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Review Article

Effective Tumor Control Following Re-Irradiation Combined with Superficial Hyperthermia of Inoperable, Locally Recurrent Breast Cancers

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Summary

Inoperable, locally Recurrent Breast Cancer (LRBC) in previously irradiated regions is a challenging disease to manage. Superficial Hyperthermia (sHT) in combination with Re-Irradiation (re-RT) offers an effective local tumor control with a total re-RT dose of 20 Gy. The low toxicity enables the application of repeated re-irradiations, especially in recurrent lymphangiosis carcinomatosa. This technology can also be applied with other superficial tumor types, e.g., in primary or radiation-associated angiosarcoma or skin metastasis.

1. Background

Breast cancer patients presenting with inoperable, locally recurrent tumors suffer from extreme psychological and physiological stress. This stress is exacerbated by the appearance of the disease as well

as by any symptoms associated with the extension of the disease such as pain, ulceration, bleeding, constriction and shortness of breath (cancer en cuirasse), lymph edema and unpleasant odor. The need for therapeutic intervention for these patients is high, but therapeutic options for recurrences in previously irradiated regions are very limited. An additional re-irradiation with effective dosage is often contra-indicated and is related to a high risk of severe side effects. Frequently, these heavily pretreated regions are resistant to systemic therapies, and the potential benefit of these therapies must then be weighed against possible side effects. Oftentimes, the goal of effective local tumor control is then abandoned.

1.1 Hyperthermia and radiation therapy

The combination of Radiotherapy (RT) with sHT provides an evidence based, effective therapeutic option for these patients. Mild Hyperthermia (HT) with tissue temperatures between 39-43°C is an efficient radio-sensitizer and can enhance antitumor immune responses. This combination provides the opportunity to significantly reduce the radiation doses and consequently, radiation toxicity. This effect is mainly achieved by (a) increased tumor perfusion, (b) improved tissue oxygenation, (c) inhibition of DNA-repair and by (d) fostering immunological effects. Therefore, HT is indicated specifically in previously irradiated target volumes, where unfavorable, hypoxic conditions are commonly present. A meta-analysis; published in 2016, demonstrated the efficiency of the combined sHT/re-RT protocol with regards to LRBC [1]. The application of this treatment scheme is no longer considered an "outsider method" and should be utilized in cases with limited therapeutic options. Bearing this in mind, it is important then that physicians and patients know that this treatment is a viable option for LRBC.

1.2 Improved technical methods

A novel technical method using thermography-controlled water-filtered infrared-A superficial hyperthermia (wIRA-sHT) provides a contact-free application of energy to large surfaces with heterogeneous body contours [2]. The heating of the surface is automatically limited to 43°C, and thus the risk of burns and blistering in scars or skin transplants is practically eliminated.

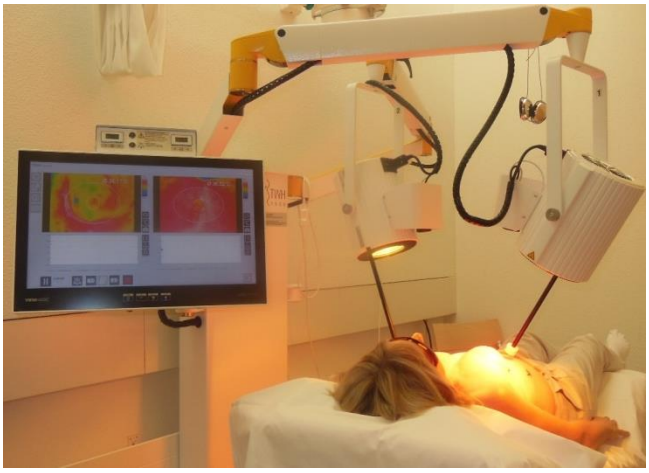

Figure 1: Therapeutic setting of water-filtered infrared-A superficial hyperthermia (hydrosun®TWH1500, Hydrosun Medizintechnik, Muellheim, Germany) in a bilateral chest wall recurrence of a breast cancer patient.

As a well-tolerated treatment protocol we recommend the following procedure: weekly wIRA-sHT for 45 – 60 min, immediately followed by re-RT. Single irradiation dose is 4 Gy, with a total dose of 20 Gy, 1x/week [3]. This treatment allows for an outpatient setting.

