

# Post Mastectomy Radiation Therapy in Breast Cancer Patients with 1 to 3 Positive Lymph Nodes: has the Debate Ended?

## Abstract

The administration of post mastectomy radiation therapy to breast cancer patients with 1 to 3 positive lymph nodes has long been regarded as a highly controversial issue. Despite the availability of some randomized trials during 90s favoring radiotherapy, the extrapolation of guidelines that apply to contemporary clinical practice is challenging. This is due to the evolution of systemic therapies such as cytotoxic chemotherapy and molecularly targeted agents that have been shown to also reduce loco regional recurrences. In this mini-review we follow the debate from its origins to the present and contemplate on the interplay between radiation and systemic therapies.

**Keywords:** Breast cancer; Post mastectomy radiation therapy; 1 to 3 lymph nodes

## Mini Review

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**Abbreviations:** PMRT: Post Mastectomy Radio Therapy; ALND: Axillary Lymph Node Dissection; EBCTCG: Early Breast Cancer Trialists Collaborative Group; LR: Loco Regional Recurrences; RSI: Radio Sensitivity Index

## Introduction

The first reference to patient's dichotomy into those with 1 to 3 and 4 or more positive lymph nodes dates back to 1968, in a paper from Fisher et al. [1] regarding the benefit of adjuvant chemotherapy [1]. This somewhat contrived bisection has, later on, been adopted by the radiation oncology community as well. Oxymoron as it may sound, chemotherapy managed to gradually phase it out from its therapeutic algorithm, yet for radiotherapy the debate goes on until today.

The first clinical trials documenting the benefit of post mastectomy radiotherapy (PMRT) were the Danish trials 82b and 82c, in premenopausal and postmenopausal women, respectively, along with the Canadian trial from British Columbia Cancer Agency [2,3]. All three trials were consistent with each other in that PMRT reduces loco regional recurrences (LR) and increases overall survival. This was a significant breakthrough at the time since it provided evidence that a loco regional intervention may have impact on a systemic endpoint.

Nonetheless, there was a common underlying problem: the large recurrence rates in the arm that did not receive PMRT, which were in direct antithesis with the rates from other trials, mostly conducted in the United States [4]. This disparity was attributed to: 1. The inadequate axillary lymph node dissection (ALND). The median dissected lymph nodes in the Danish trials and in the BCCA trial were 7 and 11, respectively. 2. The "obsolete" CMF regimen as opposed to others containing an anthracycline and 3. The suboptimal use of hormone therapy. In the Danish trial the latter was administered as tamoxifen 30 mg for 1 year

irrespective of the ER status. For all the reasons above, PMRT has been considered to be beneficial only in patients with 4 or more positive lymph nodes, as portrayed in the international guidelines of the time [5].

Breast cancer as a disease exhibits a continuous spectrum and it is almost certain that PMRT helps patients with 1 to 3 positive nodes. The fundamental question is whether the magnitude of absolute LR risk reduction, conferred by PMRT, justifies its use. The reason why loco regional recurrence rates are so important is due to their direct relation to overall survival. This connection has been demonstrated and quantified by a meta analysis from EBCTCG in 2005, where an absolute reduction of at least 10-20% in 5 year LR probability was mandated for an overall survival benefit in 15 years to be seen [6]. Granted, we should not underestimate the value of loco regional control per se and the medical and psychological burden of disease relapse in the breast.

In 2014, a large meta analysis of 22 randomized trials was published by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), concluding that the addition of PMRT patients with 1 to 3 positive lymph nodes reduced loco regional recurrences and breast cancer associated mortality, irrespective of the administration of systemic therapy (mostly CMF and/or tamoxifen) [7]. Three out of 22 trials in this meta analysis were the Danish 82 b & c and the BCCA trials. These three trials undoubtedly affected the results due to the large number of patients (~2500 patients). It follows, naturally, that any criticism towards those three trials applies to the meta analysis as well. Most importantly, though, the meta analysis showed that the benefit from PMRT was more definite in those patients that received systemic therapies, as opposed to those that they did not.

In order to perceive the effect this meta-analysis to the clinical practice one may contrast the answers of St Gallen 2013 and 2015 consensus (the EBCTCG paper was published in June 2014). As we

can see in the Table 1 the practice regarding 1 to 3 positive lymph nodes remained the same. In the case of an unfavorable histology, positive answers increased from 61.7% to 87%, whereas age by itself continued to divide the panel of experts.

