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Fast Neutron Therapy for Breast Cancer Treatment: An Effective Technique Sinking into Oblivion

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Introduction

Adjuvant radiation therapy significantly decreases breast cancer mortality [1, 2], but first-generation techniques, which relied on large irradiation fields, were associated with an increased cardiotoxicity risk. Fortunately, breast radiotherapy has evolved, and state-of-the-art radiation therapy techniques are currently able to efficiently limit heart exposure without altering tumor control, even in complex anatomic situations. In this context, particle radiation therapy is of particular interest: depth-dose curves of proton and carbon ion beams sharply increase when those particles come to rest. This physical feature, known as the Bragg peak, can be efficiently used to limit radiation doses delivered to organs at risk.

However, among the particle radiotherapy techniques evaluated to date for breast cancer treatment, fast neutron therapy (FNT) currently seems to be sinking into oblivion, despite promising clinical data. Although $>$ 35 000 patients have been treated with FNT for half a century, only a few FNT facilities are still operating worldwide (in the United States, Germany, and Russia). However, neutrons have specific radiobiologic advantages that deserve consideration. Their linear energy transfer is about 200 times greater than that of photon beams [3, 4], ranging somewhere between 20 and 100 keV/μm, and the relative biologic effectiveness (RBE) of fast neutron beams is estimated to be between 3.0 and 8.0. Lethal DNA breaks are consequently rapidly caused for a short distance, which is of particular interest when treating superficial tumors, such as chest-wall recurrences. Finally, the oxygen enhancement ratio of FNT is evaluated to be around 1.3 [3], and this minimal sensitivity to hypoxic conditions [5] may be valuable when irradiating unresectable breast tumors, which are often characterized by significant areas of hypoxic tissues [6].

Clinical data of fast neutron therapy for breast cancer treatment

The FNT experience for breast cancer treatment relies on retrospective studies and on prospective phase I and comparative phase II trials, which included around 700 patients worldwide. Interestingly, more than two-thirds of those patients were treated in Russia. For clarity, the main clinical data from those studies are summarized in the **Table**. Unfortunately, most comparative, prospective trials were nonrandomized, which limits comparison with other breast radiotherapy techniques.

The first breast FNT trials began in the 1970s, with FNT used as a single-treatment modality for locally advanced, unresectable tumors. The technical feasibility of breast FNT was first demonstrated by Halpern et al [7], who experimented with this technique between 1972 and 1978 in 28 patients with inoperable, locally advanced breast tumors; one-half of those patients had inflammatory tumors. Planned target volumes consisted of

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Editorial

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Table. Fast neutron therapy trials for breast cancer (primary tumors and chest wall recurrences).

