Postmastectomy radiotherapy for all node positive patients: The case against

Title

Postmastectomy radiotherapy for all node positive patients: The case against

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The role of postmastectomy radiotherapy (PMRT) for patients with 4 or more positive nodes is widely accepted based on the Oxford meta-analysis of randomised trials [1]. However, its role in patients with 1-3 positive nodes, where the EBCTCG metananalysis indicated similar benefits for 4 or positive nodes, remains controversial [2,3,4,5]. The motion that 'This House believes that all node positive patients need postmastectomy irradiation' was debated at the virtual European Breast Cancer Conference on October 8th 2020.

The case against:

1. Impact of PMRT in the absence of systemic therapy

If PMRT improves survival in node positive women with breast cancer it should have its optimal effect in those who have no adjuvant systemic therapy.

However, PMRT had no effect in the NSABP-B04 trial [6] that compared radical mastectomy (RM) vs total mastectomy(TM) vs TM + postoperative RT (50Gy in 25 fractions) in clinically node negative women and RM vs TM plus RT to chest wall (50 Gy in 25 fractions with 10-20Gy boost and 45Gy in 25 fractions to the internal mammary and supraclavicular nodes in clinically node positive women. In cN0 patients there was no significant reduction in distant recurrence from PMRT. In node positive women PMRT had no effect on loco-regional recurrence or distant metastases. In neither node negative nor node positive women, was there any improvement in overall survival from PMRT. The subsequent Oxford overview of PMRT trials [1] did show a survival advantage from adjuvant PMRT. While it is possible the lack of survival benefit in B04 might have been due to excess radiation induced deaths and for this reason, this trial was not included in the EBCTCG. The lack of an effect of RT in BO4 on metastatic events is however puzzling.

2. **Lack of generalisability of historical trials of PMRT to contemporary practice**

Arguments for PMRT are largely based on early trials from the Canadian [7] and Danish Groups [8,9] in node positive patients after mastectomy and systemic therapy. These landmark trials established PMRT as standard of care for patients with 4 or more positive nodes. What is less clear, is the quality of the evidence base for PMRT in patients with 1-3 positive nodes and may explain why this was made a research priority by the US National Institutes of Health in 2000 [10]. The Canadian trial [7 randomised only 318 patients to CMF, an outdated regimen, plus loco-regional irradiation or CMF alone after mastectomy between 1978-1986. In a secondary randomisation, 68 patients were randomised to +/- ovarian irradiation + prednisolone in addition to chemotherapy. No tamoxifen was given. There was a 28% benefit (RR:0.72) in disease free survival

in the ovarian suppression and prednisolone group but this treatment arm was subsequently abandoned. The median number of axillary nodes removed was 11. The Danish studies were similar in design and ran from 1982-1989. The median number of axillary nodes removed was only 7 in the Danish premenopausal and postmenopausal trials [8,9]. This small number of nodes is both studies may have led to an underestimate of the actual number of involved axillary nodes. RT was given to chest wall, axilla, infra- and supra-clavicular nodes and upper internal mammary nodes in both trials. Only a year of 30 mg tamoxifen was given to patients in the Danish 'high risk' postmenopausal trial. There is confusion from these two studies in the benefit of PMRT in relation to ER status: with the benefit being reported in ER+ patients in the Danish studies and in triple negative breast cancer in the North American studies. In both the Canadian and Danish trials, the absence of anthracyclines, taxanes or anti-HER2 therapy, inadequate endocrine therapy and limited axillary surgery makes it difficult to draw any conclusions that are relevant to current practice. The recurrence free survival at 10 years for the Canadian and two Danish trials varied between 36-48% and the mortality at 10 years varied from 46-64%. This is much higher than seen in contemporary practice. Similarly the outcomes reported from the EBCTCG meta-analysis of PMRT in patients with 1-3 positive nodes as they are largely derived from the Danish trials, and are poor by modern standards.

