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Overview

Can Interrogation of Tumour Characteristics Lead us to Safely Omit Adjuvant Radiotherapy in Patients with Early Breast Cancer?

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Abstract

Adjuvant radiotherapy after breast-conserving surgery has been an important component of the standard of care for early breast cancer. Improvements in breast cancer care have resulted in a substantial reduction in local relapse rates over recent decades. Although the proportional benefits of adjuvant radiotherapy are similar for different prognostic risk groups of patients, the absolute benefits depend on the risk of relapse and therefore vary considerably between prognostic groups. Radiotherapy is not without risk and for some patients at very low risk of relapse the risks of radiotherapy may outweigh the benefit, leading to potential overtreatment.

Randomised controlled trial (RCT) evidence shows that omission of radiotherapy in low risk early breast cancer does not reduce overall survival or increase breast cancer mortality and local recurrences are salvageable. Despite this there has not been a change in practice regarding omission of radiotherapy. The reasons for this may include challenges in patient selection. Recent advances in immunohistochemistry and genomic profiling may improve risk stratification and the development of biomarkers to directed therapies. Several RCTs have quantified the benefit of radiotherapy in reducing local relapse. Where a treatment benefit is known but is considered to be so small not to be clinically relevant then alternatives to RCTs may be considered to answer the question of need. This is because we can assess risk against a fixed 'absolute' boundary rather than needing a randomised comparator. The prospective cohort study is an alternative to the RCT design to answer the question of need for radiotherapy. The feasibility of recruitment into biomarker-directed de-escalation studies will become apparent as more studies open. The challenge is to determine if we are able to accurately risk stratify patients and avoid unnecessary toxicity, thereby tailoring the need for adjuvant breast radiotherapy on an individual patient basis.

Key words: Biomarker; breast; cancer; clinical; de-escalation; radiotherapy; trials

Statement of Search Strategies Used and Sources of Information

MEDLINE, Pubmed, EMBASE and the Cochrane library were searched in 2017 for relevant literature on biomarker-directed avoidance of radiotherapy studies. The National Institutes of Health and ClinicalTrials.gov databases were searched in 2017 for relevant ongoing and unpublished clinical trials.

Introduction

Adjuvant radiotherapy after breast-conserving surgery (BCS) has been shown to reduce the risk of a recurrence by one-half and breast cancer mortality by one-sixth in patients with early breast cancer [1]. The absolute benefit of radiotherapy is dependent on the individual's risk of relapse and can vary substantially for different prognostic risk groups of patients [1]. Radiotherapy is not without risk and this risk is dependent on factors other than breast cancer prognosis. The risks of radiotherapy may outweigh the benefit for some women at very low risk of breast cancer relapse. This overview examines the challenges and novel approaches to de-escalating breast radiotherapy through clinical research studies.

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What are the Factors Contributing to the Risk of Local Relapse?

Meta-analysis data of patients in trials of adjuvant radiotherapy after BCS suggest that local recurrence risk depends strongly on nodal status and in node-negative patients, young age, poor tumour differentiation and large tumour size indicate a high local recurrence risk [1,2]. A recently published multi-institutional cohort of 2233 consecutive breast cancer patients who underwent BCS and postoperative radiotherapy between 1998 and 2007 observed 69 local recurrences with a median follow-up of 106 months [3]. Non-luminal A subtypes (hazard ratio for luminal B 2.64, $P = 0.001$, for HER2-positive 5.42, $P < 0.0005$ and triple-negative breast cancer 4.33, $P < 0.0005$), age $\leq$ 50 years (hazard ratio 0.56 for patients older than 50 years; $P = 0.01$) and increasing nodal involvement (hazard ratio 1.06 per involved node, $P = 0.004$) were independent risk factors for increased local recurrence on multivariate analysis. Of note, high histological grade (hazard ratio 5.37, $P < 0.001$), T3 disease (hazard ratio 10.39, $P < 0.001$) and positive margins (hazard ratio 2.43, $P = 0.005$) were significantly associated with increased risk of local recurrence on univariate but not on multivariate analysis. Identifying risk factors for local recurrence may help to determine when adjuvant radiotherapy is required.

