-off of doses around sources while sparing surrounding normal tissues – indicated that BT seemed to be a more promising way to re-irradiate the tumor bed with an effective dose after a previous WBI. This method was first used in the late 1970s. The first multi-patient study was reported by Maulard et al. in 1995 [91]. He described the method of treating IBTR by limited tumorectomy and perioperative low-dose rate (LDR) BT, carried out by intraoperatively implanted plastic tubes with delayed loading of radioactive Iridium wires. The results of treatments using this technique are discussed in detail in Section 5.

According to the data reported by Miller and her colleagues, it is estimated that the number of breast cancer survivors in the United States will increase by 22% between 2019 and 2030 (from 3.8 to 4.9 million) [92]. These data suggest that the number of patients diagnosed with IBTR will increase significantly in the coming decades, which makes the issue of 2ndBCT even more topical.

2. Objectives

The objectives of the dissertation are:

1. To present the technique of intraoperative catheter implantation and perioperative breast brachytherapy, and 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

3.1. Treatment of the initial breast cancer

The study was approved by the local ethics committee and was performed with the permission of the national regulatory authority (ETT-TUKEB Nº: BM/7915- 1 /2023).

We identified 195 patients who had an IBTR following a prior 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 (SLNB) or axillary block dissection. Adjuvant RT consisted of 46 to 50 Gy WBI using a LINAC with CT-based treatment planning, administered by two tangential photon beams with conventional fractionation (2 Gy/day, 5 fractions/week). Forty-five patients (23%) received photon or electron tumor bed boost between 4 and 16 Gy. Patient, tumor, and treatment characteristics for the initial breast cancer are summarized in Table 2.

Table 2. Patient, tumor, and treatment characteristics for the initial breast cancer of 195 patients (Smanykó V, 2019 [62]).

Characteristic	n (%)
Mean age (years)	53 (range: 27-83)
Premenopausal	85 (44%)
Mean tumor size (mm)	19 (range: 1-80)
Histologic type	
Invasive ductal carcinoma	130 (67%)
Invasive lobular carcinoma	12 (6%)
Other invasive carcinoma	10 (5%)
Ductal carcinoma in situ	14 (7%)
Unknown	29 (15%)
Histologic grade	
1	29 (15%)
2	64 (33%)
3	43 (22%)
Unknown	59 (30%)

Table 2. Patient, tumor, and treatment characteristics for the initial breast cancer of 195 patients (continued) (Smanykó V, 2019 [62]).

Characteristic	n (%)
pTNM stage	
pT1 pN0	69 (35%)
pT2 pN0	21 (11%)
pT3 pN0	4 (2%)
pT1 pN1	25 (13%)
pT2 pN1	15 (8%)
pT2 pN2	2 (1%)
pT2 pN3	2 (1%)
pT3 pN0	4 (2%)
Unknown	53 (27%)
Surgical margin status	
Positive	12 (6%)
Negative	103 (53%)
Unknown	80 (41%)
Hormonal status	
ER+, PR+	58 (30%)
ER+, PR-	12 (6%)
ER-, PR+	5 (3%)
ER-, PR-	38 (19%)
Unknown	82 (42%)
Her-2 status	
Her-2 positive	37 (19%)
Her-2 negative	130 (67%)
Unknown	28 (14%)

Table 2. Patient, tumor, and treatment characteristics for initial breast cancer of 195 patients (continued) (Smanykó V, 2019 [62]).

Characteristic	n (%)
Systemic therapy	
Chemotherapy	41 (21%)
Hormonal therapy	54 (27%)
Chemo-, and hormonal therapy	21 (11%)
None	62 (32%)
Unknown	17 (9%)

ER: estrogen receptor; PR: progesterone receptor.

3.2. Treatment of ipsilateral breast tumor recurrence

Thirty-nine patients who – after detailed information and discussion about the treatment methods available – refused sMT, underwent 2ndBCS (wide re-excision) and perioperative HDR MIBT. All of the cases were presented at our institutional breast tumor board. Written informed consent was given from every patient prior to treatment. 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.

3.2.1. Second breast conserving surgery and intraoperative catheter implantation

In a case of 2ndBCT, after being confirmed by fine needle aspiration cytology or core biopsy, wide re-excision of the recurrent tumor was performed under general anesthesia by breast surgeons of our Institute. 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 (range: 4-24) 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 dosimetry system [93] (Figure 1.). Afterward, the guide needles were replaced with flexible hollow plastic catheters and secured with fixation buttons on both sides of the skin. After implantation, the wound was closed with sutures (Figure 2.).

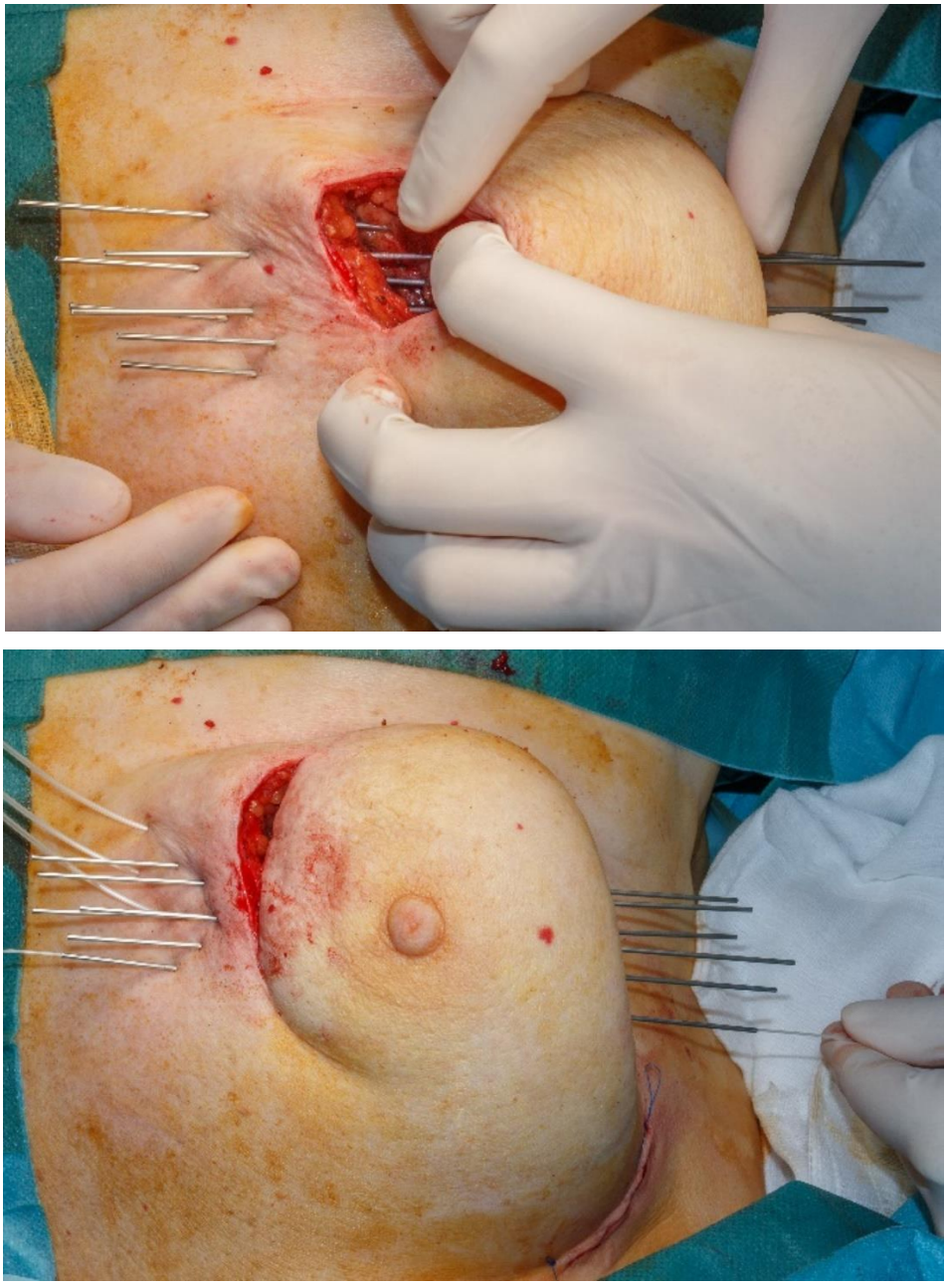

Figure 1. Needle insertion.

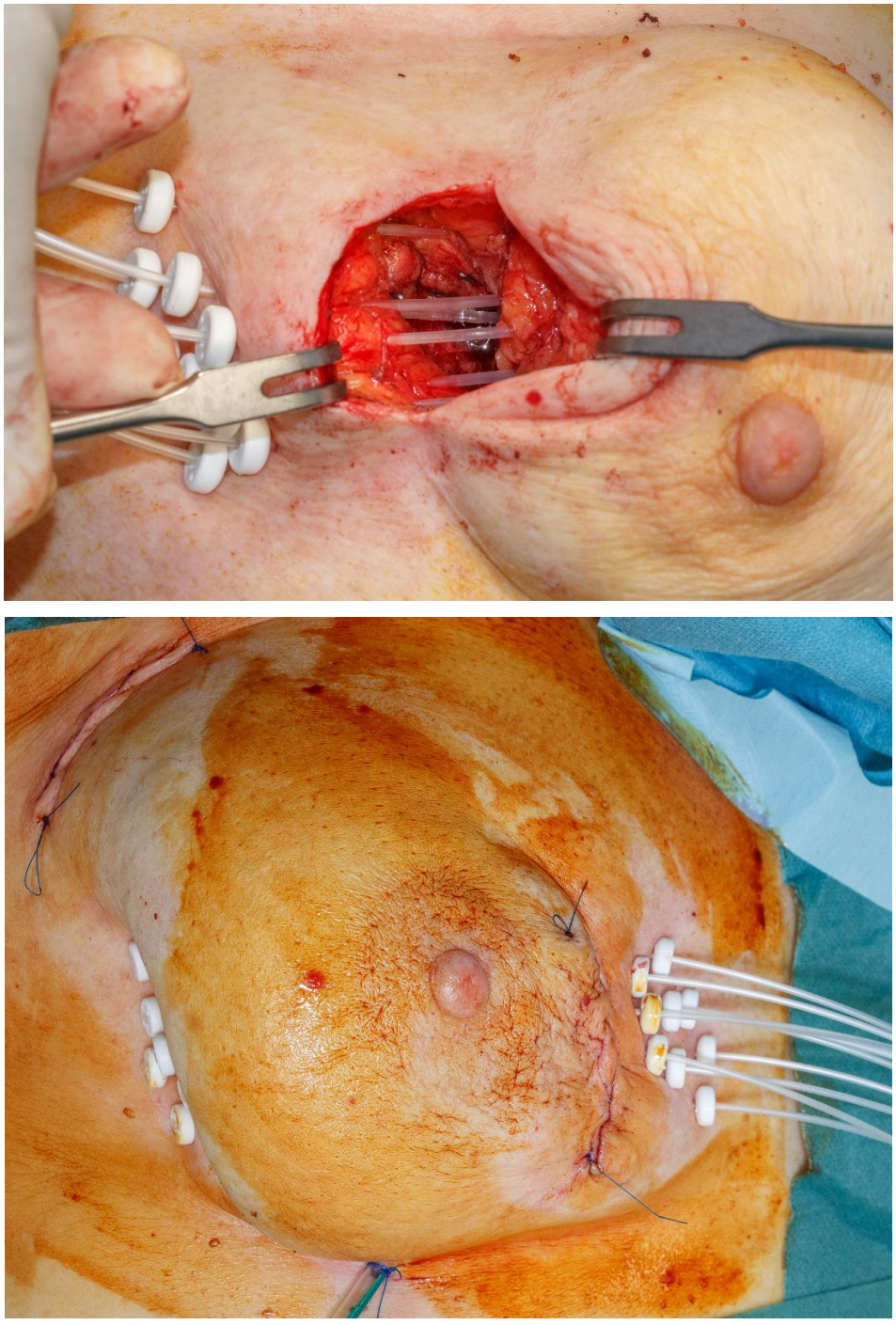

Figure 2. Plastic catheters with fixation buttons at the skin.

Assessment of axillary lymph nodes was rarely performed because at the time of primary treatment (before introduction of SLNB in Hungary) axillary block dissection was performed. Five patients (13%) in the 2ndBCT group, and 39 patients (25%) in the sMT group underwent re-SLNB.

3.2.2. Treatment planning and dosimetric aspects of perioperative multicatheter interstitial brachytherapy

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, according to the GEC-ESTRO (Groupe Européen de Curiethérapie – European Society for Radiotherapy and Oncology) recommendation [94] (Figure 3 and 4.). In one patient the exact extent of the microscopic surgical margin remained unknown due to the incision of the surgical specimen in the operation theatre, thus the maximum margin of 20 mm was used.

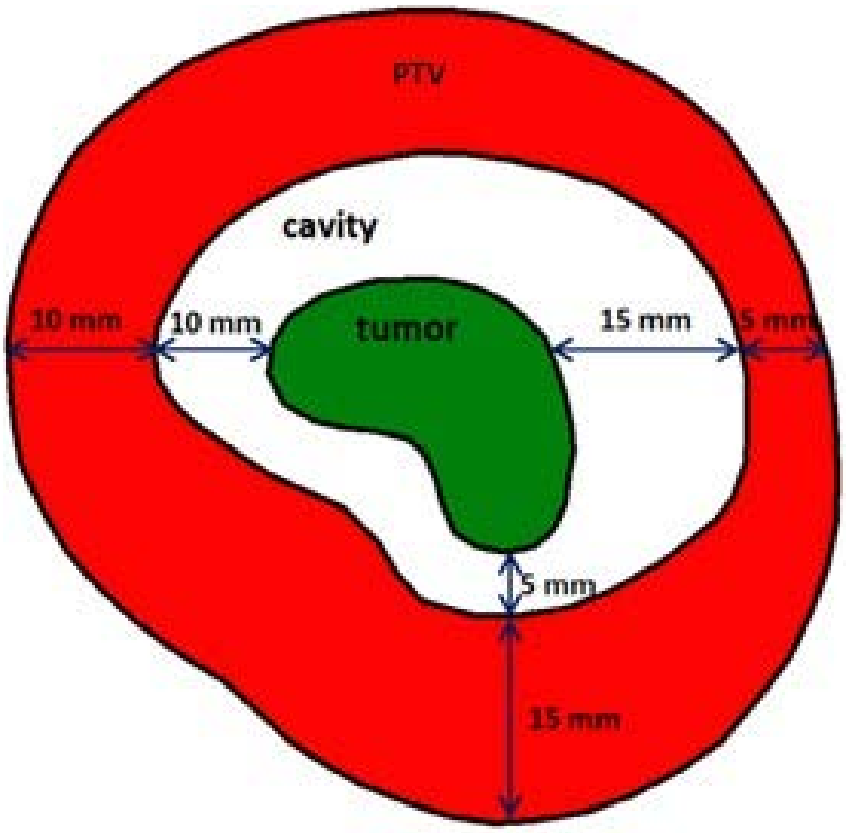

Figure 3. Schematic representation of the relation between the tumor location and the excision cavity to the planning target volume (PTV). In all directions the total margin around the tumor is 20 mm (Major T, 2016 [94]).

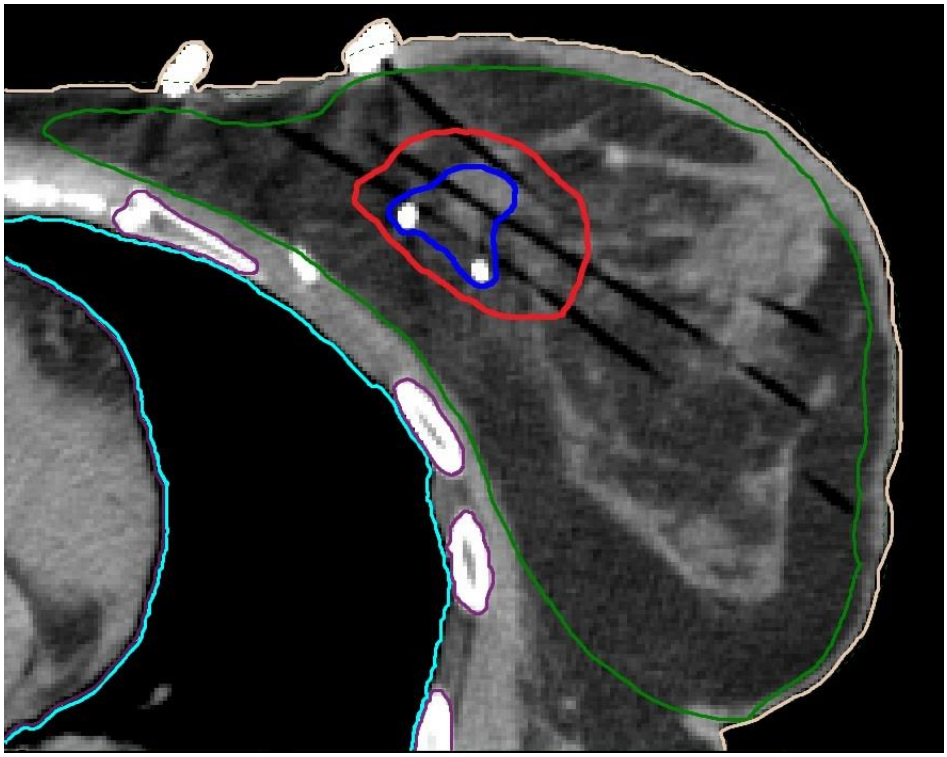

Figure 4. Target volume and contours of the organs at risk with colored lines. Blue line: tumor bed, red line: planning target volume (PTV), green line: ipsilateral breast with 5 mm rim of subcutaneous tissue beneath the skin, light purple line: ribs, dark purple line: heart, azure blue line: ipsilateral lung.

After contouring of the clinical target volume (CTV), which is equal to the planning target volume (PTV) in BT, the OARs such as heart, ribs, lung, skin, ipsilateral non-target breast, and contralateral breast were identified. After reconstruction of the catheters, geometric optimization was used during the treatment planning, which was supplemented with graphical optimization as needed to achieve the required dose-volume criteria. Later, with the development of a treatment planning system, the hybrid inverse planning optimization method (HIPO) was applied to reach an optimal dose distribution. Dose constraints were used in accordance with the ESTRO-ACROP (European Society for Radiotherapy and Oncology - Advisory Committee for Radiation Oncology Practice) guideline [95]. 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 and target coverage (at least 90% of the PTV received 100% of the

prescribed dose /PD/), and the lowest possible dose to OARs (Figure 5 and 6.). The dose nonuniformity ratio (DNR) was aimed to be equal or less than 0.35.

Initially the Plato® and later the Oncentra Brachy® treatment planning system were used for planning (Nucletron, Veenendaal, The Netherlands and Elekta Brachytherapy, Veenendaal, The Netherlands).

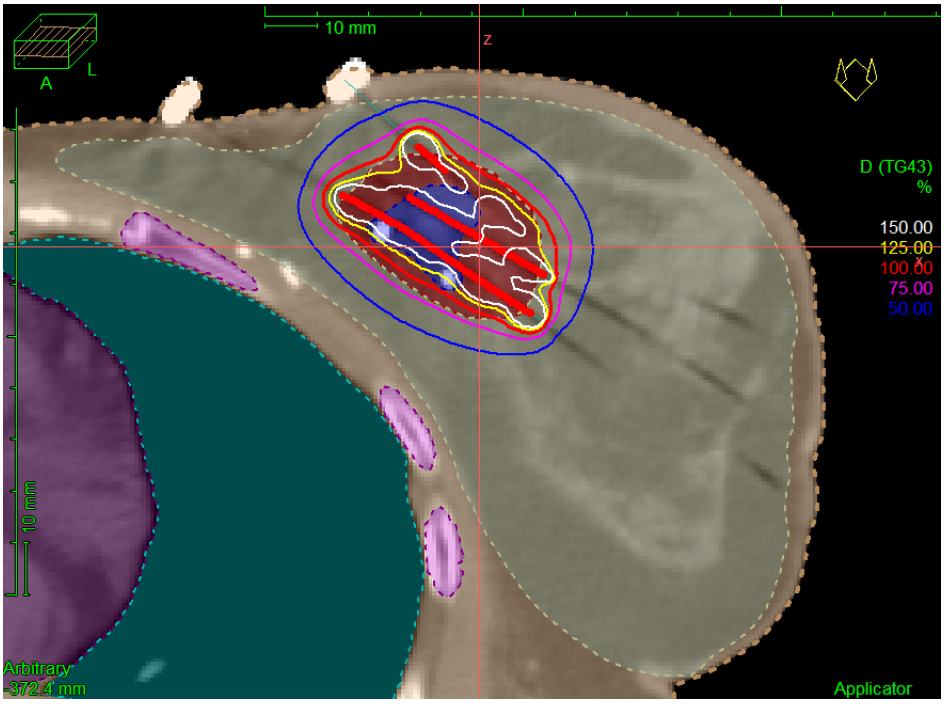

Figure 5. Conformal dose distribution on an axial CT slice.

Red area = planning target volume (PTV), different colored lines: isodose curves corresponding to dose distributions, red dots: dwell positions of the iridium source.

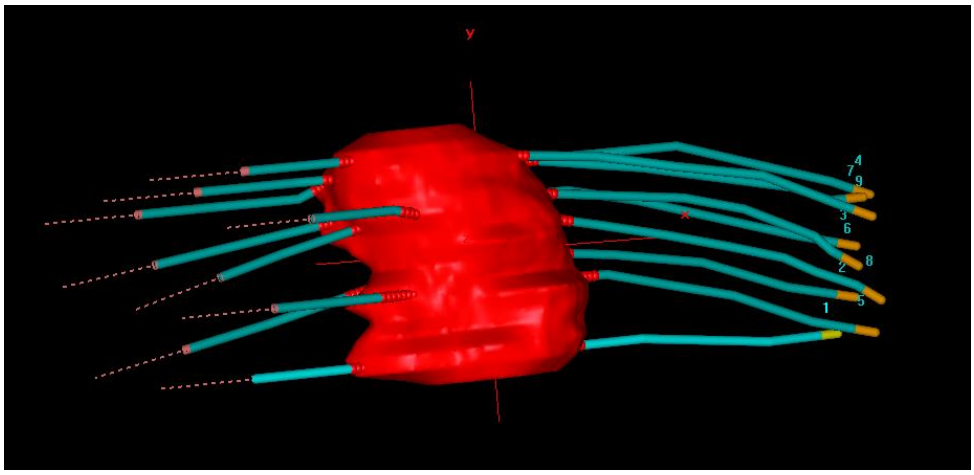

Figure 6. 3D image of the planning target volume (PTV) and reconstructed catheters.

The following dose-volume parameters were used for quantitative evaluation of plans:

- V_{PTV}: volume of the planning target volume (PTV) (cm^3).
- V100, V150, and V200: percentage of the V_{PTV} receiving at least 100%, 150%, and 200% of the PD (%).
- D90 and D100: minimum doses (in percentage of the PD) encompassing 90% and 100% of the PTV (Gy).
- D_{mean} (non-target breast): the mean dose of non-target breast (Gy);
- $D_1(x)$, $D_{0.1}(x)$: the minimal dose of the most exposed 1 and 0.1 cm^3 of the critical organ (x = heart, ribs, ipsilateral lung, skin, contralateral breast) (Gy).

