# Factors predictive of locoregional recurrence following neoadjuvant chemotherapy in patients with large operable or locally advanced breast cancer: An analysis of the EORTC 10994/BIG 1-00 study

# Factors predictive of locoregional recurrence following neoadjuvant chemotherapy in patients with large operable or locally-advanced breast cancer: an analysis of the EORTC 10994/BIG 1-00 study

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**Highlights:**

- Predictors of locoregional recurrence (LRR) may help to tailor radiotherapy
- Second study using data from a prospective trial
- Low 5-year LRR rate (4.90%), with only 76 patients with a LRR as first event
- The highest LRR risk is observed in triple negative and HER2+ subtypes.

## Abstract

**Purpose:** Identification of clinico-pathological factors predicting for a locoregional recurrence (LRR) after neoadjuvant chemotherapy (NAC) could help to decide on the optimal locoregional radiotherapy. The objective of this trial is to identify those factors in the context of a phase III trial (EORTC 10994).

**Methods:** Patients received NAC followed by surgery with or without radiotherapy. Radiotherapy was administered according to pre-specified guidelines. Patients with hormone receptor positive tumours received adjuvant hormonal therapy. A proportion of patients with Human Epidermal growth factor Receptor 2 (HER2) positive cancer received adjuvant trastuzumab. The predictive factors for LRR were identified by multivariate analysis with time to LRR as first event as the primary endpoint.

**Results:** The median follow-up was 4.8 years. In 1553 eligible patients, there were 76 LRRs with a 5-year cumulative incidence of 4.9% (95% CI: [3.76-6.04]). In multivariate analysis, breast cancer subtype was a significant predictor of LRR ($p<0.0001$): Hazard Ratio (HR) 6.44 (95% CI: [2.83-14.69]) for triple negative, 6.26 (95% CI: [2.81-13.93]) for HER2+ without trastuzumab (T), and 3.37 (95% CI [1.10-10.34]) for HER2+ with T cancers, all compared to Luminal A patients. Lack of pathological response was also associated with significantly higher LRR risk in case of ≥ 4 pathologically positive nodes, HR 2.43 (95% CI [1.34-4.40], $p<0.0001$).

**Conclusion:** Breast cancer subtype and lack of pathological response are predictive factors for high LRR after NAC.

**Key words:** Breast cancer, neoadjuvant chemotherapy, locoregional recurrence

## Introduction

Adjuvant radiotherapy indications after neoadjuvant chemotherapy (NAC) are, for now, based on the standard radiation indications (1). However, none of the studies that led to these indications included patients receiving NAC (2, 3).

With regard to identified predictive factors of locoregional recurrence (LRR), the National Surgical Adjuvant Breast and Bowel Project (NSABP) study is the only published data from prospective trials (NSABP B-18, NSABP B-27) (4, 5). Several predictive factors of 10-year LRR risk were identified in that study: age <50 years (after lumpectomy), clinical tumour size >5 cm (after mastectomy), clinical nodal status (cN+), pathological breast tumour response (ypT+) and pathological nodal status (ypN+) (6).

We therefore analysed data from the previously published EORTC 10994/BIG 1-00 neoadjuvant phase III trial (7). The EORTC study is more recent compared to the NSABP study with significant therapeutic implications for radiotherapy indications, adjuvant hormonal therapy and trastuzumab. We included two pathological factors in our analysis: the pathological response after chemotherapy and a simplified breast cancer subtype classification. The latter consists of 4 groups: luminal A-like, luminal B-like, Human Epidermal growth factor Receptor 2 (HER2) positive and triple negative (supplementary table 1). In the EORTC 10994 study, only a third of the patients with HER2-positive tumours received adjuvant trastuzumab. This treatment became the new standard of care for HER2-positive patients at the end of the EORTC 10994/BIG 1-00 trial (8, 9). Since trastuzumab treatment is known to reduce the risk of relapse including LRR (10), the HER2-positive group was further divided in two subgroups: patients who did or did not receive adjuvant trastuzumab. Our aim is to examine rates and patterns of LRR and to identify predictive factors in breast cancer patients treated with NAC.