3. Heterogeneity of the T1-2 population of patients undergoing mastectomy

The pT1-2 population is heterogeneous. It includes (i) high and low risk patients treated by modified radical mastectomy with an axillary lymph node dissection (ii) mastectomy and SNB where 1 positive or 2-3 positive nodes are found (iii) neoadjuvant chemotherapy, and axillary lymph node dissection with residual disease in 1- 3 nodes

(ypN0 or ypN1) (iv) patients having primary or delayed reconstruction. This heterogeneity argues for invidualisation of PMRT. There are differential risks based on biological factors that need to be considered (eg HER2, ER/PgR status).

4. Local recurrence rates are falling

Local recurrence rates are falling. In Edinburgh 5 and 10 year local recurrence rates after breast conserving surgery (BCS) have fallen from 6.5% and 12.4% from 1981-1989 to 1.7% and 2.4% respectively for 2005-2009. This reflects an 82% reduction in ipsilateral breast tumour recurrence since the start of the Canadian and Danish trials of PMRT. This fall is largely due to better systemic therapy and in part due to the increasing and consequent interdisciplinary discussion between surgeon, pathologist and radiologist with careful workup of the specimens. At 10 years a 26-30% recurrence rate was reported in older trials with PMRT. Very much lower rates in the range of 4-14% were reported in 15 recent series of mastectomy and systemic therapy without PMRT (Table 1).

Summary of Studies: Node Positive Patients treated with Mastectomy + Systemic Therapy But no XRT				
Institution	Accrual dates	No. Patients	Follow up Median months	Loco Regional Recurrence
MDACC	1975-94	466	116	14% @ 10y
ECOG	1978-87	1018	145	13% @ 10y
NSABP	1984-94	2957	133	13% @ 10y

BCAA	1989-97	821	92	13% @ 10y
Ankara	1990-2004	326	70	13% @ 10y
MGH	1990-2004	165	84	11% @ 10y
Shikoku Japan	1990-2002	248	82	4% @ 8 y
CALGB	1994-97	254	67	11% @ 10y
MSKCC	1995-2006	924	84	4% @ 5y
Tampa	1995-2007	204	66	10% @8y
EIO	1997-2001	262	120	10% @ 10y
MDACC	1997-2002	266	90	4% @10y
Tamjin China	2001-2005	368	86	7% @10y
MDACC	2000-2007	385	84	11% @ 8y

Table 1: Summary of studies of node positive patients treated with mastectomy and systemic therapy, but no XRT (Courtesy of Prof JM Dixon)

5. Differential benefits of PMRT within 1-3 node positive group according to risk category

Contemporary non randomised studies of PMRT are informative on the differential effects of PMRT according to risk [11] (see Figure 1)

