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Thermally boosted interstitial high-dose-rate brachytherapy in high-risk early-stage breast cancer conserving therapy — large cohort long-term results

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ABSTRACT

Background: Early-stage high-risk breast cancer (BC) is standardly treated with breast-conserving therapy (BCT), combined with systemic therapy and radiotherapy (RT) ± tumor bed boost, e.g., with interstitial high-dose-rate brachytherapy (HDR-BT). To improve local recurrence rate (LRR), BT radiosensitization (thermal boost, TB) with interstitial microwave hyperthermia (MWHT) may be an option. The paper aims to report a retrospective single-institutional study on 5- and 10-year local control (LC), distant metastasis-free survival (DMFS), disease-free survival (DFS), overall survival (OS), cosmetic outcome (CO), and late toxicity (fibrosis, fat necrosis) after thermally enhanced HDR-BT boost to the BC tumor bed.

Materials and methods: In 2006–2018, 557 early-stage (I–IIIA) high-risk BC patients were treated with BCT. If indicated, they were administered systemic therapy, then referred for 40.0–50.0 Gy whole breast irradiation (WBI) and 10 Gy interstitial HDR-BT boost (group A). Eligible patients had a single MWHT session preceding BT (group B). Based on present risk factors (RF), medium-risk (1–2 RF) and high-risk subgroups (≥ 3 RF) were formed. Patients were standardly checked, and control mammography (MMG) was performed yearly. Breast cosmesis (Harvard scale) and fibrosis were recorded. LC, DMFS, DFS, and OS were statistically analyzed.

Results: Out of 557 patients aged 57 years (26–84), 364 (63.4%) had interstitial HDR-BT boost (group A), and 193 (34.6%) were preheated with MWHT (group B). Patients in group B had a higher clinical stage and had more RFs. The median follow-up was 65.9. Estimated 5-year and 10-year LC resulted in 98.5% and 97.5%, respectively. There was no difference in LC, DMFS, DFS, and OS between groups A and B and between extracted high-risk subgroups A and B. Five- and ten-year OS probability was 95.4% and 88.0%, respectively, with no difference between groups A and B. Harvard criteria-based CO assessment revealed good/excellent cosmesis in 74.9–79.1%. Tumor bed hardening was present in 40.1–42.2%. Asymptomatic fat necrosis-related macrocalcifications were detected in 15.6%, more frequently in group B ($p = 0.016$).

Conclusions: Thermally boosted or not, HDR-BT was locally highly effective as part of combined treatment. Five- and ten-year LC, DMFS, DFS, and OS were high and equally distributed between the groups, although TB was prescribed in more advanced one with more RFs. TB did not influence CO and fibrosis. TB added to late toxicity regarding asymptomatic fat necrosis detected on MMG.

Key words: breast cancer; HDR; brachytherapy; thermal boost; hyperthermia; breast-conserving therapy

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Introduction

Early breast cancer (BC) patients are standardly treated with breast-conserving therapy (BCT). According to the risk factors, breast-sparing regular or oncoplastic surgery is preceded or followed by neo- or adjuvant chemotherapy, mostly mandatory radiotherapy (RT) ± tumor bed boost, hormonal therapy, and immunotherapy, if indicated. In the past, mutilating mastectomy was an alternative to current BCT [1–4].

The primary lesion site is of the most interest for surgery and radiation. Both methods eradicate the tumor and secure the patient from potential local relapse. Up to two decades ago, published studies delivered data confirming that adjuvant breast irradiation with increased tumor bed boost may reduce the 5-year local recurrence rate (LRR) from 7.3–13.3% to 3.6–6.3% [5–7]. Some more often advocate that RT should be administered, especially to breast cancer patients with a high risk of relapse. In that patients, matured observation prolonged to 20 years revealed that RT with boost reduces ipsilateral breast tumor recurrence (IBTR) from 31% to 15% [8]. In addition to whole breast irradiation (WBI), the extra dose (boost) may be delivered to the tumor bed in a few ways [9–11]. Here, we focus on interstitial multi-catheter (MC) high-dose-rate brachytherapy (HDR-BT), which is the most conformal and precise method of target volume irradiation [12]. As summarized by Polgar et al. on 1770 patients, HDR-BT boost results in a mean 5-year LRR of 5.5% [13]. However, there is still room for further improvements oriented on a maximally low recurrence rate.