## Methods

### Study design, eligibility and treatments

This was an unplanned analysis of the EORTC 10994/BIG 1-00 neoadjuvant phase III trial randomizing patients in a 1:1 ratio between six cycles of fluorouracil, epirubicin, cyclophosphamide and a taxane-based regimen, docetaxel for three cycles followed by epirubicin+ docetaxel for three cycles, all administered prior to primary surgery (7). The trial was registered with ClinicalTrials.gov number NCT00017095 and was approved by national and/or local ethics committees in all participating centres. All patients signed an informed consent for the clinical trial and for research on tumour samples taken before registration and randomization. Eligible patients for the EORTC 10994 trial were women aged <71 years suitable for NAC, with histologically-proven invasive carcinoma of the breast, with any large operable or locally advanced/inflammatory breast cancer. Following surgery, treatment was completed with planned radiotherapy in accordance with the guidelines described in the protocol (supplementary file). Adjuvant endocrine therapy for 5 years was mandatory for women with Oestrogen Receptor (ER) and/or Progesterone Receptor (PR) positive tumours. Patients with HER2-positive tumours were allowed to take part in adjuvant clinical trials assessing trastuzumab or to receive this treatment in the adjuvant setting when it became standard practice, but not to receive it neo-adjuvantly.

For this sub-study, a subgroup of the initial population of 1856 patients was selected based on the following criteria: (i) eligible patients from the EORTC 10994 trial (ii) patients who received at least one cycle of NAC and who underwent surgery of the primary tumour and axilla; (iii) patients who didn't receive radiotherapy before surgery; (iv) patients who did not progress on NAC; (v) patients without inflammatory breast cancer.

**Objectives and endpoints definitions**

The primary objective was to identify predictive factors for LRR as first relapse after NAC and locoregional treatment. The secondary objective was to describe the LRR rate and patterns and the time to LRR as first relapse.

The time to LRR was defined as the time in days from the date of surgery to the date of a locoregional recurrence as a first relapse. LRRs were reported by the investigators on a case report form. Regional recurrences sites were classified as skin and/or chest wall, axillary lymph nodes, internal mammary nodes and infra/supraclavicular nodes relapses. Patients who died or experienced a distant relapse or a second primary cancer prior to or within a window of 2 months following a LRR (STEEP system) were considered as having had a competing risk event at the time of the competing event (11). Patients without an event of interest or a competing risk event were censored at their last follow-up date.

**Pathology assessment**

No central pathology review was performed for this analysis. Grade, ER, PR, and HER2 status were assessed by local pathologists from biopsy taken at diagnosis and reported on a case report form. ER, PR and HER2 status was assessed by immunohistochemistry (IHC) and reported as positive or negative according to each center's local definition. HER2-positivity was defined as either HER2 gene amplification by fluorescent in situ hybridization and/or scored 3+ by IHC. As the information on Ki-67 was not available from data collected within the main EORTC 10994 study, we replaced Ki-67 by grade in order to classify tumours in luminal A-like or luminal B-like groups, based on the St Gallen 2011 consensus (supplementary table 1) (12). Pathological response was assessed by local pathologists by microscopic examination of the excised tumour and lymph nodes after completion of the NAC. Pathological complete response (pCR) was defined as no evidence of residual invasive cancer (or very few scattered tumour cells) in the primary tumour, with or without residual ductal carcinoma in situ, and in axillary lymph nodes (ypT0/is ypN0) (US FDA suggested definition) (13). Surgical margins

were defined as negative (R0) when no invasive or in situ carcinoma cell was seen on the inked section, or as positive (R1) otherwise.

**Statistical analysis**

A statistical analysis plan was prospectively defined. Eligible patients were analysed on an intent-to-treat basis. All the statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). The following variables were tested as potential predictive factors for LRR as first event: age at diagnosis, cT, cN, type of surgery (lumpectomy/quadrantectomy, mastectomy), histological type (ductal, lobular, other), surgical margins (R0, R1), pathological tumour/nodal status after NAC (ypT0/is ypN0, ypT+ (any size) ypN0, ypT+ (any size) ypN+ 1-3 nodes, ypT+ (any size) ypN+ ≥4 nodes), and simplified breast cancer subtypes classification with 6 groups, luminal A-like, luminal B-like (HER2-), HER2+ Trastu- (not treated with trastuzumab), HER2+ Trastu+ (treated with trastuzumab), triple negative, unknown.