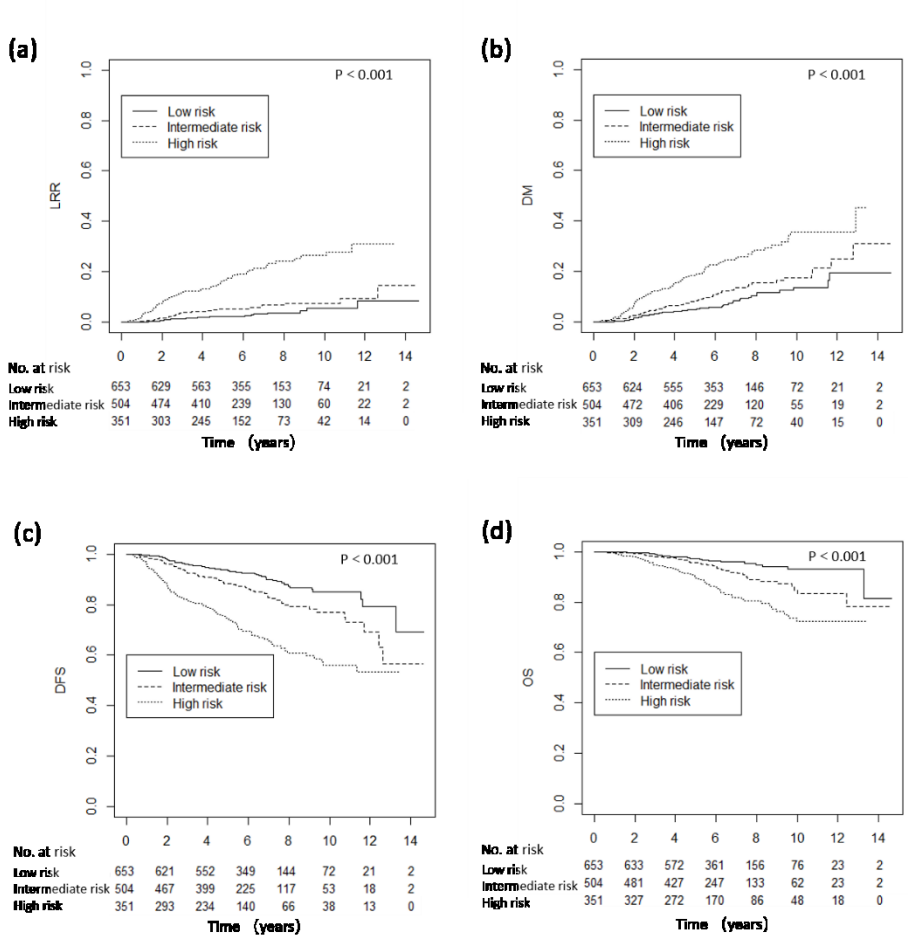

Figure 1: LRR, DM, DFS and OS curves for low-, intermediate- and high-risk groups without PMRT. LRR, loco-regional recurrence; DM, distant metastasis, DFS, disease free survival; OS, overall survival; PMRT, post-mastectomy radiotherapy.

(Reproduced from Wang et al [11])

Wang et all undertook (11) a retrospective analysis of 1986 patients with T1-T2,N1 defined according to AJCC 8th edition criteria who underwent mastectomy +/- PMRT in two Chinese institutions. They showed a modest effect on local recurrence from PMRT but no effect on distant metastases or on disease free or overall survival. There were differential effects of prognostic factors on clinical outcomes (age, site, number of involved lymph nodes) with younger patients or those with more nodes experiencing higher rates of loco-regional recurrence, distant metastases and reduced disease free

and overall survival. Significant improvements in the outcomes occurred in the high-risk group but not in the low and intermediate groups (Fig 1). Age <40 years, inner quadrant tumours,2-3 positive nodes and higher AJCC stage were identified as independent prognostic factors for loco-regional recurrence and the same factors (without 2-3 nodes) for distant metastases.

6. Efficacy of systemic therapy

Tamoxifen for 5 years reduces the relative risk of local recurrence (LR) compared to placebo by 53% (RR 0.47) and aromatase inhibitors reduce LR by an additional 26% (RR 0.74; absolute rates: 10yrs-LRR Tam-5y 3.6% vs AI-5y 3.1%, absolute benefit 0.5% [12]). Looking at chemotherapy and LR, the hazard ratio for LR in the NSABP BI3 trial in ER negative patients for the addition of chemotherapy was 0.22, a 78% reduction in events and in the NSABP B14 trial in ER positive patients was 0.29, a 71% reduction in recurrence. In HER2 positive patients treated by BCS and radiotherapy in T1-T2,N0, trastuzumab reduced 3 yr LR rates from 7% to 1% [13] and in T1-3,N0 treated by modified radical mastectomy from 6.6% to 1.5% [14].

7. Impact of neoadjuvant chemotherapy

Not all node positive patients need chest wall irradiation after neoadjuvant chemotherapy. A combined analysis was performed of the NSABP B18 (Surgery followed by 4 cycles of AC or AC followed by surgery) and the B27 trial (4 cycles of preoperative AC followed by surgery or four cycles of AC followed by four cycles of docetaxel, followed by surgery or four cycles of AC followed by surgery and then four cycles of docetaxel [15]). In the B18 trial only postmenopausal ER+ patients received tamoxifen and in B27 all ER+ patients received tamoxifen. Patients who received

tamoxifen or docetaxel had significantly lower risks of local recurrence, than those who did not. The 10 year cumulative incidence of loco-regional recurrence was negligible in patients who had tumours >5cm treated by mastectomy without irradiation who were clinically node positive and had a pathological complete response. High LRR rates occurred only in patients with residual nodal disease after chemotherapy. Pathological complete response rates in HER2 positive patients are now of the order of 60-80%, and the need for radiotherapy in such patients is unclear as they have an excellent disease free and breast cancer specific survival even without RT

Many patients who are node positive at diagnosis do not get radiotherapy as their nodes are sterilised by neoadjuvant chemotherapy. In particular in HER2 positive cancers, neoadjuvant chemotherapy and a combination trastuzumab and pertuzumab, converts 75% of these patients being converted from node positive to node negative.