The following parameters were calculated for quantitative analysis of dose distributions regarding dose homogeneity and conformality:

- Dose nonuniformity ratio (DNR): the ratio of high dose volume (irradiated by 1.5 times the PD) to reference dose volume (irradiated by the PD). A lower value means a more a homogeneous dose distribution [96].

$$DNR = \frac{V_{150}}{V_{100}}$$

- Dose homogeneity index (DHI): the higher the DHI, the more homogeneous the distribution [97].

$$DHI = \frac{V100 - V150}{V100}$$

- Conformal index (COIN): takes into account the coverage of the PTV by the PD and also the unwanted irradiation of normal tissues outside the PTV. The dose distribution is most conformal when the COIN is maximal [98].

$$COIN = \frac{PTV_{ref}}{V_{PTV}} \cdot \frac{PTV_{ref}}{V_{ref}} = CI \cdot \frac{PTV_{ref}}{V_{ref}}$$

where: V_{ref}: volume irradiated by the reference dose ($V_{ref} = V_{100}$)

PTV_{ref}: volume of PTV irradiated with the reference dose

- Coverage index (CI): shows the proportion of the target volume that receives at least the reference dose.

$$CI = \frac{V100}{100}$$

In an ideal implant the DNR is low, the DHI is high, and the CI and COIN are close to 1.

The irradiation was started 72 to 96 hours after salvage surgery. 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, at least 6 hours apart and over 3 consecutive days. Following the last fraction, the catheters were removed. After a few hours of observation, the patients were discharged home.

3.3 Patient, tumor, and treatment characteristics for ipsilateral breast tumor recurrence

There was no remarkable difference between the 2ndBCT and sMT groups in terms of the patient-related parameters at the second tumor. Although the mean size of the IBTR was significantly larger in the sMT group than in the 2ndBCT 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). In the majority of the cases in both groups the IBTR was located in or near to the tumor bed of the first operation (74% and 81%). Most of the patients had chemo- or hormonal therapy in both treatment groups (note that the patients in the sMT group had almost twice the number of hormone receptor-negative tumors than the members of the 2ndBCT group), which probably played a role in improved local control. In the 2ndBCT group adjuvant systemic treatments consisted of chemotherapy in 3 patients (8%), while 29 (74%) received endocrine therapy only, and 3 (8%) received both. No further adjuvant treatment was administered in 4 patients (10%) because of their advanced age, hormone receptor-negative status, or their refusal of systemic cytostatic therapy. In the sMT group the patient numbers were 33 (21%), 87 (56%), 15 (10%), and 21 (13%), respectively.

Patient, tumor, and treatment characteristics for the IBTR are summarized in Table 3. [62].

Table 3. Patient, tumor, and treatment characteristics for ipsilateral breast tumor recurrence (IBTR) according to salvage treatments in the total patient population of 195 (Smanykó V, 2019 [62]).

Characteristic	2ndBCT group (N=39)	sMT group (N=156)	p-value
Mean age (years)	63 (range: 36-81)	62 (range: 36-87)	0.48§
Premenopausal	4 (11%)	20 (13%)	0.82#
Mean tumor size (mm)	16 (range: 2-70)	25 (range: 2-90)	**0.0005**§
Mean time to recurrence (months)	128 (range: 36-258)	108 (range: 9-324)	0.09@
Localization of recurrence*	(n=38)	(n=96)	
In or vicinity of the tumor bed	28 (74%)	78 (81%)	0.35ß
Different quadrant	10 (26%)	18 (19%)	
Unknown	1	60	
Histologic type			
Invasive ductal carcinoma	33 (84%)	114 (73%)	0.51ß
Invasive lobular carcinoma	3 (8%)	21 (13%)	
Other invasive carcinoma	2 (5%)	11 (7%)	
Ductal carcinoma in situ	1 (3%)	10 (7%)	
Histologic grade			
1	7 (18%)	18 (11%)	0.26ß
2	11 (28%)	62 (40%)	
3	20 (51%)	64 (41%)	
Unknown	1 (3%)	12 (8%)	
Surgical margin status			
Positive	1 (3%)	13 (8%)	0.34ß
Negative	37 (94%)	134 (86%)	
Unknown	1 (3%)	9 (6%)	

2ndBCT: second breast-conserving therapy; sMT: salvage mastectomy; *: only in cases with known localization, §: Student's t-test, #: Fisher's exact test, @: Mann–Whitney U test, ß: logistic regression

Table 3. Patient, tumor, and treatment characteristics for ipsilateral breast tumor recurrence (IBTR) according to salvage treatments in the total patient population of 195 (continued) (Smanykó V, 2019 [62]).

Characteristic	2ndBCT group (N=39)	sMT group (N=156)	p-value
Hormonal status			
ER+, PR+	24 (62%)	82 (53%)	0.49ß
ER+, PR-	6 (15%)	21 (13%)	
ER-, PR+	1 (3%)	1 (1%)	
ER-, PR-	6 (15%)	44 (28%)	
Unknown	2 (5%)	8 (5%)	
Systemic therapy			
Chemotherapy	3 (8%)	33 (21%)	0.18ß
Hormonal therapy	29 (74%)	87 (56%)	
Chemo- and hormonal therapy	3 (8%)	15 (10%)	
None	4 (10%)	21 (13%)	

2ndBCT: second breast-conserving therapy; sMT: salvage mastectomy, ER: estrogen receptor; PR: progesterone receptor, ß: logistic regression

Based on the location of the first and second tumor in the total study population of 195 patients, 79% of the IBTR can be considered to be true recurrences, and 21% as new primary tumors (tumor bed recurrence or elsewhere failure). The same proportions, based on the histological type relationship of the first and second tumors, were 78% and 22%, respectively. In both groups, approximately four-fifths of the 62 distant metastases detected in the entire study population occurred in patients with true recurrence.

Based on the GEC-ESTRO ABPI classifications [99], in the 2ndBCT group 17 (44%), 11 (28%), and 11 patients (28%) belonged to low-risk (LR), intermediate-risk (IR) and high-risk (HR) categories, respectively.

Based on the recommendation of the St. Gallen Consensus Conference [100], in the 2ndBCT group 14 (36%), 10 (26%), 2 (5%), 2 (5%), 4 (10%) IBTR belonged to the Luminal A, Luminal B, Luminal Her2-positive, non-Luminal Her2-positive, and triple-negative molecular subtype groups respectively, while 7 (18%) were not classifiable.

This distribution in the sMT group was 52 (33%), 28 (18%), 11 (7%), 18 (12%), 23 (15%) in the same order, and 24 (15%) were not classifiable. Published series in the literature use various methods to classify patients into approximated molecular subtypes on the basis of available immunohistochemical information. Where the Ki-67 value was not described in the pathology report, we used histological grade as an acceptable substitute measure of proliferation rate in our analysis.

3.4. Patients' follow-up

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. Breast ultrasound and mammography were performed annually. In cases of uncertain ultrasound or mammography findings, MRI and/or histological sampling (fine needle aspiration cytology or core biopsy) of suspicious lesions were performed to differentiate between 2ndIBTR and localized late side effect (fibrosis or fat necrosis).

3.5. Evaluation of side effects and cosmetic results

The cosmetic results were assessed by the Harvard criteria [101] (Table 4.).

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 [102] (Table 5.).

To assess fat necrosis, we used the classification system previously developed by our working group [103] (Table 6.).

Table 4. Harvard criteria system for assessing cosmetic outcomes (Harris J, 1979 [101]).

Grade	Definition
Excellent	Treated breast nearly identical to untreated breast
Good	Treated breast slightly different than untreated breast
Fair	Treated breast clearly different from untreated breast, but not seriously distorted
Poor	Treated breast seriously distorted compared to untreated breast

Table 5. RTOG/EORTC late radiation morbidity scoring scheme (Cox JD, 1995 [102]).

Tissue	Grade					
	0	**1**	**2**	**3**	**4**	**5**
Skin	None	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Market atrophy; gross telangiectasia	Ulceration	Death
Subcutaneous tissue	None	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; < 10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture > 10% linear measurement	Necrosis	Death

RTOG/EORTC: Radiation Therapy Oncology Group / European Organization for Research and Treatment of Cancer.

Table 6. Scoring system for fat necrosis (Lövey K, 2007 [103]).

Grade	Definition
0	No fat necrosis
1	Asymptomatic fat necrosis (only radiologic and/or cytologic findings)
2	Symptomatic fat necrosis not requiring medication (palpable mass with or without mild pain)
3	Symptomatic fat necrosis requiring medication (palpable mass with significant pain)
4	Symptomatic fat necrosis requiring surgical intervention

3.6. Statistical methods

The primary endpoint of this study was the 5-year cumulative incidence of a 2ndIBTR. Secondary endpoints were the 5-year overall survival (defined as the time between the date of salvage treatment and the date of patient death of any cause), the 5-year cumulative incidence of regional relapse (axillary, supraclavicular, or internal mammary), the 5-year cumulative incidence of distant metastasis (observed between salvage treatment date and event occurrence), the 5-year cumulative incidence of disease-free survival (2ndIBTR, regional or distant metastasis, breast cancer death, or death from any cause) and the 5-year cumulative incidence of specific survival (death caused by the cancer). All time intervals were calculated from the date of salvage surgery. Student's t-test, Fisher's exact test, Mann–Whitney U test and logistic regression were used to compare patient, tumor, and treatment characteristics between the two treatment groups [104]. The actuarial rates of specific events and survivals were calculated using the Kaplan-Meier method [105]. Survival curves were compared using the log-rank (Mantel-Cox) test [106]. STATISTICA 12 software was used for statistical analyses (StatSoft Inc., Palo Alto, USA). The statistical significance was considered at $p < 0.05$.

4. Results

We retrospectively analyzed the outcomes of 195 women who had been presented with an IBTR after previous breast conserving surgery and WBI between 1999 and 2016. Because this was a real-world study, the size of the study population was determined by the number of patients in whom the IBTR was discovered and treated at our Institute.

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

At the 2ndBCS 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).
The mean volumes of 100%, 150%, and 200% of PD were 85.8%, 41.0%, and 18.7% of the volume of the PTV, respectively. The mean D90 and D100 were 93.0% and 56.2%.
The average DNR was 0.4. In the vast majority of cases, we were able to keep the DNR below our planned limit, but in some cases the DNR moderately exceeded the desirable value of 0.35. In those cases, the target coverage was preferred against dose homogeneity.
The mean COIN was equal to 0.51, whereas the dose homogeneity in the PTV was characterized with a DHI of 0.59.
Dose-volume parameters for the PTV are presented in Table 7.

Seventeen patients had an IBTR in the left breast, and 22 patients in the right breast. In terms of the dose-volume parameters for the organs at risk, mean D_1 and $D_{0.1}$ were 1.12 Gy and 1.3 Gy to the heart for left-sided lesions, 2.93 Gy and 3.58 Gy to the ribs, 2.11 Gy and 2.39 Gy to the ipsilateral lung, 2.72 Gy and 3.16 Gy to the skin, and 0.08 Gy and 0.13 Gy to the contralateral breast, respectively.
The detailed results can be found in Table 7.
Based on this data, with the technique of intraoperative catheter implantation we were able to keep the dose exposure of the OARs at low level, with a conformal dose distribution, good 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 [107].

Table 7. 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

PTV: planning target volume. V100, V150, V200: volume of 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, after 2ndBCT or sMT (p=0.15).

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). After the 2ndIBTR, completing mastectomy was implemented in 3 patients in the 2ndBCT group, so the final mastectomy-free survival was 92%. In one women distant metastasis was discovered prior to the 2ndIBTR, therefore no additional breast surgery was performed.

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).

The 5-year probability of distant metastasis-free survival was 76% vs. 74% in the 2ndBCT and the sMT group (p=0.41). Overall, 9 patients (23%) in the 2ndBCT group and 53 women (34%) in the sMT group developed subsequent distant metastases at mean 48 (range: 19-123) and 55 (range: 3-180) months after salvage surgery of IBTR, and all of them died of breast cancer at mean 30 (range: 6-123) and 22 (range: 0-155) months after the diagnosis of distant metastasis, respectively.

The 5-year probability of disease-free survival was 69% after 2ndBCT vs. 65% after sMT (p=0.20).

The 5-year probability of cancer-specific survival was 85% vs. 78% (p=0.51), respectively.

And the 5-year probability of overall survival was 81% vs. 66% (p=0.12), in the same order.

The above detailed, previously published results are presented by Kaplan-Meier curves in Figures 7-12. [62].

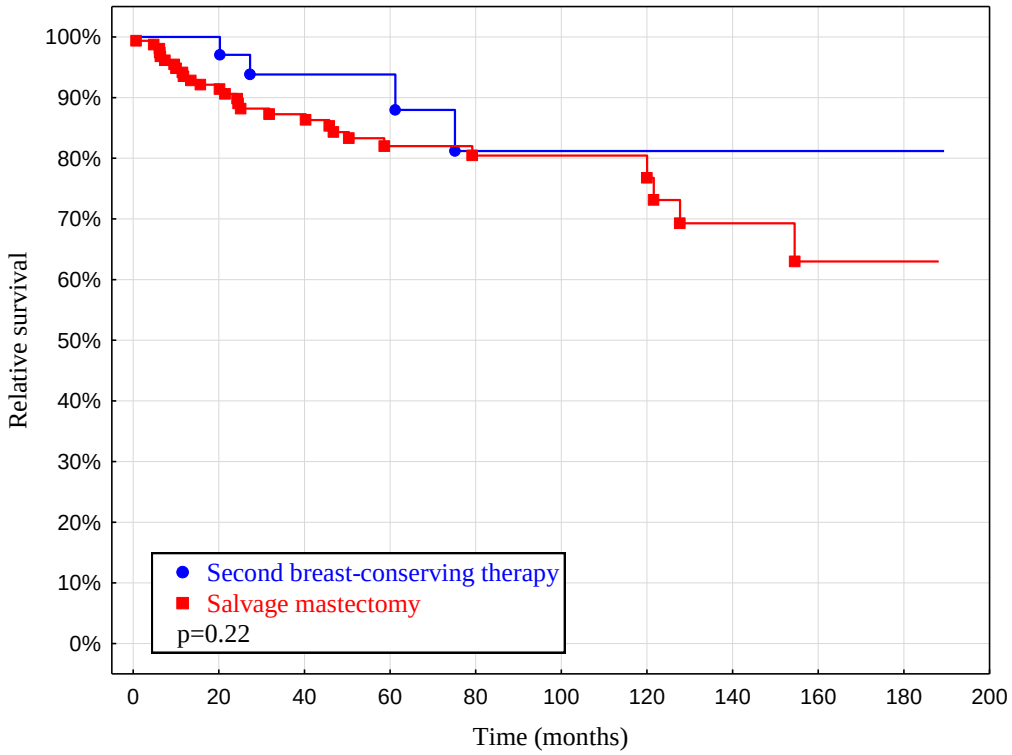

Figure 7: Second ipsilateral breast tumor recurrence-free survival after second breast-conserving therapy or salvage mastectomy (Smanykó V, 2019 [62]).

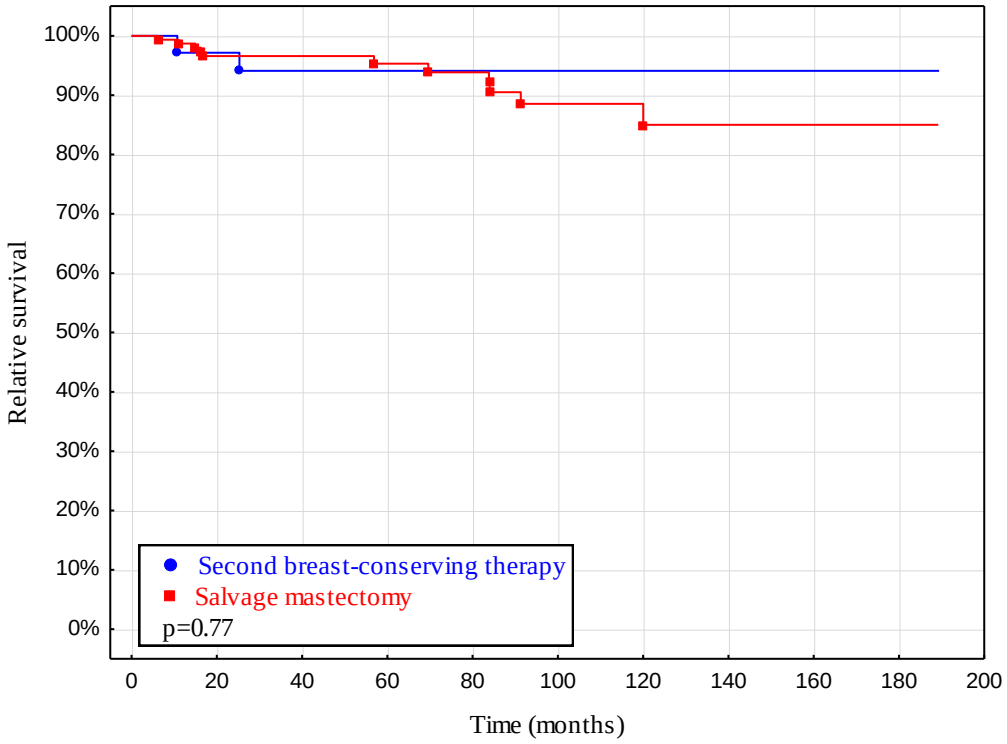

Figure 8: Regional recurrence-free survival after second breast-conserving therapy or salvage mastectomy (Smanykó V, 2019 [62]).

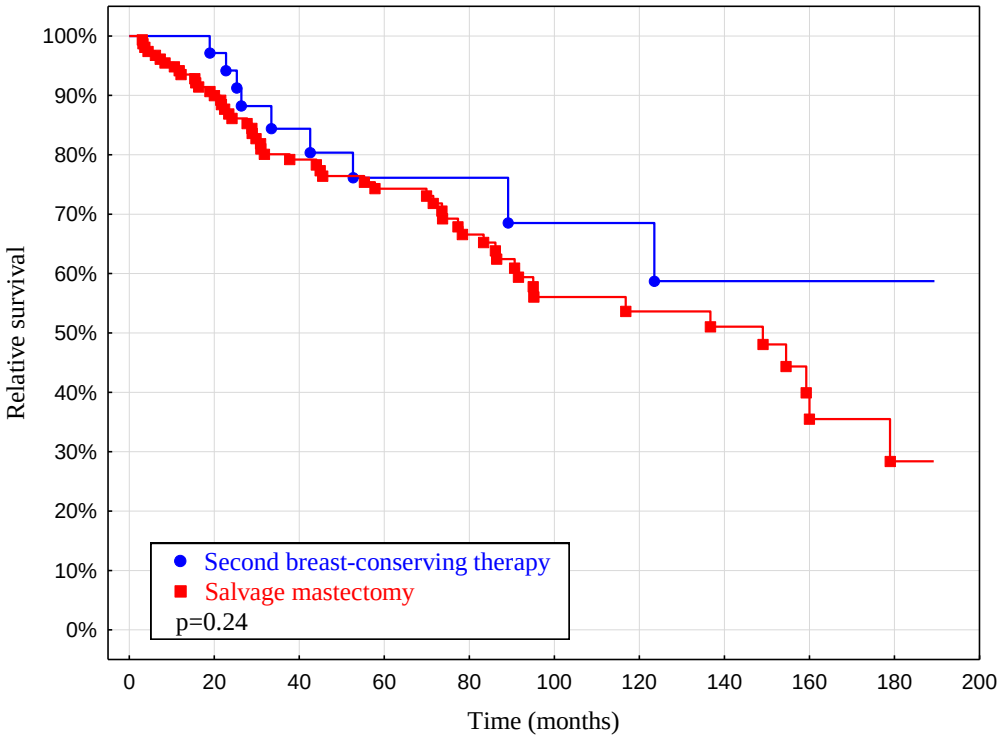

Figure 9: Distant metastasis-free survival after second breast-conserving therapy or salvage mastectomy (Smanykó V, 2019 [62]).

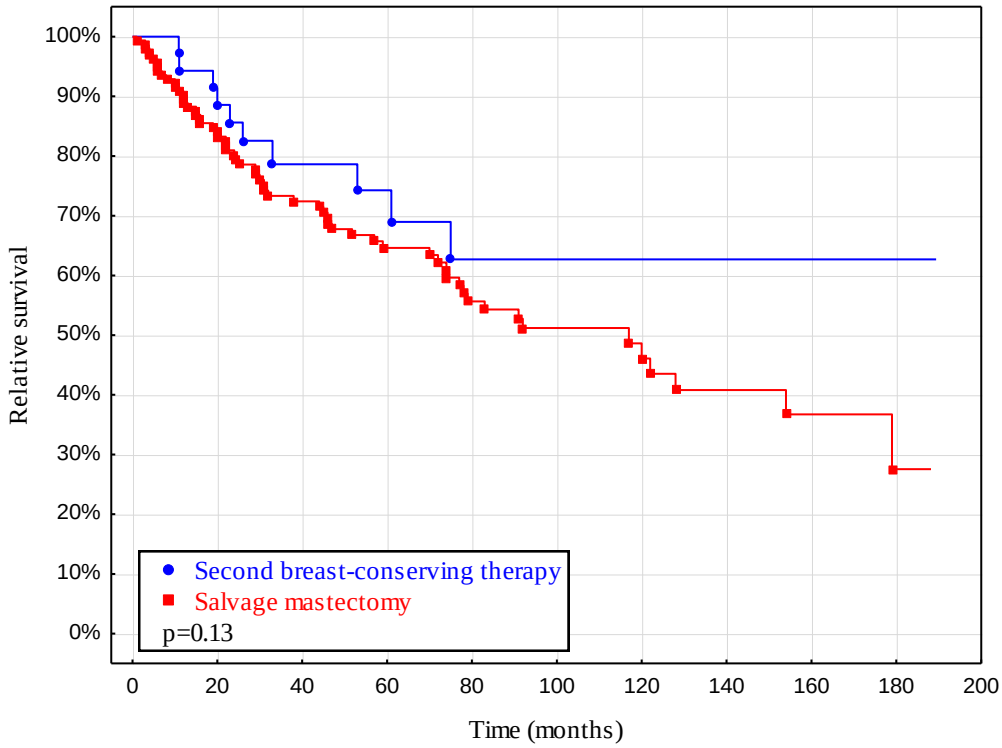

Figure 10: Disease-free survival after second breast-conserving therapy or salvage mastectomy (Smanykó V, 2019 [62]).