A backward model selection procedure was performed starting from a full multivariate Fine and Gray model containing all potential predictive factors (14). The selection procedure was stopped when all remaining factors in the model were significant at the 5% level according to the 2-sided Fine and Gray test p-value. The prognostic effect of these factors was quantified by the corresponding hazard ratio (HR) estimates with their 95% confidence interval (CI) in the final multivariate Fine and Gray model. These remaining factors were considered predictors for LRR as first relapse after NAC in this analysis. Patients with missing value(s) for one (or more) of the considered variables were excluded from the primary analysis. A sensitivity analysis was done, using a Cox model in which the competing events were censored, in order to validate the obtained results. An internal validation was also conducted via bootstrap resampling, to confirm the stability of the remaining factors. LRR cumulative incidence curves were generated using Kaplan Meier method.

## Results

### Characteristics of the patient population

Of the 1856 patients originally randomised, 1553 patients were eligible for this sub-study. The reasons for ineligibility are provided in the consort diagram (figure 1). The clinicopathological characteristics of the patients are shown in table 1.

### Rates and cumulative incidence of LRRs

Median follow-up was 4.4 years (95% CI, [4.2-4.5]) from the date of surgery. A total of 76 patients presented with a LRR as first relapse. Table 1 shows the number of patients (and rates) with LRR as first relapse according to patient and tumour characteristics. Competing events were observed in 351 patients (distant relapse in 350 and death in 1). Cumulative incidence curves of LRR as first event and of competing events are reported in figure 2. The LRR rate at 5 years was 4.9% (95% CI,[3.76-6.04]) and the local relapse only as first relapse rate at 5 years was 1.9% (95% CI,[1.2-2.8]).

### Patterns of LRRs as first event

Of the 76 patients with observed LRR as first relapse, 27 (35.5%) had local recurrences only, 4 had local and regional recurrences (5.3%) and 45 (59.2%) had regional recurrences only (one regional site or more).

Details of LRRs are provided in table 2. Sites of relapse were local in 31 patients, chest wall relapses in 28, axillary nodes in 11, internal mammary nodes in 3, infraclavicular nodes in 6 and subclavicular nodes in 8. Recurrences were preferentially isolated among patients with local recurrences (27/31 cases (87.1%)) and with infra/supraclavicular node recurrences (10/14 cases (71.4%)). They were frequently accompanied by another site of relapse among patients with regional axillary nodes recurrences (7/11 cases (63.6%)) and internal mammary node recurrences (2/3 cases (66.7%). LRRs predominantly occurred in the first 3 years of follow-up (figure 2). However, some LRRs were observed over 7 years after date of surgery.

**Predictive factors for LRRs**

Due to missing data, 48 of the 1553 eligible patients were excluded (figure 1) for the principal multivariate analysis (table 3). Two factors were identified as being independent predictors of LRR as first event after NAC: breast cancer subtype classification and pathological response ($p < 0.0001$ for both factors).

The luminal A-like group, used as the reference, had lower risk of LRR. In the final multivariate Fine and Gray model, luminal B-like, HER2+ Trastu-, HER2+ Trastu+ and triple negative groups had a higher risk of LRR: HR 2.29 (95% CI,[0.76-6.97]), 6.26 (95% CI,[2.81–13.93]), 3.37 (95% CI,[1.10–10.34]), and 6.44 (95% CI,[2.83–14.69]), respectively. Although no direct comparison was made between these groups, the risk of LRR tended to be lower among patients with HER2-positive cancer when treated with adjuvant trastuzumab.

Concerning the pathological response, the ypT0/is ypN0 group was taken as the reference group. The main difference between the groups is driven by the increased risk of LRR for the ypT+ (any size) ypN+ >4 nodes group (HR 2.43; 95% CI,[1.34–4.40]). By contrast, a lower risk of LRR was observed in the ypT+ (any size) ypN0 and ypT+ (any size) ypN+ 1-3 nodes groups (HR 0.58 [0.26–1.28] and HR 0.74 [0.36–1.52]) although the CIs were large. Of note, 16 patients with a pCR presented a LRR as first site of relapse of whom 10 presented a local relapse only (supplementary table 2).

The other tested factors (age, cT, cN, histological type, type of surgery and surgical margins) were not significantly associated with the occurrence of LRR as first relapse in this analysis.

Sensitivity analyses using a backward procedure on Cox models in which the competing events are censored, selected the same factors for prediction of LRR as first event. Internal validation via bootstrap resampling of this model confirms the stability of these two factors (supplementary table 3).

