available at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.rpor.eu/

Original article

Thermal boost combined with interstitial brachytherapy in breast conserving therapy – Assessment of early toxicity

Adam Chicheł, Janusz Skowronek, Marek Kanikowski*

Department of Brachytherapy, Greater Poland Cancer Centre, Garbary 15, 61-866 Poznań, Poland

ARTICLE INFO

Article history:
Received 11 October 2010
Received in revised form
11 December 2010
Accepted 21 February 2011

Keywords:
Hyperthermia
Brachytherapy boost
Breast cancer

ABSTRACT

Background: Hyperthermia (HT) causes a direct damage to cancerous cells and/or sensitize them to radiotherapy with usually minimal injury to normal tissues. Adjuvant HT is probably one of the most effective radiation sensitizers known and works best when delivered simultaneously with radiation. In breast conserving therapy, irradiation has to minimize the risk of local relapse within the treated breast, especially in an area of a tumor bed. Brachytherapy boost reduces 5-year local recurrence rate to mean 5,5%, so there still some place for further improvement. The investigated therapeutic option is an adjuvant single session of local HT (thermal boost) preceding standard CT-based multicatheter interstitial HDR brachytherapy boost in order to increase the probability of local cure.

Aim: To report the short-term results in regard to early toxicity of high-dose-rate (HDR) brachytherapy (BT) boost with or without interstitial microwave hyperthermia (MV HT) for early breast cancer patients treated with breast conserving therapy (BCT).

Materials and methods: Between February 2006 and December 2007, 57 stage IA–IIIA breast cancer patients received a 10 Gy HDR BT boost after conservative surgery and 42.5–50 Gy whole breast irradiation (WBI) ± adjuvant chemotherapy. 32 patients (56.1%) were treated with additional pre-BT single session of interstitial MW HT to a tumor bed (multi-catheter technique). Reference temperature was 43 °C and therapeutic time (TT) was 1 h. Incidence, severity and duration of radiodermatitis, skin oedema and skin erythema in groups with (I) or without HT (II) were assessed, significant p-value ≤ 0.05.

Results: Median follow-up was 40 months. Local control was 100% and distant metastasis free survival was 91.1%. HT sessions (median): reference temperature 42.2 °C, therapeutic time (TT) 61.4 min, total thermal dose 42 min and a gap between HT and BT 30 min. Radiodermatitis grades I and II occurred in 24 and 6 patients, respectively, differences between groups I and II were not significant. Skin oedema and erythema occurred in 48 (85.7%) and 36 (64.3%) cases, respectively, and were equally distributed between the groups. The incidence and duration of skin oedema differed between the subgroups treated with different fractionation protocols of WBI, $p = 0.006$. Skin oedema was present up to 12 months. No difference in pattern of oedema regression between groups I and II was observed, $p = 0.933$.

* *Corresponding author.* Tel.: +48 61 8850902; fax: +48 61 8850834; mobile: +48 600687369.
E-mail address: adam.chichel@wco.pl (A. Chicheł).

doi:10.1016/j.rpor.2011.02.004

Conclusion: Additional thermal boost preceding standard HDR BT boost has a potential of further improvement in breast cancer local control in BCT. Pre-BT hyperthermia did not increase early toxicity in patients treated with BCT and was well tolerated. All side effects of combined treatment were transient and were present for up to 12 months. The increase in incidence of skin oedema was related to hypofractionated protocols of WBI. The study has to be randomized and continued on a larger group of breast cancer patients to verify the potential of local control improvement and to assess the profile of late toxicity.

1. Background

Hyperthermia (HT) is one of the cancer therapies and, clinically, is considered to be an artificial way of increasing the temperature of a particular tumorous region over the physiological temperature of the body.[1–3] It is achieved by delivering heat obtained from external sources, e.g. microwaves (MW). HT is mostly understood as a range of temperatures from 40 to 48 °C maintained in a treated site for a period of about an hour.[4–8]

Many studies have already shown that high temperature[6] cause a direct damage to cancerous cells and/or sensitize them to other treatment modalities (radiotherapy, chemotherapy, gene therapy and immunotherapy) usually with minimal or no injury to normal tissues.[4,7–12] Thus, HT is extensively used as an adjuvant therapy.[2,5,9] HT has a potential of killing cells itself, induces reoxygenation, increases radiosensitivity and augments immune reactions against the tumor.[13–15] In fact, hyperthermia is probably one of the most effective radiation sensitizers known, a fact supported with extensive preclinical data and a number of large randomized clinical trials.[16,17] The most probable mechanism by which HT sensitizes cells to radiation is by interfering with the cells' ability to repair radiation-induced damage of DNA structure,[18] as predominant target of HT is protein.[8,9,19] Due to a temporary effect of heat-induced changes in protein structure, the best approach is to deliver hyperthermia and radiation simultaneously, which is difficult in common practice.

