



Original Research

Preoperative radiotherapy in breast cancer patients: 32 years of follow-up



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Abstract This study evaluates the long-term outcomes of a retrospective cohort of breast cancer (BC) patients who had received curatively intended premastectomy radiation therapy (RT). We analysed locoregional control, disease-free survival (DFS) and overall survival (OS), pathological complete remission (pCR), predictors thereof, and immediate safety. The series consisted of 187 patients with a median age of 49 years [43–60] and T2–T4 or N2 tumours. Between 1970 and 1984, they had received slightly hypofractionated RT to the whole breast, ipsilateral supraclavicular fossa and axilla ± the internal mammary chain (45–55 Gy/18 fractions of 2.5 Gy/34 days) systematically followed by a modified radical mastectomy with an axillary dissection. No other preoperative treatment was given. Among the 166 centrally reviewed tumour biopsy specimens, 22% had a triple-negative (TN) phenotype, 17% were HER2 3+ or amplified and 61% were ER+. The median follow-up was 32 years [23–35]. The 25-year locoregional control rate was 89% [93%–82%] and the 25-year DFS and OS rates were identical, 30% [24%–37%]. A pCR in the tumour and lymph nodes had been achieved in 18 among all patients (10%), but in 26% with TN disease. In the multivariate analysis, the TN status was the only predictive factor of pCR (OR = 5.49, 95% confidence interval [CI] 1.87–16.1, $p = 0.002$). Also, the pN status (HR = 1.69, [1.28–2.22], $p = 0.0002$) and TN subtype (HR = 1.80, [1.00–3.26], $p = 0.05$) exerted a significant prognostic impact on OS. The

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postoperative complication rate (grade >2) was 19% with 4.3% of localized skin necrosis. Preoperative RT followed by radical surgery is feasible and associated with good long-term locoregional control.

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1. Introduction

Preoperative radiation therapy (PreopRT) was investigated in the 1980s to permit conservative surgery but few data are available on its role before mastectomy and on the pathological complete remission (pCR) rates achieved [1]. Adjuvant radiation therapy (RT) plays an important role in the treatment of breast cancers (BC) affording a benefit for disease-free survival (DFS) and overall survival (OS) [2,3]. Complete remissions have been demonstrated with RT alone in BC [4–6]. This raises the question of whether PreopRT should currently be used in combined treatment strategies.

The aims of this study were to evaluate the long-term outcomes after PreopRT followed by mastectomy with an axillary dissection (AD), in a large retrospective cohort of BC patients specifically focused on locoregional control. The secondary end-points were the safety and feasibility of this treatment schedule, the definitions of outcome predictors and the pCR rate.

2. Patients and methods

2.1. Eligibility

This retrospective study comprised patients treated with PreopRT for non-inflammatory and non-metastatic BC between 1970 and 1984 in the Gustave Roussy centre. Patient characteristics are shown in Table 1. Patients were selected for PreopRT due to a high risk of a locoregional recurrence (LRR) after mastectomy. The written protocol had previously been established by the local Breast Cancer Tumor Committee for T2 tumours with a clinical doubling time of less than 6 months (classified as PEV1 [7]); inoperable T3 bulky tumours; non-inflammatory T4 tumours or palpable fixed N2 axillary nodes. The patients were evaluated and examined during a clinical session by three specialists (a surgeon, a radiation and medical oncologist) and had a chest X-ray, a pelvic X-ray and blood tests for staging. All treated patients gave their oral consent for the treatment. All cases including the classification and the treatment schedule were immediately registered in the institution's central computer. A core needle biopsy was performed for the baseline histological diagnosis. In five patients, a surgical excisional biopsy was done due to insufficient core biopsy material. The reference date was the start of RT.

2.2. Treatments

RT, performed with a Cobalt-60 unit, encompassing the whole breast, ipsilateral supraclavicular fossa and the axilla, delivered 45 Gy in 18 fractions of 2.5 Gy, one fraction a day, 4 days a week. The ipsilateral internal mammary chain received a total dose of 45–55 Gy. A modified radical mastectomy (MRM) with an AD was systematically performed at least 4 weeks after the completion of radiotherapy, whatever the tumour response. No patient received preoperative chemotherapy or endocrine therapy. Postoperative chemotherapy (CMF or anthracycline-based regimens) was prescribed according to institutional guidelines at that time.

2.3. Pathological assessment

Retrospectively, the hormone receptor (HR) status assessed by immunohistochemistry and the HER2 status assessed by immunohistochemistry on the biopsy and mastectomy specimens were centrally reviewed. Missing data were due to exhausted histological specimens. The cut-off for HR positivity was $\geq 10\%$ of positive tumour cells exhibiting nuclear staining. HER2 positivity was defined as a score of 3+ [8,9]. A pCR at surgery was defined as the absence of invasive or in situ carcinoma in the breast (ypT0) and axillary nodes (ypN0).

2.4. Follow-up

The 30-day morbidity and mortality following surgery were collected from patient files and defined as any event requiring medical intervention. Toxicities were classified according to the CTCAE V4.03 [10]. The patients had a clinical follow-up every 6 months for 5 years, and annually thereafter. A mammography was performed once a year. Follow-up data were last updated in June 2014.

2.5. Statistical analysis

Patient characteristics are described using rates for categorical variables and medians and the interquartile range (IQR) for continuous variables (Table 1). The median follow-up was calculated with the inverted Kaplan–Meier method [11]. Tumour event rates were calculated from the first day of radiotherapy to the date of diagnosis of the event (local or regional recurrence, or

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