

particularly invasive LR. An overview of all four of the randomised trials that compared adjuvant whole breast radiotherapy (RT) vs no RT after breast-conserving surgery for DCIS showed that RT halved the LR rate [1]. It reduced the absolute 10-year intraductal or invasive LR risk by 15.2% (12.9% vs 28.1%, $2P < 0.00001$). RT was effective irrespective of age, detection method, focality, tumour size, architecture, grade, comedonecrosis, margin status or tamoxifen use. However, there was no significant effect on breast cancer mortality or all-cause mortality.

Currently, there are no reliable predictors for invasive LR and published data is limited to identification of surrogate markers for clinical outcome. There is a consistent association between younger age and an increased LR risk. High nuclear grade and presence of comedonecrosis are strongly associated with LR and progression to invasive disease. In addition, large tumour size and involvement of surgical margin are associated with LR but the optimal margin size remains controversial. Molecular markers including oestrogen receptor status, HER2/neu oncogene over-expression and p53 tumour suppressor gene mutation have not been reliably associated with LR risk. Approaches derived from global molecular profiling are being investigated for predictive assessment of recurrence.

A principal aim of DCIS research is to determine robust biomarkers to identify women at high risk from those at lower risk of invasive LR, and enable individualised treatment. A single-arm prospective study reported a 5-year LR rate after breast-conserving surgery, without RT of 6.1% in patients with low or intermediate grade DCIS ≤ 25 mm in size and resected with margins ≥ 3 mm, and 15.3% in patients with high grade DCIS ≤ 10 mm [2]. Further research on biomarkers may enable more reliable identification of patients who have low absolute risk of LR and for whom RT may provide little absolute gain. In contrast, patients at higher risk of LR may benefit from more extensive surgery and/or RT. The addition of a tumour bed boost to whole breast RT to further reduce LR rate is being investigated in a clinical trial.

References

- [1] EBCTCG. J Natl Cancer Inst Monogr 2010;41:162-77.
- [2] Hughes et al. J Clin Oncol 2009;27:5319-24.

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Invited

The Pathology of DCIS: Take it or Leave it

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Incidence rates of ductal carcinoma in situ (DCIS) have increased over the past decades largely due to population-based screening for breast cancer. However, data from 1987 to 1999 indicate that invasive ductal carcinoma incidence rates have remained essentially constant. On pathological examination, a subgroup of neoplastic low grade intraductal lesions is even more low risk than classical cribriform ductal carcinoma in situ grade 1 with a cumulative risk on progressive disease of 0.5–1.0% per year, a risk that is comparable to developing local recurrence after breast conserving therapy. These lesions share the same histogenetic alterations and are diagnosed by a variety of terms covering a spectrum of morphological slightly different lesions ranging from columnar cell change to cribriform ductal carcinoma in situ grade I. Within this spectrum, a variety of diagnostic definitions have been proposed like atypical ductal hyperplasia, flat epithelial atypia, columnar alterations with prominent snouts and secretions (CAPSS), etc., etc. Nevertheless, one of the major challenges remains, i.e. the substantial interobserver variation in diagnosing these low risk, low grade intraductal neoplastic lesions.

In current practice, most women undergo surgery to excise the high end of the risk spectrum, i.e. the unambiguous DCIS grade I lesions, regardless of extensiveness and patient's features, such as age and co-morbidity, to exclude that the core biopsy was containing just the tip of the iceberg. For the more ambiguous lesions, patient management can vary enormously due to different opinions and interpretations of the multidisciplinary breast team. Most likely, the majority of women with such a lesion would not benefit from surgery due to the low risk of developing extensive DCIS and/or invasive ductal carcinoma. In addition, if lesions do develop from a low grade in situ component, these are almost always well differentiated, small sized, hormone receptor positive, HER2 negative invasive carcinomas with an exceptionally favorable prognosis. In fact, the risk of dying due to the disease might not be significantly higher than in the non affected population. It is therefore unsure whether surgical excision (followed by radiotherapy in case of breast conserving treatment) of such lesions can be considered as adequate treatment or overtreatment. To solve this issue, proper follow-up of patients with such lesions without surgical intervention is required to justify either surgery or a watchful waiting policy.