Breast conserving therapy (BCT), consisting of conservative surgery, radiotherapy ± brachytherapy and optional adjuvant chemotherapy, is a standard radical treatment for a vast majority of breast cancer patients. BCT is a good alternative to mastectomy in treatment of early invasive breast cancer.[20–22] The goal of irradiation is to minimize the risk of local relapse within the treated breast, especially in an area of a tumor bed which is a target volume for brachytherapy. There are many methods of increasing the dose to the tumor bed (boost).[23] The best approach is chosen depending on clinical and morphological criteria, patient's will and institutional resources and protocols,. Modern interstitial multi-catheter HDR brachytherapy offers conformal and accurate irradiation of the target volume, provided there are surgical clips left in the operated breast and treatment planning system is CT-based. Patient age of <50 years; close, microscopically positive or unknown surgical margins; and the presence of an extensive intraductal component are accepted indications for boost irradiation.[24–26]

Randomized "boost vs. no boost" trials revealed, that there is an evident benefit from administering additional dose to the tumor bed. The boost reduces 5-year local recurrence rate from 7.3–13.3% to 3.6–6.3% (p 0.04–0.0001).[27–29] Polgár et al. also summarized the results of many different HDR brachytherapy series worldwide, in which in total 1776 patients, 5-year local recurrence rate was achieved in 0–9% (mean 5.5%).[26] There is still some room for improvement in common management of early stage breast cancer in order to decrease the recurrence rate to a minimum level. This goal can be achieved by eradicating the gross tumor and all cancer cells in its surrounding (margins of healthy tissue). One of the investigated therapeutic options is additional local hyperthermia which has already proved its potential of improving the outcome of standard therapy. The main objective of such research is to find an optimal treatment which would enable achieving of up to 100% local control.

Sophisticated CT-based interstitial brachytherapy of breast cancer is based on multi-catheter implants piercing the tumor bed. The same set of elastic tubes can be successfully used for hyperthermia treatment. In this approach, tiny microwave antennas are inserted into the treated volume via brachytherapy applicators. The antennas always have to be used along with thermometers inserted for temperature measurement and adjustments. A set of CT scans used for treatment planning delivers strict geometrical information about 3D orientation of applicators within the tumor bed and enables the physician to plan the best pattern of antennas and thermometers to safely heat the target volume before irradiation. It was decided to add a single hyperthermia session (thermal boost) preceding standard brachytherapy boost in order to increase the probability of local cure.

2. Aim

To report the short-term results in regard to early toxicity of high-dose-rate (HDR) brachytherapy (BT) boost with or without interstitial microwave hyperthermia (HT) for early-stage breast cancer patients treated with breast conserving therapy (BCT).

3. Materials and methods

Between February 2006 and December 2007, 57 early-stage breast cancer patients were treated with HDR BT boost after BCT, followed by external beam radiotherapy (EBRT) to the

Table 1 – Patient and tumor characteristics.

	$n = 57$ (100%)
Age, median (range)	53 (32–71) years
≤40	5 (8.8%)
41–50	13 (22.8%)
51–60	21 (36.8%)
≥61	18 (31.6%)
T stage	
T1a	2 (3.5%)
T1b	11 (19.3%)
T1c	33 (57.9%)
T2	8 (14%)
Tx	3 (5.3%)
N stage	
N0	37 (64.9%)
N1	17 (29.8%)
N2	3 (5.3%)
Clinical stage	
IA	27 (47.4%)
IB	1 (1.7%)
IIA	21 (36.8%)
IIB	2 (3.5%)
IIIA	3 (5.3%)
ns	3 (5.3%)
Tumor histology	
Invasive ductal carcinoma	47 (82.5%)
Invasive lobular carcinoma	2 (3.5%)
Tubular carcinoma	4 (7%)
Other	4 (7%)
Tumor grade	
G1	20 (35.1%)
G2	24 (42.1%)
G3	10 (17.5%)
Gx	3 (5.3%)
Receptor status	
ER pos/neg/ns	39 (68.4%)/15 (26.3%)/3 (5.3%)
PgR pos/neg/ns	36 (63.1%)/18 (21.6%)/3 (5.3%)
HER2 1+/2++/3+++	18 (31.6%)/10 (17.5%)/1 (1.7%)
neg/ns	13 (22.8%)/15 (26.4%)

Abbreviation: ns – not specified, ER – estrogen receptor, PgR – progesterone receptor, neg – negative, pos – positive.

whole breast (WBI) and in 34 cases (59.6%) by chemotherapy, if indicated. All patients underwent conservative surgery with axillary lymph nodes dissection in vast majority of them. In 5 patients (8.8%) sentinel node biopsies (SNB) were performed. Detailed clinical and pathological data are listed in Table 1. All except 3 patients were treated with hypofractionated regimens of EBRT. Equivalent total doses normalized to 2 Gy per daily fraction were similar, ranging from 46 to 50 Gy (Table 2). Patients were irradiated according to a 3D conformal technique conventionally delivered in opposed tangential fields with photon energy of 6 MV.