**Table 1:**

| Clinical Scenario                         | St Gallen     |          |
|---|---------------|----------|
|   | 2013          | 2015     |
| N+ 1-3 LNs                                | 29.8/63.8/6.4 | 32/64/4  |
| N+ 1-3 LNs plus unfavorable Histology     | 61.7/31.9/6.4 | 87/7/7   |
| N+ 1-3 LNs plus young age (<40 years old) | 55.1/40.8/4.1 | 51/37/12 |

The results of the EBCTCG meta analysis are congruent with the interim reports from the Canadian MA. 20 and the EORTC 22922/10925 trials [8,9]. The majority of patients in these trials were treated with breast conserving surgery and were randomized to breast/chest wall radiation with or without regional nodal irradiation. These trials demonstrated a modest reduction in distant metastasis in addition to improved loco regional relapse.

### Evolution of systemic therapies and radiotherapy

During last decades, the advancement of systemic therapies has been considerable. Cytotoxic chemotherapy has been intensified with the introduction of anthracyclines, taxanes and dose-dense regimens. The administration of hormone therapy has been standardized and aromatase inhibitors have been developed. Anti-HER2 targeted therapies changed the natural course of HER2 positive cancer. For instance, in the first phase III trials the addition of trastuzumab to chemotherapy reduced loco regional recurrences almost by half [10]. The screening of women has been intensified resulting in more women been diagnosed with early stage breast cancer. Also, our ability to diagnose lymph nodes metastases at the microscopic level has been evolved with the aid of serial sub gross sectioning. Thus, a woman that nowadays is classified as N+, she could had been N- at the time of the Danish trials and she would not had received PMRT. For all these reasons, it is expected that the absolute benefit from PMRT to be smaller than 30 years before [7].

Similarly, radiotherapy has evolved tremendously during the last decades. The invention of computed tomography, treatment planning systems, multi-leaf collimators and IMRT are only a fraction of the breakthroughs. The administration of radiotherapy nowadays is far more efficient in terms of dose coverage and homogeneity and safer than 50 years ago [11]. For example, the survival benefit seen for RT in older trials, dating back to 1958, was to some extent negated by the deleterious effects on the heart seen with mean doses as high as 15.8 Gy [12]. In modern cohort of patients, though, breast cancer mortality does not appear to depend on the laterality of breast cancer [13]. Thus, it is expected that the relative benefit of PMRT to be larger nowadays [7] Nielsen et al studied the failures of pattern in the 82 b & c cohorts and found out that patients irradiated with ortho voltage equipment had a larger risk of LR failure, although this did not translate into a risk reduction of distant metastases [14].

### Loco regional and systemic therapies: antagonism or synergy?

Radiation and systemic therapies are, at times, considered as antagonistic to each other in an either-or scenario. This may hold true for certain low risk breast cancers for which both treatments are sufficiently effective, but for most of the cases they act synergistically [15]. This debate parallels with the controversy regarding the natural history of breast cancer. The Halstedian theory of orderly progression accepts axillary nodes as local and the supra clavicular nodes as regional disease [16]. On the contrary, Fisher's theory views breast cancer as a systemic disease regulated by intrinsic factors in tumor cells and not by the anatomical considerations of the affected organ. Systemic therapies avert distant relapses allowing loco regional control to translate into an overall survival benefit.

To further expand on the topic, in a post hoc analysis, Kyndi et al [17] assigned 82 b & c patients into three prognostic groups of LR risk based on the number of positive lymph nodes, tumor size and histological grade [17]. The largest absolute reduction (36%) in 5 year LR probability after radiotherapy was seen in the poor prognostic group, yet this did not translate into overall survival benefit (0% reduction in mortality). Apparently, patients in the poor prognostic group suffered a systematic relapse which neutralized any loco regional control benefit. Contrariwise, patients in the good and intermediate prognostic groups had a less prominent LR risk reduction which in fact led to an increased overall survival.