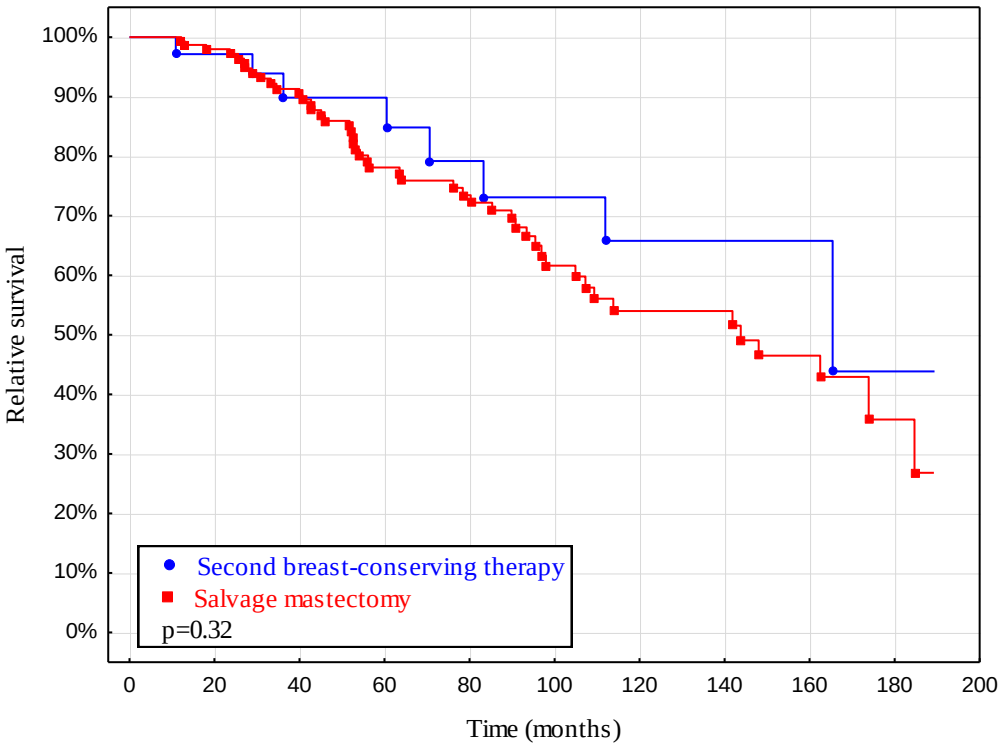

Figure 11: Cancer-specific survival after second breast-conserving therapy or salvage mastectomy (Smanykó V, 2019 [62]).

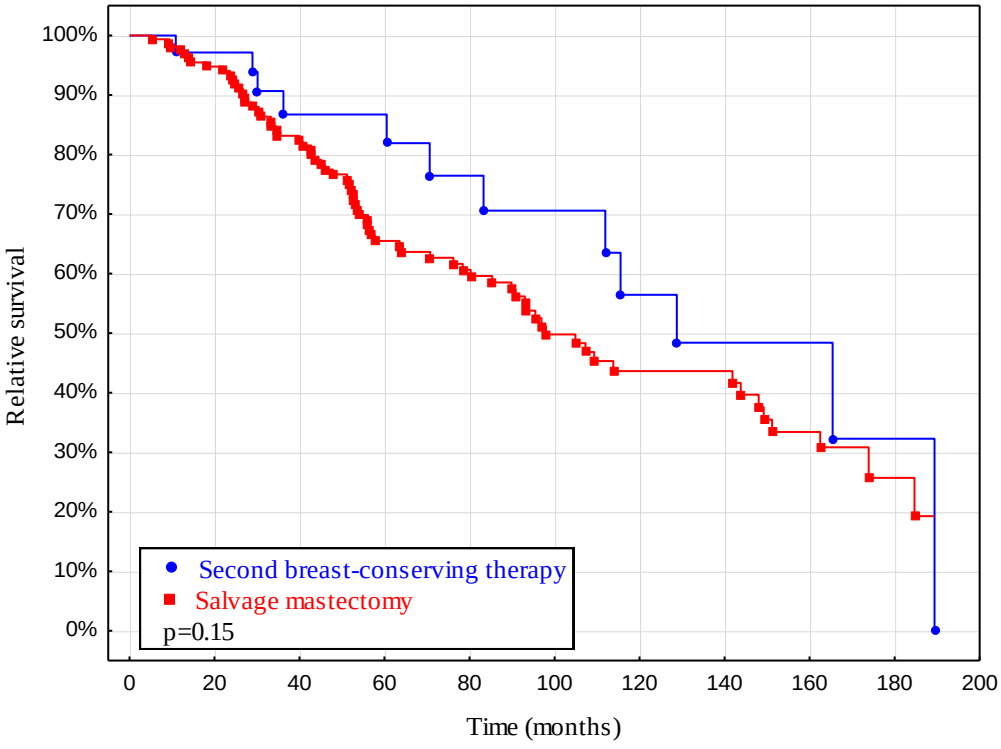

Figure 12: Overall survival after second breast-conserving therapy or salvage mastectomy (Smanykó V, 2019 [62]).

Three patients (2%) developed second primary non-breast malignancies in the sMT group (including one renal cancer, one lung cancer, and one ovarian cancer), and also 3 patients (8%) in the 2ndBCT group (including one colon cancer, one lung cancer, and one hypernephroma).

Contralateral breast tumor occurred in 18 patients (9%) in the sMT group and in 2 patients (5%) in the 2ndBCT group.

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.

The results are summarized in Table 8.

The long-term side effects of patients who received MIBT as APBI due to primary breast cancer are also available at our Institute [108]. With a median follow-up of 17 years, the combined rate of excellent and good cosmetic results was 82%, the rate of grade 3 late skin toxicity was 0%, and the rate of grade 3 fibrosis was 2%.

Our data show, that 2ndBCT (following a previous BCS and WBI) results in worse late side effects and cosmetic outcomes compare to BT for primary breast cancer.

However, it is important to note that in our case we are talking about a second course of BCT, therefore the side effects of the first and second treatment course are summed up. Furthermore, that in this case the goal is to avoid mutilating surgery.

Table 8. Cosmetic results and late radiation side effects after second breast-conserving therapy of 39 patients (Smanykó V, 2019 [62]).

Characteristic	n (%)
Cosmetic results	
Excellent	4 (10%)
Good	23 (60%)
Fair	6 (15%)
Poor	6 (15%)
Skin side effects	
Grade 0	4 (10%)
Grade 1	21 (54%)
Grade 2	11 (28%)
Grade 3	3 (8%)
Fat necrosis	
Asymptomatic (Gr1)	7 (18%)
Symptomatic (Gr2-4)	0 (0%)
Subcutaneous tissue (fibrosis)	
Grade 0	17 (44%)
Grade 1	12 (31%)
Grade 2	9 (23%)
Grade 3	1 (2%)

5. Discussion

For a long time, "salvage" mastectomy was the only accepted treatment strategy for management of an IBTR after BCS and WBI. According to the literature, the average rate of the 2ndIBTR is close to 10% after sMT (range: 0-22%) [33, 41-55] (Table 1.). Voogd et al. [33] reported the results of a retrospective study with the largest number of patients – treated in the 1980's – who underwent sMT after the diagnosis of an IBTR. The median follow-up after sMT was 52 months, and 51 out of the 229 patients (22%) developed a 2ndIBTR.

However, since the 1960s, several authors have also published that 2ndBCS is a viable alternative in selected patients [33, 41-48, 58-61]. The literature addressing this question suggests that the rate of 2ndIBTR after repeated BCS has been reported as high as 28% (range: 4-50%). The largest series with 2ndBCS used as monotherapy published by Gentilini et al. [60]. After a median follow-up of 81 months, a 2ndIBTR occurred in 47 of 161 patients (29%), and the five-year cumulative incidence of 2ndIBTR was 29%.

The largest study directly comparing the two treatment methods was reported by Salvadori et al. [41]. 2ndIBTR were reported in 4 patients out of 133 (3%) after sMT, and 8 patients of 57 (14%) after repeated wide excision. The five-years incidence of 2ndIBTR was higher in the re-excision group (19%), compared to the sMT group (4%) (p-value not reported). In Hungary, Fodor and co-workers published their results on this topic [42]. After a median follow-up of 165 months, the incidence of 2ndIBTR was 28% (9 of 32 patients) in the 2ndBCS group, and 16% (5 of 32 patients) in the sMT group (p=0.22). Therefore, based on these investigations, the 2ndIBTR ratio is higher after repeated BCS than after sMT [33, 41-48].

The comparison of these two treatment methods is summarized in Table 1. [62].

Re-irradiation after 2ndBCS may decrease the risk of 2ndIBTR [89], but re-irradiation of the whole remaining breast with an effective dose is considered inappropriate due to the high risk of serious late side effects. However, the previous promising results of APBI as part of primary BCT for selected patients has led to a renewed interest in partial breast re-irradiation in the salvage setting as a means of improving local tumor control while minimizing the toxicity of a second course of irradiation.

Partial breast re-irradiation may be delivered with either an external beam technique or BT.

The use of EBRT may still be interesting from the point of view of its wide availability, however particular caution should be exercised with regard to the potential side effects caused by re-irradiation of the remaining mammary gland, skin, lung, and heart.

For the first time, Mullen et al. [90] published a study of external beam re-irradiation as a part of the 2ndBCT. Between 1986 and 1993, sixteen patients who had an IBTR after an initial breast cancer cured by BCS and WBI underwent repeated lumpectomy and 50/2 Gy electron re-irradiation to the operative area. At 75 months follow-up, 4 patients (25%) had further local failure. There were no severe late sequelae.

A few years later, Deutsch et al. [89] reported the results of thirty-nine women with an IBTR after previous BCS and WBI who were treated with excision of the recurrent tumor and 50/2 Gy electron re-irradiation to the operated area. After a median follow-up of 51 months, 2ndIBTR occurred in 8 patients (21%). The 5-year overall survival was 78%, and the rate of an excellent or good cosmetic result was 75%.

In 2019, Arthur et al. presented the results of the RTOG-1014 trial, which evaluated oncologic outcome and toxicity after a second conservative treatment combining lumpectomy with 45 Gy tumor bed external beam photon re-irradiation (1.5 Gy twice daily for 30 fractions, during 15 days), using a 3-dimensional conformal technique. From fifty-eight patients with a median follow-up of 66 months, 4 patients (6.8%) reported 2ndIBTR, representing a 5-year cumulative incidence of 5.2%. The 5-year overall survival was 95%. Grade 1, 2, and 3 late skin side effects were 25%, 26%, and 7%, respectively. It should be noted that the median IBTR size was just 10 mm, and the cohort included 40% of DCIS [109]. The outcomes of these studies are summarized in Table 9.

The largest experience and the most abundant literature of re-irradiation after a 2ndBCS is with MIBT carried out by an intraoperative catheter implantation technique [91, 110-124]. The disadvantage of this approach is that it requires dedicated technical equipment and experience in order to execute correctly this procedure, because the dose distribution optimization starts at the time of catheter implantation in the operating room. Our comparison of the results of these studies are summarized in Table 10. [62].

Table 9. Results of external beam radiotherapy as re-irradiation after repeated breast-conserving surgery.

Author	Technique	Fraction x dose (Gy)	Median FUP (months)	Patients	2ndIBTR (%)	5-year 2ndIBTR (%)	5-year OS (%)	Excellent and good cosmesis (%)
Mullen [90]	electron	25x2	75	16	25%	NR	NR	NR
Deutsch [89]	electron	25x2	51	39	21%	NR	78%	75%
Arthur [109]	photon (3D-CRT)	30x1.5 (BID)	66	58	7%	5%	95%	NR
Chen [125]	photon (3D-CRT)	30x1.5 (BID)	23	34	6%	3%*	NR	NR

*: 2-year actuarial rate; 2ndIBTR: second ipsilateral breast tumor recurrence, Gy: gray; FUP: follow-up period; 3D-CRT: 3-dimensional conformal radiotherapy; BID: twice daily fractionation.

Table 10. Results of brachytherapy as re-irradiation after repeated breast-conserving surgery (Smanykó V, 2019 [62]).

Author	Technique	Fraction x dose (Gy)	Median FUP (months)	Patients	2ndIBTR (%)	5-year 2ndIBTR (%)	5-year OS (%)	Excellent and good cosmesis (%)
Hannon-Levi JM [110]	LDR	1x30; 1x45-50	50	69	16%	25%; 14%	92%	NR
Hannon-Levi JM [111]	LDR PDR HDR	1x30-55 49-50/0.6-1‡ 5-10x3.6-4.4	47	217	4%	6%	89%	85%
Guix B [112]	HDR	12x2.5	89	36	3%	11%§	97%§	94%
Trombetta M [113]	HDR ¶	10x3.4	40	18	11%	NR	NR	83%
Chada M [114]	LDR	1x30; 1x45	36	15	7%	11%*	100%*	100%
Maulard C [91]	LDR	1x30	48	15	26%	NR	61%	62%
Resch A [115]	PDR	40-50/0,6-1‡	59	9	0%	0%	100%†	55%
Kauer-Dorner D [116]	PDR	50.1/0.6-1‡	57	39	5%	7%	87%	37%
Trombetta M [117]	LDR HDR	1x45-50 10x3.4	38	26	4%	NR	NR	92%
Houvenaeghel G [118]	LDR	1x45-56	73	62	26%	17%	80%	NR
Montagne L [119]	LDR HDR	1x30-55 8-10x3.4	71	143	4%	3%@	91%@	85%

Table 10. Results of brachytherapy as re-irradiation after repeated breast-conserving surgery (continued) (Smanykó V, 2019 [62]).

Author	Technique	Fraction x dose (Gy)	Median FUP (months)	Patients	2ndIBTR (%)	5-year 2ndIBTR (%)	5-year OS (%)	Excellent and good cosmesis (%)
Forster T [120]	PDR HDR	49.8-50.4/0.5-0.7‡ 32-32.4x3.8-4	66	19	1%	0%	100%	NR
Chatzikonstantinou G [121]	HDR	8x4	70	20	10%	13%	92%	75%
Cozzi S [122]	HDR	10x3.4 or 8x4	61	40	5%	3%	85%	57%
Vavassori A [123]	HDR	10x3.4	74	31	10%	10%	87%	100%
Hannon-Levi JM [124]	LDR PDR HDR	1x30-55 49-50/0.6-1‡ 5-10x3.6-4.4	74	377	4%	3%	87%	80%
Present study	HDR	5x4.4	59	39	10%	6%	81%	70%
Range for all patients			**36-89**	**1175#**	**0-26%**	**0-25%**	**61-100%**	**37-100%**

Gy: gray; FUP: follow-up period; 2ndIBTR: second ipsilateral breast tumor recurrence; OS: overall survival; LDR: low-dose-rate; PDR: pulsed-dose-rate; HDR: high-dose-rate; NR: not reported; §: 10-year actuarial rate; ¶: patients were treated with intracavitary HDR brachytherapy using the MammoSite® or the Contura® balloon applicators; *: 3-year actuarial rate; ‡: total dose/pulse dose; †: disease-free survival; #: total number of patients; @: 6-year actuarial rate.

First, in 1989, Recht et al. [54] reported a patient who refused sMT following an IBTR after BCS and WBI, and therefore was treated with wide excision supplemented by an Iridium-192 implant at the tumor site. The patient died 72 months after the intervention of intercurrent illness without evidence of further failure.

The first multi-patient study was reported by Maulard et al. in 1995 [91]. He described the method of treating IBTR by limited tumorectomy and perioperative low-dose rate (LDR) BT, carried out by intraoperatively implanted plastic tubes with delayed loading of radioactive Iridium wires. From 1977 to 1990, 15 patients were treated and the delivered dose was 30 Gy. After a median follow-up of 48 months, 4 patients (26%) presented with a 2ndIBTR. The 5-year overall survival was 61%. Cosmetic results were evaluable in 8 patients, with no or minor sequelae in 5 women (62%). It is interesting to note, that in the same study 23 patients were treated with exclusive split-course BT, delivering 60-70 Gy by two implants at a one-month interval. After a median follow-up of 36 months, 4 patients (17%) developed a 2ndIBTR, the overall survival was 50%, and 2 patients underwent a mastectomy due to serious late side effects.

Guix and coworkers performed the study with the longest follow-up [112]. Between 1990 and 2001, 36 women were treated with IBTR by re-excision of the recurrence tumor and using 30 Gy (12x2.5 Gy) HDR MIBT. After a median follow-up of 89 months, the 10-year 2ndIBTR rate was 11%, and the 10-year overall survival rate was 97%. The rate of a good and excellent cosmetic result was 94%.

In 2004, French researchers from Marseilles and Nice published their results from 69 patients with IBTR treated with lumpectomy and LDR MIBT [110]. The prescribed total dose was 30 Gy or 45-50 Gy. The 5-year local control and overall survival were 77% and 92%, respectively. Women who treated by a minimum 50 Gy dose of BT to the breast had better 5-year local tumor control rates than those who treated by <50 Gy (86% vs. 75%, p=0.095). Nevertheless, patients who received a cumulative total dose (EBRT plus BT) >100 Gy had significantly higher rates of grade 2-3 toxicity compared to those who received <100 Gy (33% vs. 4%, p=0.005). Likewise, women who received >46 Gy dose of BT had higher rates of grade 2-3 side effect compared to those who received <46 Gy (36% vs. 14%, p=0.005).

In 2013, the GEC-ESTRO Breast Cancer Working Group presented a collaborative analysis [111]. In this study, conducted between 2000 and 2010, 217

patients were treated by MIBT in 8 European oncology centers. The mean total dose of re-irradiation was 46 Gy (range: 30-55 Gy), 50 Gy (49-50.4 Gy) and 32 Gy (22-36 Gy) with low-dose-rate (LDR), pulsed-dose-rate (PDR) and high-dose-rate (HDR) techniques, respectively. With a median follow-up of 47 months, the authors reported the actuarial 5- and 10-year 2ndIBTR rates of 6% and 7%, while the actuarial 5- and 10-year overall survival rates were 89% and 76%, in the same order. Good to excellent cosmesis was achieved in 85% of the patients.

Between 2004 and 2012, Trombetta et al. [113] performed a study with 18 patients, in which after a 2ndBCS used a special balloon applicator instead of separate catheters for repeated BT. This spherical, liquid filled device was inserted into the surgical cavity at the time of salvage surgery. An HDR radioactive source was passing through the device via a catheter, while it treated the tumor bed with 1 cm margins. A total dose of 34 Gy (10x3.4 Gy) was delivered in two fractions per day. After a median follow-up of 39 months, 2ndIBTR was observed in 2 patients (11.1%). The combined rate of excellent and good cosmetic results was 83%, although one patient had to undergo mastectomy 9 months after the procedure due to a chronic abscess next to the balloon applicator.

In 2021, GEC-ESTRO Breast Cancer Working Group made the first propensity score-matched cohort analysis study on patients who diagnosed by an IBTR between 1995 and 2017 [124]. This retrospective study with the participation of 15 European cancer centers processed 377 – 377 patients who were treated with 2ndBCS and perioperative MIBT or sMT. Matching (1:1) was achieved, including 10 clinical/pathologic data related to the IBTR. The median follow-up was 73.8 and 75.4 months. No significant differences were observed between the 2ndBCT and sMT groups for 5-year cumulative incidence of 2ndIBTR (2.8% vs 2.3%, p=0.4). Overall survival was 86.7% and 87.5% (p=0.7), respectively. According to the Harvard criteria system, cosmetic results in the 2ndBCT group were acquired from 212 women (56%), and were rated as excellent or good in 80%. Factors associated with oncological outcomes were investigated by univariate and multivariate analysis. In multivariate analysis, time between primary and salvage treatment (<36 months) and IBTR size (≥30 mm) were considered to be prognostic factors for all oncologic outcome items except for 2ndIBTR-free survival. Patient age (<48 years) was a prognostic factor for specific survival. The

period of salvage surgery (treated before 2002) was a prognostic for disease-free and metastatic disease-free survival. These results may further help us identify the indications for 2ndBCT more accurately.

Recently, intraoperative radiotherapy (IORT) has emerged in the literature as a new therapeutic modality for the treatment of primary breast tumors, with predominantly negative results. In this technique, a special device is used to deliver a high dose of X-ray or electron beam to the surgical cavity in a single fraction, immediately after 2ndBCS in the operating theatre. However, there are only very few studies about IORT in the management of IBTR, and they have clear weaknesses, such as incoherent patient selection, short follow-up time, lack of a control group, and very low patient numbers [126-128]. For the above reasons, this technique will not be discussed in detail.

In 1999, at our institution we introduced the 2ndBCS with re-irradiation using perioperative HDR MIBT in selected cases for the management of IBTR developed after a previous breast-conserving operation and WBI. Our early results were reported elsewhere [129-130]. In this current study, 39 women who were presented with an IBTR after a previous BCT were salvaged by re-excision and perioperative HDR MIBT. The data of these women were compared to 156 patients who were salvaged with sMT during the same period. The 5-year actuarial rate of a 2ndIBTR was 6% after 2ndBCT and 18% after sMT (p=0.22). In the literature, these rates are roughly 8% (range: 0-25%) and 18% (4-45%), respectively. In the 2ndBCT group, the good-to-excellent cosmesis was achieved in 70% of the patients. Although our results lag behind the previously mentioned results of the GEC-ESTRO propensity score-matched study, we attribute this to our more cautious fractionation scheme. We chose a moderate fractionation because we wanted to avoid the undesirable late side effects resulting from the re-irradiation. In the first larger study of re-irradiation with interstitial BT, in which patients were first treated in 1975, the prescribed doses delivered through the LDR technique were 50 Gy and 30 Gy in Marseilles and Nice, respectively [110]. Based on our calculations, 22 Gy in 5 fractions with the HDR technique is equal to 36 Gy with the LDR technique for late side effects (if the α/β value for breast cancer and late side effects is 4, and the dose rate is 1 Gy/hour) [78-79].

It should also be noted that, whereas most studies focus on detailed presentations of salvage surgery, applied doses and methods of RT, only limited information is

available on the use of adjuvant systemic treatment. As presented in the CALOR study, women with isolated ER-negative IBTR benefit significantly from adjuvant cytostatic therapy after salvage surgery, but no benefit of chemotherapy was observed for patients with ER-positive tumors, compared to endocrine treatment alone [131]. With the use of the most up-to-date adjuvant systemic therapy, the risks of a 2ndIBTR could probably be reduced as well.

Interestingly, only a few studies have specifically investigated whether the IBTR was a true in-field recurrence or a second primary tumor. Molecular biology-based studies have shown that only 60% of IBTR are clonally related to the original tumor [132]. In the study of Nishimura et al., the IBTR was classified based on the pathological matching of the first and second tumors, and patients with a second primary tumor had improved 5-year rates of overall survival (91% vs. 76%, p=0.063) and distant disease-free survival (93% vs. 61%, p=0.003) [30]. Another study also found that on the basis of tumor location, histological type, and immunohistochemical characteristics, patients classified as having new primary tumor had significantly better 10-year disease-specific and overall survival rates than those classified as true recurrence, and patients with true recurrence were more likely to develop distant metastasis after IBTR (42.2% vs. 13.2%, p<0.001) [31]. These evidences suggests that second primary tumors generally have a better prognosis than true recurrences and may therefore be more appropriate for a 2ndBCT.

In 2010, GEC-ESTRO proposed a three-group classification to select patients most suitable for APBI. [99]. In their study, Montagne et al. examined whether the oncological outcomes of IBTR patients could be influenced by their belonging to an APBI classification group [119]. Between 2000 and 2016, 143 patients underwent 2ndBCT treated with lumpectomy and re-irradiation performed by LDR (30–55 Gy) or HDR (28–34 Gy) MIBT. Sixty (42%), sixty-one (43%), and twenty-two patients (15%) were classified as low-risk (LR), intermediate-risk (IR), and high-risk (HR), respectively. Among the six patients who presented a 2ndIBTR, 5 belonged to the HR group (4 of them with positive surgical margin) and 1 was in the IR group. With a median follow-up of 71 months, the 6-year 2ndIBTR-free survival rates for LR, IR, and HR patients were 100%, 96%, and 93%, respectively (p=0.003). No significant differences were found between the three groups for regional-free, specific, or metastasis-free survival. In univariate analyses, HR group (p=0.001), positive margins (p<0.001), and lympho-vascular

invasion (p=0.009) were considered as significant prognostic factors for 2ndIBTR. In multivariate analyses, the HR group (p=0.009) was the only prognostic factor. In our study, in the 2ndBCT group 17 (44%), 11 (28%), and 11 patients (28%) were classified as LR, IR, and HR. Among the four patients who presented a 2ndIBTR, 1 belonged to the LR group and 3 were in the IR group, and the 5-year 2ndIBTR-free survival rates were 100%, 82%, and 100%, respectively. Of course, due to the low number of patients, these values are not comparable with the results of the above-mentioned study.