All 57 patients were administered 10 Gy single fraction boost with radioactive source of ^{191}Ir (remote afterloader microSelectron HDR, Nucletron BV, Veenendaal, the Netherlands). The method of implantation (multi-catheter technique) and treatment planning are described in details elsewhere.[24] 32 patients (56.1%) were selected for interstitial MW hyperthermia preceding brachytherapy boost. Selection was not randomized and based on clinical performance of the patients and their informed consent. Final decisions to add hyperthermia had been made after implantation of elastic tubes into the breast gland. Patients with sufficiently large breasts, in which minimal skin-to-skin interstitial applicator distances were found to be at least 6–7 cm. It was done in order to avoid unintended heating of the skin (risk of blisters) as active length of interstitial MW antennas is about 4.5 cm. Such approach leads to skin sparing and eliminates pain complaints during a HT session. Details concerning treated locations (quadrants) are listed in Table 2.

Each HT session was planned to last about 90 min, including preparation and insertion of antennas and thermometers into the tubes. Proper catheters were selected to be implanted with active MW antennas or thermometers after the assessment of post-implant CT scans to appropriately cover tumor bed with intended pattern of isotherms. Hypothetical ideal temperature distribution within heated volume is presented in Fig. 1. Prescribed reference temperature was 43 °C. Intended therapeutic time (TT, the time with temperature maintained above 40 °C) was 1 h and the time interval between the termination of heating and the start of HDR irradiation was as short as reasonably possible.

The median follow-up for all patients was 40 months (range 1–49 months). Patients were investigated (clinical examination, blood samples, photo documentation) every 3 months in the first 2 years after the treatment and every 6 months in the following years. First mammography (for monitoring of local relapse, necrosis and/or fibrosis) was scheduled 6–12 months after the completion of treatment and then annually. Special attention of the study was paid to early toxicity of the treatment. Incidence of late toxicity and cosmetic results are to be reported in the future after substantially longer follow-up. Presence, severity and duration of radiodermatitis, skin oedema and erythema after completed treatment were assessed (individual impact of surgery on the presence and severity of oedema was not specifically analyzed). The key point of the paper is to assess the difference between the incidence of symptoms listed above in the group of patients treated with a standard BT boost and that in the group with additional thermal boost. Mann–Whitney *U*-test was used to evaluate the differences between the groups. The Kaplan–Meier method was used to calculate the actuarial rates and patterns of healing in symptomatic patients with breast oedema. A p-value of ≤ 0.05 was considered statistically significant.

4. Results

56 patients were included in the calculations as one patient was observed in other institution: 24 patients treated with a standard HDR BT boost (group I) and 32 with additional HT preceding BT (group II). During a median follow-up of 40 months, none of the patients developed local recurrence. 5 patients (8.9%) developed distant metastases: 2 and 3 in groups I and II, respectively (Table 3). All patients were alive at the time of analysis.

The most frequent location of thermal boost was upper lateral quadrant. HT was prescribed only once in case of a tumor bed located in the lower medial quadrant (Table 2). There was a noticeable trend in the difference between groups I and II in respect to treated quadrants ($p = 0.064$, Fisher's exact test).

Table 2 – Treatment protocols and treated sites.

BT-HDR boost 10 Gy	All 57 patients (100%)
HT T_{ref} 43 °C/60 min	32 (56.1%)
EBRT	
50 Gy/#2 Gy [EQD2 50.0 Gy]	3 (5.3%)
45 Gy/#2.25 Gy [EQD2 46.9 Gy]	19 (33.3%)
42,5 Gy/#2.5 Gy [EQD2 46.0 Gy]	35 (61.4%)
Chemotherapy	
Yes	34 (59.6%)
No	23 (40.4%)

	All	BT-HDR + HT	BT-HDR alone
Tumor location (breast)			
Right	27 (47.4%)	12 (21.1%)	15 (26.3%)
Left	30 (52.6%)	20 (35.1%)	10 (17.5%)
Tumor location (quadrant)			
ULQ	29 (50.9%)	18 (31.6%)	11 (19.3%)
UMQ	6 (10.5%)	5 (8.8%)	1 (1.7%)
LLQ	9 (15.8%)	5 (8.8%)	4 (7%)
LMQ	8 (14%)	1 (1.7%)	7 (12.3%)
RA	5 (8.8%)	3 (5.3%)	2 (3.5%)
Total	57 (100%)	32 (56.1%)	25 (43.9%)

Abbreviation: T_{ref} – reference temperature set at 43 °C, ULQ – upper lateral quadrant, UMQ – upper medial quadrant, LLQ – lower lateral quadrant, LMQ – lower medial quadrant, RA – retroareolar.

Median number of interstitial MW antennas used for HT sessions was 3 and median number of thermometers was 3, as well. Median reference temperature reached 42.2 °C and median therapeutic time (TT) was 61.4 min, which enabled the treated volume to be delivered with median 42 min of total thermal dose. Median gap between HT and BT was 30 min (Table 4).

