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Internal mammary node irradiation in breast cancer: does benefit outweigh risk?

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We have known for around three decades that breast radiation therapy (RT) not only reduces the risk of local relapse but also breast cancer death[1-2], albeit potentially causing major cardiac events many years later[3]. The balance of benefit versus harm is particularly relevant for internal mammary node (IMN) RT, where patients are usually at greater risk of relapse by virtue of having higher stage disease, but heart doses can be higher due to the close proximity of the internal mammary chain. Uncertainties around the therapeutic ratio prompted clinical trials testing regional nodal (including IMN) RT, with three studies reporting in 2015[4-6].

Poortmans et al[7] report fifteen-year results evaluating internal mammary and medial supraclavicular lymph node chain (IM-MS) irradiation, updating their 2015 publication[4]. Eligible patients were ≤75 years with stage I-III breast adenocarcinoma either with lateral tumours and positive axillary lymph nodes or medial/central tumours with or without positive nodes. Randomisation was to IM-MS RT delivered in 50Gy in 25 fractions versus no IM-MS RT. The primary endpoint was 10-year overall survival, aiming to detect an increase from 75% to 79% (HR=0.82).

Around 4000 patients were enrolled from 1996-2004. Overall survival at 15.7 years' median follow-up was 73.1% versus 70.9% (HR 0.95; 95%CI 0.84-1.06; p=0.36) for IM-MS RT versus control, disease-free survival 60.8% versus 59.9% (0.93; 0.84-1.03; p=0.18) and breast cancer mortality was statistically significantly lower with IM-MS RT at 16.0% versus 19.8% (0.81; 0.70-0.94; p=0.0055). There were no significant differences in the incidence of cardiovascular deaths, second cancers or contralateral breast cancers.

We congratulate the authors on this large, high-quality trial. Planned analyses at 10, 15 and 20 years show insight into the importance of late effects of breast RT. The RT techniques used might be considered outdated, but the stringent quality assurance provides reassurance that RT was carried out to a consistently high standard[8]. It is, however, disappointing that this update shows no overall survival advantage with IM-MS RT. One possible explanation is the relatively low event rate given that a more favourable risk group was recruited compared with MA20 and Danish Breast Cancer Group (DBCG) trials[4-6] (Table). The Danish study has the highest risk population and showed a statistically significant improvement in overall survival and breast cancer mortality with IMN RT at 8.9 years' median follow-up; the highest absolute overall survival benefit was for patients with N2 tumours.

Table: Axillary lymph node involvement in 3 IMN RT trials

Involved axillary nodes	EORTC (%)[4]	MA20 (%)[5]	DBCG (%)[6]
0	44	10	0
1-3	43	85	60
>3	13	5	40

The EORTC trial 10-year overall survival rates were better than anticipated, reducing statistical power to detect a difference (74% power for HR=0.82 using observed rate in control group). This is a common issue for breast cancer trials that report years after initial study design.

The apparent discrepancy between lack of overall survival benefit despite a statistically significant difference in breast cancer mortality may partially be explained by missing data on cause of death, which is only an issue for cause-specific survival analyses. Commonly, analyses attribute deaths following metastases to breast cancer. Around 12.5% of deaths in the IM-MS RT group had cause unknown compared with 7.2% in the control group. If the "unknowns" were mostly breast cancer deaths, the difference in breast cancer mortality rates would be smaller, reducing the statistical significance.

At first glance, we may feel reassured by the lack of a statistically significant difference in late cardiac toxicity. However, it is questionable whether even a 4000-patient trial has the statistical power to detect a difference in these important but relatively rare major cardiac events[1]. In addition, we know that cardiac toxicity can continue to manifest decades after RT.

The Early Breast Cancer Trialists Collaborative Group carried out an interim meta-analysis of randomised trials investigating regional node (including IMN) RT, separating studies that began 1961-1978 and 1989 onwards[10]. The older trials showed that regional nodal RT had little effect on breast cancer mortality whilst statistically significantly increasing overall mortality. The newer trials demonstrated significantly reduced breast cancer mortality *and* overall mortality. The *proportional* benefit of regional nodal RT was similar across subgroups, but the greatest *absolute* mortality reduction was in patients with $\geq$4 lymph nodes positive. The meta-analysis will be repeated with updated data will inform international IMN RT guidelines as there is currently huge variation in eligibility[10].

What about future IMN RT research? It is important to develop internationally agreed dose constraints, whilst continuing to investigate technical solutions to improve the therapeutic gain. This includes testing the potential benefit of proton beam therapy for those patients whose plans are suboptimal with even the best photon techniques.

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Declaration of Interest
We declare no competing interests.

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