As the local treatment goal is to eradicate the gross tumor and oncologically sterilize the tumor's surroundings, considering that radiation fails in some parts, we investigated a combination of BT with interstitial microwave hyperthermia (MWHT). Our proposal was thermal boost (TB) preceding HDR-BT boost in a timely manner. As such, hyperthermia (HT) is a well-known, effective, and approved radiation sensitizer that interferes with radiation-dependent cellular proteins and may reduce tumor α/β ratio [14–18]. We developed an original and feasible technique of combining interstitial MWHT (thermal boosting) with standard interstitial MC HDR-BT. We recently described it in detail elsewhere, along with short- and long-term results of our limited initial patients' group [19–21]. Based on those findings and observed safety in other clinical practices, we focused on patients presenting at least one local recurrence risk factor and endangered by a higher probability of local failure.

The paper is a retrospective single-institutional report on 5- and 10-year local control (LC), distant metastasis-free survival (DMFS), disease-free survival (DFS), overall survival (OS), cosmetic outcome (CO), and late toxicity (fibrosis, fat necrosis) in high-risk early-stage BC patients treated with HDR-BT boost with or without interstitial MWHT thermal boost.

Materials and methods

Between February 2006 and December 2018, 557 diverse early-stage (I–IIIA) high-risk BC patients were conservatively treated with BCT. All that had indications were administered adjuvant chemotherapy and started immunotherapy and hormonal therapy. Then, they were referred for 40.0–50.0 Gy whole breast irradiation (WBI). The irradiation course was always finalized with a 10 Gy interstitial HDR-BT boost. When referred for interventional radiotherapy (brachytherapy), each tumor bed volume was carefully assessed regarding its ratio related to the rest of the treated breast, distance to the skin, and predicted post-implant applicators coordinates and distances. Patients considered eligible were proposed additional BT preceding a single session of interstitial hyperthermia. Eligibility criteria included well-known risk factors predicting local recurrence: age ≤ 40–50 years, premenopausal status, T2 tumors larger than 3 cm, multifocal tumors, grade 3, positive nodes, indications for chemotherapy, HER2-positivity, triple-negative tumors, high Ki-67 ≥ 30%. Based on them, we grouped the patients into a medium-risk group with 1 or 2 risk factors and a high-risk group characterized by at least three risk factors or more. We could not randomize the patients eligible for MWHT as the selection was based on a few critical features that had been assessed before the decision: adequate breast volume, relatively large and rather deep-seated tumor bed, enough skin-to-skin distance, predicted at least three application planes, safe deep plane-to-bone structures distance, lack of seroma

or hematoma. The final enrollment was possible after the post-implant CT scan assessment. After such personal tailoring, if selected, the patient was informed in detail about the offered oncological approach to enhance interstitial HDR-BT to increase the local cure probability thermally. All patients signed an individual informed consent form. In an oncological setting, HT administered concomitantly with radiation (including interstitial BT) is an accepted and reimbursed treatment option in the authors' country.

As mentioned above, interstitial MW thermal boost planning and delivery followed by HDR-BT boost were meticulously described in detail in our previous communications [12, 19]. Briefly, MWHT sessions were performed with a 915 MHz BSD-500 system (BSD Medical Corporation, Salt Lake City, UT, United States) and HDR-BT with a ^{191}Ir radioactive source (microSelectron-HDR, Nucletron BV/Elekta, Veenendaal, The Netherlands). HT always preceded BT. For both methods, the same disposable interstitial application was used. We followed all temperature prescriptions (minimal and reference temperature), thermometry rules (multiple measurements), the time interval between heating and irradiation (up to two hours), and HT quality assurance (QA) requirements being in force since Radiation Therapy Oncology Group (RTOG) guidelines release and their later updates [22, 23].

Most of our patients were regularly checked on control visits every three months for the first two years of follow-up, every six months in 3–5 years after treatment completion, and yearly later. After five years, if not recurrent, some patients were sent for further controls to their general practitioners and were lost for follow-up. However, we verified all patients' life statuses in a national registry and archived the confirmed death dates. Control mammography was regularly performed once a year, with the first one starting six months after BT. There was the assumption on check-ups to note the treated breast presentation according to the four-grade Harvard scale (very good/excellent, good, poor/satisfactory, and bad cosmetic result) [24] and the presence of tumor bed induration.