Although it is obvious that 2ndBCT is clearly associated with a better quality-of-life and cosmetic result than sMT, some studies have quantified this comparison. Jendrian et al. investigated differences in psychosocial outcomes among patients who underwent 2ndBCT or sMT after the treatment of IBTR. They found that women after 2ndBCT (n=46) showed significantly better results than women after sMT (n=61) with respect to role functioning (p=0.043), emotional functioning (p=0.028), social functioning (p=0.016), and body image (p=0.001) [56].

Nowadays, the increasingly popular oncoplastic surgery could become an important part of repeated BCT, as the breast is even more mutilated than during primary conserving surgery; however, it is considered a relative contraindication for RT as the tumor bed can no longer be accurately identify.

While mastectomy with immediate reconstruction may seem like a promising salvage treatment, its effect on body image, self-confidence, and quality of life remains questionable. Patients undergoing mastectomy with immediate reconstruction generally overestimated how well they would feel at one year later. In the work of Lee et al., these differences were statistically significant for satisfaction with sexual attractiveness clothed (p=0.03), sexual attractiveness unclothed (p<0.001), breasts unclothed (p=0.01), and experienced numbness (p<0.01). Patients who had more pain (p<0.001) or were less happy (p=0.02) than expected, were more likely to regret their choice of surgery [133].

Although all results discussed above could be valuable in the future as we build our knowledge concerning the ideal patient selection to treat with 2ndBCT, there is still no uniformly accepted patient selection criteria system. In 2016, expert panel of the German Society of Radiation Oncology (DEGRO, Deutsche Gesellschaft für Radioonkologie) presented their guideline, which has suggested selection criteria for a second breast-conserving approach. Based on this, patients who meet the following

criteria are found to be the most suitable: an isolated, unifocal, <3 cm local recurrence, a long interval between the primary treatment and the appearance of IBTR (>48 months), a patient aged >50 years, and the patient's strong preference for a 2ndBCT [134]. With these conditions, MIBT is the recommended method, while external-beam or intraoperative partial breast re-irradiation is acceptable only in a clinical trial.

The weakness of our study is its retrospective (non-randomized) nature, but it is practically impossible to organize a prospective randomized trial due to the patients' reluctance to accept randomization between breast conserving therapy or mastectomy.

The absence of some data could be also considered a limitation. For example, detailed pathological data from a few cases were not documented in sufficient details, mainly for patients who suffered their disease in an earlier period. Furthermore, comorbidities that could have had a competitive effect on clinical outcome (e.g., overall survival) were not part of this study. For example, regarding radiation-induced heart disease after RT of the left sided breast cancer, no data are available focusing on a safe radiation-free interval when considering re-irradiation. However, according to a study, after the first course of irradiation women already had a 1.77-fold higher risk of dying of cardiac disease than those who had not received RT [135]. In addition, during the relatively long period of our study, some diagnostic and therapeutic methods for IBTR evolved, thus some patients did not benefit from contemporary treatment possibilities (e.g., repeated SLNB or newer systemic therapies).

Finally, it may be worth noting that the long latency until the IBTR – which occurred in our study up to 27 years after first BCT – implies that it may be advisable to extend the follow-up even beyond the usually suggested 5 years.

6. 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 show a similarity to our previous results of ABPI for primary breast cancer, executed by the postoperative catheter implantation technique. Since then, this approach has been routinely used in our clinical work.

2. Based on the results of our study, the 2ndBCS with perioperative HDR MIBT results in similar, 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 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.

7. Summary

Local failure after primary BCT is a challenge for both surgeons and radiation oncologists to minimize morbidity while maintaining optimal treatment outcomes.

Because the majority of patients have a good prognosis after treatment of early-discovered IBTR, patient satisfaction and quality of life have become increasingly important. Although sMT is still currently accepted as a benchmark in cases of IBTR (whether it is seen as a true recurrence or as a new primary tumor), patients undergoing sMT may suffer from reduced self-esteem and impaired body self-image, followed by physical and emotional distress which negatively impact their quality of life. Hence, second breast preservation is always worth considering, however, 2ndBCS alone is associated with a significantly higher further recurrence rate compared with sMT. Historically, repeated RT of the breast was contraindicated following a prior WBI due to concerns about intolerable morbidity with a second course of irradiation.

To our knowledge, this study is the first to directly compare 2ndBCT with perioperative HDR MIBT to sMT in patients who were treated at the same institute and during the same period. Based on our results and the data published previously by others, 2ndBCS with perioperative HDR MIBT is a feasible and safe option for the management of IBTR, resulting in equivalent 5-year oncological outcomes compared to standard sMT. HDR MIBT decreases the risk of a 2ndIBTR with low rate of late side-effects and acceptable cosmetic results.

When choosing between these two salvage strategies, which appear to achieve similar local control, it should be taken into account the breast size after the primary conservative surgery (the possibility of preserving a reasonable cosmetic result), histopathological factors of the recurrent tumor, the patients' age, the time since first treatment, and the skin-related consequences of the first course of irradiation. A close interdisciplinary collaboration between the radiation oncology and surgical communities is required to maximize patient care. Finally, the patient's request remains crucial after detailed information about the benefits and risks of each salvage treatment.

Although there is no currently available phase III non-inferiority study available, there is growing evidence that 2ndBCT is safe and has excellent local control, overall survival, cosmesis, and patient satisfaction.

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9. 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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Hungarian-language peer-reviewed publications:

1. Smanykó V, Mészáros N, Újhelyi M, Fröhlich G, Stelczer G, Major T, Mátrai Z, Polgár C. (2018) Második emlőmegtartó műtét és szövetközi sugárkezelés az emlődaganat lokális kiújulásának kezelésére. Orv Hetil, 159: 430-438.
   IF:0,564

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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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   IF:1,315

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Második emlőmegtartó műtét és szövetközi sugárkezelés az emlődaganat lokális kiújulásának kezelésére

Ötéves eredmények

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Bevezetés és célkitűzés: Második emlőmegtartó műtét és nagy dózisteljesítményű szövetközi sugárkezelés eredményeinek bemutatása azonos oldali emlődaganat kiújulása miatt kezelt betegeknél.
Módszer: Korai invazív emlőrák előzetes emlőmegtartó kezelése után jelentkező helyi daganatkiújulás miatt 1999 és 2015 között 33 betegnél végeztünk második emlőmegtartó műtétet perioperatív szövetközi sugárkezeléssel. A második emlőmegtartó műtét során a tumorágyba átlagosan 8 (tartomány: 4–24) darab flexibilis katétert ültettünk be. A perioperatív időszakban a tumorágy és annak 1–2 cm-es biztonsági zónájának területére adott összdózis 22 Gy volt (5 × 4,4 Gy, 3 nap alatt). Adjuváns szisztémás kezelésként 24 beteg (73%) egyedüli endokrin kezelésben, 6 beteg (18%) pedig kemoterápiában részesült. A túlélési eredményeket a Kaplan–Meier-módszerrel elemeztük. A késői mellékhatásokat és a kozmetikai eredményeket feljegyeztük.
Eredmények: A második emlőmegtartó kezeléstől számított követési idő középértéke 61 hónap (tartomány: 26–189 hónap) volt. A követési idő alatt 4 betegnél (12,1%) alakult ki második lokális recidíva. A második helyi daganatkiújulás, a regionális daganatkiújulás és a távoli áttétképződés ötéves valószínűsége 6,3%, 6,1% és 14,9% volt, azonos sorrendben. Az ötéves betegségmentes, daganatspecifikus és teljes túlélés 76,2%, 92,4% és 89,2% volt. Kiváló, jó, megfelelő és rossz kozmetikai eredményt 4 (12%), 19 (58%), 4 (12%) és 6 (18%) betegnél állapítottunk meg. Grade 2-es és 3-as fibrosis 9 (27%) és 1 (3%) betegnél alakult ki. Tünetmentes zsírnekrózist 7 (21%) betegnél figyeltünk meg.
Következtetés: A második emlőmegtartó műtét perioperatív szövetközi sugárkezeléssel biztonságos lehetőség az emlődaganat helyi kiújulásának kezelésére. A szövetközi sugárkezelés elfogadható kozmetikai eredmények és kevés késői mellékhatás mellett csökkentheti a második lokális kiújulás valószínűségét, így válogatott esetekben a standard mastectomiát helyettesítheti.
Orv Hetil. 2018; 159(11): 430–438.

Kulcsszavak: emlőrák, helyi daganatkiújulás, második emlőmegtartó műtét, sugárkezelés, brachytherapia

Second breast conserving surgery and interstitial radiotherapy for the treatment of breast tumor local recurrences

Five-year results

Introduction and aim: To report the clinical outcomes of second breast-conserving therapy with perioperative interstitial radiotherapy for the treatment of ipsilateral breast tumor recurrences.
Method: Between 1999 and 2015, 33 patients, presenting with an ipsilateral breast tumor recurrence after previous breast conserving therapy, were salvaged by re-excision and perioperative high-dose-rate interstitial brachytherapy. A median of 8 (range: 4–24) catheters were implanted into the tumor bed intraoperatively. A total dose of 22 Gy in

5 fractions of 4.4 Gy was delivered to the tumor bed with a margin of 1–2 cm, on 3 consecutive days. The adjuvant systemic treatments consisted of hormonal therapy for 24 patients (73%) and chemotherapy for 6 patients (18%). The survival results were estimated by the Kaplan–Meier method. Late side effects and cosmetic results were also registered.
Results: The median follow-up time following the second breast conserving therapy was 61 months (range: 26–189 months). During the follow-up, 4 patients (12.1%) developed second local recurrence. The five-year actuarial rates of the second local, regional and distant recurrence were 6.3%, 6.1%, and 14.9%, respectively. The five-year probabilities of disease-free, cancer-specific and overall survival were 76.2%, 92.4%, and 89.2%, respectively. Four (12%), 19 (58%), 4 (12%) and 6 (18%) patients had excellent, good, fair and poor cosmetic results, respectively. Grade 2 and 3 fibrosis developed in 9 (27%) and 1 (3%) patients. Asymptomatic fat necrosis was detected in 7 (21%) women.
Conclusion: Second breast conserving therapy with perioperative high-dose-rate interstitial brachytherapy is a safe and feasible option for the management of ipsilateral breast tumor recurrences. Interstitial brachytherapy may decrease the risk of second local relapse with acceptable cosmetic results and low rate of late side effects. Hence, in selected cases it can provide a feasible alternative to salvage mastectomy.

Keywords: breast cancer, local recurrence, second breast conserving surgery, radiotherapy, brachytherapy

Smanykó V, Mészáros N, Újhelyi M, Fröhlich G, Stelczer G, Major T, Mátrai Z, Polgár Cs. [Second breast conserving surgery and interstitial radiotherapy for the treatment of breast tumor local recurrences. Five-year results]. Orv Hetil. 2018; 159(11): 430–438.

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Semmelweis Ignác születése 200. évfordulójának évében a *Szerkesztőség* felkérésére készített tanulmány.

Rövidítések

DCIS = ductalis carcinoma *in situ;* DEGRO = (Deutsche Gesellschaft für Radioonkologie) Német Onkoradiológiai Társaság; EMT = emlőmegtartó terápia; ER = ösztrogénreceptor; GEC-ESTRO = (Groupe Européen de Curiethérapie – European Society for Radiotherapy and Oncology) az Európai Brachytherapiás Társaság Emlőrák Munkacsoportja; Gy = gray; HDR = (high-dose-rate) nagy dózisteljesítményű; IDC = invazív ductalis carcinoma; ILC = invazív lobularis carcinoma; LDR = (low-dose-rate) alacsony dózisteljesítményű; LR = lokális recidíva; MASZT = mastectomia; NA = nincs adat; OS = (overall survival) teljes túlélés; PDR = (pulsed-dose-rate) pulzáló dózisteljesítményű; PR = progeszteronreceptor; RTOG/EORTC = (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer) az Európai Rákkutató és Rákkezelési Szövetség Sugárterápiás Onkológiai Munkacsoportja

Az emlőrák a leggyakoribb női daganatos betegség. 2012-ben világszerte 1,67 millió új esetet regisztráltak, ami az összes új daganatos betegség 25,1%-át adta [1]. A Nemzeti Rákregiszter adatai szerint Magyarországon 2014-ben 8049 új megbetegedést jelentettek be [2]. A korai stádiumú emlőrák általánosan elfogadott kezelése az emlőmegtartó műtét és a maradék emlő posztoperatív besugárzása [3–5]. A megfelelő ellátás ellenére az azonos oldali lokális recidíva (LR) aránya 10 év után 8–11% körül van [6, 7]. Ezen esetekben a „salvage" mastectomia a standard kezelés, de a páciensek részéről felmerül az igény egy jobb életminőséggel és jobb kozmetikai eredménnyel járó második emlőmegtartó terápia iránt. Az irodalmi adatok szerint „salvage" mastectomia után a második helyi kiújulás valószínűsége megközelítőleg 10% (tartomány: 3–22%) [8–23]. Ugyanez az arány ismételt emlőmegtartó műtét után 26% (tartomány: 4–50%) [8–16, 24–27]. A maradék emlő ismételt besugárzásával csökkenthető lenne a második lokális kiújulás aránya, de a teljes emlő reirradiációját nem ajánlják a súlyos késői mellékhatások magas kockázata miatt. Válogatott esetekben a szövetközi multikatéteres sugárkezeléssel (brachytherapiával) végzett egyedüli részleges emlőbesugárzás eredményessége már bizonyított [28–30]. Ez a technika lehetőséget biztosít arra, hogy csak a tumorágy területére korlátozva további besugárzást adhassunk le, a környező egészséges szövetek megkímélésével.

Vizsgálatunk célja az előzetes emlőmegtartó kezelés után kialakult azonos oldali emlőrák-recidívák kezelésében az ismételt emlőmegtartó műtét és a perioperatív nagy dózisteljesítményű (high-dose-rate, HDR) szövetközi sugárkezelés hatékonyságának meghatározása volt.

Módszer

1999 márciusa és 2015 márciusa között 33, korábban primer emlőtumor miatt konzervatív műtéttel és teljesemlő-besugárzással ellátott betegnél végeztünk azonos oldali emlőrecidíva miatt második emlőmegtartó műtétet intraoperatív katéterbeültetéssel és perioperatív szövetközi sugárkezelést. A betegek második emlőmegtartó kezelését a következő feltételek egyidejű fennállása esetén végeztük el: izolált, egygócú, azonos oldali emlőreci-

díva, klinikai és mammográfiás vizsgálattal ≤3 cm-es tumorméret, a bőrfelszíntől legalább 2 cm távolságra elhelyezkedő kiújulás, a beteg határozott preferenciája az ismételt emlőmegtartó műtét irányában. Kizáró ok volt az egyidejű regionális vagy távoli áttét jelenléte, illetve a multifokális/multicentrikus lokális recidíva.

Az elsődleges emlőrák ellátása minden betegnél széles excízió és hónalji blokkdissectio vagy őrszemnyirokcsomó-biopszia volt. A posztoperatív sugárkezelés során a maradék emlő 46–50 Gy dózisú fotonirradiációját tangenciális mezőkből végeztük, konvencionális frakcionálással (2 Gy/nap, 5 frakció/hét). Tizenkét beteg 4–16 Gy dózisú kiegészítő tumorágy „boost" besugárzásban is részesült. Adjuváns kemoterápiában 4 beteg (12%), hormonkezelésben 12 beteg (36,5%), míg kemo- és hormonterápiában 5 beteg (15%) részesült. A betegek és a daganatok patológiai jellemzőit az első műtét, illetve a második emlőmegtartó műtét idején az *1. és a 2. táblázatban* foglaltuk össze.

1. táblázat | A betegek és a daganatok patológiai jellemzői az első emlőmegtartó kezeléskor

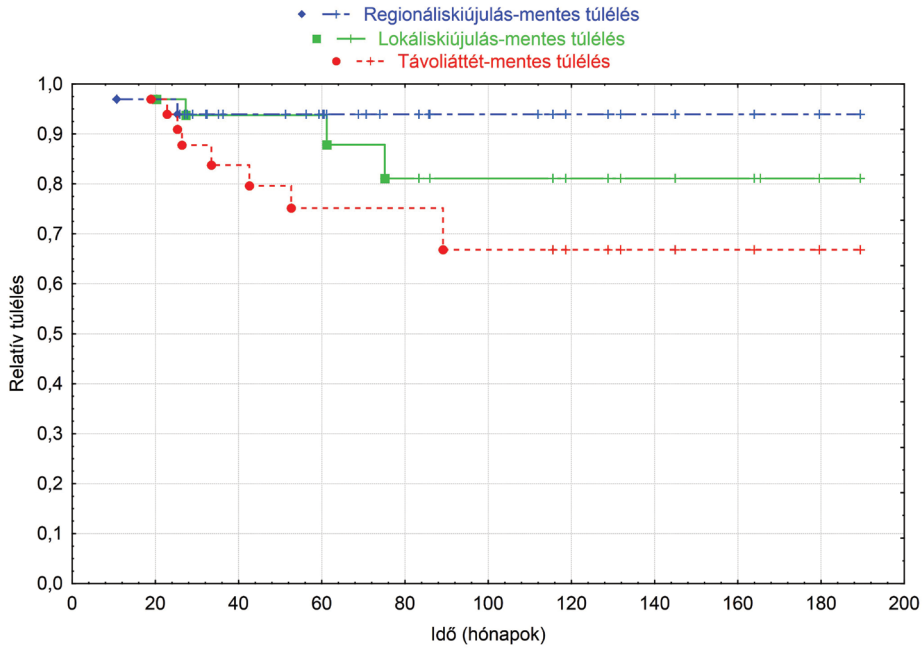
Jellemzők	n = 33
Átlagos életkor (tartomány)	52 év (33–72)
Premenopauza	11 (33%)
Tumorméret (tartomány)	16 mm (4–40)
Szövettani típus	
IDC	24 (73%)
ILC	2 (6%)
Egyéb invazív	4 (12%)
Ismeretlen	3 (9%)
Szövettani fokozat	
Grade 1	7 (21%)
Grade 2	15 (46%)
Grade 3	8 (24%)
Ismeretlen	3 (9%)
pTNM-status	
pT1 pN0	15 (46%)
pT2 pN0	2 (6%)
pT1 pN1mi	1 (3%)
pT1 pN1a	6 (18%)
pT2 pN1a	4 (12%)
Ismeretlen	5 (15%)
Sebészi szél	
Pozitív	15 (46%)
Negatív	1 (3%)
Ismeretlen	17 (51%)
Hormonreceptor-status	
ER+, PR+	11 (33%)
ER+, PR–	2 (6%)
ER–, PR+	0
ER–, PR–	4 (12%)
Ismeretlen	16 (49%)

ER = ösztrogénreceptor; IDC = invazív ductalis carcinoma; ILC = invazív lobularis carcinoma; PR = progeszteronreceptor

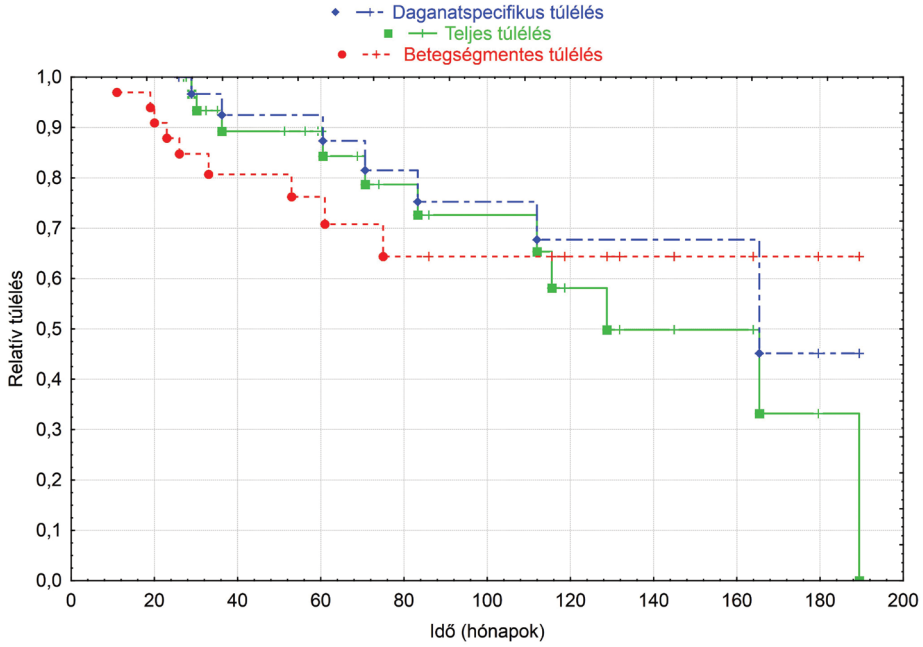
2. táblázat | A betegek és a daganatok patológiai jellemzői a kiújult daganat kezelésekor

Jellemzők	n = 33
Átlagos életkor (tartomány)	63 év (37–78)
Premenopauza	3 (9%)
Tumorméret (tartomány)	16 mm (2–70)
A recidíváig eltelt átlagos idő (tartomány)	125 hónap (36–258)
A recidíva lokalizációja	
Tumorágy-recidíva	18 (55%)
Tumorágyhoz közeli recidíva	5 (15%)
Tumorágyon kívüli recidíva	9 (27%)
Ismeretlen	1 (3%)
Szövettani típus	
IDC	28 (87%)
ILC	2 (6%)
Egyéb invazív	2 (6%)
DCIS	1 (1%)
Szövettani fokozat	
Grade 1	7 (21%)
Grade 2	9 (27%)
Grade 3	16 (49%)
Ismeretlen	1 (3%)
Sebészi szél	
Pozitív	0
Negatív	32 (97%)
Ismeretlen	1 (3%)
Hormonreceptor-status	
ER+, PR+	20 (61%)
ER+, PR–	6 (18%)
ER–, PR+	1 (3%)
ER–, PR–	4 (12%)
Ismeretlen	2 (6%)

DCIS = ductalis carcinoma *in situ;* ER = ösztrogénreceptor; IDC = invazív ductalis carcinoma; ILC = invazív lobularis carcinoma; PR = progeszteronreceptor



1. ábra | Regionáliskiújulás-mentes túlélés, lokáliskiújulás-mentes túlélés és távoliáttét-mentes túlélés a második emlőmegtartó kezelés után



2. ábra | Daganatspecifikus túlélés, teljes túlélés és betegségmentes túlélés a második emlőmegtartó kezelés után

A második emlőmegtartó kezelés során a korábban aspirációs citológiával vagy vastagtű-mintavétellel igazolt LR széles kimetszését általános érzéstelenítésben végeztük. A műtét során a tumorágyat 6 darab titániumklippel jelöltük, azután a nyitott műtéti üreg mellett a sebüreg méretétől függően 1–5 síkban (átlag: 2), 4–24 darab (átlag: 8) egymással párhuzamos vezetőtűt szúrtunk a tumorágyba, majd helyükre műanyag flexibilis utántölthető katétereket vezettünk be. A fémtrokárok eltávolítása után a katéterek végeit a bőrfelszínen műanyag gombokkal rögzítettük, amit a sebüreg zárása követett. A második–negyedik posztoperatív napon a besugárzástervezéshez izocentrikus röntgenfelvételeket vagy CT-vizsgálatot készítettünk az implantált emlőről. Céltérfogatként a tumorágyat és annak biztonsági zónáját (20 mm mínusz a tér hat irányában megadott ép sebészi szélek) kontúroztuk be úgy, hogy a pectoralis izmokat és a bőrfelszín alatti 5 mm vastagságú területeket kihagytuk.