2. Results

A retrospective analysis of 201 patients with inoperable, previously irradiated LRBC treated with the aforementioned protocol was published in 2020 [4]. The size of local recurrences was recognized as one of the most important prognostic factors. Therefore, a novel size classification was proposed and the treatment results were related to the tumor extensions. Response rates were as follows: in Class I (largest diameter ≤ 10 cm): CR (complete remission) = 76%, PR (partial remission) = 24%; in Class II (>100 cm^2, but limited to the ipsilateral chest wall): CR = 61%, PR = 36%, NC (no change) = 3%; in Class III (extension beyond ipsilateral chest wall): CR = 36%, PR = 61%, PD (progressive disease) = 2%; and in Class IV (extension from both chest wall to the back, classical "cancer en cuirasse"): CR 2%, PR 83%, NC 10%, PD 5%. The overall response rate for the patients in this analysis was 95%, which means that only a small percentage did not report any clinical benefit. In 2/3 of the patients with CR, the local control could be maintained and in more than half of the patients with PR, a local progression free situation could be achieved during life time. However, this is despite above-average previous radiation doses and tumor extensions, in comparison to other studies. In addition, the re-RT dose used was the lowest one ever reported in the literature (see Table 1).

Authors & year	n	HT technique used	Total RT-dose (Gy)	CR	HT related toxicity ≥ G2
a. Randomized trials					
Vernon et al. [5]	56	100 – 1000 MHz	32	38 % (RT) 78% (HT-RT)	23%
Jones et al. [6]	39	434 MHz	30 – 66	24 % (RT) 68% (HT-RT)	21%
b. Non-randomized trials / retrospective analyses					
Oldenborg et al. [7]	414	434 MHz	32 (20 – 40)	58%	13%
Linthorst et al. [8]	248	434 MHz	32	70%	23%
Bakker et al. [9]	262	434 MHz	32	n.r.	26%
Notter et al. [4]	201	wIRA	20	43% (2-76%)*	0.5%

Table 1: Results of combined superficial hyperthermia & re-irradiation in locally recurrent breast cancer. n = number of patients treated, HT = hyperthermia, RT = radiotherapy, MHz = (megahertz, microwave technique),

wIRA = water-filtered infrared-A, CR = complete remission, n.r. = not reported, * remission according to size classes of macroscopic disease.

2.1. Side effects

The reported side effects of this treatment protocol were very low with 114 (57%) of the 201 patients presenting with no acute side effects at all, 65 (33%) with acute skin reactions grade I, and 4 (2%) with acute skin reactions grade II. Chronic reactions like hyperpigmentation grade I (26%) and new teleangiectasias grade II (3%) were observed in 56 patients. This low toxicity allows physicians to use this treatment scheme multiple times, even several times in the same formerly treated region. This could be advantageous for the management of lymphangiosis carcinomatosa (involvement of lymphatic drainage system of the skin by cancer cells) with the tendency to recur again and again.

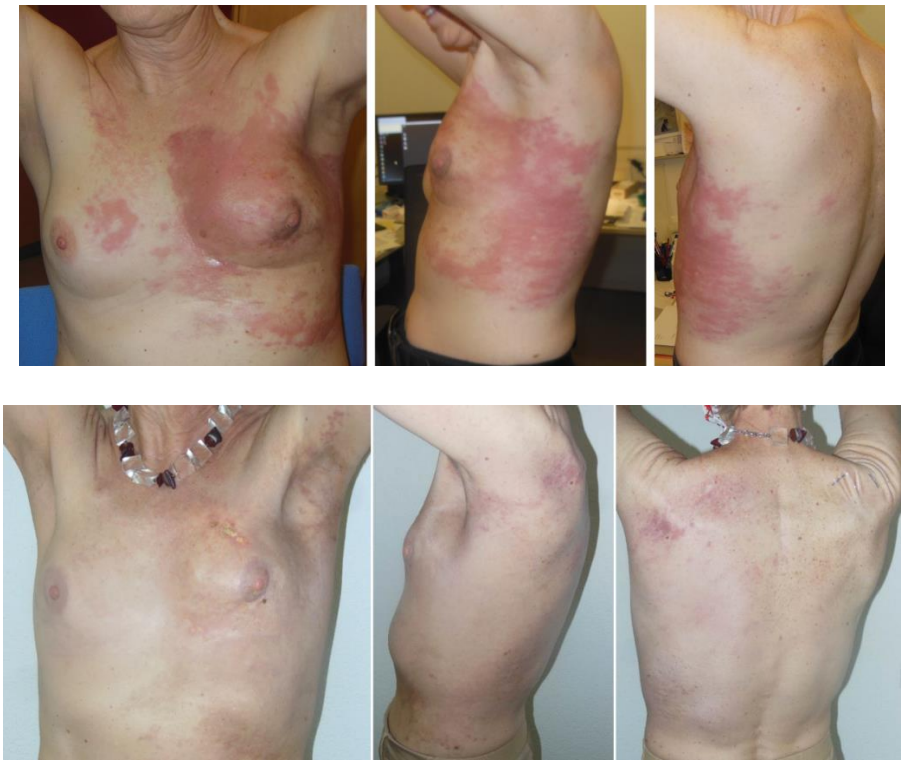

Figure 2: Upper panel: Cancer en cuirasse before combined treatment (January 14, 2020). Lower panel: Result 4 ½ weeks after completion of combined treatment of anterior and left lateral chest wall, back and supraclavicular fossa, each region with 5 x 4 Gy 1x/week and wIRA-sHT (June 24, 2020).

