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Over-irradiation

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ABSTRACT

Decreasing the burden of radiation therapy (RT) for breast cancer includes, next to complete omission, several ways to tailor the extent of RT. Possible options for this include lowering of the total dose, such as selective omission of the boost, hypofractionated RT to shorten the duration of treatment, the selective introduction of partial breast irradiation and anatomy based target volume contouring to decrease the size of the irradiated volumes.

Elective regional nodal irradiation showed in several randomised trials and meta-analyses to significantly impact on local-regional control, disease-free survival, breast cancer mortality and overall survival. The generalisability of these results remains complex in the light of the decreasing use of axillary lymph node dissection, the use of more effective adjuvant systemic therapy, the increasing use of primary systemic therapy and continuously improving RT techniques.

In general, the use of RT compensates for the decreasing extent of surgery to the breast and the axillary lymph nodes, eliminating residual tumour cells while maintaining better aesthetic and functional results. In some occasions, however, the indications for the extent of RT have to be based on limited pathological staging information. Research is ongoing to individualise RT more on the basis of biological factors including gene expression profiles. When considering age, treatment decisions should rather be based on biological instead of formal age.

The aim of this review article is to put current evidence into the right perspective, and to search for an appropriate appreciation of the balance between efficacy and side effects of local-regional RT.

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Introduction

Breast cancer (BC) is the commonest cancer in women in the industrialised western countries with an increased age-standardised incidence using the standard world population of about 50 per 100,000 women in 1975 to about 100 per 100,000 women in 2010 [1]. This can be explained mainly by a changed reproductive pattern in combination with an increasing life expectancy, although other factors including life-style do contribute as well. Over the same period, the mortality rate decreased – after an initial rise – from about 20 to just above 15 per 100,000 women. This decrease in relative mortality from 40% to 15% in 45 years, which can be explained by a combination of earlier diagnosis combined with improved treatments, led to the development of

less mutilating or intensive treatment approaches. Most of these involve local-regional treatments including breast conserving therapy (BCT), the sentinel lymph node biopsy (SLNB) procedure and selective avoidance of axillary clearance.

Postoperative radiation therapy (RT) is an integral component of BCT. Whole breast RT alone reduces the 10-year risk of any first recurrence (including local-regional and distant) by 15% and the 15-year risk of BC related mortality by 4% [2]. The addition of a higher boost dose to the primary tumour bed further reduces the relative local recurrence risk by about 50% and is thereby indicated for patients with unfavourable risk factors for local control including age <51, grade 3 tumours and (focally) non-radical tumour excision [3,4].

With decreasing local recurrence rates following improved diagnostic approaches as well as local and systemic treatments, the need for RT of the intact breast after local tumour excision is put into question, even for high-risk patients [5; Fig. 1]. While these results led to omission of a boost dose to the primary tumour bed in patients without high-risk factors for local recurrence, only limited

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data focussing especially on elderly patients receiving adjuvant endocrine treatment, is available to support any strong recommendations on omission of RT.

The current debate about regional nodal irradiation (RNI) treatment follows trials that have shown that axillary clearance is not required after removal of an involved SLNB while regional RT demonstrated to be beneficial by preventing distant metastases.

The intention of this review article is to put the current evidence into the right perspective and to search for an appropriate appreciation of the balance between efficacy and side effects of both local-regional and systemic treatments.

Local treatment for low risk patients

Treatment for low-risk patients with cancer is a matter of debate in several disease sites. In the CALGB 9343 trial, 636 patients, >70 years of age with early stage oestrogen receptor positive BC, were randomised between tamoxifen alone and tamoxifen combined with whole breast irradiation. The 5-year local-regional recurrence rate was 4% and 1%, respectively ($p < 0.001$) [6]. In a similar randomised trial accruing 769 patients of 50 years or older, Fyles et al. obtained 5 year local-regional recurrence rates of 7.7% versus 0.6%, respectively ($p < 0.001$) [7]. In the accompanying editorial, Smith and Ross stated that whole breast irradiation might not be always necessary for all women undergoing BCT for early stage BC. They noted however that patient selection remains difficult, that late recurrences might be a concern (in the series of Fyles et al., after 8 years of follow up, the difference was already 15.2% versus 3.6% in favour of RT for the patients with a good prognosis [Fyles A, personal communication]) and that the value of more recent endocrine treatment is not yet known [8].