In February and March 2023, each patient's data was retrospectively verified and recorded regarding the last follow-up, current health and life status, disease presence, eventual treatment sequelae, and the previous mammography findings.

Data was collected in an MS Excel spreadsheet, from which descriptive statistics were elucidated. Tests and graphs were produced with Statistica 13 (Statsoft, Tulsa, OK, United States). The Mann-Whitney test was used to compare categorical and continuous variables without normal spread. The variables in the nominative scale were assessed with a Chi-square test. LC, DMFS, DFS, and OS were analyzed with the Kaplan–Meier method and compared with the log-rank test. The influence of selected variables on late toxicity was analyzed with logistic regression analysis. We considered the p-values < 0.05 statistically significant.

Results

Clinical results

We treated and collected data from 557 early BC patients presenting local recurrence risk factors. The median patient's age was 57 years (range 26–84 years). Of them, 364 (63.4%) were administered solitary interstitial HDR-BT boost (group A), and another 193 (34.6%) were preheated with a single session of interstitial MWHT (group B). Group A and B did not differ regarding age and age intervals, T-stage, tumor histology and grading, hormonal receptors, and HER2 status. However, we identified that group B was characterized more by higher N-stage ($p < 0.001$), clinical stage ($p = 0.004$), Ki67 count ($p = 0.048$), more frequent axillary lymph node dissection ($p < 0.001$), less favorable cancer molecular subtypes ($p < 0.001$), and more frequent chemotherapy administration ($p = 0.007$). In consequence, after patients' allocation to medium- (1–2 risk factors) and high-risk (≥ 3 risk factors) subgroups, we identified 61.5% of patients from group A in medium-risk and 52.8% of patients from group B in high-risk cohorts, respectively ($p = 0.011$). We also revealed that patients with more risk factors (group B) were more often treated with hypofractionated WBI regimens ($p = 0.001$). Almost half were prescribed 42.5 Gy in 17 fractions by 2.5 Gy. More detailed information regarding patients' characteristics is presented in Table 1.

As presumed, all who started TB completed the heating after a mean of 61 minutes (range