Radiodermatitis occurred in 30 patients, grades I and II in 24 and 6 patients, respectively. Distribution of radiodermatitis amongst groups slightly differed, but the differences were not significant. The incidence and duration of skin oedema was similar in both groups. Similar results were found for the incidence and duration of skin erythema (for details see Table 3). One significant difference in incidence and duration of skin

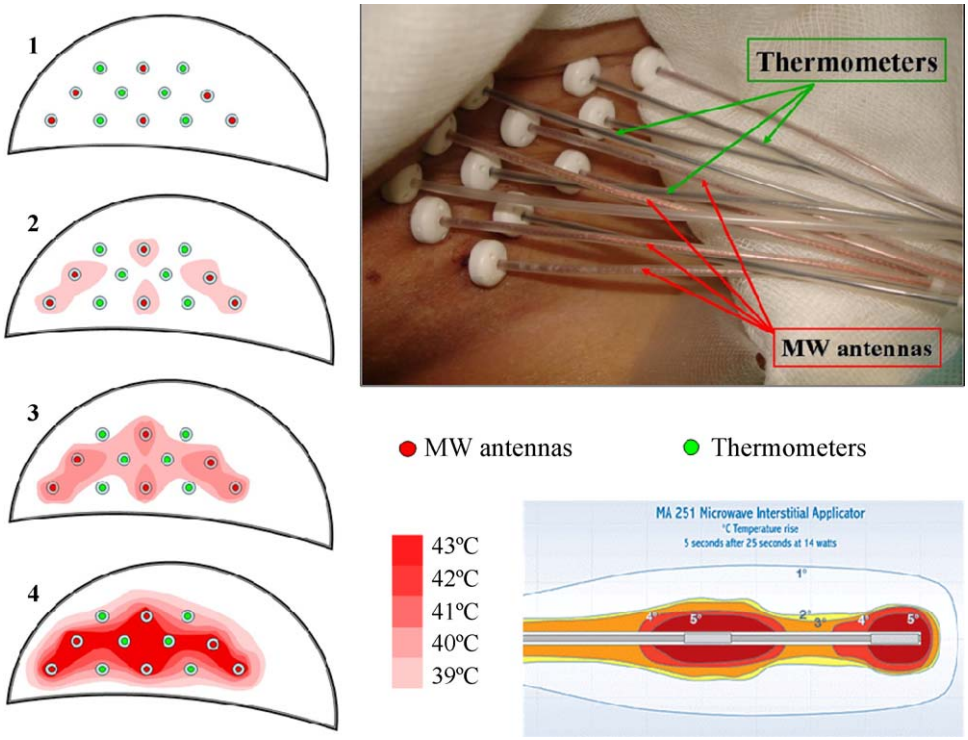

Fig. 1 – Temperature distribution within the tumor bed. Left 1–4: hypothetical "ideal" increase in temperature distribution within the tumor bed during single hyperthermia session. Upper right: a set of microwave (MW) antennas and thermometers inserted into interstitial flexible applicators. Lower right: a schematic distribution of isotherms around the antenna (BSD-500, MW hyperthermia system operating on 915 MHz, BSD Medical).

Table 3 – Observation results, $n = 56$.[a]

	BT alone group I	BT + HT group II	[p]
Radiodermatitis			
Grade 0	13 (54.2%)	13 (40.6%)	0.432 (ns)
Grade I	12 (37.5%)	19 (46.9%)	0.505 (ns)
Grade II	2 (8.3%)	4 (12.5%)	0.676 (ns)
Oedema, yes/no (%)	21/3 (87.5%)	27/5 (84.4%)	0.933 (ns)
Duration, median (range)	4 (1–11) months	4 (1–12) months	0.721 (ns)
Skin erythema yes/no (%)	16/36 (66.7%)	20/32 (62.5%)	0.811 (ns)
Duration, median (range)	1 (0–8) months	1 (0–10) months	
Local control (all, $n = 56$)	100%	100%	ns
Local control (min. 1 year)[b]	100%	100%	ns
Distant metastases	2/24 (8.3%)	3/32 (9.4%)	ns
Follow-up, median (range)		40 (3–49) months	

[a] One patient out of 57 was followed-up only once after one month and was excluded from analysis.
[b] Local control in patients with minimum 1 year long observation, $n = 49/56$ (in first year of follow-up metastases occurred in 3 patients, 4 patients were not observed after the oedema regressed).
Abbreviations: ns – not significant.

Table 4 – Details of delivered hyperthermia sessions.

Treated patients	32/57 (56.1%)
MW antennas; median (range)	3 (0–6)[a]
Interstitial thermometers; median (range)	3 (1–6)[a]
Mean MW energy; median (range)	3,7 (1.4–5.7) Watt
Reference temperature; **mean/median** (range)	**41,6/42,2** (39.2–42.8) °C
Therapeutic TT (≥40 °C); **median** (range)	**61.4** (0–65.3) **min**
Total thermal dose; median (range)	42 (0–60) min
Gap between HT and BT; median (range)	30 (5–60) min

[a] In one patient superficial MW applicator and interstitial thermometers were used.
Abbreviations: MW – microwaves, TT – treatment time, HT – hyperthermia, BT – brachytherapy.