## Discussion

The first notable observation of this study is the low 5-year LRR rate (4.90%), with only 76 / 1553 patients presenting with a LRR as first event. In the retrospective studies published from 2002 to 2005, the 5-year LRR rate was higher (ranging from 10-27%) (15-18) decreasing in more recent publications (ranging from 4.6-11%) (19-23). In the NSABP study, the 10-year LRR rate was 11.1% (6). Given that pre-operative breast MRI was exceptionally performed at that time and radiopaque markers were rarely inserted in the tumours, it may be that the lower LRR observed in EORTC trial could be due to improvements in radiotherapy, hormonal therapy and trastuzumab use. Adjuvant radiotherapy was more widely used in EORTC trial, with strict guidelines provided in the study protocol (see Appendix). The indications of adjuvant hormone therapy have evolved in recent years. In NSABP B-18 trial, only patients >50yrs received tamoxifen. In EORTC trial, tamoxifen (or aromatase inhibitors for postmenopausal patients) was given to all patients with positive ER and/or PR cancers; one third of patients with HER2-positive cancer received adjuvant trastuzumab.

The second key finding of our study is the demonstration of a statistically predictive role of breast cancer subtypes on LRR risk after NAC, particularly for triple negative and HER2-Positive subtypes (irrespective of adjuvant trastuzumab treatment). In EORTC trial, the highest LRR risk was observed in triple negative and HER2+ Trastu- groups with high HRs (6.44 and 6.26, respectively). Although breast cancer subtypes were not analysed in NSABP study (6), the role of subtypes on LRR risk had been suggested in smaller retrospective studies (20,21,23). Our analysis corroborated these initial results with greater robustness. Regarding the role of adjuvant trastuzumab, estimated LRR risk was nearly two times higher for HER2 Trastu- than for HER+ Trastu+ cancers. Although no direct comparison could be made between these 2 groups, adjuvant trastuzumab certainly plays a role. Its protective effect on LRR after NAC had been suggested in two recently published retrospective studies from the MDACC and the Korean groups (22,23). Luminal A-like and luminal B-like (HER2-negative)

cancers showed lower LRR rates. However, breast luminal A and B cancers continue to relapse beyond 5 years after the initial diagnosis, whereas later relapses of other subtypes are rare. We acknowledge that the follow-up might be to short. Hence, another analysis of the EORTC study based on long-term follow-up data is planned in late 2017.

In our study, pathological response was the only other predictive factor for LRR. The main difference between the groups was not driven by a decreased risk in patients achieving a pCR group, but by an increased risk of LRR for the ypTx (any size) ypN+ ≥4 nodes subgroup. Our finding is consistent with literature, pathological nodal involvement having already been identified as a predictor of LRR, with a greater risk when 4 nodes or more were involved (6,15,16,21). The ongoing NSABP B-51/RTOG 1304 phase III trial will enlighten the real benefit of postmastectomy regional node radiotherapy for cN+ypN0 patients (NCT01872975).

Our study has several limitations. First, though precise guidelines for adjuvant radiotherapy were provided (supplementary file), data as to precisely what radiotherapy was given to each patient was not captured in the CRFs. Second, the number of local and/or regional recurrence events in this study was low, therefore the analysis was only powered to pick up large effects for such small groups. This may explain why several factors previously identified in the literature, such as surgical margins, age, clinical tumour status (cT) and clinical nodal status (cN), despite being tested, were not retained in this multivariate analysis (6, 15-17, 19, 22, 23).

## Conclusion

Despite the low number of events observed in our analysis, we identified triple negative and HER2-positive breast cancer subtypes, regardless of adjuvant trastuzumab treatment, as being at high risk of developing loco-regional recurrence during the first 5 years after surgery. Thus, breast cancer subtype should be taken in consideration when considering regional nodal radiotherapy following surgery. Pathological involvement of at least 4 nodes was also found to

be predictive of a higher LRR risk. Importantly, even when a pCR was obtained after NAC, some patients experienced a LRR and based on this observation, a de-escalation of adjuvant radiotherapy indication should not be considered outside of a prospective trial in patients achieving a pCR.

## Funding

The sponsor of the trial (EORTC) designed and coordinated the trial. The funding sources had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the study data and the final responsibility for the decision to submit for publication. Trial design, conduct, and analysis were done at the EORTC Headquarters independently from all funding bodies.