Table 1. Patient characteristics

Feature	HDR-BT Alone Group A (n = 364; 63.4%)	HDR-BT + Thermal Boost Group B (n = 193; 34.6%)
Age, median (range) years	57 (26–84)	*p = 0.49
≤ 40	24 (6.6%)	13 (6.7%)
41–50	101 (27.8%)	53 (27.5%)
51–60	109 (29.9%)	67 (34.7%)
≥ 61	130 (35.7%)	60 (31.1%)
T stage		*p = 0.13
T1a	14 (3.9%)	8 (4.1%)
T1b	42 (11.5%)	15 (7.8%)
T1c	151 (41.5%)	79 (40.9%)
T2	113 (31.0%)	68 (35.3%)
Tx	44 (12.1%)	23 (11.9%)
N stage		*p = 0.001
N0	225 (70.1%)	109 (56.5%)
N1	75 (20.6%)	62 (32.1%)
N2a	34 (9.3%)	22 (11.4%)
Clinical stage		*p = 0.004
I	161 (44.3%)	61 (31.6%)
IIA	138 (37.9%)	88 (45.6%)
IIB	31 (8.5%)	17 (8.8%)
IIIA	16 (4.4%)	14 (7.3%)
n.d.	18 (4.9%)	13 (6.7%)
Tumor histology		^p = *0.09*
Ductal invasive carcinoma	311 (85.5%)	164 (85.0%)
Lobular invasive carcinoma	26 (7.1%)	11 (5.6%)
Tubular carcinoma	3 (0.8%)	4 (2.1%)
Not specified (post-chemo)	24 (6.6%)	14 (7.3%)
Grading		*p = 0.77
G1	75 (20.6%)	37 (19.2%)
G2	158 (43.4%)	79 (40.9%)
G3	117 (32.2%)	66 (34.2%)
Not specified (post-chemo)	14 (3.8%)	11 (5.7%)
Estrogen receptor status		^p = *0.17*
ER (+)	276 (75.8%)	134 (69.4%)
ER (–)	88 (24.2%)	56 (29.0%)
n.d.	0 (0.0%)	3 (1.6%)
Progesteron receptor status		^ p = *0.61*
PgR (+)	266 (73.1%)	135 (69.9%)
PgR (–)	98 (26.9%)	55 (28.5%)
n.d.	0 (0.0%)	3 (1.6%)
Ki-67 (n = 353)		*p = 0.048
mean value (range) (%)	27.7 (1–90)	32.0 (34–85)
n.d.	112 (30.8%)	92 (47.7%)
HER2 status†		^p = 0.81
Positive (+)	73 (20.1%)	39 (20.2%)
Negative (–)	286 (78.6%)	145 (75.1%)
n.d.	5 (1.3%)†	9 (4.7%)†
Lymph node treatment		^p < 0.001
ALND	135 (37.1%)	110 (57.0%)
SNB ‡	229 (62.9%)	83 (43.0%)
Immunohistochemistry		^p < 0.001
Luminal A	87 (23.9%)	27 (14.0%)
Luminal B	93 (25.5%)	42 (21.7%)
HER2 positive	39 (10.7%)	14 (7.3%)
TNBC	53 (14.6%)	33 (17.1%)
Luminal B/HER2 positive	31 (8.5%)	25 (13.0%)
n.d. (no Ki67 data)	61 (16.8%)	52 (26.9%)
Immunotherapy (TZM)		^p = 0.43
Yes	46 (12.6%)	20 (10.4%)
No	318 (87.4%)	173 (89.6%)
Chemotherapy treatment		^p = 0.007
Yes	203 (55.8%)	136 (70.5%)
No	161 (44.2%)	57 (29.5%)
Risk groups		^p = 0.011
Low (no risk factors)	0 (0.0%)	0 (0.0%)
Medium (1-2 risk factors)	224 (61.5%)	91 (47.2%)
High (≥ 3 risk factors)	140 (38.5%)	102 (52.8%)
External Beam RT regimen		^p = 0.001
50.0 Gy/2.0 Gy/25 fx	165 (45.4%)	60 (31.1%)
45.0 Gy/2.25 Gy/20 fx	32 (8.8%)	35 (18.1%)
42.5 Gy/2.5 Gy/17 fx	142 (39.0%)	92 (47.7%)
40.0 Gy/2.35 Gy/17 fx	23 (6.3%)	1 (0.5%)
40.0 Gy/2.67 Gy/15 fx	0 (0.0%)	5 (2.6%)
n.d.	2 (0.5%)	0 (0.0%)

^test χ^2; *test M-U; †at the time of the study, HER2 status was not standardly assessed for all patients, and Ki67 status as well; ‡at the time of the study, SNB was not a standard yet. ALND — axillary lymph node dissection; fx — fractions; n.d. — no data; RT — radiotherapy; SNB — sentinel node biopsy; TNBC — triple negative breast cancer; TZM — trastuzumab

33–66 minutes) and began BT in a mean of 25 minutes (range 5–75 minutes). The average achieved reference temperature was 41.6°C (38.8–42.7°C). All solitary and combined sessions were finalized without unexpected complications.

The median follow-up resulted in 65.9 months (range 0.0–195.5). Thirty-two patients (5.7%) were present only for the first control visit or never reappeared. They were excluded from clinical outcomes (except OS), CO, and late toxicity calculations. For the remaining 525/557 (94.3%) patients, estimated 5-year and 10-year LC resulted in 98.5% and 97.5%, respectively. There was no difference in LC, DMFS, DFS, and OS between groups A and B (Fig. 1A, C, E, G). Also, there was no difference in LC, DMFS, DFS, and OS between extracted high-risk subgroups A and B (Fig. 1B, D, F, H). We identified only 11 (2.1%) local recurrences (8 in group A, 3 in group B). Distant metastases were noted more frequently and appeared in 30 (5.7%) patients (19 in group A, 11 in group B). We noticed 62 (11.1%) deaths (37 in group A, 25 in group B), of which the minority of 25 (40.3%) cases was related to BC dissemination. 17 (27.4%) patients died of independent second malignancy, and 20 (32.3%) in consequence of comorbidities. The cumulative median OS was 86.6 months (6–205 months). Five- and ten-year OS probability was 95.4% and 88.0%, respectively, with no difference between groups A and B (p = 0.88) (Fig. 1G).