Author/Year	Type of Study	Treatment	Tumor characteristics	OS	LC/DFS/RFS	Toxicity
Catterall 1987 *[8]* **(Hammersmith)**	Retrospective 17 pts	7.5 MeV neutrons	**Primary BC** T4 : 17 pts	2.2 y	CR : 16 pts	Ulceration Gr. 3-4 : 3 pts Fibrosis : 17 pts
Halpern 1990 *[7]* **(MD Anderson)**	Retrospective 28 pts	Breast 16 MeV neutrons (22.6 nGy) : 3 pts 50 MeV neutrons (22.1 nGy) : 12 pts 50 Mev neutrons (9.34 nGy) + photons : 9 pts Axilla 50 MeV neutrons (17.2-25.0 nGy) : 4 pts 50 MeV neutrons (4.77-10.0 nGy) + photons : 8 pts	**Primary BC** T4d : 14 pts N+ : 23 pts	3.6 y	CR : 9 pts PR : 18 pts	Ulceration Gr. 3-4 : 5 pts Edema Gr. 3 : 4 pts Brachial plexopathy : 6 pts
Murray 2005 *[9]* **(Cap Town)**	Comparative phase I/II 27 pts	A : 27 MeV neutrons (16 nGy) : 16 pts B : Photons (60 Gy) : 11 pts	**Primary BC** N+ : 16 pts M+ : 10 pts	A : 1.8 y B : 1.1 y *(NS)*	CR A : 3 pts B: 4 pts PR A : 3 pts B: 2 pts	Gr. 3 : A : 5 pts B: 5 pts Gr. 4: A : 1 pts B: 2 pts
Specht 2015 *[3]* **(Munich)**	Retrospective 46 pts	<12 mo. recurrence : neutrons (10 nGy) >12 mo. recurrence : electrons (30Gy) + neutrons (6 nGy)	**Chest wall recurences**	*NA*	CR : 68% PR : 29% 3-y LC : 55%	No Gr. 3-4
Ragulin 2015 *[10]* **(Obninsk)**	Comparative phase II 201 pts	A : 1 MeV neutrons (2-3 nGy) + photons (to 60 GyEBR) : 95 pts B : Photons (60 Gy) : 106 pts	**Primary BC** T4 : 157 pts N+ : 194 pts	10-y OS (p<0.02) : A : 32.8% B : 17,1%	CR (p<0.001) : A : 28.4 % B : 0.9 % 10-y DFS (p<0.02) : A : 29.5% B : 4.4%	Ulceration Gr. 3-4 : A : 1 pt B : 1 pt
Startseva 2015 *[11]* **(Tomsk)**	Comparative phase II 246 pts	neoadjuvant chemotherapy (CMF/FAC) Pre-operative loco-regional radiation therapy : A : 6.3 MeV neutrons (7.2 nGy, breast) ± lymph node photon RT (if N+) : 108 pts B : photons (hyperfractionated, 35-40 Gy) : 40 pts C : photons (normofractionated, 40-44 Gy) : 38 pts D : no RT : 83 pts Mastectomy ± hormonotherapy	**Primary BC** (T2-4 N0-2 M0)	10-y OS (p<0.05) : A : 70,8% B : 42,4% C : 54,2% D : 40,6%	Local recurrence (p<0.05) : A : 2.0% B : 15.0%% C : 23.7% D : 31.3%	No Gr. 3-4
Velikaya 2016 *[12]* **(Tomsk)**	Comparative phase II 227 pts	Locally recurrent BC : 114 pts A : 6.3 MeV neutrons (30-40 Gy EBR) : 26 pts or 6.3 MeV neutrons + photons (50-60 Gy EBR) : 44 pts B : photons (60 Gy) : 44 pts Locally advanced BC : 113 pts Neoadjuvant/adjuvant chemotherapy (CMF/FAC) Mastectomy ± hormonotherapy Post-operative locoregional radiation therapy : C : 6.3 MeV neutrons (16.7-29.9 Gy EBR) : 65 pts D : electrons (38-44 Gy) : 48 pts	**Chest wall recurences** *or* **Primary BC** (T2-4 N0-3 M0-1)	Chest wall recurences 8-y OS (p<0.01) : A : 87.6% B : 54.3% Locally advanced BC 7-y OS (p<0.01) C : 85.4% D : 43.3%	Chest wall recurences Re-recurrence (p<0,05) A : 4% B : 39% Locally advanced BC 7-y RFS (p=0.04) C : 93.4% D : 77.5%	Chest wall recurences Lung fibrosis : 14 pts (Gr. 3: 1 pt) Skin toxicity : 16 pts Locally advanced BC Lung fibrosis : 4 pts (no Gr. 3) Skin toxicity : 3 pts

Abbreviations: OS: overall survival; LC: local control; DFS: disease-free survival; RFS: relapse-free survival; nGY, nanogray; pt, patient; CR, complete response; PR, partial response; BC: breast cancer; NS, not significant; NA, not applicable; RT, radiotherapy; EBR, external beam radiation; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; FAC, 5-fluorouracil, doxorubicin, cyclophosphamide.

the whole breast, irradiated with tangential fields and the axilla lymph node area [7]. That first study provided evidence of a high local control rate: 96% of the patients experienced partial or complete response. Unfortunately, the RBE had been underestimated during FNT treatment planning, and some irradiation fields overlapped, which resulted in major adverse events: overall, there were 5 necrotic skin ulcers (18%; 4 patients [14%] had to receive skin grafts) and 6 brachial plexopathies (21%). Therefore, subsequent breast FNT trials tried to reduce the total neutron dose delivered to the planned target volume. This pragmatic attitude did not, however, alter tumor control. Catterall et al [8] used lower neutron doses in 17 patients with 20