Table 5 – Incidence of oedema due to total dose and fractionation of external beam radiotherapy (EBRT).

Total/fraction dose	42.5/2.5 Gy	45/2.25 Gy	50/2 Gy	[p]
Oedema, yes/no (%)	33/34 (97.1%)	13/19 (68.4%)	2/3 (66.7%)	0.006
HT, yes/no (%)	19/15 (55.9%)	12/7 (63.2%)	0/3 (0.0%)	ns

oedema was revealed for groups with or without concomitant skin erythema. In 34 patients who developed both oedema and erythema, the former lasted significantly longer (median: 5 months) in comparison with a group of 14 patients with solitary oedema (2.5 months), $p = 0.044$. The incidence and duration of skin oedema also differed between the subgroups of patients who had been treated with different fractionation protocols of EBRT. The shorter was the course of radiotherapy and the higher the fraction dose, the more severe and

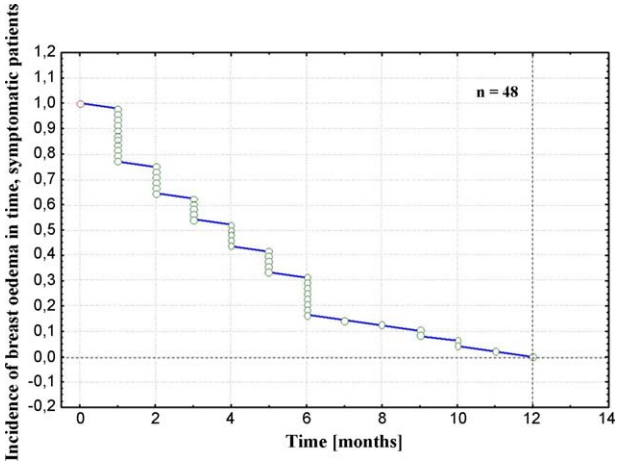

Fig. 2 – Duration of breast oedema in all symptomatic patients, $n = 48$ (both groups).

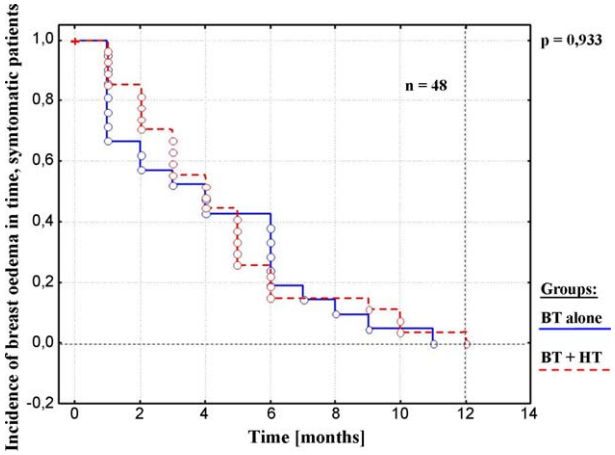

Fig. 3 – Duration of oedema in symptomatic patients ($n = 48$) in groups treated with brachytherapy alone (BT) or with combination with hyperthermia (BT + HT).

longer lasting was the breast oedema, without any influence of additional HT, $p = 0.006$ (Table 5).

Skin oedema itself occurred in 48 cases (85.7%) and persisted up to 12 months. It healed most often (71.4%) during first 6 months of observation (Fig. 2). There was no difference in pattern of oedema regression between groups I and II, $p = 0.933$ (Fig. 3).

5. Discussion

In 2007, Horsman and Overgaard[16] presented a review of pre-clinical rationale for combining HT with radiation and summarized the clinical data showing its efficacy. A meta-analysis of 23 published trials, in which 1861 patients were randomized to thermoradiation or radiation alone, showed a highly significant improvement in locoregional control ($p < 0.0001$). It is relevant for many anatomical sites like the breast and chest wall, cervix, rectum, bladder, melanoma, glioblastoma and head and neck. In case of head and neck and pelvic tumors, 3 studies reported significant improvement also in overall survival.[30–33]

Amongst the above, Vernon et al.[34] presented a large breast study that reported results from five randomized trials which failed to prove benefit in overall survival, but showed a clear improvement in local control when HT had been added to radiation.

It is worth noticing that none of the studies found any significant increase in acute toxicity[31–37] and only one reported a slight increase in late reactions.[32] HT delivered alone or in combination with other cancer treatments is generally well tolerated and, if the temperature does not exceed 44.0 °C, rarely affects normal tissues. Only higher thermal depositions can lead to blistering, burns, pain or necrosis.[8,12] Results of this paper stand in agreement with the above with regard to early toxicity.