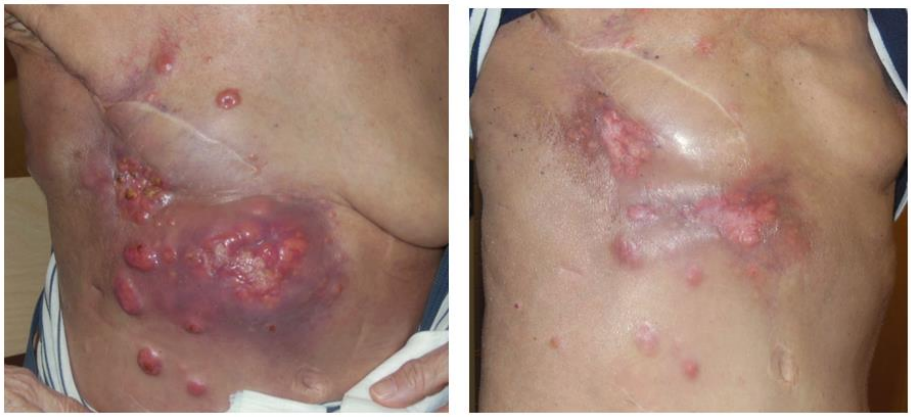

Figure 3: Locally recurrent breast cancer. Left panel: before combined treatment (March 1, 2017). Right panel: 6 weeks after 5 x 4 Gy 1x/week and wIRA-sHT. Distinct regression and relief of pain (July 5, 2017)

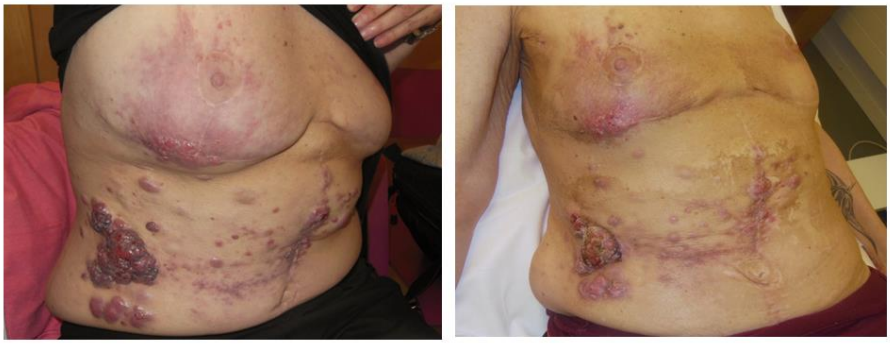

Figure 4: Metastatic lesions of an advanced ovarian cancer within the abdominal wall, skin metastases and extension to the right breast. Resistance to different attempts with chemotherapy. Left panel: before combined treatment (October 22, 2019). Right panel: 4 weeks after 5 x 4 Gy 1x/week and wIRA-sHT: distinct relief of pain, drying of the ulcerating lesions, higher comfort and reduced unpleasant odor. Good palliative effect (January 7, 2020)

3. Outlook

Comparative confirmatory phase III trials comparing sHT/re-RT versus best supportive care (without tumor-directed therapy) are not feasible for LRBC due to patient related factors and ethical considerations [10]. Patients with heavily pre-treated recurrences may refuse randomization, may also insist on the immediate start of treatment with the intention of effective local tumor control or distinct relief of symptoms. Comparative studies with sHT/re-RT with reduced doses versus re-RT alone using conventional

doses would either exclude or compromise those patients who are at risk of unacceptable cumulative toxicity. Moreover, the highly individual differences in lesions sizes, type and number of pre-treatments, resistances to other therapies, comorbidities etc. impede randomization into comparable groups. It is stated, that sHT immediately followed by low dose re-RT is an acceptable treatment protocol for therapeutic consideration [11]. Patients with

microscopic disease after resection of a LRBC with R1 margins (non-radical operation) or with a high risk of local recurrence due to limited resection margins, also profit from the combined sHT-re-RT [4,12]. The presented treatment schedule can also be used to treat other superficial tumor entities, e.g., primary skin cancer (melanoma and non-melanoma tumors), Merkel-cell carcinoma, cutaneous lymphomas, skin metastasis, primary or radiation-associated angiosarcomas etc. The latter of the tumor entities, is a rare disease that has also been proven to have a clinical benefit following a sHT/re-RT treatment scheme [13].

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