Editorial

It's PRIMETIME. Postoperative Avoidance of Radiotherapy: Biomarker Selection of Women at Very Low Risk of Local Recurrence

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After 40 years of improving, increasing and extending adjuvant breast cancer therapies, there are increasing concerns about overtreatment, with TIME magazine featuring this controversy on their October 2015 front cover. This editorial discusses the rationale and design of a new study, PRIMETIME, which investigates the omission of radiotherapy after breast-conserving surgery (BCS) in patients at very low risk of recurrence.

Side-effects from Breast Radiotherapy May Now Outweigh Potential Benefit in Some Patients

Radiotherapy is part of the current standard of care and in the UK is recommended by the National Institute for Health and Care Excellence for all women with early invasive breast cancer after BCS. Radiotherapy to the conserved breast halves the rate of cancer relapse (local, regional or distant) and reduces breast cancer mortality by about one sixth [1]. These proportional benefits vary little between different subgroups, but the absolute benefits (number of women per 100 for whom relapse is prevented) vary substantially according to patient and tumour characteristics and can be very low. For example, the UK PRIME II trial (2003–2009) reported a 5 year local relapse rate of 1.3% (95% confidence interval 0.2–2.3) in low risk early breast cancer patients (tumour ≤3 cm, oestrogen receptor positive, node negative) after BCS and radiotherapy compared with 4.1% (95% confidence interval 2.4–5.7) after no radiotherapy (P = 0.002) [2]. There was no excess of distant relapse, second cancers or deaths, suggesting that local relapses after BCS can be salvaged with further surgery (± radiotherapy) without increasing the risk of breast cancer death. In an unplanned subgroup analysis, oestrogen receptor-rich patients receiving radiotherapy had only a 2.4% absolute gain in local relapse over non-irradiated patients.

Side-effects after breast radiotherapy still occur with modern techniques, and the rates and severity are the same irrespective of the magnitude of radiotherapy benefit. The 10 year analysis of the UK START trials testing radiotherapy fractionation in women with early breast cancer reported moderate/severe chronic adverse effects (breast shrinkage, pain, tenderness or hardness) in up to one-third of patients [3]. These side-effects impair quality of life and can cause psychological distress. Even using intensity-modulated radiotherapy, 12% of patients have been reported to have poor cosmesis at 5 years [4]. Breast cancer radiotherapy increases rates of major coronary events by 7.4% per Gray mean heart dose, with the absolute risk of radiation-induced cardiac toxicity increasing substantially in patients with pre-existing cardiac risk factors [5].

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These risks of radiotoxicity support the assertion that if patients with a very low risk of local relapse can be reliably identified, then they may benefit from avoiding breast radiotherapy after complete microscopic excision of primary tumour. Identification of these individuals relies increasingly on the use of tumour biomarkers in the primary tumour.

Risk Stratified Medicine using Biomarkers

Cancer treatment has entered an era of tailored medicine, which may be personalised to the individual or may stratify patient groups of similar risk. Basic clinico-pathological parameters (e.g. tumour size, grade, receptor status and nodal involvement) are being enhanced and even superseded by tumour genotyping. For example, a 21 gene expression assay in breast cancer allows the identification of patients with very low recurrence rates in the absence of adjuvant chemotherapy, who would previously have received chemotherapy based on routine clinicopathological parameters only [6].

Genotyping techniques are expensive. By contrast, immunohistochemical (IHC) biomarkers are a relatively inexpensive alternative that allows sub-typing of tumours into genetically distinct categories based on IHC phenotype. IHC biomarkers have been shown to provide prognostic information on local relapse after radiotherapy [7]. IHC4+clinical (IHC4+C) is a refinement of IHC phenotyping that combines protein expression of oestrogen receptor, progesterone receptor, HER2 and Ki67 with clinicopathological parameters to identify breast cancer patients at very low, low, intermediate or high risk of distant disease recurrence [8]. The TransATAC translational study on ATAC trial (Arimidex, Tamoxifen Alone or Combined) showed that IHC4+C provided comparable or more accurate prognostic information than commercially available genotyping assays (Risk of Recurrence Score and OncotypteDX, respectively) for postmenopausal women treated with endocrine therapy [9]. The IHC4+C score will be used within the PRIMETIME study to identify patients at very low risk of recurrence.