Egy páciensnél a műtéti specimenre való rámetszés miatt pontos mikroszkopikus sebészi szél nem volt meg-

adható, így a maximális 20 mm-es biztonsági margót alkalmaztuk.

A számítógépes besugárzástervezés során a katétereken belüli aktív forráspozíciókat úgy határoztuk meg, hogy a dóziseloszlás minél homogénebb legyen, a dózisfelület pedig minél jobban illeszkedjen a céltérfogat alakjához. A kezelést a műtét után 48–72 órával indítottuk, és HDR utántöltéses („afterloading") besugárzókészülékkel végeztük. Az előírt 22 Gy összdózist 5 frakcióban, 4,4 Gy frakciódózisokkal, 3 egymást követő nap alatt szolgáltattuk ki, napi kétszeri besugárzással, a kezelések között legalább 6 óra szünetet tartva. A céltérfogat átlagosan 60 cm^3 volt (tartomány: 21–130 cm^3). Az utolsó frakció után a katétereket eltávolítottuk, és a betegeket néhány órás megfigyelés után otthonukba bocsátottuk. Adjuváns szisztémás kezelésként a betegek többsége (73%) egyedüli endokrin kezelésben részesült, kemoterápiát 6 beteg (18%) kapott. Három betegnél (9%) az előrehaladott életkor, hormonreceptor-negatív status vagy a citosztatikus szisztémás kezelés elutasítása miatt nem történt további adjuváns ellátás.

Az első és a második emlőrák végleges szövettani típusa 27 betegnél (82%) volt azonos, 3 betegnél (9%) különböző, további 3 betegnél (9%) pedig pontosan nem meghatározható viszonyú.

A betegeket az első két évben háromhavonta, az ötödik évig félévente, majd évente hívtuk vissza kontrollvizsgálatra. Mammográfiás és emlőultrahang-vizsgálatot évente végeztünk. A kozmetikai eredményeket a Harvard-beosztás [31], a késői melléhatásokat az Európai Rákkutató és Rákkezelési Szövetség Sugárterápiás Onkológiai Munkacsoportjának (RTOG/EORTC, Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer) osztályozási rendszere [32] alapján értékeltük. A követési időt a második emlőmegtartó műtét napjától számítottuk. A túlélési eredmények ötéves valószínűségét a Kaplan–Meier-módszerrel [33] számítottuk ki. A statisztikai feldolgozáshoz a STATISTICA 12 (StatSoft Inc., Palo Alto, CA, USA) programot használtuk.

Eredmények

A 61 hónapos medián követési idő (tartomány: 26–189 hónap) alatt négy esetben (12,1%) alakult ki az azonos oldali emlőben második lokális recidíva. A második helyi daganatkiújulás ötéves valószínűsége emlőmegtartás és reirradiáció után 6,3% volt *(1. ábra)*. A második lokális recidíva kialakulása után 3 betegnél végeztünk komplettáló mastectomiát, így a mastectomiamentes túlélés 91% volt. Egy betegnél a második lokális recidíva felfedezése előtt távoli áttéteket mutattak ki, ezért ismételt műtét nem történt. Azonos oldali axillaris metasztázis megjelenését 2 betegnél (6,1%) észleltük. Az ötéves regionáliskiújulás-mentes túlélés 93,9% volt *(1. ábra)*. Összesen 8 beteg (24,2%), a második emlőmegtartó műtétet követő 19–89. hónapban kialakult távoli áttét következtében a követés 29–165. hónapja között elhalálozott. Az ötéves távoliáttét-mentes túlélés 75,1% volt *(1. ábra)*. Az ötéves betegségmentes túlélés 76,2%, a daganatspecifikus túlélés 92,4%, a teljes túlélés 89,2% volt *(2. ábra)*.

3. táblázat Kozmetikai eredmények és késői mellékhatások a második emlőmegtartó kezelés után

Kozmetikai eredmény	n (%)
Kiváló	4 (12%)
Jó	19 (58%)
Megfelelő	4 (12%)
Rossz	6 (18%)
Bőrmellékhatás	
Grade 0	2 (6%)
Grade 1	17 (52%)
Grade 2	11 (33%)
Grade 3	3 (9%)
Zsírnekrózis	
Tünetmentes	7 (21%)
Tünettel járó	0 (0%)
Fibrosis	
Grade 0	11 (33%)
Grade 1	12 (37%)
Grade 2	9 (27%)
Grade 3	1 (3%)

Második primer tumor 3 betegnél (9%) alakult ki: egy vastagbélrák, egy veserák és egy tüdőrák; a követés 168., 106., illetve 105. hónapjában. Ellenoldali emlőrák a követési idő alatt 1 betegnél (3%) jelentkezett. A kozmetikai eredményeket és a késői mellékhatásokat a *3. táblázatban* foglaltuk össze. A kiváló és jó kozmetikai eredmények együttes aránya 70% volt. Súlyos fokú (Grade 3) bőrmellékhatás 3 (9%), fibrosis pedig 1 (3%) betegnél alakult ki. Panaszt okozó (szimptomatikus) zsírnekrózis nem fordult elő. Ismételt műtéti beavatkozást igénylő (Grade 4) mellékhatás (fibrosis, bőr- vagy zsírnekrózis) egy esetben sem alakult ki.

Megbeszélés

Hosszú időn keresztül az ún. „salvage" mastectomia volt az egyetlen elfogadott kezelés az emlőmegtartó műtétet és posztoperatív teljesemlő-besugárzást követően kialakult lokális emlődaganat-kiújulások kezelésére [8–16, 22, 23]. Az 1990-es évektől azonban egyre több munkacsoport számolt be a második emlőmegtartó műtéttel elért eredményeiről [24–27] *(4. táblázat)*. Hazánkban *Fodor és mtsai* [9] közölték a második emlőmegtartó műtéttel vagy mastectomiával kezelt betegek klinikai eredményeinek összehasonlítását, amelyben a második

4. táblázat | A második emlőmegtartó műtét (sugárkezelés nélkül) és a „salvage” mastectomia eredményeinek összehasonlítása

Szerző	Medián követési idő (hónap)	Betegszám		2. LR (%)		Ötéves LR (%)		Ötéves OS (%)	
		2. EMM	MAST	2. EMM	MAST	2. EMM	MAST	2. EMM	MAST
Salvadori B [8]	73	57	133	14%	3%	19%	4%	85%	70%
Fodor J [9]	165	32	32	28%	16%	NA	NA	NA	NA
Dalberg K [10]	72	14	65	50%	18%	33%	12%	NA	NA
Voogd AC [11]	52	20	229	40%	22%	NA	NA	NA	NA
Alpert TE [12]	165	30	116	7%	7%	NA	NA	58%*	66%*
Komoike Y [13]	43	30	11	30%	0%	37%†	0%†	90%†	91%†
Abner AL [14]	39	16	123	31%	6%	NA	NA	NA	79%
van der Sangen MJ [15]	NA	8	89	50%	11%	NA	NA	NA	NA
Kurtz JM [16]	35	34	36	9%	3%	22%	4%	NA	NA
Kurtz JM [24]	72	52	–	23%	–	21%	–	79%	–
Kurtz JM [25]	51	50	–	32%	–	38%	–	67%	–
Gentilini O [26]	81	161	–	4%	–	29%	–	84%	–
Ishitobi M [27]	40	78	–	22%	–	21%	–	NA	–
Doyle T [17]	44	–	112	–	3%	–	NA	–	86%
Beard HR [18]	55	–	59	–	12%	–	NA	–	NA
Botteri E [19]	60	–	121	–	15%	–	NA	–	73%
Lindford AJ [20]	66	–	60	–	10%	–	NA	–	93%
Tanabe M [21]	55	–	118	–	9%	–	9%	–	NA
Recht A [22]	32	–	65	–	8%	–	37%	–	NA
Osborne MP [23]	28	–	46	–	15%	–	45%	–	76%
Összes vizsgálat	*28–165*	*582*	*1415*	*26,1%*	*9,9%*	*19–38%*	*0–45%*	*58–90%*	*66–93%*

2. EMM = második emlőmegtartó műtét; 2. LR = második lokális recidíva; MAST = mastectomia; NA = nincs adat; OS = teljes túlélés; †hároméves lokális recidíva és teljes túlélés; *tízéves teljes túlélés

LR-ek aránya 28% és 16% volt, azonos sorrendben. A vizsgálatok alapján az ismételt szervmegtartó műtét után a második LR aránya magasabb volt, mint „salvage” mastectomia után [8–16].

Bár a második emlőmegtartó műtét után végzett ismételt besugárzás csökkentheti a második lokális kiújulás gyakoriságát, a teljes emlő reirradiációját nem ajánlják a késői radiogén mellékhatások magas kockázata miatt. Második emlőmegtartó terápia részeként külső besugárzással végzett reirradiáció eredményeit *Deutsch és mtsai* [34] közölték. Vizsgálatukban 39 reexcízión átesett betegnél 50 Gy dózisú elektronbesugárzást adtak csak a tumorágy területére. Második lokális kiújulás 51,5 hónapos medián követési idő alatt 8 betegnél (20,5%) alakult ki, a kiváló és jó kozmetikai eredmények együttes aránya 75%, míg az ötéves teljes túlélés 77,9% volt.

Az ismételt emlőmegtartó műtét utáni reirradiáció témájában a legtöbb közlemény a szövetközi sugárkezelés módszerének alkalmazásával született [35–44]. Ezen vizsgálatok eredményeit az *5. táblázatban* foglaltuk összse. Elsőként, 1989-ben *Recht és mtsai* [22] számoltak be egy betegről, aki korábbi emlőmegtartó műtétet és teljesemlő-besugárzást követően kialakult LR mellett elutasította a mastectomiát, ezért széles excízióban és irídium sugárforrással végzett implantációban részesült. A páciens 72 hónappal a beavatkozás után daganatmentesen halt meg. Két francia munkacsoport 2004-ben közölt közös eredményeket 69 betegről, akik második emlőmegtartó műtét után alacsony dózisteljesítményű (low-dose-rate, LDR-) technikával kaptak szövetközi sugárkezelést, intézetenként eltérő 30 Gy vagy 45–50 Gy dózisban [35]. Az ötéves második lokálisrecidívamentes túlélés nem szignifikáns mértékben, de magasabb volt azoknál a betegeknél, akik legalább 50 Gy dózisú szövetközi sugárkezelést kaptak, mint azoknál, akik 50 Gy-nél kisebb dózisú ismételt besugárzásban részesültek (85,5% versus 74,4%; p = 0,095). Ugyanakkor a Grade 2–3-as mellékhatások aránya szignifikánsan magasabb volt, amennyiben a külső és a szövetközi sugárkezelések összegzett dózisa meghaladta a 100 Gy-t, mint ahol ennél kevesebb volt (32,5% versus 4%; p = 0,005). Szintén több volt a súlyosabb mellékhatás abban az esetben, ha a szövetközi sugárkezeléssel leadott dózis meghaladta a 46 Gy-t (36% versus 13,6%; p = 0,007).

A legnagyobb betegszámú multicentrikus vizsgálatot az Európai Brachytherapiás Társaság (GEC-ESTRO, Groupe Européen de Curiethérapie – European Society for Radiotherapy and Oncology) Emlőrák Munkacso-

5. táblázat | A második emlőmegtartó műtét és a szövetközi sugárkezeléssel végzett reirradiáció eredményei

Szerző	Dózis-teljesítmény	Frakciószám × dózis (Gy)	Medián követési idő (hónap)	Betegszám	2. LR (%)	Ötéves LR (%)	Ötéves OS (%)	Kiváló és jó kozmetikai eredmények (%)
Hannoun-Levi JM [35]	LDR	1 × 30; 1 × 45–50	50	69	15,9%	25%; 14%	91,8%	NA
Chadha M [39]	LDR	1 × 30; 1 × 45	36	15	6,7%	11%*	100%*	100%
Maulard C [40]	LDR	1 × 30	40	15	26,7%	NA	61%	16%
Resch A [41]	PDR	40–50/0,6–1‡	59	9	0%	0%	100%†	55%
Kauer-Dorner D [42]	PDR	50,1/0,6–1‡	57	39	5,1%	7%	87%	37%
Guix B [37]	HDR	12 × 2,5	89	36	2,7%	10,6%§	96,7%§	94%
Trombetta M [43]	LDR HDR	1 × 45–50 10 × 3,4	38	26	3,8%	NA	NA	92%
Hannoun-Levi JM [36]	LDR PDR HDR	1 × 30–55 49–50/0,6–1‡ 5–10 × 3,6–4,4	47	217	4,1%	5,6%	88,7%	85%
Houvenaeghel G [44]	LDR	1 × 45–56	73	62	25,8%	17%	80%	NA
Trombetta M [38]	HDR#	10 × 3,4	40	18	11,1%	NA	NA	83%
A jelen vizsgálat	HDR	5 × 4,4	61	33	12,1	6,3%	89,2%	70%
Összes vizsgálat			*36–89*	*539*	*10,4%*	*5,6–25%*	*61–100%*	*16–100%*

2. LR = második lokális recidíva; Gy = gray; HDR = magas dózisteljesítmény (high-dose-rate); LDR = alacsony dózisteljesítmény (low-dose-rate); NA = nincs adat; OS = teljes túlélés; PDR = pulzáló dózisteljesítmény (pulsed-dose-rate); #üregi HDR-technikával kezelt betegek MammoSite® vagy Contura® ballon-applikátorral; *hároméves lokális recidíva és teljes túlélés; †betegségspecifikus túlélés; ‡összdózis/egyszeri pulzus dózisa; §tízéves lokális recidíva és teljes túlélés

portja közölte 2013-ban [36]. A tanulmány 217 azonos oldali lokális kiújulás miatt 2000 és 2010 között második emlőmegtartó műtéttel és multikatéteres szövetközi sugárkezeléssel ellátott beteg adatait dolgozta fel nyolc európai intézet közreműködésével. A reirradiáció dózisának középértéke LDR- és pulzáló dózisteljesítményű (pulsed-dose-rate, PDR-) technika esetén 46 Gy (tartomány: 30–55 Gy) és 50,4 Gy (tartomány: 49–50 Gy), míg HDR-technika alkalmazásakor 32 Gy (tartomány: 22–36 Gy) volt. Negyvenhét hónap medián követési idő után a második lokális kiújulás öt- és tízéves valószínűsége 5,6% és 7,2% volt, azonos sorrendben. Az öt- és tízéves teljes túlélés egyenként 88,7% és 76,4% volt. A kozmetikai eredmény 85%-ban kiváló vagy jó volt.

A leghosszabb követési idővel rendelkező vizsgálatot *Guix és mtsai* [37] végezték: 1990 és 2001 között 36 betegnél alkalmaztak izolált emlőrecidíva miatt második lumpectomiát és 30 Gy (12 × 2,5 Gy) dózisú HDR szövetközi sugárkezelést. Nyolcvankilenc hónap medián követési idő után a második lokális kiújulás tízéves valószínűsége 10,6%, a tízéves teljes túlélés 96,7% volt. A kiváló és jó kozmetikai eredmények együttes aránya 94% volt.

Intézetünkben 1999-ben vezettük be a második emlőmegtartó műtéttel kombinált intraoperatív emlőtűzdelést és perioperatív HDR szövetközi sugárkezelést az azonos oldali emlőrecidívák válogatott eseteinek kezelésére. Korai eredményeinket az előzőekben más folyóiratokban közöltük [45, 46]. Jelen vizsgálatunkban 33 betegnél végeztünk előzetes emlőmegtartó műtét és posztoperatív külső besugárzás után kialakult LR miatt reexcíziót, intraoperatív tumorágytűzdelést és perioperatív HDR szövetközi sugárkezelést. Az ötéves második lokáliskiújulás-mentes túlélés 93,7%, a teljes túlélés 89,2%, a kiváló és jó kozmetikai eredmények együttes aránya 70% volt. Eredményeink hasonlóak az irodalomban közölt korábbi tanulmányok eredményeihez.

Vizsgálatunk gyenge pontja annak retrospektív (nem randomizált) jellege, de a „salvage" mastectomia és a második emlőmegtartó kezelés eredményességét összehasonlító prospektív randomizált vizsgálat kivitelezése a gyakorlatban nem lehetséges, mivel a beválasztásra alkalmas betegek emlőmegtartó műtét iránti preferenciája a gátját képezi a véletlen besorolásnak.

A Német Onkoradiológiai Társaság (DEGRO, Deutsche Gesellschaft für Radioonkologie) 2016-ben megjelent gyakorlati irányelvei alapján az alábbi beválasztási kritériumok esetén javasolják az azonos oldali emlőrecidíva kombinált szervmegtartó kezelését: izolált, unicentrikus, 3 cm-nél kisebb recidíva; 50 évnél idősebb életkor; 48 hónapnál hosszabb idő a primer és a kiújult daganat között; illetve a beteg kifejezett preferenciája az emlőmegtartás iránt [47]. Ezen feltételek teljesülése mellett sugárterápiás technikaként a legtöbb tapasztalatot adó multikatéteres szövetközi besugárzást ajánlják, míg az ismételt parciális külső besugárzást vagy az intraoperatív radioterápiát csak klinikai vizsgálat keretében tartják elfogadhatónak.

A GEC-ESTRO Emlőrák Munkacsoportja jelenleg is dolgozik a „salvage" mastectomia és a szövetközi sugárkezeléssel együtt végzett második emlőmegtartó műtét

eredményességét összehasonlító retrospektív adatbázisának frissítésén, immár 14 centrum közreműködésével, amelyben az Országos Onkológiai Intézetben működő Emlőrák Munkacsoportunk is részt vesz. Ezek az összesített eredmények további segítséget nyújthatnak majd az ismételt emlőmegtartó kezelés indikációs körének pontosabb meghatározásához.

Következtetés

A jelen vizsgálat eredményei és a korábban közlésre került irodalmi adatok alapján a második emlőmegtartó műtét perioperatív szövetközi sugárkezeléssel (brachytherapiával) biztonságos lehetőséget kínál az emlődaganat lokális kiújulásának kezelésére, hasonló ötéves onkológiai eredményeket biztosítva, mint a standard „salvage" mastectomia. A szövetközi sugárkezelés elfogadható kozmetikai eredmények és kevés késői mellékhatás mellett csökkentheti a második lokális kiújulás valószínűségét. A jövőben további, nagyobb betegszámú vizsgálatok szükségesek, hogy meghatározhassuk a második emlőmegtartó kezelés pontos klinikai értékét a „salvage" mastectomiával szemben.

Anyagi támogatás: A közlemény megírása, illetve a kapcsolódó kutatómunka során a szerzők anyagi támogatásban nem részesültek.

Szerzői munkamegosztás: S. V.: Adatfeldolgozás, a nemzetközi irodalom áttekintése, a kézirat elkészítése. M. N.: Intraoperatív katéterimplantáció, a sugárkezelés kivitelezése. Ú. M.: Adatfeldolgozás. F. G.: Besugárzástervezés, statisztikai elemzés. S. G., M. T.: Besugárzástervezés. M. Z.: Az emlőmegtartó műtétek elvégzése. P. Cs.: A kezelési módszer magyarországi bevezetése, témavezetés, intraoperatív katéterimplantáció, sugárkezelés kivitelezése, adatelemzés, a kézirat revíziója. A cikk végleges változatát valamennyi szerző elolvasta és jóváhagyta.

Érdekeltségek: A szerzőknek nincsenek érdekeltségeik.

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„Tuta viam omnium tutissima."
(Mindig a járt út a veszélytelenebb.)

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Breast/Soft Tissue

Second breast-conserving surgery and interstitial brachytherapy vs. salvage mastectomy for the treatment of local recurrences: 5-year results

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ABSTRACT

PURPOSE: The purpose of this study was to report the clinical outcomes of a second breast-conserving therapy (2nd BCT) with perioperative interstitial brachytherapy (iBT) vs. those of salvage mastectomy (sMT) in the treatment of ipsilateral breast tumor recurrences (IBTRs).

METHODS AND MATERIALS: Between 1999 and 2015, 195 patients with IBTR after a previous breast-conserving treatment were salvaged either with reexcision and perioperative high-dose-rate iBT (n = 39), or with sMT (n = 156). In the 2nd BCT group, a total dose of 22 Gy in five fractions of 4.4 Gy was delivered to the tumor bed with intraoperatively implanted catheters for 3 consecutive days.

RESULTS: The median followup time was 59 months (1–189) in the 2nd BCT, and 56 months (3–189) in the sMT group. The mean size of IBTR was 16 mm (2–70) vs. 24 mm (2–90), respectively (p = 0.0005), but there were no other significant differences in patient- or IBTR-related parameters between the two groups. During the followup period, 4 of 39 (10.2%) and 28 of 156 (17.9%) second local recurrences (2nd LR) occurred in the 2nd BCT and the sMT group, respectively. The 5-year actuarial rate of 2nd LR was 6% vs. 18% (p = 0.22), the 5-year probability of disease-free, cancer-specific and overall survival was 69% vs. 65% (p = 0.13), 85% vs. 78% (p = 0.32), and 81% vs. 66% (p = 0.15), respectively. In the 2nd BCT group, the rate of good to excellent cosmesis was 70%.

CONCLUSIONS: 2nd BCT with perioperative high-dose-rate iBT is a safe and feasible option for the management of IBTR, resulting in similar 5-year oncological outcomes and better cosmetic results compared with sMT.

Keywords: Breast cancer; Local recurrence; Second breast-conserving therapy; Salvage mastectomy; Brachytherapy

Introduction

Breast cancer is the most common cancer among women with an estimated 1.67 million new cases diagnosed in 2012, representing 25.1% of all new cancerous diseases (1). According to the National Cancer Registry, in 2014, 8049 new cases were reported in Hungary (2). Nowadays, the standard of care for early-stage breast cancer is breast-conserving surgery (BCS) with postoperative radiotherapy (RT) (3, 4, 5). In spite of adequate local treatment, the rate of ipsilateral breast tumor recurrence (IBTR) has been reported to be within the range of 8–11% in 10 years (6, 7). In such cases, salvage mastectomy (sMT) is currently considered as the gold-standard treatment, but—after detailed information and discussion—a large number of patients would prefer a second breast-conserving therapy (2nd BCT) resulting in better quality of life and cosmetic outcome. According to the literature, the rate of the second local recurrence (2nd LR) is close to 10% after the sMT (range: 3–22%) (8–23). This rate, after repeated BCS without RT, has been reported as high as 26% (range: 4–50%) (8–16, 24–27). Theoretically, re-irradiation after second BCS may decrease the chance of

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2nd LR, but unfortunately, the reirradiation of the whole breast with the sufficient dose is considered inappropriate due to the high risk of serious late side effects. In selected cases, multicatheter interstitial brachytherapy (iBT) was successfully used as partial-breast irradiation after BCS (28–32). Owing to the ability to focus radiation on a limited area, while sparing surrounding normal tissues, this technique is a promising method to reirradiate the tumor bed with an effective dose after previous BCS and whole-breast irradiation (WBI).