### Molecular subtypes and LR risk after mastectomy

In 2010, Voduc et al. [18] used semi quantitative immune histochemical techniques to partition breast cancer into certain molecular subtypes, namely luminal A, luminal B, basal-like, HER2 enriched, etc. He then observed that all subtypes, besides luminal A, had an increased risk of LR recurrence post mastectomy when radiotherapy was omitted [18]. There are several weaknesses in this study that prevent us from extrapolating its conclusions in the contemporary practice. The cohort's patients were treated between 1986-1992 and none received trastuzumab; Herceptin(R) got and FDA approval in 1998. Also, only 25% of patients received chemotherapy. In 2014 Moo et al explored whether molecular subtypes could be used as a means to select patients with T1,T2 breast cancer and 1 to 3 positive lymph nodes after mastectomy for PMRT [19]. On a multivariate analysis only age and the presence of lympho vascular invasion were independent prognostic factors, whereas MSTs not. 37% of the cohort received trastuzumab and 67% received chemotherapy with an anthracycline/taxane combination. It appears that in the modern era MSTs cannot stratify patients by their LR risk.

### Phase III trials

The inconsistencies in the available evidence regarding the use of PMRT in patients with 1 to 3 positive nodes are further intensified by the paucity of randomized trials. The SWOG 9927 phase III trial randomized patients with stage II breast cancer and 1 to 3 positive axillary nodes to PMRT or observation, but was prematurely closed in 2003 due to lack of accrual [20]. Another phase III trial, the SUPREMO (Selective Use of Postoperative

Radiotherapy after Mastectomy) trial completed accrual and is currently at the follow-up stage [21]. Besides the absence of randomized trials, by the time their results are published the original therapies might have become outdated by current standards, particularly in diseases where a long follow-up is needed, such as breast cancer.

### Biomarkers and personalized medicine

The development of biomarker-based tools to influence therapeutic decisions is a central premise of the so called personalized medicine. The criteria which affect the recommendation of radiation therapy are still clinical and pathological in their nature. Radiation oncology has called for radio sensitivity predictive assays for several decades, yet only recently has there been noticeable progress in the context of breast cancer with the introduction of RSI (Radio sensitivity Index) [22] and gene profiles [23].

One of the important aspects of the SUPREMO trial is the TRANS-SUPREMO sub trial, which will aim at identifying a “molecular signature” predictive of loco regional recurrence risk and resistance to radiotherapy [21]. Similarly to how the 21-gene recurrence score (Oncotype DX) predicts the risk of systemic relapse and resistance to chemotherapy.

Although RS has been validated to assess the risk of distance recurrence in hormone receptor-positive women, there has been interest in extending its scope. Jegadeesh et al. [24] found that among mastectomy patients the 5 years LRR rate was 27.3% in patients with RS > 24 versus 10.7% in those with RS ≤ 24 (p=0.04) [24]. Mamounas et al. [25] studied the prognostic impact of RS in locoregional recurrence in node negative patients and found a significant association [25]. The authors conclude that as RS expands to node positive patients [26], it could become an important tool to identify subgroups with 1 to 3 positive nodes at low versus high risk for LRR who may or may not benefit from PMRT.

### Conclusion

Clinical trials are meant to be interpreted in the historical context when they were conducted, although by the time their results are published the standard of care may have changed. The tremendous evolution of systemic therapies renders the therapeutic value of PMRT in patients with 1 to 3 positive lymph nodes less clear, and the astounding technical innovation of radiation therapy invalidates to a certain extent its reported treatment related toxicities. The development of biomarkers and molecular tests that will stratify patients with regard to their loco regional risk cannot be adequately emphasized.