Study Design

PRIMETIME is a prospective, biomarker-directed case-cohort study. It will utilise the highly successful collaborations established by the National Cancer Research Institute Standardisation of Radiotherapy (START) trial testing hypofractionation, and consolidated by the IMPORT, FAST-Forward and PRIME trials. The study rationale is to obtain high-quality, practice-changing, clinical evidence supporting the safe avoidance of radiotherapy for a highly selected subgroup of breast cancer patients, who are deemed to be at such low risk of local relapse that the potential benefits associated with radiotherapy are unlikely to outweigh the known risks.

This study aims to recruit women aged ≥60 years who have undergone BCS for invasive disease, with complete resection of tumour tissue. The final pathology will determine study eligibility, with IHC4+C defining whether patients are ‘very low’ risk (<5% probability of distant relapse at 10 years) and eligible for radiotherapy avoidance or not ‘very low’ risk and therefore require radiotherapy according to standard care (Figure 1). All patients will be recommended a minimum of 5 years of adjuvant endocrine therapy as per local policy.

To ensure sufficient time for IHC4+C calculation, there will be two stages to patient recruitment: (i) preoperative following diagnostic biopsy and (ii) postoperative following definitive surgery and multidisciplinary team confirmation of eligibility.

Stage 1: Patients preoperatively assessed as potentially eligible for study entry will be approached before definitive BCS (Figure 1). Following explanation of the PRIMETIME study, consent will be sought for sample provision to a central laboratory for IHC4+C testing.

Stage 2: Following definitive BCS and confirmation of eligibility, patients will be offered the option of participating in the study. Patients with a ‘very low’ risk of relapse, based on IHC4+C will be recommended avoidance of radiotherapy. Patients with a ‘low’, ‘intermediate’ or ‘high’ risk of relapse, will be recommended radiotherapy. For all

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patients, regardless of risk category, all other anti-cancer treatments will be administered and managed according to local practice.

The primary end point is ipsilateral breast disease rate at 5 years. PRIMETIME requires recruitment of 2400 patients at the preoperative stage, to allow 1550 patients to actively avoid radiotherapy, based on a local relapse rate, in the absence of radiotherapy, of ≤4% at 5 years. The two-stage study design necessitates engagement of the surgical community to facilitate recruitment at the preoperative stage. The study has been designed through collaboration between surgeons and clinical oncologists, with surgeons being key members of the protocol development group. This study has been reviewed by the Association of Breast Surgery (ABS) Academic and Research Committee who will be key members of the protocol development group. The study has been designed through collaboration between surgeons and clinical oncologists, with surgeons being key members of the protocol development group. This study has been reviewed by the Association of Breast Surgery (ABS) Academic and Research Committee who will recommend ABS badging once ethical approval is granted.

Stage 1, which requires recruitment of 1150 women, was chosen in part because the effect of radiotherapy on local recurrence, that the reduction in local recurrence rates provided by radiotherapy is not clinically relevant. A simple cohort study will facilitate rapid accrual, as patient acceptance of randomisation is recognised to negatively affect recruitment. In addition, the PRIMETIME design is in line with a similar Canadian cohort study, LUMINA, allowing future meta-analysis.

**Conclusion**

PRIMETIME has a novel design utilising biomarker selection of patients at ‘very low’ risk of recurrence for avoidance of breast radiotherapy within a prospective cohort study with at least 10 years of follow-up. It is expected that IHC4+C will prove an effective, yet inexpensive method for risk stratification that can be adopted as part of standard care. In addition, it is anticipated that this study will pave the way for the use of routine National Health Service outcome data as a cost-effective method of long-term follow-up in future trials. In an era where overdiagnosis and overtreatment are a regular source of media and patient concern, this study could not be more timely.

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**References**