In a later trial, 869 women with favourable prognosis early stage BC treated by lumpectomy plus tamoxifen or anastrozole were randomly assigned to either whole breast RT or no RT. After a median follow-up of 53.8 months, the 5-year recurrence rate was 5.1% in the non-radiation and 0.4% in the radiation group, respectively ($p = 0.0001$, hazard ratio (HR) 10.2). Overall relapse rate was also significantly higher in the non-radiation group: 6.1% vs. 2.1%; $p = 0.002$, HR 3.5. As in the earlier trials, no significant differences were found for the rate of distant metastases and for overall survival (OS) [9].

Results after long-term follow-up were only reported for the CALGB 9343 trial: after a median follow-up of 12.6 years, 10-years local-regional recurrence rate was 10% for patients after tamoxifen only vs. 2% after combined tamoxifen with whole breast RT. There was no significant difference for any of the other endpoints, with a 10-year OS of 66% vs. 67%, respectively [10,11].

The BASO-2 trial randomised 1135 low-risk patients in a study with a 2×2 factorial design with or without RT and with or without tamoxifen, allowing trial entry to either comparison or both. After 10 years of follow-up, both RT and tamoxifen reduced the local recurrence rate to a similar extent (HR 0.37, CI 0.22–0.61, $p < 0.001$ and HR 0.33, CI 0.15–0.70, $p < 0.004$, respectively). The annual local recurrence rate after lumpectomy alone was 1.9%, compared to 0.7% with RT alone, 0.8% with tamoxifen and 0.0% with both treatments combined. The authors concluded that even in these low-risk patients, the local recurrence risk after surgery alone was still very high, although there was no demonstrated negative effect on survival [12].

In the recently published PRIME II study, 1326 women were randomised between whole breast RT or no RT following lumpectomy and adjuvant endocrine treatment. After a median follow-up of 5 years, a statistically significant reduction in ipsilateral breast tumour recurrence by the addition of whole breast RT to adjuvant endocrine treatment after lumpectomy was confirmed (from 4.1% to 1.3%, $p = 0.0002$). No differences for the other endpoints were found. The authors concluded that the 5-year local recurrence rate might be low enough to consider omission of post-operative RT in a selected group of patients [13].

In interpreting the clinical significance of these findings, we should mind the generalisability of the results for the whole population of older patients with endocrine-sensitive tumours (Table 1). Firstly because, irrespective of the entry criteria, a disproportionately high number of patients with very low risk features based on for example tumour diameter and tumour grade was generally recruited. Secondly, the question which most authors did not answer, is what the benefit to be derived from endocrine therapy for these patients with a very low risk profile might be.

Patients affected by low risk BC, particularly in the elderly, are a unique population with regards to prognosis and potential comorbidities, therefore minimizing treatment to warrant a good profile of quality of life without compromising survival is crucial. As it is difficult to demonstrate a survival advantage at 5–10 years in

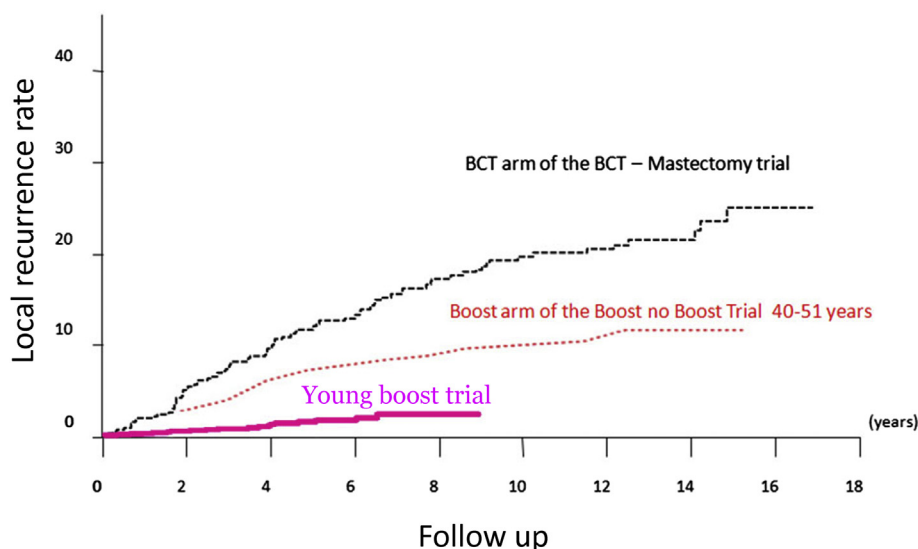


Fig. 1. Local breast recurrence rate in three consecutive trials on breast conserving therapy from 1980 till 2012 (modified from [5]).

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