### References

1. Fisher B, Ravdin RG, Ausman RK, Slack NH, Moore GE, et al. (1968) Surgical adjuvant chemotherapy in cancer of the breast: results of a decade of cooperative investigation. *Ann Surg* 168(3): 337-356.
2. Overgaard M, Jensen MB, Overgaard J, Hansen PS, Rose C, et al. (1999) Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 353(9165): 1641-1648.
3. Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, et al. (1997) Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 337(14): 949-955.
4. Taghian A, Jeong JH, Mamounas E, Anderson S, Bryant J, et al. (2004) Patterns of loco regional failure in patients with operable breast cancer treated by mastectomy and adjuvant chemotherapy with or without tamoxifen and without radiotherapy: results from five National Surgical Adjuvant Breast and Bowel Project randomized clinical trials. *J Clin Oncol* 22(21): 4247-4254.
5. Recht A, Edge SB, Solin LJ, Robinson DS, Estabrook A, et al. (2001) Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 19(5): 1539-1569.
6. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, et al. (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 366(9503): 2087-2106.
7. McGale P, Taylor C, Correa C, Cutter D, Duane F, et al. (2014) Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 383(9935): 2127-2135.
8. Whelan TJ, Olivetto I, Ackerman I, Chapman JW, Chua B, et al. (2011) NCIC-CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. *J Clin Oncol* 29(15): LBA1003.
9. Poortmans P, et al. (2013) Irradiation of the internal mammary and medial supraclavicular lymph nodes in stage I to III breast cancer: 10 years results of the EORTC radiation oncology and breast cancer groups phase III trial 22922/10925. *Eur J Cancer* 47.
10. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, et al. (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 353(16): 1673-1684.
11. Harris JR (2014) Fifty years of progress in radiation therapy for breast cancer. *Am Soc Clin Oncol Educ Book* 21-25.
12. Sarah C Darby, Marianne Ewertz, Paul Mc Gale, Anna M Bennet, Ulla Blom Goldman, et al. (2013) Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 368: 987-998.
13. Rutter CE, Chagpar A B, Evans SB (2014) Breast cancer laterality does not influence survival in a large modern cohort: implications for radiation-related cardiac mortality. *Int J Radiat Oncol Biol Phys* 90(2): 329-334.
14. Danish Breast Cancer Cooperative Group, Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J (2006) Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. *J Clin Oncol* 24(15): 2268-2275.
15. Poortmans P (2014) Postmastectomy radiation in breast cancer with one to three involved lymph nodes: ending the debate. *Lancet* 383(9935): 2104-2106.
16. Halsted WSI (1907) The Results of Radical Operations for the Cure of Carcinoma of the Breast. *Ann Surg* 46(1): 1-19.
17. Kyndi M, Overgaard M, Nielsen HM, Sorensen FB, Knudsen H, et al. (2009) High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. *Radiother Oncol* 90(1): 74-79.

18. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, et al. (2010) Breast cancer subtypes and the risk of local and regional relapse. *J Clin Oncol* 28(10): 1684-1691.
19. Moo TA, McMillan R, Lee M, Stempel M, Ho A, et al. (2014) Impact of molecular subtype on locoregional recurrence in mastectomy patients with T1-T2 breast cancer and 1-3 positive lymph nodes. *Ann Surg Oncol* 21(5): 1569-1574.
20. Southwest Oncology Group. Protocol S9927: Randomized trial of post-mastectomy radiotherapy in stage II breast cancer in women with one to three positive axillary nodes.
21. Kunkler IH, Canney P, van Tienhoven G, Russell NS, MRC/EORTC (BIG 2-04) SUPREMO Trial Management Group (2008) Elucidating the role of chest wall irradiation in "intermediate-risk" breast cancer: the MRC/EORTC SUPREMO trial. *Clin Oncol* 20(1): 31-34.
22. Eschrich SA, Fulp WJ, Pawitan Y, Foekens JA, Smid M, et al. (2012) Validation of a radiosensitivity molecular signature in breast cancer. *Clin Cancer Res* 18(18): 5134-5143.
23. Tramm T, Mohammed H, Myhre S, Kyndi M, Alsner J, et al. (2014) Development and validation of a gene profile predicting benefit of postmastectomy radiotherapy in patients with high-risk breast cancer: a study of gene expression in the DBCG82bc cohort. *Clin Cancer Res* 20(20): 5272-5280.
24. Jegadeesh NK, Kim S, Prabhu RS, Oprea GM, Yu DS, et al. (2015) The 21-gene recurrence score and locoregional recurrence in breast cancer patients. *Ann Surg Oncol* 22(4): 1088-1094.
25. Mamounas EP, Tang G, Fisher B, Paik S, Shak S, et al. (2010) Association Between the 21-Gene Recurrence Score Assay and Risk of Locoregional Recurrence in Node-Negative, Estrogen Receptor-Positive Breast Cancer: Results From NSABP B-14 and NSABP B-20. *J Clin Oncol* 28(10): 1677-1683.
26. Albain KS, Barlow WE, Shak S, Hortobagyi GN, Livingston RB, et al. (2010) Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol* 11(1): 55-65.
27. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart Gebhart M, et al. (2013) Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol* 24(9): 2206-2223.
28. 14th St Gallen International Breast Cancer Conference Primary Therapy of Early Breast Cancer, Vienna, Austria 18 - 21 March 2015.