Cosmetic outcome (CO)

Harvard criteria-based CO assessment of 507/557 (91.0%) patients revealed good to excellent cosmesis in 74.9%, poor/satisfactory in 21.5%, and bad in 3.6% in group A, and good to excellent cosmesis in 79.1%, poor/satisfactory in 18.1%, and bad in 2.8% in group B; p = 0.32 (Tab. 2). Of note, we failed to record the CO of 50 patients as it was not reported in clinical files by any of the patients' controlling specialists.

Late toxicity

Tumor bed hardening was assessed and recorded in 508/557 (91.2%) patients. It was present in 42.2% of patients treated with sole HDR-BT and 40.1% of patients additionally preheated; p = 0.58 (Tab. 2). The fibrosis was not graded according to any of the available scales. Recordings were somewhat subjective, providing only knowledge about partial breast hardening presence or absence.

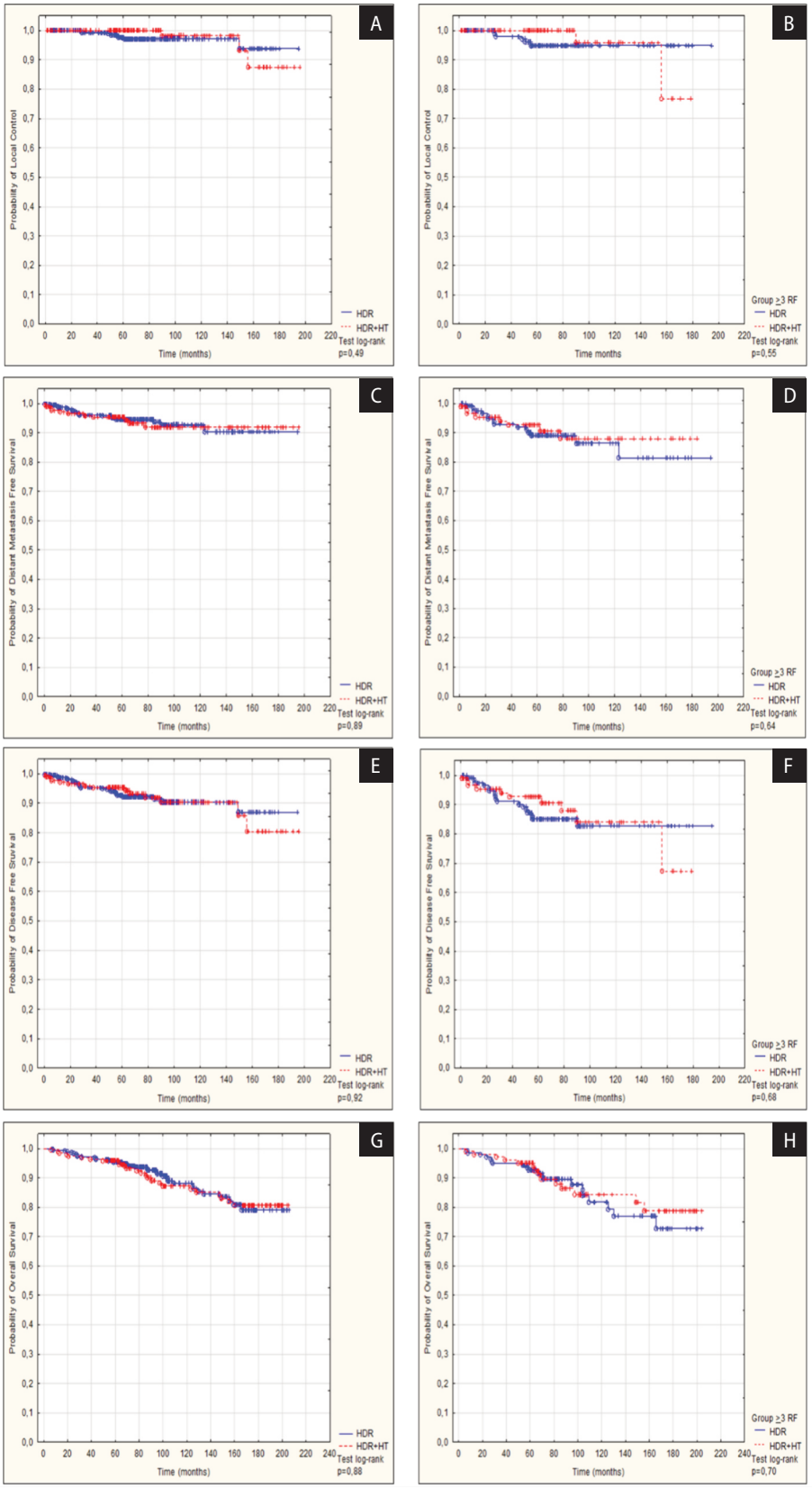
Control mammography (MMG) is standardly performed to detect early and not yet palpable in-breast recurrences. In rare cases, magnetic resonance (MR) replaces MMG. However, imaging gives some more information about the treated breast tissue and possible treatment side effects. Most often, it finds no changes at all (here: 62/508; 12.2%), tissue scarring (246; 48.4%), tissue scarring with tiny benign calcifications (121; 23.8%), tissue scarring with asymptomatic fat necrosis-related macrocalcifications (79; 15.6%), or symptomatic massive fat necrosis (here: none). We identified asymptomatic fat necrosis more frequently in the thermally boosted group; p = 0.016 (Tab. 2). Neither of the patients presented inflammatory disorders needing drug prescribing or surgical intervention.