What are the Benefits of Adjuvant Breast Radiotherapy?

Historical data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) analysis of >10 000 patients randomised into trials of BCS with and without radiotherapy have shown radiotherapy to the conserved breast halves the rate at which a disease recurs and reduces the breast cancer death rate by about a sixth [1,4]. There have been a number of improvements in breast cancer care and a reduction in local relapse rates than those reported in trials on which the EBCTCG meta-analysis was based [5]. Earlier cancer detection, improvements in the quality and standardisation of surgery, developments in systemic therapies and radiation techniques may have contributed to the reduced rates of local relapse [5]. Although the relative benefit from breast radiotherapy remains the same, the absolute benefit is much smaller by virtue of the decreased local relapse rate. As breast cancer survival increases, the late permanent effects of radiotherapy become more apparent and greater patient advocate voice and survivorship awareness have highlighted the problems patients face regarding long-term adverse effects.

What are the Risks of Adjuvant Breast Radiotherapy?

Despite advances in radiation techniques, rare life-threatening side-effects may occur. A large case–control study in 2168 patients showed an increased rate of major coronary events by 7.4%/Gy mean heart dose with breast radiotherapy, with no apparent 'safe' threshold dose to the heart [6]. The absolute risk of radiation-induced cardiac toxicity increases considerably in patients with pre-existing cardiac risk factors [6]. A meta-analysis that included >700 000 women showed that breast radiotherapy was significantly associated with an additional second cancer risk, the highest being second lung cancer risk (relative risk 1.66; 95% confidence interval 1.36–2.01) and the second in incidence was second oesophageal cancer risk (relative risk 2.17; 95% confidence interval 1.11–4.25) that increased over time at least 15 years after treatment [7]. A meta-analysis of trials of women randomly assigned to radiotherapy versus no radiotherapy yielded a lung cancer incidence $\geq$10 years after radiotherapy rate ratio of 2.10 (95% confidence interval 1.48–2.98; $P < 0.001$) and for cardiac mortality, the rate ratio was 1.30 (95% confidence interval 1.15–1.46; $P < 0.001$). Smoking was found to determine the net effect of radiotherapy on mortality [8].

More commonly, radiotherapy can lead to normal tissue effects affecting the treated breast. For example, the 10 year analysis of the UK START trials reported moderate/severe chronic adverse effects, including breast shrinkage, pain, tenderness and hardness [9], leading to impaired quality of life and psychological distress [10].

Given the potential risk of toxicity associated with adjuvant breast radiotherapy there is an increasing view among clinicians that in patients at very low risk of local relapse the side-effects of radiotherapy may outweigh the benefits.

What is the Evidence to Date?

Several studies have randomly assigned women with early breast cancer to receive hormonal therapy with or without radiotherapy and have shown small but significantly improved local control rates in patients receiving radiotherapy [11–15].

The Cancer and Leukaemia Group (CALGB) and PRIME II trials recruited women over 70 and 65 years, respectively. Fyles *et al.* [11] recruited women >50 years, but almost three-quarters of women were aged >60 years. The BASO II trial recruited women <70 years. There is no agreed age cut-off as to what constitutes an older patient.

The CALGB 9943 trial randomly assigned 636 women $\geq$70 years with stage I oestrogen receptor-positive disease and tumour size $\leq$2 cm to receive BCS and tamoxifen with or without radiotherapy and showed that radiotherapy did not improve 5 year overall survival or disease-free survival or decrease the rate of mastectomy for recurrence. In patients receiving radiotherapy there was a small but statistically significant improvement in local relapse. Local relapse was 1% (95% confidence interval 0–2%) in patients receiving radiotherapy versus 4% (95% confidence interval 2–7%, $P < 0.001$) in patients not receiving radiotherapy [13]. The CALGB 10 year local recurrence rates were 2% (95% confidence interval 1–4%) and 9% (95% confidence interval 6–13%) for those who did and did not receive radiotherapy,

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