As regards breast cancer radiosensitivity, Niedbala et al.[38] presented interesting data concerning response to PDR and LDR with and without mild HT (41 °C) using two human breast carcinoma cell lines: MCF7 (parental wild type) and the variant C716 (more radioresistant over-expressing a DNA repair enzyme polymerase β). The study showed that the PDR and LDR treatment combined with mild HT caused significant radiosensitization when compared to PDR and LDR irradiation alone in terms of the clonogenic and comet assays with both cell lines. This supports the concept of the inhibition of DNA damage repair mechanisms in cells exposed to elevated temperature.

A vast majority of available data concerning HT in breast cancer treatment is focused on unoperable, locally advanced or recurrent malignancies. Hartmann et al.[39] investigated breast conservation rates after preoperative chemotherapy, radiotherapy and hyperthermia in 158 patients with stage IIA–IV breast cancers. Radiation treatment involved an interstitial brachytherapy boost of 10 Gy immediately preceded with a local hyperthermia session (43.5–44.5 °C over 60 min) and a course of external beam radiotherapy of 50 Gy (5×2 Gy weekly). 142/158 patients underwent salvage surgery. In 74 (52%) breast-conserving therapy was possible, in 53 (37%) flap-supported surgery was done. After a median follow-up of 20 months one patient (0.6%) developed isolated local recurrence and in 14 patients locoregional recurrences occurred in combination with distant metastases.

Dooley et al.[12] presented fresh data emerging from their randomized study on externally applied focused microwave thermotherapy (FMT) for preoperative treatment of early-stage invasive breast cancer. Interim results of the study (assessed 75 patients out of 222 planned) are suggestive of a reduction in positive margins in the preoperative thermotherapy plus BCT arm compared with surgery alone (0 vs. 9.8%, $p = 0.13$).

Jones et al.[40] presented a novel therapeutic program for locally advanced breast cancer. 18 patients were given concurrent chemotherapy, HT and radiation followed by mastectomy. Radiation therapy consisted of 50 Gy delivered from external fields and a boost to 60–65 Gy for those not undergoing surgery. HT was administered twice a week and tumor oxygenation was measured. 15/18 patients responded with complete (6) and partial (9) response. 13/18 patients underwent mastectomy with 3 pathological complete responses. As stated in conclusion, HT may offer a strategy for improving tumor oxygenation with consequent treatment response, which may depend on thermal dose. The latter was continued by Jones et al.[41] in a prospective randomized trial of superficial tumors ($\leq$3 cm depth) comparing radiotherapy vs. HT combined with radiotherapy, using the parameter describing the number of cumulative equivalent minutes at 43 °C exceeded by 90% of monitored points within the tumor (CEM 43 °C T_{90}) as a measure of thermal dose, as trials generally lack rigorous thermal dose prescription and administration. 121 patients were enrolled; 109 (89%) were deemed heatable and were randomly assigned. The complete response rate was 66.1% in the HT arm (microwave spiral strip applicators, 433 MHz) and 42.3% in the no-HT arm. Previously irradiated patients had the greatest incremental gain in complete response: 23.5% no-HT arm vs. 68.2% HT arm. No overall survival benefit was seen. They concluded that adjuvant hyperthermia with a thermal dose of more than 10 CEM 43 °C T_{90} confers a significant local control benefit in patients with superficial tumors receiving radiation therapy. CEM 43 °C T_{90} appears to be the most useful dosimetric parameter in clinical research.[1,42,43] RTOG guidelines being in force precisely describe rules of thermometry necessary for CEM calculations and assurance of hyperthermia quality.[8,44]

Ben-Yosef et al.[45] reported a simple and convenient thermoradiation delivery system to treat locally recurrent breast cancer. They treated 15 women with external beam radiotherapy (electrons or photons, total dose 30–40 Gy in previously irradiated fields or 50–70 Gy in non-irradiated fields) followed by at least two hyperthermia sessions to each HT field (45 °C over 45 min started within 10 min after irradiation, no invasive thermometry). As a result, 10/15 patients had complete or partially-infilled response. The only major side effect was ulceration in 3 patients (one healed, one remained and one developed recurrence).

Arunachalam et al.[46] went a step further. Over the years, they designed and improved a novel ThermoBrachytherapy Surface Applicator (TBSA) for combined simultaneous thermobrachytherapy of diffuse chest wall recurrences. MW hyperthermia delivered simultaneously with HDR brachytherapy enables the increase of the thermal enhancement ratio

(TER) of the latter from 1.5 to 2.5 or higher. The method of delivering hyperthermia described in this paper has to be sequentional as the same applicators are used for inserting heating antennas and a stepping source of iridium. This requires the time between hyperthermia session and the start of irradiation to be as short as possible. With proper work flow the time interval can be as short as 5 min.

At this point in time, hyperthermia is being combined with radiation therapy, chemotherapy or radiochemotherapy and, most lately, with gene or immunotherapy.[4,5,7,9–11] Still, all the regimens have a status of scientific research or clinical trials.[8] Despite a strong rationale for combining HT with radiation, HT is still an out-of-routine clinical practice. One of the reasons for that may be the need to have a high quality equipment, which has to be operated by dedicated and well trained personnel,[8,16] HT sessions are obviously time consuming and rarely reimbursed.[45] Some more clinical trials have to be closed and summarized to firmly re-confirm hyperthermia as a standard cancer treatment.