Therefore, the aim of this study was to evaluate the feasibility and efficacy of second breast-conserving operation with reirradiation using perioperative high-dose-rate (HDR) iBT for the treatment of IBTR developed after a previous breast-conserving treatment, compared with standard sMT.

Methods and materials

We retrospectively analyzed the outcome of 195 women who had been presented with an IBTR after previous conservative surgery and WBI, between 1999 and 2016.

For the treatment of the initial breast cancer, all patients underwent wide excision and axillary block dissection or sentinel lymph node biopsy. Postoperative RT consisted of 46–50 Gy WBI administered using two tangential photon beams with conventional fractionation (2 Gy/day, 5 fractions/week). 45 patients (23%) received a tumor bed boost of 4–16 Gy. Patient, tumor, and treatment characteristics for initial breast cancer are summarized in Table 1.

Table 1
Patient, tumor, and treatment characteristics for initial breast cancer of 195 patients

Characteristic	*n* (%)
Mean age (years)	53 (range: 27–83)
Premenopausal	85 (44%)
Mean tumor size (mm)	19 (range: 1–80)
Histologic type	
Invasive ductal carcinoma	130 (67%)
Invasive lobular carcinoma	12 (6%)
Other invasive carcinoma	10 (5%)
Ductal carcinoma *in situ*	14 (7%)
Unknown	29 (15%)
Histologic grade	
1	29 (15%)
2	64 (33%)
3	43 (22%)
Unknown	59 (30%)
pTNM stage	
pT1 pN0	69 (35%)
pT2 pN0	21 (11%)
pT3 pN0	4 (2%)
pT1 pN1	25 (13%)
pT2 pN1	15 (8%)
pT2 pN2	2 (1%)
pT2 pN3	2 (1%)
pT3 pN0	4 (2%)
Unknown	53 (27%)
Surgical margin status	
Positive	12 (6%)
Negative	103 (53%)
Unknown	80 (41%)
Hormonal status	
ER+, PR+	58 (30%)
ER+, PR−	12 (6%)
ER−, PR+	5 (3%)
ER−, PR−	38 (19%)
Unknown	82 (42%)
Systemic therapy	
Chemotherapy	41 (21%)
Hormonal therapy	54 (27%)
Chemotherapy and hormonal therapy	21 (11%)
None	62 (32%)
Unknown	17 (9%)

ER = estrogen receptor; PR = progesterone receptor.

39 patients who refused sMT underwent second BCS and perioperative HDR multicatheter iBT. The other 156 women underwent standard sMT. Patients were treated with 2nd BCT when the following conditions were met: isolated (without regional and distant metastasis), unicentric, parenchymal tumor recurrence; clinical and mammographic examination $\leq$ 3 cm tumor size, recurrence at least 2 cm from the skin surface; and the patient's strong preference for repeated BCS. Exclusion criteria were the multifocal or multicentric LR.

In case of 2nd BCT—after aspiration cytology or core biopsy confirmed—wide reexcision of the recurrent tumor was performed under general anesthesia. During reoperation, the walls of the excision cavity were marked with four to six titanium clips. With an open surgical wound, a median of 8 (range: 4–24) guide needles in one to three planes were placed in the tumor bed, spaced 15–20 mm apart. Afterward, the guide needles were replaced with plastic catheters and secured with fixation buttons at the skin. After implantation, the wound was closed with sutures. On the second-fourth postoperative day, isocentric X-ray films or CT scans were taken of the implanted breast, and computerized treatment planning was performed.

As a target volume, the tumor bed plus an additional margin (20 mm minus the intact surgical margins given in the six main directions) were contoured by excluding the pectoral muscle and a 5 mm rim of subcutaneous tissue beneath the skin, according to the Groupe Européen de Curiethérapie–European Society for Radiotherapy and Oncology (GEC-ESTRO) recommendation (33). In 1 patient, owing to the incision of the surgical specimen, the exact extent of the microscopic surgical margin remained unknown, and a maximum margin of 20 mm was used. During treatment planning, active source positions within the catheters were determined, and conformal dose distribution was calculated. The irradiation was started 48 to 72 h after salvage surgery. Patients were treated with an HDR remote afterloading unit using an Iridium-192 source.

A total dose of 22 Gy was delivered to the tumor bed, in 5 fractions of 4.4 Gy, provided at least 6 h apart and with a twice-a-day fractionation, over 3 days. After the last fraction, the catheters were removed, and after a few hours of

Table 2
Patient, tumor, and treatment characteristics for recurrent breast cancer according to salvage treatments

Characteristic	2nd BCT patients *n* (%)	sMT patients *n* (%)	*p*-value
Mean age (years)	63 (range: 36–81)	62 (range: 36–87)	0.48
Premenopausal	4 (11%)	20 (13%)	0.82
Mean tumor size (mm)	16 (range: 2–70)	25 (range: 2–90)	**0.0005**
Mean time to recurrence (months)	128 (range: 36–258)	108 (range: 9–324)	0.09
Localization of recurrence[a]	(*n* = 38)	(*n* = 96)	
In or vicinity to the tumor bed	28 (74%)	78 (81%)	0.35
Different quadrant	10 (26%)	18 (19%)	
Unknown	1	60	
Histologic type			
Invasive ductal carcinoma	33 (84%)	114 (73%)	0.51
Invasive lobular carcinoma	3 (8%)	21 (13%)	
Other invasive carcinoma	2 (5%)	11 (7%)	
Ductal carcinoma *in situ*	1 (3%)	10 (6%)	
Histologic grade			
1	7 (18%)	18 (11%)	0.26
2	11 (28%)	62 (40%)	
3	20 (51%)	64 (41%)	
Unknown	1 (3%)	12 (8%)	
Surgical margin status			
Positive	1 (3%)	13 (8%)	0.34
Negative	37 (94%)	134 (86%)	
Unknown	1 (3%)	9 (6%)	
Hormonal status			
ER+, PR+	24 (62%)	82 (53%)	0.49
ER+, PR−	6 (15%)	21 (13%)	
ER−, PR+	1 (3%)	1 (1%)	
ER−, PR−	6 (15%)	44 (28%)	
Unknown	2 (5%)	8 (5%)	
Systemic therapy			
Chemotherapy	3 (8%)	33 (21%)	0.18
Hormonal therapy	29 (74%)	87 (56%)	
Chemotherapy and hormonal therapy	3 (8%)	15 (10%)	
None	4 (10%)	21 (13%)	

2nd BCT = second breast-conserving therapy; ER = estrogen receptor; PR = progesterone receptor; sMT = salvage mastectomy.
Bolded value indicates the significant difference.
[a] Only in cases with known localization.

observation, the patients were discharged. The mean volume of the planning target volume was 58 cm^3 (range: 21–130 cm^3). The average dose nonuniformity ratio (the ratio of high dose volume to reference dose volume) was 0.4 (range: 0.24–0.52).

In both groups, most patients had chemotherapy or hormonal therapy (note that the patients in the sMT group had almost twice the number of ER/PR-negative tumors than the members of the 2nd BCT group), which probably played a role in improving local control. Adjuvant systemic treatments in the 2nd BCT group consisted of chemotherapy in 3 patients (8%), whereas 29 (74%) received endocrine therapy and 3 (8%) received both. No further adjuvant treatment was administrated in 4 patients (10%) because of their advanced age, hormone receptor-negative status, or their refusal of systemic cytostatic therapy. In the sMT group, the respective patient numbers were 33 (21%), 87 (56%), 15 (10%), and 21 (13%) in the same order. Patient, tumor, and treatment characteristics for the recurrent tumors are summarized in Table 2.

In the 2nd BCT group, the histological type of first and second breast cancer was the same in 28 patients (72%), different in 7 patients (18%), and not exactly determinable in 4 patients (10%). In the sMT group, this ratio was 105 (67%), 25 (16%), and 26 patients (17%), respectively.

During followup, patients were controlled every 3 months in the first 2 years after salvage treatment, every 6 months in the first 5 years, and every year thereafter. Mammography and breast ultrasound were performed annually. In case of uncertain mammography and ultrasound findings, breast MRI and/or aspiration cytology of suspicious lesions were performed to differentiate between 2nd LR and localized fibrosis or fat necrosis. The cosmetic results were assessed using the Harvard criteria (34). Skin side effects and fibrosis were scored by the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme (35). All time intervals were calculated from the date of salvage surgery. The actuarial rates of specific events and survivals were calculated using the Kaplan–Meier method (36). STATISTICA 12 software (StatSoft Inc., Palo Alto, CA) was used for statistical analyses.

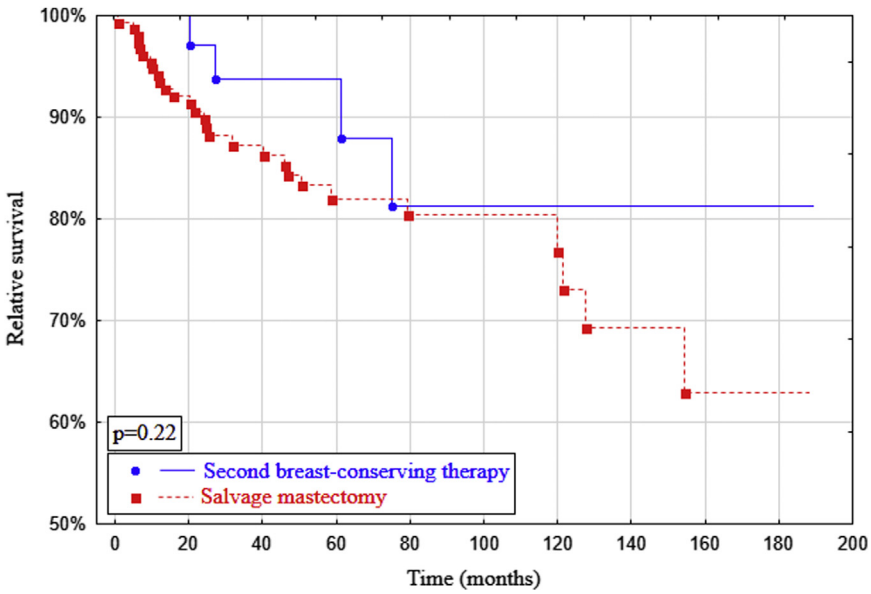

Fig. 1. Second local recurrence–free survival after second breast-conserving therapy or salvage mastectomy.

Results

There was no significant difference between the two groups in terms of the patient-related parameters, such as age and menopausal status. Although, the mean size of the recurrent tumors was larger in the sMT group than in the 2nd BCT group (25 mm vs. 16 mm, $p = 0.0005$), no other significant difference was found in the pathological characteristics of the recurrences (e.g., histologic type, grade, margin status, receptor status) between the two groups. The IBTR was located in or near the tumor bed of the first operation in most of the cases in both groups.

At a median followup of 59 months, a 2nd LR occurred in 4 patients (10.2%) in the 2nd BCT group, and at a median followup of 56 months, in 28 women (17.9%) in the sMT group. The 5-year actuarial rate of a 2nd LR was 6% after 2nd BCT vs. 18% after sMT ($p = 0.22$) (Fig. 1.). In the 2nd BCT group, after the 2nd LR, completing mastectomy was performed in 3 patients, so the ultimate mastectomy-free survival was 92%. In 1

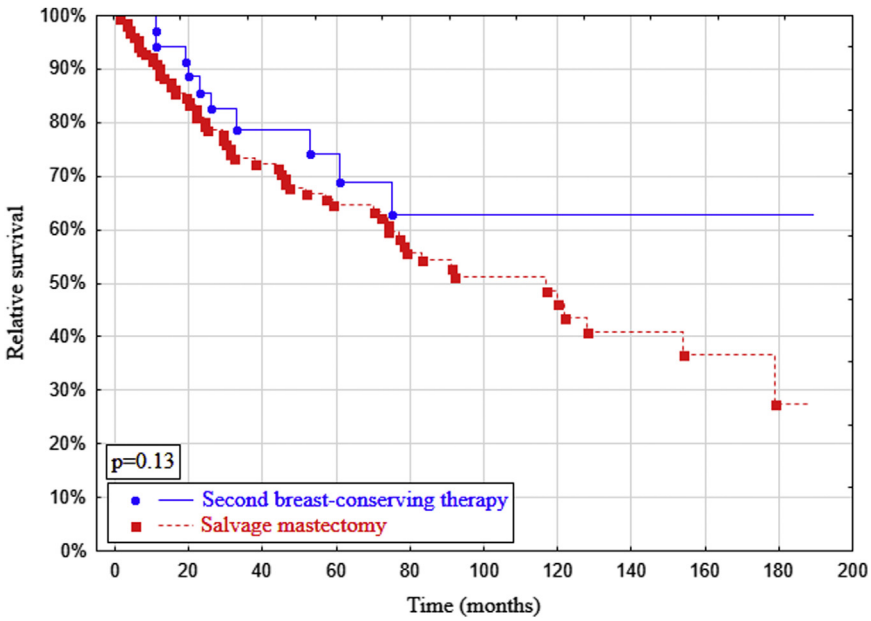

Fig. 2. Disease-free survival after second breast-conserving therapy or salvage mastectomy.

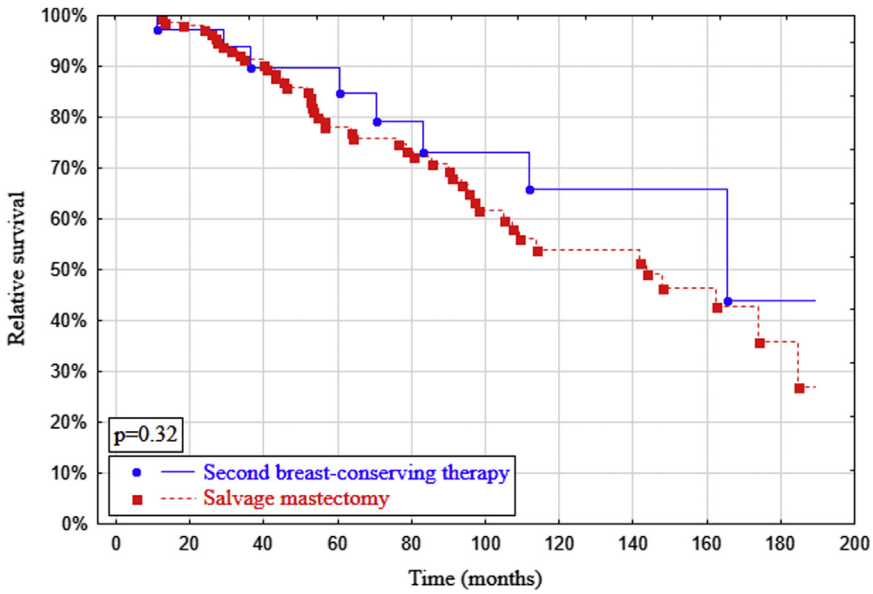

Fig. 3. Cancer-specific survival after second breast-conserving therapy or salvage mastectomy.

patient, distal metastases were detected before the 2nd LR; therefore, no repeat surgery was performed. Ipsilateral axillary metastasis occurred in 2 patients (5.1%) in the 2nd BCT group, and in 11 patients (7.1%) in the sMT group. The 5-year probability of regional recurrence-free survival was 94% after 2nd BCT vs. 95% after sMT ($p = 0.77$). The 5-year probability of disease-free survival was 69% after 2nd BCT vs. 65% after sMT ($p = 0.13$) (Fig. 2.). Overall, 9 patients (23%) in the 2nd BCT group and 53 patients (34%) in the sMT group developed subsequent distant metastases 19 to 124 and 3 to 180 months after IBTR, and all of them died of breast cancer 11 to 165 and 12 to 184 months after salvage treatment, respectively. The 5-year probability of distant metastasis-free survival was 76% vs. 74% ($p = 0.24$), the 5-year probability of cancer-specific survival was 85% vs. 78% ($p = 0.32$), and the 5-year probability of overall survival was 81% vs. 66% ($p = 0.15$), respectively (Figs. 3 and 4.) Three patients (8%) developed second primary malignancies in the 2nd BCT group (including one hypernephroma, one colon,

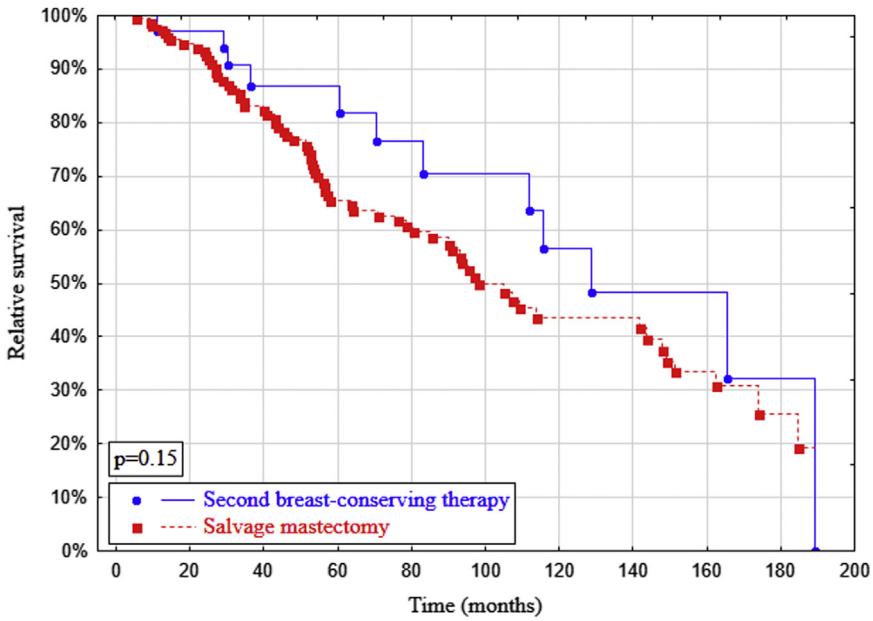

Fig. 4. Overall survival after second breast-conserving therapy or salvage mastectomy.

Table 3
Cosmetic results and late radiation side effects after the second breast-conserving therapy

Characteristic	*n* (%)
Cosmetic results	
Excellent	4 (10%)
Good	23 (60%)
Fair	6 (15%)
Poor	6 (15%)
Skin side effects	
Grade 0	4 (10%)
Grade 1	21 (54%)
Grade 2	11 (28%)
Grade 3	3 (8%)
Fat necrosis	
Asymptomatic	7 (18%)
Symptomatic	0 (0%)
Fibrosis	
Grade 0	17 (44%)
Grade 1	12 (31%)
Grade 2	9 (23%)
Grade 3	1 (2%)

and one lung cancer), and also 3 patients (2%) in the sMT group (including one lung cancer, one renal cancer, and one ovarian cancer). Contralateral breast cancer occurred in 2 patients (5%) in the 2nd BCT group and in 18 patients (9%) in the sMT group.

After the 2nd BCT, cosmetic results were evaluated based on Harvard criteria. Among these, 4 (10%), 23 (60%), 6 (15%), and 6 patients (15%) had excellent, good, fair, and poor cosmetic results, respectively. Grade 2 and 3 fibrosis developed in 9 (23%) and 1 patient (2%), respectively; grade 2 and 3 late skin toxicity occurred in 11 (28%) and 3 patients (8%), respectively. Asymptomatic fat necrosis was detected in seven women (18%) and required no surgical intervention (Table 3.).

Discussion

For a long time, "salvage" mastectomy was the only accepted strategy for treating an LR after BCS and WBI. According to the publications, the rate of the 2nd LR is close to 10% after the sMT (range: 3–22%) (8–23) (Table 4.) Voogd *et al.* (11) reported the results of a retrospective study with the largest number of patients—treated in the 80s—who underwent sMT after an LR in the breast. The median followup after the diagnosis of LR was 52 months, and 51 of the 229 patients (22%) developed a 2nd LR.

However, since the 1990s, second BCS was also reported by several authors as a viable alternative in selected cases (24–27). Gentilini *et al.* (26) published the results of the largest series with second BCS used as monotherapy. After a median followup of 81 months, a 2nd LR occurred in 47 of 161 patients (29%). Five-year cumulative incidence of a second local event after IBTR was 29%.

Table 4
Results of second conservative surgery (without radiotherapy) vs. salvage mastectomy

Author	Median FUP (months)	No. of patients		2nd LR (%)		5-year 2nd LR (%)		5-year OS (%)	
		2nd BCS	sMT	2nd BCS	sMT	2nd BCS	sMT	2nd BCS	sMT
Salvadori B (8)	73	57	133	14%	3%	19%	4%	85%	70%
Fodor J (9)	165	32	32	28%	16%	NR	NR	NR	NR
Dalberg K (10)	72	14	65	50%	18%	33%	12%	NR	NR
Voogd AC (11)	52	20	229	40%	22%	NR	NR	NR	NR
Alpert TE (12)	165	30	116	7%	7%	NR	NR	58%[a]	66%[a]
Komoike Y (13)	43	30	11	30%	0%	37%[b]	0%[b]	90%[b]	91%[b]
Abner AL (14)	39	16	123	31%	6%	NR	NR	NR	79%
van der Sangen MJ (15)	NA	8	89	50%	11%	NR	NR	NR	NR
Kurtz JM (16)	35	34	36	9%	3%	22%	4%	NR	NR
Doyle T (17)	44	-	112	-	3%	-	NR	-	86%
Beard HR (18)	55	-	59	-	12%	-	NR	-	NR
Botteri E (19)	60	-	121	-	15%	-	NR	-	73%
Lindford AJ (20)	66	-	60	-	10%	-	NR	-	93%
Tanabe M (21)	55	-	118	-	9%	-	9%	-	NR
Recht A (22)	32	-	65	-	8%	-	37%	-	NR
Osborne MP (23)	28	-	46	-	15%	-	45%	-	76%
Kurtz JM (24)	72	52	-	23%	-	21%	-	79%	-
Kurtz JM (25)	51	50	-	32%	-	38%	-	67%	-
Gentilini O (26)	81	161	-	29%	-	29%	-	84%	-
Ishitobi M (27)	40	78	-	22%	-	21%	-	NR	-
Present study	56	-	156	-	18%	-	18%	-	66%
All patients (range)	28–165	582[c]	1571[c]	4–50%	0–22%	19–38%	0–45%	58–90%	66–93%

FUP = followup period; NR = not reported; OS = overall survival; sMT = salvage mastectomy; 2nd BCS = second breast-conserving surgery; 2nd LR = second local recurrence.

[a] 10-year actuarial rate.

[b] 3-year actuarial rate.

[c] total number of patients.

The largest study comparing the two treatment methods was reported by Salvadori *et al.* (8). Four of 133 (3%) intramammary recurrences were reported after sMT, and 8 of 57 (14%) after repeated local resection. The incidence of 2nd LR at 5 years was higher in the reexcision group (19%), compared with the mastectomy group (4%) (p-value not reported). In the study of Fodor *et al.* (9) after 165 months, the incidence of 2nd LR was 16% (5 of 32 patients) in the sMT group, and 28% (9 of 32 patients) in the second BCS group ($p = 0.22$). Therefore, based on the investigations, the 2nd LR ratio was higher after repeated BCS than after sMT (8–16).