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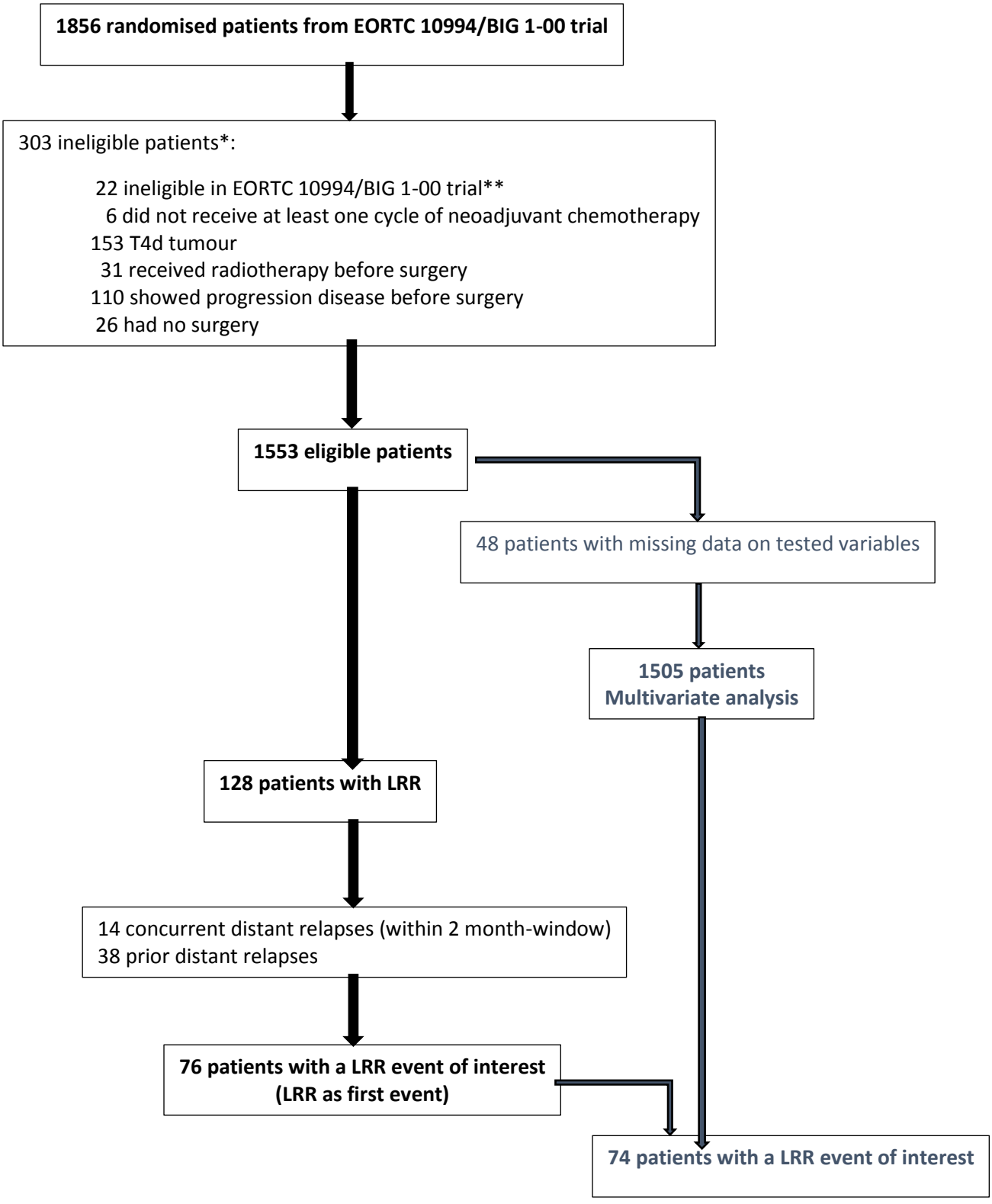
## Figure Legends

**Figure 1:** Consort diagram. *Patients can be excluded for more than one criteria;
**Ineligibility reasons in EORTC 10994 trial are displayed in the final analysis publication (7).