tumors, who presented with locally advanced, unresectable, ulcerated breast cancer, and obtained an excellent control rate of 95% (n = 19 tumors) with complete responses and fewer skin toxicities. Finally, at the end of the 20th century, because of further technical progresses and a better understanding of fast neutron radiobiology, breast FNT became comparable to photon radiotherapy, in term of skin toxicity. A randomized controlled trial [9] conducted between 1996 and 1999 in South Africa compared FNT with photon radiotherapy in 27 patients with inoperable, locally advanced or metastatic breast cancer: no increased toxicity risk was observed. Unfortunately, that trial was closed prematurely because of recruitment issues, and it consequently lacked the power to provide evidence for any clinical benefit of FNT over photon radiotherapy. Recently, Ragulin et al [10] conducted a phase II trial in Russia, which included 201 patients, comparing mixed photon-FNT radiotherapy with photon radiotherapy for inoperable, locally advanced breast cancer, mostly $T4N^{+}$ tumors. That trial showed a significant increase of 10-year overall survival (OS) and 10-year disease-free survival (DFS) in the photon-FNT group (10-y OS, 32.8% versus 17.1%, $P < .02$; 10-y DFS, 29.5% versus 4.4%, $P < .02$), whereas the toxicity profiles were strictly comparable between each group.

Naturally, considering FNT as a single modality for breast cancer management would hardly be conceivable currently; multidisciplinary approaches combining recent chemotherapy protocols, surgical procedures, and modern radiotherapy techniques have become established practice. The most recent breast FNT trials have thus evaluated FNT in a multimodality approach. Startseva et al [11] conducted a large phase II trial, which included 246 patients, comparing preoperative FNT with photon radiotherapy, after neoadjuvant chemotherapy and before radical mastectomy. All patients included had locally advanced breast cancers with pejorative prognostic factors, such as resistance to neoadjuvant chemotherapy or multicentricity [11]. In that study, the preoperative FNT group had a significantly greater 10-year OS (70.8% versus 54.2%, $P < .05$) and a significantly lower local recurrence rate (2.0% versus 23.7%, $P < .05$). Toxicity profiles were comparable, and no grade 3 or 4 toxicity was observed. In the adjuvant setting, postmastectomy FNT was similarly compared with photon radiotherapy [12] in a phase II trial, which included 113 patients diagnosed with locally advanced breast tumors and multiple pejorative prognostic factors, after chemotherapy and radical mastectomy: 7-year OS and 7-year relapse-free survival (RFS) rates appeared substantially higher in the FNT group (7-y OS, 85.4% versus 43.3%, $P < .01$; 7-y RFS, 93.4% versus 77.5%, $P = .04$). However, even if no grade 3 toxicity was reported in the FNT group, 4 patients (3.5%) developed grade 2 lung fibroses.

Finally, FNT has been efficiently used for chest wall recurrence irradiation. Between 1985 and 2013, Specht et al [3] evaluated FNT clinical efficacy in 46 patients in Munich with chest wall recurrences; 68% of those patients exhibited a complete response, and 3-year local control was 55%. No grade 3 or 4 events were reported. In a larger phase II trial, Velikaya et al [12] compared FNT with electron radiotherapy in 114 chest wall recurrences. It appeared in this study that FNT was associated with a significantly better clinical outcome: 8-year OS was in favor of FNT (87.6% versus 54.3%, $P < .02$) and the rerecurrence rate was also significantly lower in the FNT group (4% versus 39%, $P < .05$). However, one grade 3 lung fibrosis was reported in the FNT group.

Discussion

Major skin complications, which characterized the first breast FNT trials and which were the most feared complications, are no longer current in the era of modern FNT. Consequently, FNT could potentially have a place in the multidisciplinary management of complex breast cancer situations. Although FNT is probably of limited value in most classic clinical situations, it did, however, demonstrate its clinical value for the treatment of refractory chest wall recurrences or unresectable advanced breast tumors with pejorative prognostic factors in a multimodal approach.

Nowadays, reirradiation of unresectable chest wall recurrence in previously irradiated regions may be one of the most interesting applications of FNT because therapeutic options are relatively limited in this context. In this situation, FNT is associated with an excellent local control rate, and it seems to be better tolerated than most other recently evaluated treatments, such as the hyperthermia-radiotherapy combination [13] or brachytherapy [14].

Soon, FNT is expected to become more conformal and substantially safer because of the ongoing development in intensity-modulated neutron therapy [15]. However, lack of funding might be a nonnegligible pitfall for the therapy.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no conflicts of interest to disclose.

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