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Omission of radiotherapy in elderly patients with early breast cancer: 15-Year results of a prospective non-randomised trial

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Abstract ***Background:*** Whether radiotherapy (RT) is beneficial in elderly (⩾70 years) patients undergoing conservative surgery for early breast cancer has long been controversial. Recent randomised trials show that most elderly patients do not benefit from RT. We started a prospective non-randomised trial to address this issue in 1987 and now present results for the 627 consecutive pT1/2cN0 patients recruited, and treated by conservative surgery (quadrantectomy) and tamoxifen, and assigned non-randomly to RT or no RT.

Methods: We used multivariate competing risks models to estimate 15-crude cumulative incidence (CCI) of ipsilateral breast tumour recurrence (IBTR), distant metastasis and breast cancer mortality. The models incorporated a propensity score as a measure of probability of receiving RT based on baseline characteristics, to account for the lack of randomisation.

Results: For pT1 patients, 15-year CCIs of IBTR, distant metastasis and breast cancer death were indistinguishable in the RT and no RT groups. For pT2 patients, 15-year CCI of IBTR was much higher in those not given RT (14.6% versus 0.8%, $p = 0.004$), although breast cancer mortality and distant metastasis did not differ significantly between RT and no RT.

Conclusions: Consistent with the findings of recent randomised trials, our long-term data indicate that most elderly, ER-positive patients with pT1 cN0 breast cancer treated by quadrantectomy do not benefit from RT. The 14.6% CCI of IBTR in our pT2 patients is an additional finding not presented in the trials and suggests that RT should be administered to elderly patients with pT2 disease.

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1. Introduction

The meta-analysis of 10,801 breast cancer patients from 17 randomised trials published by the Early Breast Cancer Trialists' Collaborative Group in 2011 [1], showed that radiotherapy (RT) after breast-conserving surgery not only reduces the risk of breast cancer recurrence but also improves overall survival. However, although the incidence of breast cancer increases with advancing age [2] – and around 40% of breast cancers occur in women over 65 years – most of the randomised trials that assessed postoperative breast RT excluded patients over 70 years [3–6] and it was unclear for many years whether RT after breast-conserving surgery is beneficial in elderly patients. An early trial carried out at our Institute [3], which recruited patients with tumour $\leqslant$2.5 cm, found in an *ad hoc* analysis, that the incidence of cancer recurrence in the no RT arm declined markedly with age, and the authors suggested that RT may not be necessary in older women. By contrast, another early trial, published in 1992 [4], did not identify a subgroup of patients at low risk of local recurrence who could be spared RT; in particular, for women over 50 years with tumour up to 2 cm who did not receive RT, the recurrence rate at 7 years was 22% [5].

In 2013, the long-term results of the CALGB 9343 randomised trial were published [7]. This trial recruited women aged 70 years or older with T1N0 ER-positive breast cancer, treated with lumpectomy and tamoxifen, and randomised to either postoperative RT or no RT. Fewer local relapses occurred in the RT arm (2% versus 9%) without, however, affecting breast cancer mortality, distant disease-free survival, or breast conservation, after a median follow-up of 12.6 years.

In 1987 we initiated a prospective non-randomised study to investigate whether breast RT can be safely avoided in elderly patients ($\geqslant$70 years) undergoing conservative surgery (quadrantectomy) and prescribed tamoxifen. Here we present 15-year results of that study. Whether or not RT was given depended on patient preference and the treating surgeon's opinion. No patients were formally contraindicated for RT. We used a propensity score with multivariable analyses to adjust for the imbalance in baseline characteristics between the two groups.

2. Patients and methods

2.1. Patients

Of 1451 consecutive breast cancer patients $\geqslant$70 years presenting at the Milan National Cancer Institute between January 1987 and December 1992, we evaluated 627 consecutive cN0 patients (430 pT1; 197 pT2 [$\leqslant$3 cm]) who underwent conservative surgery with or without postoperative RT. Patients with involved resection margins, multifocal lesions, synchronous bilateral breast cancer, distant metastasis at diagnosis, previous cancer at another site, or contraindication for RT, were excluded.

2.2. Treatment

Two hundred and seven patients received postoperative RT, 420 patients did not. RT was administered to the residual breast using a cobalt unit or 6-MeV photons to deliver 50 Gy (daily target dose 2 Gy) in the two opposing tangential fields. In all cases, a 10 Gy boost was administered to the tumour bed. The irradiation aimed to treat the breast only, with no attempt to include the axillary, supraclavicular or internal mammary nodes in the irradiation field.

Axillary dissection was performed in 134/430 (31%) patients with pT1 disease, and 33/197 (17%) patients with pT2 disease. After surgery, regardless of hormone receptor status, all women were prescribed 20 mg tamoxifen daily for at least 3 years.

2.3. Hormone receptor status

Hormone receptor status was determined by the dextran-coated charcoal technique [8]. Cancers with oestrogen receptor (ER) concentration above 10 fmol/mg cytosol protein were considered ER positive; those with progesterone receptor (PgR) above 25 fmol/mg were considered PgR positive. Cancers with receptor content below these values were considered receptor negative.

2.4. Follow-up

Patients were seen every 6 months for the first 5 years and annually thereafter. Mammography and chest X-ray were performed once a year and bone scan every 2 years. Gynaecological examination with pelvic ultrasound was performed annually since patients were receiving tamoxifen. Disease status or cause of death was ascertained from clinical records, by consulting general practitioners or from mortality databases. Median follow-up was 188.1 months in the no RT group and 208.9 months in the RT group. No patients were lost to follow-up.

2.5. Statistical methods

During follow-up possible events were ipsilateral breast tumour recurrence (IBTR), axillary relapse, distant metastasis, contralateral breast cancer, new primary at non-breast site, breast cancer death and death for any other cause. These events compete with each other to occur first, so competing risk methods were used to estimate crude cumulative incidences (CCIs) of events of

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