

Post-mastectomy radiotherapy after neoadjuvant chemotherapy in breast cancer patients: A review

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Contents

1. Introduction	180
2. Background	181
2.1. Neoadjuvant chemotherapy and mastectomy: a “jungle” of risk factors	181
2.2. What happens in the absence of PMRT?	182
2.3. Impact of pathological complete response on the final treatment outcome	184
2.4. A distinct entity: inflammatory breast cancer (IBC)	185
2.5. Post-NAC PMRT to breast peripheral lymphatics: when and what to irradiate?	185
3. Discussion	186
4. Conclusions	187
Conflict of interest	188
Reviewers	188
References	188

Abstract

Neoadjuvant chemotherapy followed by surgery is nowadays used in a significant number of patients presenting with locally advanced breast cancer. Most studies clearly demonstrate that, after mastectomy, local regional recurrences can be observed even when pathologic complete response is achieved after neoadjuvant chemotherapy, especially in patients with large size tumour and unfavourable pathologic factors. Retrospective studies remain the main source of information guiding the selective use of radiotherapy after neoadjuvant chemotherapy and mastectomy. This is one of the reasons why there are still many uncertainties regarding the indications of postmastectomy radiotherapy in this patient population. In addition, the extension of irradiation fields to peripheral lymphatics remains somewhat poorly defined in the literature. Finally combining the assessment of clinical and pathologic factors with the use of biomolecular assays should help oncologists determine with more accuracy which patients should receive post-mastectomy radiotherapy following neoadjuvant chemotherapy.

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1. Introduction

Originally used in patients presenting with bulky tumours with the objective of improving treatment outcome

after breast conserving surgery, neo-adjuvant chemotherapy (NAC) subsequently saw its indications extended even to small, T1 tumours, as exemplified by NSABP B18 and B27 studies [1]. In these neo-adjuvant trials, in which 28% (B18) and 14% (B27) of the tumours were staged cT1, the broad spectrum of stages made the failure risk assessment somewhat confusing. As first-line treatment, NAC has anyway been shown to lead to local regional

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down-staging and distant metastasis risk reduction. When post-NAC local treatment consists of mastectomy and axillary dissection, post-operative radiotherapy (denoted here as post-NAC PMRT) has to be delivered selectively. The decision to irradiate or not this population of patients first derived from indications provided by early retrospective studies [2,3], and later on from data generated by prospective NSABP B-18 and B-27 trials [1]. Yet indications for post-mastectomy irradiation still remain to define with more precision for patients primarily treated with chemotherapy.

The objective of this review is to revisit the most recent datasets on the pre- and post-NAC risk factors, with the objective to identify the most robust predictive and prognostic variables for disease control and survival. Its ultimate goal is to help physicians determine which criteria should drive the decision to irradiate or not breast cancer patients treated with neoadjuvant chemotherapy and mastectomy.

2. Background

Indications of adjuvant radiotherapy following mastectomy as primary treatment

In 1986, a Swedish randomized trial in 960 women with stages 1–3 disease treated with mastectomy yielded a significant difference in recurrence rates between irradiated patients and surgical controls (hazard ratio (HR): 0.65; $p < 0.001$) [4]. In 1997, the British Columbia Cancer Agency in Vancouver published the results of a randomized study in which 318 premenopausal women with node-positive breast cancer had been assigned, after modified radical mastectomy, to receive chemotherapy plus radiotherapy to the chest wall and regional lymph nodes, or chemotherapy alone. After a follow-up of 15 years, the women assigned to the latter arm had a 33% reduction in recurrence rate and 29% reduction in mortality from breast cancer (HR: 0.67 and 0.71, respectively) [5]. The same year, the final results of a randomized trial conducted by Danish Breast Cancer Cooperative Group and based on the same concept as the latter trial, demonstrated in 1708 with pathological stages II–III breast cancer both a significant reduction in local regional failure risks and overall survival rates at 10 years in the radiotherapy arm (9 vs. 32% and 54 vs. 45%, respectively; $p < 0.001$ in both cases) [6]. In 2014, the EBCTCG reported on a meta-analysis of individual data for 8135 women in 22 trials, treated with mastectomy and axillary surgery randomly assigned to treatment groups of radiotherapy to chest wall and regional lymph nodes versus the same surgery but no radiotherapy. While PMRT had no significant effect on prognosis in 700 women with no positive nodes, it was shown to reduce overall regional recurrence and breast cancer mortality in 1314 patients with 1 to 3 positive nodes ($2p = 0.00006$ and 0.01 , respectively). The corresponding $2p$ values in the 1772 patients with 4 or more positive nodes were 0.0003 and 0.04 , respectively) [7]. In various studies published at the turn of the century, the risk of

loco-regional recurrences in patients with upfront mastectomy was found to increase with T and N stage, in younger patients, in case of oestrogen receptor-negative disease, and in the presence of extracapsular extension (ECE) in the lymph nodes [8,9].

In 2014, two reports elicited a boarder range of selection criteria for adjuvant radiotherapy following primary mastectomy.

Reviewing the most recent data from the literature, Wenz et al. [10] yielded improved overall survival and local control rates following PMRT for T4 tumours, positive resection margins, >3 positive lymph nodes and in T3 N0 patients with risk factors such as lymphovascular invasion (LVI), G3 grading, close margins, invasive lobular subtype, negative hormone receptor status and young age. A 1a level of evidence was reached for the use of PMRT in patients with 1–3 positive lymph nodes. The authors concluded that PMRT is mandatory in patients with T4 tumours and/or positive lymph nodes and/or positive resection margins. PMRT should also be strongly considered in patients with T3 N0 tumours and risk factors, particularly when two or more risk factors are present.

In a cohort of 898 cases, the Cambridge group [11] designed indices categorized as high (H) risk, intermediate (I) risk and low (L) risk to select PMRT patients. The independent prognostic factors for local regional recurrences included the number of positive lymph nodes, lymphovascular invasion, tumour size and grade, and margin status. The 5-year actuarial loco-regional recurrence (LRR) rates were 6%, 2% and 2% for the H, I and L risk groups. The 5-year actuarial overall survival rates were 67%, 77% and 90%, respectively. The authors concluded that PMRT was recommended for H and I risk groups.

These recommendations are undoubtedly useful to the oncologist, for they can guide him/her in NAC setting but, to provide accurate information on the place of PMRT in patients treated primarily with chemotherapy, they have to combine the prognosticators identified in these reports with other parameters such as biologic features and response to systemic treatment.

2.1. Neoadjuvant chemotherapy and mastectomy: a “jungle” of risk factors

Several reports from MD Anderson Cancer Center in Houston analyzed the clinical and pathological factors which had a significant impact on treatment outcome after NAC and PMRT. The first one, published by Huang in 2004, showed that there were statistically significant differences in cause-specific survival rates in favour of the use of PMRT in case of 4 or more pathologic nodes (at 10 years, 69 vs. 46%, $p = 0.005$), notwithstanding the fact that more unfavourable factors had been found in the group of patients receiving radiotherapy: indeed, in the surgical and PMRT groups, the incidences of T3–4 stages were 56 and 84%, respectively. The corresponding figures for N2–3 stages were 20 and 43% [12]. In the

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