**Title:**

**It's PRIMETIME. Post-operative avoidance of radiotherapy: biomarker selection of women at very low risk of local recurrence**

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On behalf of the PRIMETIME Protocol Working Group

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**Editorial:**

After 40 years of improving, increasing and extending adjuvant breast cancer therapies, there are increasing concerns about overtreatment, with TIME magazine featuring this contoversy on their October 2015 front cover. This editorial discusses the rationale and design of a new study, PRIMETIME, that investigates the safe avoidance of radiotherapy (RT) following 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 package 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% CI 0·2-2·3) in low risk early breast cancer patients (tumour ≤3cm, oestrogen receptor [ER] positive, node negative) following BCS and RT compared to 4.1% (95% CI 2·4-5·7) after no RT (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 (± RT) without increasing the risk of breast cancer death. In an unplanned subgroup analysis, ER-rich patients receiving RT had only a 2.4% absolute gain in local relapse over non-irradiated patients.

Side effects following breast RT 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 RT 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 may have poor cosmesis at 5 years[4]. Breast cancer RT increases rates of major coronary events by 7.4%/Gy mean heart dose, with absolute risk of radiation induced cardiac toxicity increasing substantially in patients with pre-existing cardiac risk factors[5].

These risks 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 RT 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 identification of patients with very low recurrence rates in the absence of adjuvant chemotherapy,

who would previously have received chemotherapy based on routine clinico-pathological parameters only[6].

Genotying techniques are expensive. In 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 following radiotherapy[7]. IHC4+clinical (IHC4+C) is a refinement of IHC phenotyping that combines protein expression of ER, progesterone receptor (PgR), HER2 and Ki67 with clinico-pathological parameters to identify breast cancer patients at low, intermediate or high risk of distant disease recurrence [8]. The TransATAC translational study on ATAC trial (Arimidex, Tamoxifen Alone or Combined) demonstrated that IHC4+C provided comparable or more accurate prognostic information than commercially available genotyping assays (Risk of Recurrence Score and OncotypeDX 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 cohort study. It intends to utilise the highly successful collaborations established by the NCRI Standardisation of Radiotherapy (START) trial testing hypofractionation, and consolidated by the IMPORT and FASTForward 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 do not outweigh the known risks.

This study aims to recruit women aged ≥60 years who have undergone breast conserving surgery 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 must be recommended a minimum of 5 years 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 MDT confirmation of eligibility.

Stage 1: Patients preoperatively assessed as potentially eligible for study entry will be approached before definitive breast conserving surgery (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 breast conserving surgery 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 patients, regardless of risk category, all other anti-cancer treatments will be administered and managed according to local practice.

The primary endpoint is ipsilateral breast disease rate at 5 years. PRIMETIME requires recruitment of 2400 patients at the pre-operative stage, to allow 1550 patients to actively avoid of 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 pre-operative stage. The study has been designed through a collaboration between surgeons and clinical oncologists, with surgeons being a fundamental part of the trial management group. This study has the support of the Association of Breast Surgery. Given the previous success of surgical-clinical oncology collaboration with IMPORT high (which necessitated cavity clip insertion at surgery, and achieved a 93% compliance rate) we anticipate similar successful teamwork. PRIMETIME also has strong support from patient advocates who have been involved in every stage of the study evolution and will continue to play an active role.

Follow-up data will be collected prospectively during routine clinical follow up. Given that this group of patients can relapse after 5 years following treatment, it is essential that outcomes are monitored for at least 10 years. This includes yearly mammograms for 10 years for those patients not receiving radiotherapy. As a further aim of this study, we shall determine the accuracy of outcomes reported on Cancer Services and Outcomes Dataset (COSD), the National Radiotherapy Dataset (RTDS), the Systemic Anti-Cancer Therapy Dataset (SACT) and the Hospital Episodes Statistics (HES) compared to prospective research data collection. This will allow us to validate the use of routinely collected NHS outcome data as a new cost-effective method of long term research data collection.