6. Conclusion

Additional thermal boost preceding standard high-dose-rate brachytherapy boost has a potential of further improvement in breast cancer local control in breast conserving therapy. A single session of interstitial hyperthermia before BT boost did not increase early toxicity in patients treated with BCT. Such treatment was feasible and well tolerated. All side effects of combined treatment were transient and healed spontaneously in up to 12 months. The increase in the incidence of skin oedema was related to hypofractionated protocols of external whole breast irradiation. To verify the potential of local control improvement and to assess the profile of late toxicity, the study has to be randomized and continued on a larger group of breast cancer patients.

REFERENCES

1. Dewhirst MW, Gibbs Jr FA, Roemer RB, Samulski TV. Hyperthermia. In: Gunderson LL, Tepper JE, editors. *Clinical radiation oncology*. 1st ed. New York, NY: Churchill Livingstone; 2000. p. 256–82 [chapter 14].
2. Dębicki P. Hipertermia mikrofalowa w leczeniu gruczołu krokowego. Problemy fizyczne i techniczne. 1st ed. Wydawnictwo Politechniki Gdańskiej; 1999.
3. Glossary. Int J Hyperthermia 2003;19(3):385–90.
4. Sneed PK, Stauffer PR, Li GC, Stege GJJ. Hyperthermia. In: Leibel SA, Phillips TL, editors. *Textbook of radiation oncology*. 2nd ed. Saunders; 2004. p. 1569–96 [chapter 70].
5. Wust P, Hildebrandt B, Sreenivasa G, et al. Hyperthermia in combined treatment of cancer. *Lancet Oncol* 2002;**3**:487–97.
6. Falk MH, Issels RD. Hyperthermia in oncology. *Int J Hyperthermia* 2001;**17**(1):1–18.
7. Overgaard J, Horsman MR. Hyperthermia. In: Steel GG, editor. *Basic clinical radiobiology*. 2nd ed. Edward Arnold; 1997. p. 212–21.
8. Chicheł A, Skowronek J, Kubaszewska M, et al. Hyperthermia – description of a method and a review of clinical applications. *Rep Pract Oncol Radiother* 2007;**12**(5):267–75.
9. van der Zee J. Heating the patient: a promising approach? *Ann Oncol* 2002;**13**:1173–84.
10. Jones EL, Samulski TV, Vujaskovic Z, Prosnitz LR, Dewhrist MW. Hyperthermia. In: Perez CA, Brady LW, Halperin EC, Schmidt-Ullrich RK, editors. *Principles and practise of radiation oncology*. 4th ed. Lippincott Williams & Wilkins; 2004. p. 699–735 [chapter 24].
11. Kapp DS, Hahn GM, Carlson RW. Principles of hyperthermia. In: Bast Jr RC, Kufe DW, Pollock RE, et al, editors. *Cancer medicine e*. 5. 5th ed. Hamilton, Ontario: B.C. Decker Inc.; 2000.
12. Dooley WC, Vargas HI, Fenn AJ, et al. Focused microwave thermotherapy for preoperative treatment of invasive breast cancer: a review of clinical studies. *Ann Surg Oncol* 2010;**17**:1076–93.
13. Asea A, Kraeft SK, Kurt-Jones EA, et al. HSP70 stimulates cytokine production through a CD 14-dependent pathway, demonstrating its dual role as chaperone and cytokine. *Nat Med* 2000;**6**:435–42.
14. Repasky E, Issels R. Introduction: physiological consequences of hyperthermia: heat, heat shock proteins and the immune response. *Int J Hyperthermia* 2002;**18**(6):486–9.
15. Li GC, Mivechi NF, Wietzel G. Heat shock proteins, thermotolerance and their relevance to clinical hyperthermia. *Int J Hyperthermia* 1995;**11**:459–88.
16. Horsman MR, Overgaard J. Hyperthermia: a potent enhancer of radiotherapy. *Clin Oncol* 2007;**19**:418–26.
17. Horsman MR, Overgaard J. Overcoming tumor resistance resulting from hypoxia. In: Steel GG, editor. *Basic clinical radiobiology for radiation oncologists*. 3rd ed. London: Edward Arnold; 2002. p. 169–81.
18. Roti Roti JL, Introduction:. Radiosensitization by hyperthermia. *Int J Hyperthermia* 2004;**20**(2):109–14.
19. Hildebrandt B, Wust P, Ahlers O, et al. The cellular and molecular basis of hyperthermia. *Crit Rev Oncol Hematol* 2002;**43**:33–56.
20. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;**347**:1233–341.
21. Veronesi U, Cacinelli N, Mariani L, et al. Twenty-year follow-up of a randomized trial comparing breast conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;**347**:1227–32.
22. Bartelink H, Horiot JC, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med* 2001;**345**:1378–87.
23. Hammer J, Mazeron JJ, van Limbergen E. Breast boost – why, how, when? *Strahlenther Onkol* 2001;**177**:33–6.
24. Kubaszewska M, Dymnicka M, Skowronek J, et al. CT-image based conformal high-dose-rate brachytherapy boost in the conservative treatment of stage I–II breast cancer – introducing the procedure. *Rep Pract Oncol Radiother* 2008;**13**(5):227–39.
25. Polgár C, Major T. Current status and perspectives of brachytherapy for breast cancer. *Int J Clin Oncol* 2009;**14**: 7–24.
26. Polgár C, Jnvry L, Major T, et al. The role of high-dose-rate brachytherapy boost in breast-conserving therapy: long-term results of the Hungarian National Institute of Oncology. *Rep Pract Oncol Radiother* 2010;**15**(1):1–7.
27. Polgár C, Fodor J, Orosz Z, et al. Electron and brachytherapy boost in the conservative treatment of stage I–II breast cancer: 5-year results of the randomized Budapest boost trial. *Radiother Oncol* 2002;**62**(Suppl. 1):S15.
28. Bartelink H, Horiot JC, Poortmans P, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year