Discussion

This study presents long-term oncological results, cosmetic outcomes, and late toxicity of an originally altered postoperative adjuvant setting. After surgical breast-conserving therapy, we investigated thermally augmented interstitial HDR-BT boost complement to EBRT. Based on available data, radiation combined with HT is proven effective in recurrent, locally advanced, or inoperable BC [25–28]. Here, long-term conservative treatment results relate to a unique HT application adjuvant to tumor bed-boosting HDR-BT in high-risk BC patients. The study is a natural continuation of previous works [19–21].

Inspired by Hartmann et al. and Gardner et al., we intended to increase the probability of eradicating potentially invasive cells in the tumor bed and its surroundings [29, 30]. Based on recent reports, we are still aware that HT sensitizes the cells to radiation and, thus, should enhance the treatment efficacy [31]. The works of Dooley et al. on pre-mastectomy-focused MW thermotherapy of early-stage BC supported our idea to boost HDR-BT thermally [32].

From the time of our method implementation till now, we could not find any other research results concerning non-strict tumor heating with potentially cancerous cell-containing tissue. As we



Clinical result	Probability	All patients	Fig. 1	Group A	Group B	*p-value*	Fig. 1	Group A high-risk	Group B high-risk	*p-value*
LC	5-year	98,50%	a	97,70%	100,00%	*0,49*	*b*	94,60%	100,00%	*0,55*
	10-year	97,50%		97,20%	98,20%			94,60%	95,80%	
DMFS	5-year	94,80%	c	94,50%	95,20%	*0,89*	*d*	88,90%	92,70%	*0,64*
	10-year	92,50%		92,60%	92,00%			86,40%	87,80%	
DFS	5-year	93,60%	e	92,30%	95,20%	*0,92*	*f*	85,10%	92,70%	*0,68*
	10-year	90,30%		90,30%	90,30%			82,60%	84,00%	
OS	5-year	95,40%	g	95,20%	95,80%	*0,88*	*h*	92,50%	95,10%	*0,70*
	10-year	88,00%		88,20%	87,30%			81,70%	84,30%	

Figure 1. Graphs representing the probability of local control (LC) for: **A.** High-dose-rate (HDR) group A (solid blue line) and high-dose-rate + hyperthermia (HDR+HT) groups (red dotted line); **B.** HDR and HDR + HT high-risk subgroups with ≥ 3 risk factors; distant metastases-free survival (DMFS) for: **C.** HDR and HDR + HT groups; **D.** HDR and HDR + HT high-risk subgroups; disease-free survival (DFS) for: **E.** HDR and HDR + HT groups; **F.** HDR and HDR + HT high-risk subgroups; overall survival (OS) for: **G.** HDR and HDR + HT groups; **H.** HDR and HDR + HT high-risk subgroups, respectively. RF — risk factor

Table 2. Long-term treatment sequelae

Feature	HDR-BT alone Group A	HDR-BT + Thermal Boost Group B
Cosmetic effect (n = 507)†		*p = 0.32
n	330 (100.0%)	177 (100.0%)
Very good	98 (29.7%)	57 (32.2%)
Good	149 (45.2%)	83 (46.9%)
Poor	71 (21.5%)	32 (18.1%)
Bad	12 (3.6%)	5 (2.8%)
Tumor bed hardening (n = 508)°		^p = 0.58
n	330 (100.0%)	178 (100.0%)
Yes	140 (42.4%)	71 (40.1%)
No	190 (57.6%)	107 (60.5%)
Fat tissue necrosis (n = 508)°		^p = 0.016
n	330 (100.0%)	178 (100.0%)
Yes	42 (12.7%)	37 (20.8%)
No	288 (87.3%)	141 (79.2%)

^test χ^2; *test M-U; †50 patients had no information concerning cosmetic outcome registered; °49 patients had no information concerning tumor bed hardening or mammography results registered

proved previously, the method may be challenging to implement, but it is feasible and very well tolerated by patients.