The situation is different in patients after neoadjuvant chemotherapy (NACT). Whilst level 1 evidence is lacking – NSABP B-51 has not been closed yet – data are accumulating that with minimal disease in sentinel lymph nodes after NACT, a high rate of metastases can be expected in the remaining non-sentinel axillary lymph nodes (30). ALND is therefore recommended in these cases, anyway. According the German AGO guidelines, PMRT including RNI should be given in these patients.

8. Axillary micrometastases

Patients with axillary micrometastases on SNB undergoing mastectomy usually avoid chest wall radiotherapy but many of these patients have axillary macro metastases. In the IBCSG 23-01 [16] and AATRM studies [17] 13% of patients with micro metastases randomised to axillary lymph node dissection had metastases in other non sentinel

nodes. In the IBCSG 23-01 study only 6% of patient received adjuvant irradiation. So currently there are node positive patients who have only micrometastases on SNB. 13% who have macrometastases who avoid chest wall radiotherapy. It is also possible that leaving intact functioning axillary lymph low volume disease may be eliminated by mechanisms of immune surveillance [16].

9. Guidelines on the use of postmastectomy radiotherapy

Guidelines on PMRT vary. The UK National Institute for Care and Clinical Excellence (NICE) recommends PMRT for all patients with nodal macrometastases (NICE,2018[18]). However, despite its inclusion of PMRT as a standard of care for 1-3 positive nodes, NICE guidelines also state that there is moderate quality evidence from one systematic review (N=1,481) that there is no clinically important effect of PMRT to the chest wall and lymph nodes on overall survival at 20 years for women with node-positive invasive breast cancer. The overall recommendation and the caveat on the evidence base seem inconsistent.

The ASCO/ASRO/SSO guidelines on PMRT [19] take a more nuanced approach. They do not advocate PMRT for all node positive patients. They argue that: 'recent evidence suggest that the findings may not be clinically applicable to all patients with 1-3 positive nodes in the current era, when many of these patients are at much lower risk of recurrence' and 'multiple studies from North America, Europe and Asia treated with mastectomy and systemic therapy without irradiation since 1990 have reported lower 5-10 year actuarial LRF rates with the most recent LRF rates lower than 10%. In addition: 'Some subsets are likely to have such a low risk of LRF that the absolute benefit of PMRT is outweighed by its potential toxicities. 'Clinicians… should consider

factors that may decrease the risk of LRF, attenuate the benefit of reduced breast cancer specific mortality and/or increase the risk of complications resulting from PMRT'. 'Consider no radiotherapy if aged 40-45/limited life expectancy of older age or comorbidities/lower tumor burden/only single positive node and/or small size of nodal metastases or substantial response to neoadjuvant chemotherapy/ biological characteristics with better outcomes and survival and or greater effectiveness of systemic therapy'.

The St Gallen International consensus is more prescriptive recommending PMRT for patients with 1-3 positive nodes with triple negative histology [20].

The German AGO guidelines [21] PMRT to the chest wall for high risk patients with 1-3 positive nodes may be offered. However for low risk patients with 1-3 positive nodes, PMRT should be discussed but not for low risk patients where the evidence of benefit is equivocal (see Table 2).