results of the randomized boost vs. no boost EORTC 22881-10882 trial. *J Clin Oncol* 2007;**25**:3259–65.
29. Romestaing P, Lehingue Y, Carrie C, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol* 1997;**15**:963–8.
30. Sneed PK, Stauffer PR, McDermott MW, et al. Survival benefit of hyperthermia in prospective randomized trial of brachytherapy boost (hyperthermia for glioblastoma multiforme). *Int J Radiat Oncol Biol Phys* 1998;**40**:287–95.
31. Datta NR, Bose AK, Kapoor HK, et al. Head and neck cancers: results of thermoradiotherapy versus radiotherapy. *Int J Hyperthermia* 1990;**6**:479–86.
32. Valdagni R, Amichetti M. Report of long-term follow-up in a randomized trial comparing radiation therapy and radiation therapy plus hyperthermia to metastatic lymphnodes in stage IV head and neck patients. *Int J Radiat Oncol Biol Phys* 1993;**28**:163–8.
33. González González D, van Rhoon GC, et al. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective, randomised, multicentre trial. *Lancet* 2000;**355**:1119–25.
34. Vernon CC, Hand JW, Field SB, et al. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. *Int J Radiat Oncol Biol Phys* 1996;**35**:731–44.
35. Emami B, Scott C, Perez CA, et al. Phase III study of interstitial thermoradiotherapy compared with interstitial radiotherapy alone in the treatment of recurrent or persistent human tumors: a prospectively controlled randomized study by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1996;**34**:1097–104.
36. Harima Y, Nagata K, Harima K, et al. A randomized clinical trial of radiation therapy versus thermoradiotherapy in stage IIIB cervical carcinoma. *Int J Hyperthermia* 2001;**17**:97–105.
37. Overgaard J, González González D, Hulshof MC, et al. Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma. *Lancet* 1995;**345**:540–3.
38. Niedbala M, McNamee JP, Raaphorst GP. Response to pulsed dose rate and low dose rate irradiation with and without mild hyperthermia using human breast carcinoma cell lines. *Int J Hyperthermia* 2006;**22**(1):61–75.
39. Hartmann KA, Audretsch W, Carl UM, et al. Peroperative irradiation and interstitial radiotherapy-hyperthermia boost in breast tumors > or =3 cm. The Düsseldorf experience. *Strahlenther Onkol* 1997;**173**(10):519–23.
40. Jones EL, Prosnitz LR, Dewhirst MW, et al. Thermochemoradiotherapy improves oxygenation in locally advanced breast cancer. *Clin Cancer Res* 2004;**1**(10): 4287–93.
41. Jones EL, Oleson JR, Prosnitz LR, et al. Randomized trial of hyperthermia and radiation for superficial tumors. *J Clin Oncol* 2005;**23**(13):3079–85.
42. Sapareto SA, Dewey WC. Thermal dose determination in cancer therapy. *Int J Radiat Oncol Biol Phys* 1984;**10**:787–800.
43. Oleson JR, Samulski TV, Leopold KA, et al. Sensivity of hyperthermia trial outcomes to temperature and time: implications for thermal goals of treatment. *Int J Radiat Oncol Biol Phys* 1993;**25**:289–97.
44. Dewhirst M, Phillips TL, Samulski TV, et al. RTOG quality assurance guidelines for clinical trials using hyperthermia. *Int J Radiat Oncol Biol Phys* 1990;**18**:1249–59.
45. Ben-Yosef R, Vigler N, Inbar M, et al. Hyperthermia combined with radiation therapy in the treatment od local recurrent breast cancer. *IMAJ* 2004;**6**:392–5.
46. Arunachalam K, Maccarini PF, Craciunescu OI, et al. Thermal characteristics of ThermoBrachytherapy Surface Applicators (TBSA) for treating chestwall recurrence. *Phys Med Biol* 2010;**55**(7):1949–69.