Reirradiation after second BCS may decrease the chance of 2nd LR (37). Unfortunately, reirradiation of the whole breast with an effective dose is considered inappropriate because of the high risk of serious late side effects. However, the earlier promising results of partial-breast irradiation as part of upfront BCT for selected patients has led to a renewed interest in partial-breast reirradiation in the salvage setting as a means to improve local control while minimizing toxicity from a second course of radiation. Partial-breast irradiation may be delivered with either external-beam irradiation or brachytherapy. Deutsch *et al.* (37) reported the results of external-beam reirradiation as a part of the 2nd BCT. Thirty nine women with an IBTR after lumpectomy and WBI were treated with excision of the recurrence and 50 Gy RT to the operative area using electrons. After a median followup of 51 months, 8 patients (21%) developed 2nd LR. The rate of an excellent and good cosmetic result was 75%, and the 5-year overall survival was 78%.

The 5-year oncology outcomes of the Radiation Therapy Oncology Group 1014 study—a prospective phase II trial of 3D conformal photon-electron combination partial-breast reirradiation—which started in 2010, have not been published yet; but after a 1-year followup, the grade ≥3 treatment-related skin, fibrosis, and breast pain adverse events were less than 2% (38).

The largest experience of reirradiation after a 2nd BCT is with iBT (39–48). The results of these studies are summarized in Table 5. In 2004, a French study presented the results of 69 patients with IBTR treated with lumpectomy and low-dose-rate iBT (39). The prescribed dose was 30 Gy or 45–50 Gy. The 5-year local control and the overall survival was 77% and 92%, respectively. Patients who received a brachytherapy dose of at least 50 Gy had better 5-year local tumor control rates than those who received <50 Gy (86% vs. 75%, $p = 0.095$). Nevertheless, patients who received a cumulative total dose (teletherapy + brachytherapy) to the breast >100 Gy had significantly higher rates of grade 2–3 toxicity compared with those who received <100 Gy (33% vs. 4%, $p = 0.005$). Similarly, patients who received a brachytherapy dose >46 Gy had higher rates of grade 2–3 toxicity compared with those who received <46 Gy (36% vs. 14%, $p = 0.005$).

In 2013, the GEC-ESTRO Breast Cancer Working Group presented a collaborative analysis with the largest number of patients (40). In this study, 217 patients were treated between 2000 and 2010 by multicatheter iBT in eight European institutions. The mean dose of reirradiation was 46 Gy (range: 30–55 Gy) with low-dose-rate, 50.4 Gy (49–50 Gy) with pulsed-dose-rate, and 32 Gy (22–36 Gy) with HDR technique. With a median followup of 47 months,

Table 5
Results of brachytherapy as reirradiation after repeat breast-conserving surgery

Author	Technique	Fraction × dose (Gy)	Median FUP (months)	Patients	2nd LR (%)	5-year 2nd LR (%)	5-year OS (%)	Excellent and good cosmesis (%)
Hannon-Levi JM (39)	LDR	1 × 30; 1 × 45–50	50	69	15.9%	25%; 14%	92%	NR
Hannon-Levi JM (40)	LDR	1 × 30–55	47	217	4%	6%	89%	85%
	PDR	49–50/0.6–1[d]						
	HDR	5–10 × 3.6–4.4						
Guix B (41)	HDR	12 × 2.5	89	36	3%	11%[a]	97%[a]	94%
Trombetta M (42)	HDR[b]	10 × 3.4	40	18	11%	NR	NR	83%
Chada M (43)	LDR	1 × 30; 1 × 45	36	15	7%	11%[c]	100%[c]	100%
Maulard C (44)	LDR	1 × 30	40	15	27%	NR	61%	16%
Resch A (45)	PDR	40–50/0,6–1[d]	59	9	0%	0%	100%[e]	55%
Kauer-Dorner D (46)	PDR	50.1/0.6–1[d]	57	39	5%	7%	87%	37%
Trombetta M (47)	LDR	1 × 45–50	38	26	4%	NR	NR	92%
	HDR	10 × 3.4						
Houvenaeghel G (48)	LDR	1 × 45–56	73	62	26%	17%	80%	NR
Present study	HDR	5 × 4.4	59	39	10%	6%	81%	70%
All patients (range)			36–89	545[f]	3–27%	0–25%	61–100%	16–100%

FUP = followup period; Gy = gray; HDR = high-dose-rate; LDR = low-dose-rate; NR = not reported; OS = overall survival; PDR = pulsed-dose-rate; 2nd LR = second local recurrence.

[a] 10-year actuarial rate.

[b] patients were treated with intracavitary HDR brachytherapy using the MammoSite or the Contura balloon applicators.

[c] 3-year actuarial rate.

[d] total dose/pulse dose.

[e] disease-free survival.

[f] total number of patients.

the authors reported actuarial 5- and 10-year 2nd LR rate of 6% and 7%, whereas the actuarial 5- and 10-year overall survival rates were 89% and 76%, respectively. Good to excellent cosmesis was achieved in 85% of the patients. The study with the longest followup was performed by Guix *et al.* (41). Between 1990 and 2001, 36 women were treated with IBTR by excision of the recurrence and 30 Gy (12 × 2.5 Gy) HDR iBT. After a median followup of 89 months, the 10-year 2nd LR rate was 11%, and the 10-year overall survival rate was 97%. Good to excellent cosmesis was achieved in 94% of patients.

In 1999, we introduced at our institution the second breast-conserving operation with reirradiation using perioperative HDR iBT in selected cases for the treatment of IBTR developed after a previous BCT. Our early results have been reported elsewhere (49, 50).

In this study, 39 patients who were presented with an IBTR after a previous BCT were salvaged by reexcision and received perioperative HDR iBT. The data of these patients were compared with 156 women, who were salvaged with simple mastectomy during the same period. The 5-year actuarial rate of a 2nd LR was 6% after 2nd BCT and 18% after sMT ($p = 0.22$). In the literature, this rate is roughly 11% (range: 0–25%) and 19% (0–45%), respectively. In the 2nd BCT group, the good to excellent cosmesis was 70%.

The weakness of our study is its retrospective (nonrandomized) nature, but it is practically impossible to conduct a prospective randomized trial because of the patients' reluctance for accepting randomization between 2nd BCT and sMT.

The German Society of Radiation Oncology (Deutsche Gesellschaft für Radioonkologie) expert panel guidelines—published in 2016—have suggested selection criteria for a second breast-conserving approach as follows: an isolated, unifocal, <3 cm recurrence, in a patient aged >50 years, a long interval between the primary treatment and recurrence (>48 months), and the patient's preference of a 2nd BCT (51). With these conditions, multicatheter iBT is the recommended method, whereas repeated external-beam partial-breast irradiation or intraoperative RT is acceptable only in a clinical trial.

Currently, GEC-ESTRO Breast Cancer Working Group is also working on updating the retrospective database of comparison between sMT and second BCS with perioperative iBT, collaborating with 15 European cancer centers (52). These results may further help us determine the indications for 2nd BCT more accurately.

Conclusions

To our knowledge, this is the first study directly comparing 2nd BCT with perioperative HDR iBT to sMT in patients who were treated during the same period and at the same institute. Based on the results of our study and the data reported previously by others, a second BCS with perioperative HDR iBT is a safe and feasible option for the management of IBTR, resulting in similar 5-year oncological outcomes compared with a standard sMT. HDR iBT decreases the risk of a 2nd LR with acceptable cosmetic results and a low rate of late side effects.

Further studies with higher numbers of patients are required to define the value of a second BCS with reirradiation as compared with sMT.

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Clinical Investigation

Salvage Mastectomy Versus Second Conservative Treatment for Second Ipsilateral Breast Tumor Event: A Propensity Score-Matched Cohort Analysis of the GEC-ESTRO Breast Cancer Working Group Database

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Purpose: Second conservative treatment has emerged as an option for patients with a second ipsilateral breast tumor event after conserving surgery and breast irradiation. We aimed to address the lack of evidence regarding second breast event treatment by comparing oncologic outcomes after conservative treatment or mastectomy.

Methods and Materials: Oncologic outcomes were analyzed using a propensity score-matched cohort analysis study on patients who received a diagnosis of a second breast event between January 1995 and June 2017. Patient data were collected from 15 hospitals/cancer centers in 7 European countries. Patients were offered mastectomy or lumpectomy plus brachytherapy. Propensity scores were calculated with logistic regression and multiple imputations. Matching (1:1) was achieved using the nearest neighbor method, including 10 clinical/pathologic data related to the second breast event. The primary endpoint was 5-year overall survival from the salvage surgery date. Secondary endpoints were 5-year cumulative incidence of third breast event, regional relapse and distant metastasis, and disease-free and specific survival. Complications and 5-year incidence of mastectomy were investigated in the conservative treatment cohort.

Results: Among the 1327 analyzed patients (mastectomy, 945; conservative treatment, 382), 754 were matched by propensity score (mastectomy, 377; conservative treatment, 377). The median follow-up was 75.4 months (95% confidence interval [CI], 65.4-83.3) and 73.8 months (95% CI, 67.5-80.8) for mastectomy and conservative treatment, respectively ($P = .9$). In the matched analyses, no differences in 5-year overall survival and cumulative incidence of third breast event were noted between mastectomy and conservative treatment (88% [95% CI, 83.0-90.8] vs 87% [95% CI, 82.1-90.2], $P = .6$ and 2.3% [95% CI, 0.7-3.9] vs 2.8% [95% CI, 0.8-4.7], $P = .4$, respectively). Similarly, no differences were observed for all secondary endpoints. Five-year cumulative incidence of mastectomy was 3.1% (95% CI, 1.0-5.1).

Conclusions: To our knowledge, this is the largest matched analysis of mastectomy and conservative treatment combining lumpectomy with brachytherapy for second breast events. Compared with mastectomy, conservative treatment does not appear to be associated with any differences in terms of oncologic outcome. Consequently, conservative treatment could be considered a viable option for salvage treatment.

Introduction

With 2.1 million new cases in 2018, breast cancer was the most commonly diagnosed cancer and the leading cause of cancer death in women.[1] Forecasts for 2040 predict 29.5 million (+39%) new cancer cases and 16.4 million cancer deaths.[2]

For primary breast cancer, the local relapse rate after conservative treatment combining lumpectomy plus external beam irradiation ranges between 4% and 6% at 10 years[3,4] and between 10% and 15% at 20 years of follow-up.[5,6] According to data reported by Miller et al, the number of breast cancer survivors in the United States will increase by 22% between 2019 and 2030 (3.8 vs 4.9 million, respectively).[7] These data suggest that the number of patients experiencing a second ipsilateral breast tumor event will increase dramatically during the next decades.

Fisher et al[6] and Veronesi et al[5] aimed to avoid mastectomy for patients with primary breast cancer and successfully followed the evidence-based medicine process by conducting prospective randomized phase 3 trials comparing mastectomy versus breast conservative treatment based on lumpectomy plus irradiation. Since then, the breast-conserving approach has been considered the standard treatment for localized breast cancer. Currently, salvage mastectomy is adopted as the usual standard treatment for second breast cancer events. However, there is no convincing argument for not applying the rationale used for primary breast tumors (ie, avoiding deleterious mutilation) to second breast events. Furthermore, encouraging results after second conservative treatment combining lumpectomy plus tumor bed reirradiation have been reported.[8,9]

To effectively compare oncologic outcomes after salvage mastectomy or second conservative treatment, a randomized phase 3 trial assessing these 2 salvage options would be needed. However, in this context, randomization would be difficult to achieve, mainly for methodologic and ethical reasons.[9,10] Regarding methodology, whatever the chosen primary oncological endpoint, the objective would not be to improve the clinical results, but rather to offer the possibility of second breast preservation. Consequently, a randomized trial would require a noninferiority design involving a large number of patients to evaluate the outcome of second breast events, which are rare clinical occurrences. Such a trial would probably take more than 10 years to complete, and at a prohibitive cost. Regarding ethical considerations, it remains difficult to obtain a signed consent form from a patient who is made aware of the

50/50 chance of need for a second conservative treatment. Consequently, patient enrollment would be problematic and would render such a randomized phase 3 trial technically unfeasible and possibly unethical.

In the absence of randomized data clearly supporting the use of salvage mastectomy as the standard treatment for second breast events, the main goal of this study was to use a European oncology database to perform a matched treatment analysis comparing oncologic outcomes after salvage mastectomy compared with second conservative treatment (lumpectomy plus reirradiation of the tumor bed).

Methods and Materials

Study design and participants

Based on the database of the GEC-ESTRO Breast Cancer Working Group, this study was a propensity score-matched analysis of real-world observational clinical practices across 15 academic hospitals/cancer centers in 7 European countries (Austria, Belgium, France, Germany, Hungary, Spain and Switzerland; Table E3). To protect privacy, the database encrypts patients' personal information and provides researchers with anonymous identification numbers associated with relevant information including sex, age, treatment procedures, and prescriptions. The researchers were provided with no direct identification data. Consequently, patient consent was not required to access the database. To fulfill the conditions for exemption, the present study was approved by the Ethical Committee of the Institutional Review Board at the Antoine Lacassagne Breast Cancer Board (no. 18001). The board also specifically waived the consent requirement. For our analysis, we used data from 1995 to 2017 retrieved and analyzed before the General Data Protection Regulation.

We included all women diagnosed between January 1995 and June 2017 with a histologically proven second ipsilateral breast tumor event occurring after conservative treatment of the primary (lumpectomy plus whole breast irradiation). Patients of all ages presented no evidence of skin involvement or distant metastatic disease, had no history of contralateral breast cancer, had a tumor staged T1-2, and had at least 12 months between primary and salvage surgery. Patients were offered mastectomy alone (without reirradiation) or, for those refusing mastectomy, conservative treatment combining lumpectomy plus tumor bed reirradiation with multicatheter interstitial brachytherapy. Patient selection for conservative treatment took into account tumor stage, multicentricity, breast size, and potential sequalae of the first conservative treatment.[11] Negative histologic margins were mandatory. Axillary lymph node evaluation was rarely performed because, at the time of primary tumor treatment before 1995 and the introduction of sentinel lymph node biopsy, axillary dissection was performed.

Procedures

For patients receiving conservative treatment, brachytherapy was delivered as described elsewhere.[8] Briefly, patients underwent lumpectomy combined with intra- or postoperative catheter implantation according to the Paris system recommendations.[12] After analysis of the final pathologic report, tumor bed brachytherapy-based irradiation was performed at either low, pulsed, or high dose rates, depending on the treatment period and the technique available in each center (Table E1).

For patients who underwent mastectomy, no postoperative irradiation was delivered, and immediate or delayed breast reconstruction was discussed with the patient and performed at the discretion of each surgical team. Patient-, tumor-, and treatment-related data were collected by each center and pooled in the GEC-ESTRO Breast Cancer Working Group database. The treatment period was also collected and used in the analysis because this may have had an influence on oncologic outcomes. Patients followed up every 6 months during the first 5 years, then yearly with clinical examinations and mammograms.

Outcomes

Given the need for equivalent comparisons of oncologic outcomes between the mastectomy and conservative treatment cohorts, we investigated comparable treatment failure patterns in the 2 groups. Thus, the primary endpoint of this observational study was overall survival, defined as the time between the date of salvage surgery and the date of patient death of any cause. Patients who were still alive at the time of analysis or who were lost to follow-up were censored at the date of last news. Secondary endpoints were 5-year cumulative incidence of third ipsilateral breast tumor, regional relapse (axilla, supraclavicular fossa, and internal mammary chain) and distant metastasis observed between salvage surgery date and event occurrence. Disease-free survival (third breast event, regional relapse, distant metastasis, breast cancer death, or death from any cause) and specific survival were defined as the time length between salvage surgery date and occurrence of the first tumor-related event or occurrence of death from breast cancer, respectively. For each patient, follow-up was estimated between the date of salvage surgery and date of last news.

Because the conservative treatment cohort had undergone the investigated salvage procedure, we also took as a secondary endpoint for this treatment group the 5-year cumulative incidence of mastectomy due to any cause. Late toxicities (Common Terminology Criteria for Adverse Events version 4) and cosmetic outcomes (Harvard criteria) were investigated.[13]

Statistical analysis

Because this was a real-world match-paired study, the sample size was determined by the number of women

whose data were included in the GEC-ESTRO Breast Cancer Working Group database. Demographic, diagnostic, clinicopathologic, and treatment-specific information was retrieved for each patient entered in the database. Due to the extensive duration of the study period (22.5 years; January 1, 1995 to June 30, 2017) and possible changes in treatment strategies (local and systemic), the outcomes after second breast event treatment were analyzed over 3 different periods: from January 1, 1995 to December 31, 2001, from January 1, 2002 to December 31, 2009, and from January 1, 2010 to June 30, 2017. In the event of missing data, a multiple imputation by chained equations[14] was performed with 20 imputed data sets.

To minimize the significantly different baseline characteristics between the women in the 2 compared groups and their effect on the oncologic outcome assessment (Table E2), a 1:1 ratio propensity score analysis was performed with a caliper of 0.1.[15] The propensity score was calculated using a logistic regression model and was based on the following variables: patient age at the time of second breast event, length of time between primary and salvage surgery, recurrence period, tumor size, histologic type and grade, hormonal receptor and Her2 status, hormone therapy, and chemotherapy. Subsequently, the standardized mean differences were calculated for all variables included in the propensity score before and after matching to assess the effect of pairing on imbalance (Fig. E1). A 10% standardized difference was considered the limit of an acceptable correct balance. Categorical data were shown as frequencies and percentages and continuous variables as minimums, maximums, and means with standard deviations. All survival curves were estimated with a 95% confidence interval (CI) using the Kaplan-Meier method, taking time baseline as the date of salvage surgery. Baseline characteristic comparisons for unmatched and matched data sets were performed using the χ^2 or Fisher's exact tests for categorical data and the Student t test or Mann-Whitney U test for continuous variables. The median follow-up and its 95% CI were calculated using the Schemper method.[16] Median follow-up and survival curves were compared using the log-rank test. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% CIs for the relation between treatment and survival. The proportional hazards ($P > .05$) assumption was checked using statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals.[17] A sensitivity analysis was performed by repeating the primary analysis, stratified by treatment center to establish whether conservative treatment could negatively affect oncologic outcome.

To identify prognostic factors for oncologic outcome, univariate and multivariate Cox models were performed on the matched data set using propensity score calculation variables and type of salvage local treatment. The final multivariate Cox regression model was performed using backward stepwise elimination with Akaike information criteria as the stopping rule.

Data entry and management were performed on the capture system (Ennov Clinical). All statistical analyses were considered statistically significant at P values of $<.05$ (2-sided) and were performed using SAS software version 9.4 and R 3.6.0 using package Matching, survey, Reshape2, and mice on Windows.

Results

Of the 1400 patients identified in the GEC-ESTRO Breast Cancer Working Group database as having experienced a second breast event diagnosed between January 1995 and June 2017, 1327 patients met the inclusion criteria and constituted the final study population of patients with a nonmetastatic second breast event. Of these, 945 (71%) had undergone mastectomy (standard pathway) and 382 (29%) conservative treatment (Fig. 1). We excluded 73 patients who presented a time length between primary and salvage surgery of less than 12 months (n = 40), a second breast event date before January 1, 1995 (n = 31), and bilateral breast cancer (n = 2). All demographic, clinicopathologic, and treatment-related variables for the entire cohort are presented in Table 1, according to type of salvage surgery. Multiple imputation was performed to complete missing data for tumor size (20%), histologic type (16.8%), histologic grade (21.7%), Her2 status (22.8%), and hormone therapy (19.1%).

In the unmatched data set, compared with patients who underwent conservative treatment, patients treated with mastectomy were generally younger with longer median follow-up and a shorter time between primary and salvage surgery. They also had more unfavorable tumor characteristics (tumor $\geq$ 30 mm, histologic grade 3, negative hormonal receptor status) and more often received adjuvant chemotherapy and less frequently hormonal therapy.

Conservative treatment was used more frequently after 2002 compared with the period from 1995 to 2002. Radiation therapy−specific data for the conservative treatment cohort are shown in Table E1 and Figure E2. On the basis of the variables retained in these regression models, propensity scores for the use of mastectomy and conservative treatment were calculated to enable independent patient matching. The 1:1 matching for mastectomy versus conservative treatment resulted in 377 matched pairs and a sample size of 754 patients (Table 1).

Regarding death from any cause, 315 (84%) of 377 patients survived in the conservative treatment group compared with 310 (82%) in the mastectomy group. After a median follow-up of 75 months (interquartile range, 42-119) for the matched 1:1 data set, Kaplan-Meier analysis and the log-rank test showed that conservative treatment was associated with similar overall survival compared with mastectomy, with 5-year overall survival rates of 86.7% versus 87.5% for conservative treatment and mastectomy, respectively (HR, 0.91; 95% CI, 0.64-1.28; P = .6) (Table 2; Fig. 2).

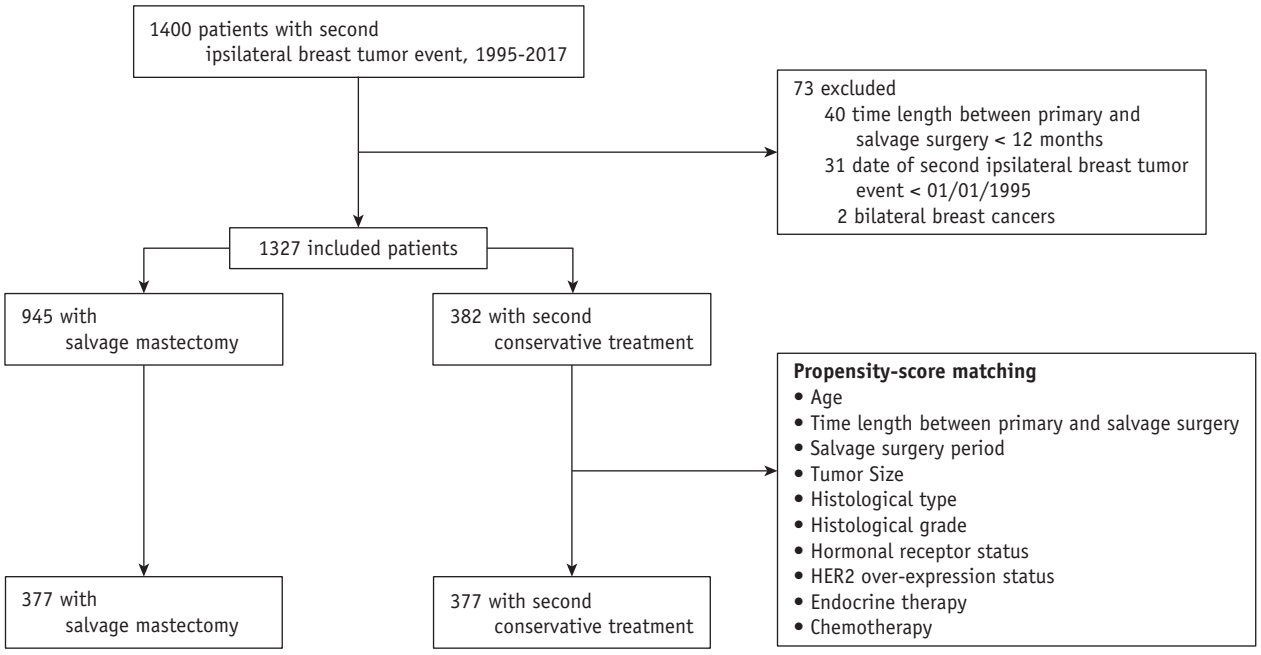

Fig. 1. Flow chart.