In our large group of high-risk BC patients, we discovered that patients selected for TB were burdened with a higher risk of loco-regional and distant recurrence yet achieved the same and excellent long-term LC, DMFS, DFS, and OS compared to the HDR-BT alone cohort. It might be the effect of tumor bed heating and more frequent hypofractionated RT regimens. Nevertheless, due to perfect long-term LC in both groups, we failed to prove or at least suggest that TB enhances HDR-BT boost clinical results. Whether thermally enhanced or not, our HDR-BT boost achieved comparable or slightly better 5-year LC than published in other series resulting in 93.7–96.4% probability of local cure [5–7, 13].

There is no doubt that young BC patients with present recurrence risk factors need efficient and individually tailored treatment at every step, from surgery, through systemic therapy, to irradiation with boost [33–35]. Our results add some information on possible very effective management. Vrieling et al., based on EORTC Trial, proved again in 2017 the importance of the boost that cuts the 20-year ipsilateral BC recurrence rate by half [8].

Available example studies implementing interstitial HDR-BT boost report the cosmetic outcome as high as good to excellent in 80–97% [36, 37]. The paper presents retrospective data on good to excellent CO in 74.9% (group A) and 79.1% (group B), p = 0.32. The interpretation may be difficult as different researchers use different tools for assessing the cosmesis, also in terms of prospective or retrospective scenarios, still searching for eventual poor cosmesis predictors [38]. However, TB did not worsen CO in our cohort, and the above-mentioned patient selection (larger breast cups were easier qualified) might not significantly influence, yet slightly improve the score.

Related to the cosmesis, tumor bed induration may be clinically relevant. We identified palpable fibrosis in two-fifths of our patients. Some proportion of it was already present after surgery, although it was not verified and noted at the patient presentation. In 2014, Bartelink et al. presented a cumulative 20-year incidence of fibrosis in patients that received the boost (71.4%) and those not boosted (57.2%), p < 0.0001. The difference was also significant for the incidence of severe fibrosis, 5.2% versus 1.8% [39]. Our study follow-up is too short to allow any comparison with their very long-term results.

Multiple modality treatment may cause fat necrosis (FN) in a part of the treated breast. It is instead scarcely reported (2–52%), rarely causes clinical problems (e.g., worsens the cosmesis), and is most often detected in asymptomatic patients on their control mammograms [40–42]. In our series, asymptomatic FN-related macrocalcifications were seen on MMG in 15.6% of patients, more often in the heated group. Well-planned HDR-BT with all dose-volume constraints met prevents the FN formation possibility. However, unique problematic FN formations may develop even after 20 years post-treatment [43].

The study's weaknesses were noted and listed. Although the patient cohort was relatively large and exceeded five hundred, their analysis was retrospective, some patients were lost from follow-up, and some data were incomplete. Also, selecting appropriate candidates for adjuvant HT was specific and somehow exclusionary, so patient groups A and B were not ideally balanced. Breast size,

post-surgical breast and scar presentation, tumor bed size and location, remnant seroma or hematoma presence, and interstitial implant volume had to be considered. However, only a personalized approach based on meticulous individuals' presentations was possible to perform safe and high-quality HT sessions. Nevertheless, all these features made the randomization option impossible.

Conclusions

Interstitial HDR-BT boost with or without TB for high-risk early-stage BC patients treated with BCT was feasible and well-tolerated. Thermally boosted or not, HDR-BT was locally highly effective as part of combined treatment. The probability of 5-year and 10-year LC, DMFS, DFS, and OS was equally distributed between the groups. TB kept the clinical outcomes (LC, DMFS, DMFS, OS) on the same level, although it was prescribed in more advanced group with more RFs. TB did not influence CO and fibrosis. TB added to late toxicity regarding asymptomatic fat necrosis detected on MMG.

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