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Proffered paper oral

Adjuvant Radiotherapy After Breast-conserving Surgery for Ductal Carcinoma in Situ – Fifteen-year Results of the EORTC Randomized Phase III Trial 10853

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Background: The incidence of ductal carcinoma in situ (DCIS) has increased in the last decades due to mammographic screening and accounts currently for 25% of the new breast cancers. We present the 15-years results of a randomized controlled trial that investigated the role of adjuvant radiotherapy (RT) after a local excision (LE) for DCIS.

Patients and Methods: Between 1986 and 1996, 1010 patients with a complete excision of DCIS < 5 cm were randomized to no further local treatment or RT (50 Gy in 25 fractions to the whole breast).

Results: After a median follow up of 15.8 years, radiotherapy continued to reduce the risk of a local recurrence (LR) (HR = 0.52; 95% CI = 0.40–0.68); the LR free rate was 69% in the LE arm, which was increased to 82% in the LE+RT arm. There were comparable reductions in the incidence of a DCIS LR (HR = 0.49; 95% CI = 0.33–0.73) and an invasive LR (HR = 0.49; 95% CI = 0.33–0.73). The 15-years cumulative incidence for LE alone compared to LE+RT for DCIS LR was 14.9% versus 7.5% respectively, and for an invasive LR this was 15.5% vs. 9.8% respectively.

When the hazard rate of a LR was analysed within three time windows (0–5, 5–10 and from 10 year onwards), this was estimated as 2.0% (95% CI = 1.4–2.6) during the first 5 years in the group receiving RT and 4.0% (95% CI = 3.2–4.8) in the group treated only with LE, 1.2% (95% CI = 0.8–1.7) and 2.0% (95% CI = 1.4–2.8) respectively in the next five years, and 0.6% (95% CI = 0.4–1.0) and 1.3% (95% CI = 0.8–1.9) respectively from 10 year onwards. The protecting effect of RT on a DCIS LR was similar throughout all time frames, the effect of RT on an invasive LR was observed mainly in the first 5 years after treatment.

The differences in LR in both arms did not lead to a difference in distant metastasis (HR = 0.99, 95% CI = 0.61–1.61) or death (HR = 1.02; 95% CI = 0.71–1.44).

Women with a DCIS LR had a similar survival prognosis after the event as compared to those without a LR. However, after an invasive LR their prognosis was significantly worse as compared to the non-recurring patients; this is reflected by a HR of 5.2 (95% CI = 3.1–8.7) for overall mortality and a HR of 17.7 (95% CI = 8.9–35.2) for breast cancer related mortality.

Conclusion: At 15 years, almost 1 in 3 women developed a LR after LE for DCIS. RT reduced this risk by 50%, equally divided over invasive or DCIS recurrences. The majority of the LRs occurred within five years after treatment; radiotherapy seemed to have a continuous protecting effect with respect to DCIS recurrence; but only a temporary protecting effect with respect to invasive recurrences in the first 5 years after treatment. Although no survival difference was seen between the two treatment groups, women who experienced an invasive recurrence had a significant worse survival compared to women who had a DCIS recurrence or no recurrence at all.

Thursday, 22 March 2012

15:30–17:00

CLINICAL SCIENCE SYMPOSIUM

Barriers to Effective Care

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Invited

External Barriers to Effective Care in Clinical Research

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Therapeutic drug development in oncology has reached new heights in recent years with the emergence of targeted agents. More than 20 years on from the development of trastuzumab to treat HER2+ breast cancer, clinicians still only have limited registered therapeutics for treatment i.e. trastuzumab and lapatinib. This phenomenon is not specific to breast