As shown in Table 2, no significant differences were observed between the conservative treatment and mastectomy groups for 5-year cumulative incidence of third ipsilateral breast tumor (2.8% vs 2.3%; HR, 1.4; 95% CI, 0.66-2.94; $P = .4$), 5-year cumulative incidence of regional relapse (2.3% vs 1.6%; HR, 2.3; 95% CI, 0.88-6.10; $P = .08$), 5-year cumulative incidence of distant metastasis (9.3% vs 14.1%; HR, 0.77; 95% CI, 0.52-1.12; $P = .2$), 5-year disease-free survival (82.5% vs 78.6%; HR, 0.92; 95% CI, 0.68-1.24; $P = .6$), and 5-year specific survival (91.2% vs 91.8%; HR, 0.81; 95% CI, 0.53-1.21; $P = .3$) (Fig. 2).

To verify whether conservative treatment could negatively affect the oncologic outcome, post hoc sensitivity analysis stratified by treatment center was performed. With a total of 428 patients (214 in each treatment cohort), no significant differences for overall survival were observed between the 2 groups (HR, 0.91; 95% CI, 0.57-1.43; $P = .7$). Similar results were noted for oncological secondary endpoints (Table E4; Fig. E3). These results confirmed that oncologic outcome after second breast event was not significantly affected by the type of salvage treatment (conservative treatment or mastectomy).

Factors associated with oncological outcomes for the matched data set (754 patients) were investigated by univariate and multivariate analysis, including propensity score items and salvage local treatment. In multivariate analysis, tumor size ($\geq$30 mm) and time between primary and salvage surgeries ($<$36 months) were considered to be prognostic factors for all oncologic outcome items except for third breast event−free survival. Salvage surgery period (patients treated before 2002) was prognostic for metastatic disease-free survival and disease-free survival. Age ($<$48 years) was a prognostic factor for specific survival (Table E5).

In the conservative treatment cohort (n = 377), 283 patients (75%) experienced postsalvage treatment complications, which are summarized in Table 3. Grade 3 and worse toxicities were observed in 9.5% of patients, mostly cutaneous (24.7%) and subcutaneous fibrosis (42.1%). Breast deformation, hyperpigmentation, telangiectasia, and ulceration were observed in 12.4%, 10.2%, 8.8%, and 1.8% of cases, respectively.

Among the 377 patients who underwent conservative treatment, 15 (4%) received postsalvage treatment mastectomy after a third breast event (11 patients) or complications (grade 3, 2 patients; grade 4, 2 patients), leading to a 5- and 10-year cumulative incidence of mastectomy of 3.1% (95% CI, 1.00-5.10) and 6.7% (95% CI, 2.80-10.40), respectively (Fig. E4). According to the Harvard criteria, cosmetic results were obtained from 212 patients (56.2%) and were rated as excellent (99 patients; 46.7%), good (71 patients; 33.5%), fair (27 patients; 12.7%), and poor (15 patients; 7.1%).

Discussion

In our real-world multicenter cohort of patients with a nonmetastatic second breast event, breast-conserving surgery plus tumor bed reirradiation with interstitial brachytherapy resulted in a 5-year overall survival rate that was not significantly different from patients treated with mastectomy. To our knowledge, the present study is the first population-based analysis specifically comparing these 2

Table 1 Baseline characteristics for patients who underwent salvage mastectomy versus those who received second conservative treatment before and after propensity matching

	Unmatched (complete) data set			Matched (1:1) data set		
	Salvage mastectomy (N = 945)	Second conservative treatment (N = 382)	*P* value	Salvage mastectomy (N = 377)	Second conservative treatment (N = 377)	*P* value
Age (minimum-maximum), y	60 (27.8-89.3)	64 (27.5-90.3)	<.001*	62.7 (31.1-89.3)	62.4 (27.5-90.3)	.74*
Time between primary and salvage surgery (range), y	8.34 (1-35.3)	10.56 (1.1-35.3)	<.001*	10.1 (1.1-35.3)	10.3 (1.1-35.3)	.61*
Salvage surgery period			.004†			.95†
On or before December 31, 2001	133 (14.1%)	29 (7.6%)		30 (8.0%)	29 (7.7%)	
January 1, 2002-December 31, 2009	413 (43.7%)	185 (48.4%)		187 (49.6%)	184 (48.8%)	
On or after January 1, 2010	399 (42.2%)	168 (44.0%)		160 (42.4%)	164 (43.5%)	
Median follow-up, mo	78 (71.9-83.9)	73.2 (67.5-78.8)	.03‡	75.4 (65.4-83.3)	73.8 (67.5-80.8)	.9‡
Tumor size			<.001†			.88†
Strictly inferior <30 mm	750 (79.4)	355 (92.9)		349 (92.6)	350 (92.8)	
Inferior or equal ≥30 mm	195 (20.6)	27 (7.1)		28 (7.4)	27 (7.2)	
Histologic type			.051†			.673†
Invasive ductal (no special type)	772 (81.7)	334 (87.4)		327 (86.7)	323 (85.7)	
Invasive lobular and others	173 (18.3)	48 (12.6)		50 (13.3)	54 (14.3)	
Histologic grade			<.001†			.9†
1	80 (8.5)	72 (18.8)		62 (16.4)	66 (17.5)	
2	489 (51.7)	187 (49.0)		188 (49.9)	183 (48.5)	
3	376 (39.8)	123 (32.2)		127 (33.7)	128 (34.0)	
Hormonal receptor status			.078†			.66†
Positive	696 (73.7)	299 (78.3)		287 (76.1)	292 (77.5)	
Negative	249 (26.3)	83 (21.7)		90 (23.9)	85 (22.5)	
Her2 status			.684†			.44†
Nonoverexpressed	793 (83.9)	324 (84.8)		307 (81.4)	315 (83.6)	
Overexpressed	152 (16.1)	58 (15.2)		70 (18.6)	62 (16.4)	
Hormone therapy			.02†			.48†
Yes	574 (60.7)	258 (67.5)		262 (69.5)	253 (67.1)	
No	371 (39.3)	124 (32.5)		115 (30.5)	124 (32.9)	
Chemotherapy			<.001†			.79†
Yes	329 (34.8)	84 (22.0)		87 (23.1)	84 (22.3)	
No	616 (65.2)	298 (78.0)		290 (76.9)	293 (77.7)	

* Wilcoxon's test.
† χ^2 test.
‡ Log-rank's test.

types of salvage options by means of a propensity score matching method, given that a phase 2 trial requiring enrollment of approximately 3600 patients would be difficult to perform (Material and Methods E1).[9,10,18]

In the medical literature, mastectomy has always been presented as the standard of care for a second breast event. Nevertheless, since the early 1990s, conservative treatment based on lumpectomy alone or combined with tumor bed reirradiation has been investigated in small retrospective cohorts.[19] GEC-ESTRO[8] reported consistent results from a cohort of 217 patients (median follow-up, 47 months) treated with lumpectomy plus brachytherapy. Recently, Arthur et al[9] presented the results of the RTOG-1014 trial, which evaluated oncologic outcome and toxicity after conservative treatment combining lumpectomy with tumor bed external beam reirradiation (65 patients; median follow-up, 66 months). Walstra et al[20] considered second conservative surgery combined with reirradiation to be a "reasonable alternative" to mastectomy in selected patients with a second breast event. Retrospective unmatched comparisons between mastectomy and conservative treatment have been reported. However, these studies were based on small samples or single institution analyses, leading to debatable conclusions due to inevitable selection

Table 2 Comparison of oncological outcome at 5 and 10 years between salvage mastectomy (n = 377) and second conservative treatment (n = 377) after propensity score matching

Oncologic outcomes	No. of cumulative events, n (%)	At 5 y, % (range)	At 10 y, % (range)	HR (95% CI)	*P* value
Cumulative incidence of third ipsilateral breast tumor event					
Salvage mastectomy	12 (3.2)	2.3 (0.7-3.9)	3.8 (1.1-6.5)	1	.4
Second conservative treatment	16 (4.2)	2.8 (0.8-4.7)	6.3 (2.5-9.9)	1.4 (0.66-2.94)	
Cumulative incidence of regional relapse*					
Salvage mastectomy	6 (1.6)	1.6 (0.0-3.1)	2.3 (0.2-4.3)	1	.08
Second conservative treatment	13 (3.4)	2.3 (0.6-3.9)	5.8 (1.8-9.6)	2.3 (0.88-6.10)	
Cumulative incidence of distant metastasis					
Salvage mastectomy	61 (16.2)	14.1 (10.0-18.0)	24.9 (18.0-31.2)	1	.2
Second conservative treatment	46 (12.2)	9.3 (5.9-12.6)	16.4 (10.5-21.3)	0.77 (0.52-1.12)	
Disease-free survival†					
Salvage mastectomy	87 (23.0)	78.6 (74.0-83.5)	67.8 (61.4-74.8)	1	.6
Second conservative treatment	80 (21.2)	82.5 (78.2-87.0)	71.6 (65.3-78.6)	0.92 (0.68-1.24)	
Specific survival					
Salvage mastectomy	50 (13.3)	91.8 (88.6-95.1)	79.3 (73.2-85.9)	1	.3
Second conservative treatment	41 (10.8)	91.2 (87.9-94.7)	84.0 (78.7-89.7)	0.81 (0.53-1.21)	
Overall survival					
Salvage mastectomy	67 (17.8)	87.5 (83.0-90.8)	74.7 (67.4-80.6)	1	.6
Second conservative treatment	62 (16.4)	86.7 (82.1-90.2)	75.4 (68.3-81.2)	0.91 (0.64-1.28)	

* Regional relapse defined as axilla, supraclavicular fossa, and internal mammary chain.
† Any breast cancer-related event, including local, regional, or distant relapse; breast cancer death; or death from any cause.

bias.[21-23] Two propensity score matching analyses, although based on the same Surveillance, Epidemiology, and End Results database, reported contradictory and inconclusive results.[18,24] Furthermore, they regrouped in the second conservative treatment cohorts undifferentiated repeat lumpectomy with or without reirradiation.

We reported an overall survival rate after conservative treatment of 86.7% and 75.4% at 5 and 10 years, respectively (Table 2; Appendix E1, p 6). GEC-ESTRO[8] reported similar results with 88.7% and 76.4% at 5 and 10 years, respectively, whereas Arthur et al[9] described a 5-year overall survival rate of 95% with a cohort including 40% of ductal carcinoma in situ. In the propensity score matched-pair analysis reported by Su et al,[18] the authors did not observe any significant difference in terms of overall survival between mastectomy and lumpectomy plus reirradiation (HR, 1.15; 95% CI, 0.87-1.53; $P = .35$).

Regarding third breast event−free survival, we did not observe a significant difference between mastectomy and conservative treatment at 5 and 10 years (97.7% vs 97.2% and 96.2% vs 93.7%, respectively). In the GEC-ESTRO study,[8] the rates of third ipsilateral breast event−free survival were 94.4% and 92.8% at 5 and 10 years, respectively, and 94.8% at 5 years in the RTOG-1014 trial.[9] We can note these very encouraging results in cohorts treated with partial breast reirradiation regardless of partial breast irradiation classification criteria.[25] This technique was also only validated for primary low-risk breast cancers.[26] However, Montagne et al[11] reported that, in cases of second conservative treatment, this classification was an independent prognostic factor for a third breast event.

We did not observe a significant difference in terms of cumulative incidence of a third breast event at 5 and 10 years ($P = .4$); however, with longer follow-up, this risk could be higher after second conservative treatment compared with mastectomy (2.8% vs 2.3% and 6.3% vs 3.8% at 5 and 10 years, respectively). Nevertheless, this appears to not have a significant negative effect on specific or overall survival (84% vs 79.3% and 75.4% vs 74.7% at 5 and 10 years, respectively). Interestingly, for primary breast cancer and with a 20-year medical follow-up, Veronesi et al[5] reported a similar observation with a local relapse cumulative incidence of 8.8% versus 2.3% ($P < .001$) after conservative treatment or mastectomy, respectively, but without significant deleterious effect on specific or overall survival.

Regarding distant metastasis-free survival, we observed no significant difference between mastectomy and conservative treatment at 5 and 10 years (85.9% vs 90.7% and 75.1% vs 83.9%, respectively). These results are consistent with those already reported by GEC-ESTRO[8] (at 5 years: 88.9%; 95% CI, 84.3-93.9) and Arthur et al[9] (at 5 years: 95%; 95% CI, 85-98).

Interestingly, for primary breast cancer in hypofractionated versus conventional whole breast irradiation randomized trials, the 5-year cumulative incidence of local recurrence (second breast event) was approximately 2.8% (range, 1.7%-5.2%) (Table E6), whereas in phase 3 partial

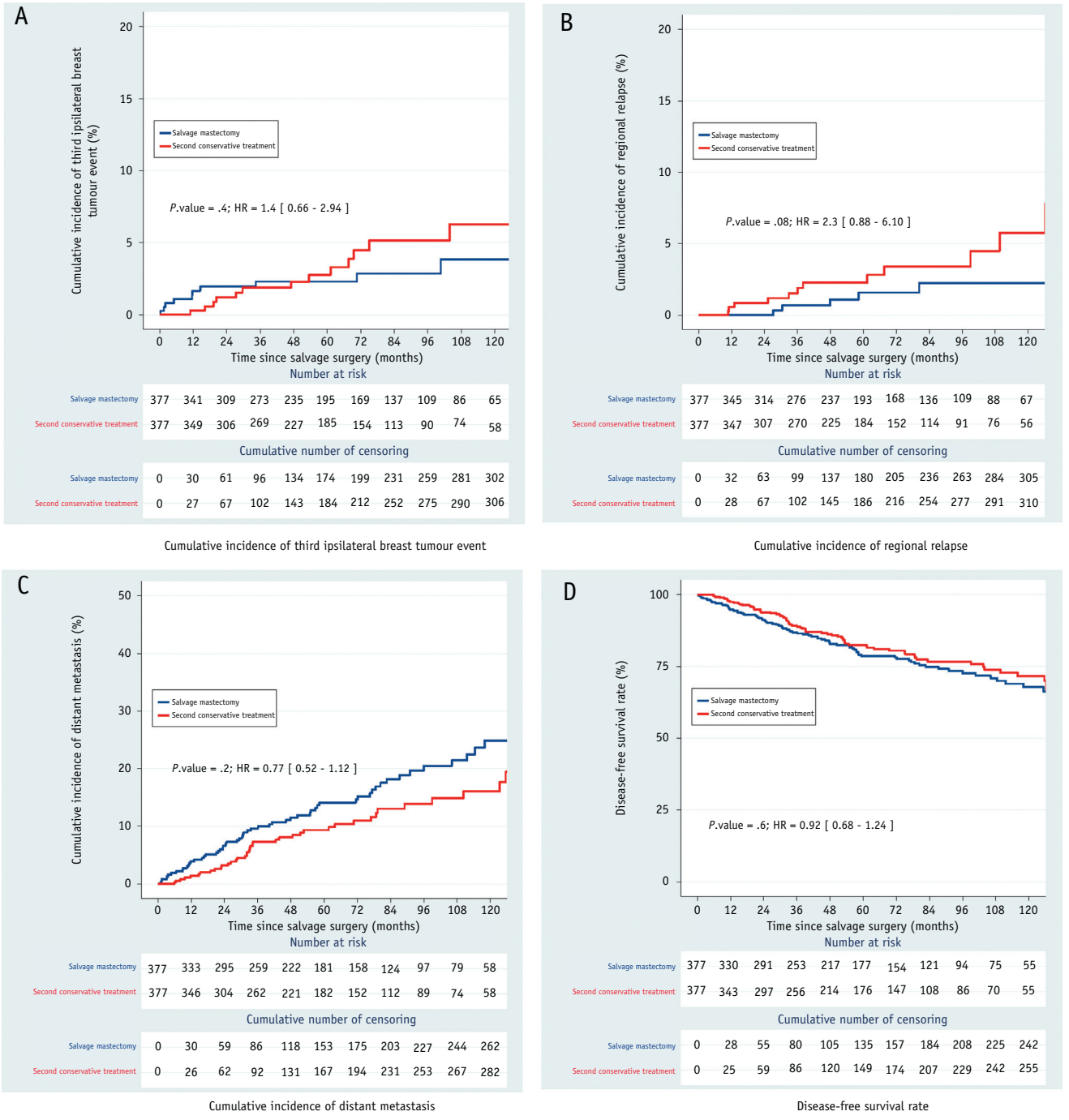

Fig. 2. Comparison of the oncological outcome between salvage mastectomy (n = 377) and second conservative treatment (n = 377) in the matched data set. (A) Cumulative incidence of third ipsilateral breast tumor event. (B) Cumulative incidence of regional recurrence. (C) Cumulative incidence of distant metastasis. (D) Disease-free survival rate. (E) Specific survival rate. (F) Overall survival rate.

breast irradiation trials, the rate was 1.7% (range, 0.4%-4.6%) (Table E6). With a 5-year cumulative incidence of third breast events of 2.8%, second conservative treatment with partial breast reirradiation appears to offer comparable results. However, in the conservative treatment cohort, the 5-year cumulative incidence of distant metastasis was 9.3%, which is higher than the results observed in partial breast irradiation trials (2.7% [range, 0.8%-5.7%]) (Table E7) and slightly higher than those observed in hypofractionated trials (7.8% [range, 4.7%-12.6%]) (Table E7). These results suggest that local control is not clinically prejudiced by a second conservative treatment. In fact, the oncologic outcome could be mainly influenced by distant metastasis progression from the second breast event itself

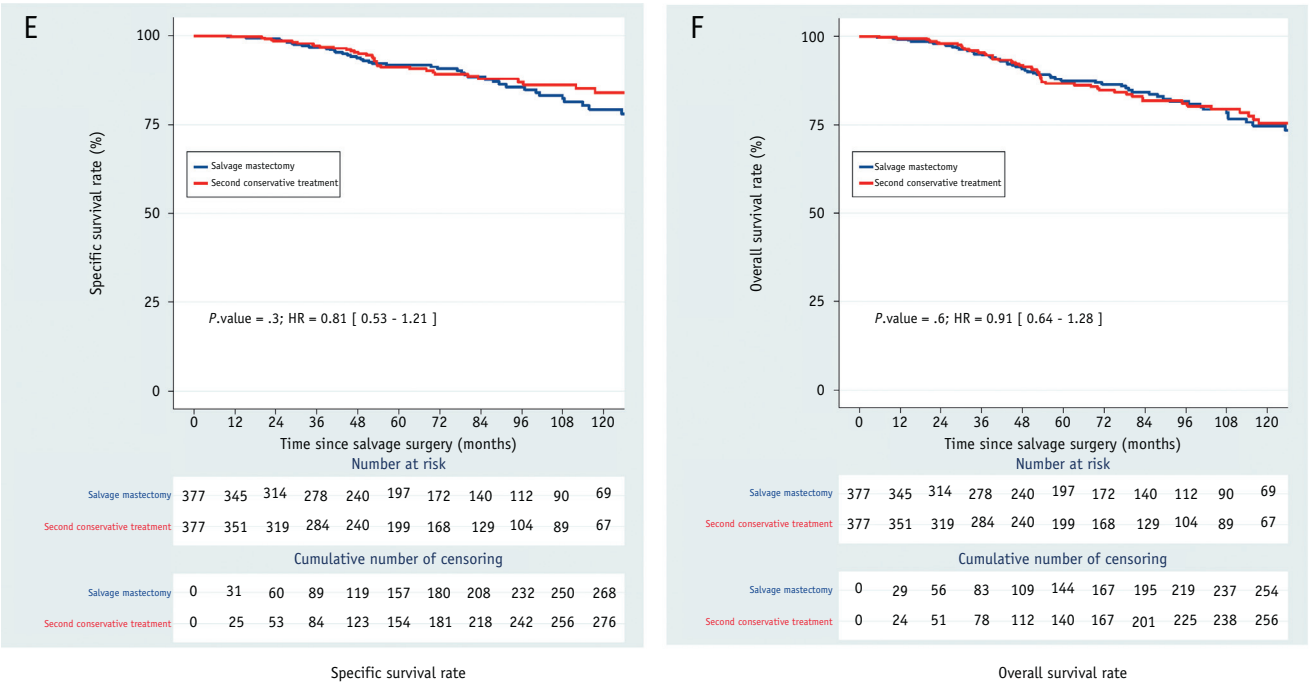

Fig. 2. (Continued)

but also by the primary tumor specifically in cases involving a short time between primary and salvage breast surgery (<36 months). This latter situation results in these patients being recommended for systematic staging and in-depth discussion regarding systemic therapies (Fig. E5).

This analysis contains a number of limitations. As in all observational studies, and despite extensive corrections, our results could have been influenced by unknown residual confounding. During the long study period, diagnostic methods and therapeutic strategies for second breast events evolved, leading us to assume that some patients in our cohort did not benefit from current treatment options (repeat sentinel lymph node biopsy or systemic therapies). The absence of some data in our study could be considered a limitation. For example, data from primary tumors were not systematically and exhaustively recorded, mainly for patients who experienced their second breast event before 2005. In addition, comorbidities that could have had a competitive effect on clinical outcome were not taken into account. Nevertheless, we believe that our key message remains unaffected.

Despite these limitations, our results provide convincing evidence that conservative therapy with re-lumpectomy and salvage brachytherapy is at least equivalent to mastectomy for the treatment of second ipsilateral breast tumor events. Even if mastectomy with immediate reconstruction is still the most commonly proposed salvage treatment, its effect on body image, self-confidence, and quality of life remains heavy.[27,28] Furthermore, van Maaren et al[29] even reported an improvement in long-term overall survival after conservative treatment versus mastectomy for primary breast cancer.

Table 3 Complications (type and grade) observed in the second conservative treatment cohort (283 complications observed for 377 patients)

	Grade 1		Grade 2		Grade 3		Grade 4		Total	
Complications	n	%	n	%	n	%	n	%	n	%
Cutaneous fibrosis	47	34.8	21	17.4	2	8.0	0	0.0	70	24.7
Sub-cutaneous fibrosis	38	28.1	67	55.4	13	52.0	1	50.0	119	42.1
Telangiectasia	15	11.2	9	7.4	1	4.0	0	0.0	25	8.8
Hyperpigmentation	21	15.6	7	5.8	1	4.0	0	0.0	29	10.2
Ulceration	1	0.7	0	0.0	3	12.0	1	50.0	5	1.8
Deformation	13	9.6	17	14.0	5	20.0	0	0.0	35	12.4
Total	135	47.7	121	42.8	25	8.8	2	0.7	283	100

Conclusions

These findings can inform the decision-making process in patients with second breast events and support the implementation of conservative treatment as a validated salvage therapy. In this context, reirradiation of the tumor bed is warranted to improve local control (as for primary disease).[18] Currently, interstitial brachytherapy after re-lumpectomy provides the most consistent data with the longest follow-up. However, investigations are currently ongoing into different reirradiation techniques that could encourage the spread of the second conservative approach for patients who refuse salvage mastectomy.[30]

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