PRIMETIME is designed as a cohort study, rather than a randomised trial, after extensive discussions with the funders (Cancer Research UK), the trialists, UK Breast Intergroup, National Cancer Research Institute Breast Clinical Studies Group and patient advocates. This study design was chosen in part because the impact of radiotherapy on local recurrence rates is already known, and thus does not need determining by a randomised trial. PRIMETIME aims to define a subgroup of women at sufficiently low risk of 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 impact on recruitment. In addition, 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 follow up. It is hoped 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 use of routine NHS outcome data as a cost-effective method of long term follow up in future trials. In an era of overdiagnosis and overtreatment being a regular source of negative media attention, this study could not be more timely.

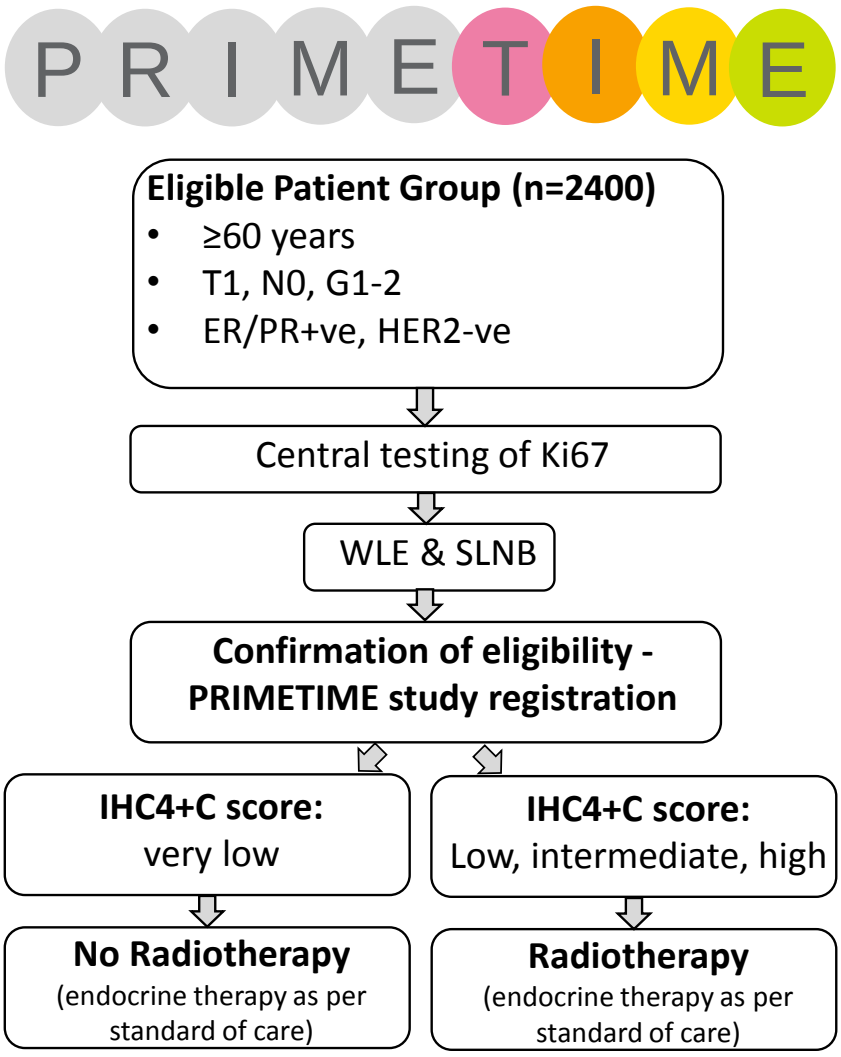


**Figure 1: Schema for PRIMETIME Study.** ER+, Oestrogen Receptor Positive; IHC4+C, Immunohistochemistry4 + Clinical Score; WLE, wide local excision; SLNB, sentinel lymph node biopsy; ET, endocrine therapy; RT, radiotherapy. Eligibility criteria, to allow risk group determination, includes final pathology confirmation of AJCC staging of pT1/pN0/M0; grade 1 or 2 invasive breast cancer; oestrogen (ER) and progesterone receptor (PR) positive and human epidermal growth factor receptor (HER2) negative according to local practice; and a IHC4+C recurrence probability score.

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**Figure 1 Study Schema**