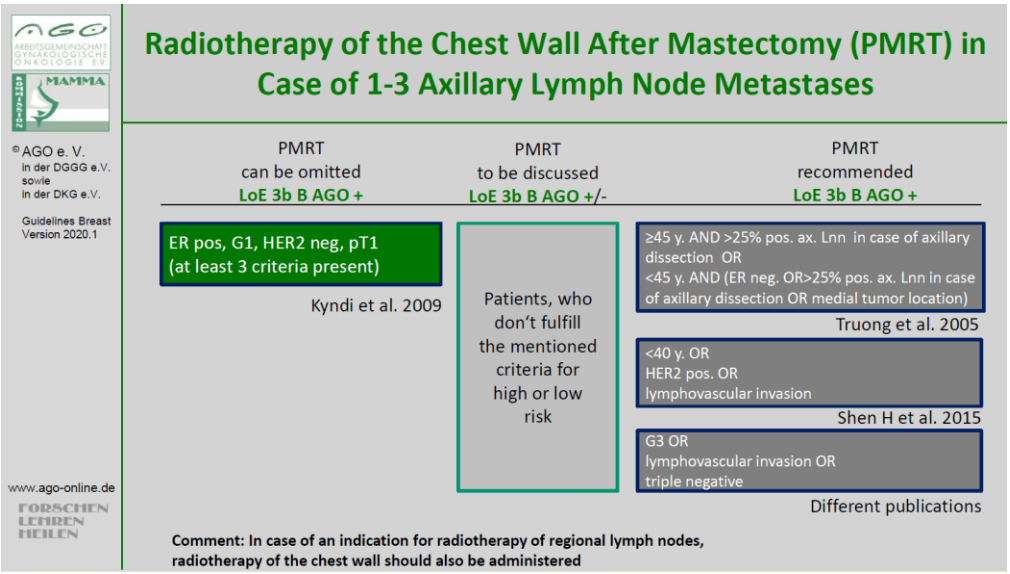

Table 2: Radiotherapy of the chest wall after mastectomy (PMRT) in case of 1-3 axillary lymph node metastases (Reproduced with permission of the German AGO guidelines [ref 21]).

The AGO guidelines (level of evidence 3b) suggest that PMRT can be omitted in patients with 1-3 positive nodes where the tumour is ER positive, G1, HER2 negative, pT1 where at least three of the factors are present [22]. For patients > 45 years and >25% of positive nodes after axillary lymph node dissection [23] or < 40 years of age or HER2 positive or lymphovascular invasion present [24] or Grade 3 or lymphovascular invasion or triple negative, PMRT is recommended. For patients in neither high or low risk groups, the evidence for PMRT is equivocal.

10. Radiation induced toxicity

PMRT is associated with an increase in loss of breast implants. In addition, it adversely effects breast reconstruction and patients' quality of life. A meta-analysis of breast reconstruction [25] showed that patients received PMRT have a hazard ratio of capsular contracture of 4.1 and reconstruction implant failure of 3.6. In addition, there is increased cardiac morbidity and mortality with left sided tumours and of second malignancies [26]. These risks are further compounded in current smokers [27] and in long term smokers, the absolute risk of modern radiotherapy may outweigh the benefits. The latter consideration is rarely considered in MDT decision making. We should wait for definitive evidence from the MRC SUPREMO trial [28] on outcomes of PMRT in the 1-3 node positive group and not advocate PMRT for all node positive patients.

11. Integration of biological factors in selection of patients for post mastectomy radiotherapy

Most trials investigating the role of PMRT have defined an intermediate risk group based on TNM staging (generally stage II), which relies heavily on nodal status as one of the most important prognostic factors. One of the limitations of the 2014 Oxford overview of PMRT is the absence of stratification for molecular subtypes and that the LRR and overall survival advantages of modern endocrine therapy and anti-HER2 therapy were not considered [5]. Biological characteristics of the primary tumour such as grade, immune-histological type (triple negative HER-2 positive, luminal A and luminal B) can influence loco-regional recurrence risk as well as distant metastases risk. However, in current practice these risks are modulated by systemic therapy. Data from NACT trials indicate that achieving a pCR in both the primary tumour and lymph nodes is a more important prognostic factor than initial nodal status. [29, 30]. Analysis of TRANS-SUPREMO [31] will hopefully shed more light on relevant biological prognostic factors within this "intermediate risk" group to differentiate which patients can safely allow avoidance additional radiotherapy. In future gene signatures [32] may be able to distinguished RT responders from non responders. However, the recent St Gallen/Vienna 2021 consensus does not recommend the use of gene expression signatures for decision-making on PMRT.

In conclusion, we believe that 'adjuvant radiotherapy for all node positive patients' remains an open question and that more level 1 evidence is required to inform best PMRT practice for patients with 1-3 positive nodes.

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