**Figure 2:** Cumulative incidence of locoregional relapse as first event and related competing risks. Locoregional relapse as first relapse is indicated in red, competing events such as distant relapse or second cancer prior to or concurrent with locoregional relapse or death are in blue and all aforementioned events in cyan.

**Figure 1**




Abbreviation: LRR: locoregional recurrence.

**Figure 2**

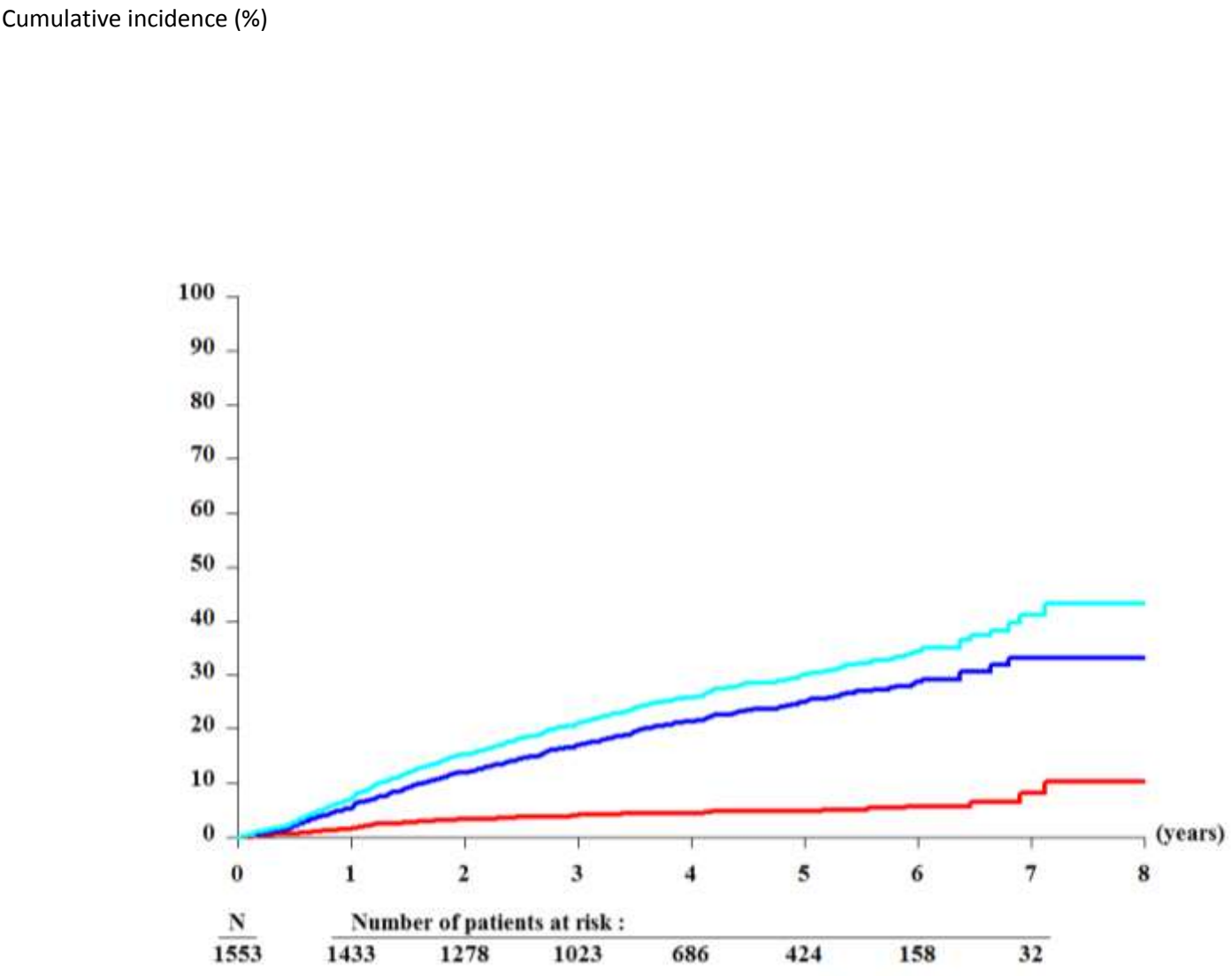

Cumulative incidence (%)
100
90
80
70
60
50
40
30
20
10
0
(years)
0
1
2
3
4
5
6
7
8
N
Number of patients at risk :
1553
1433
1278
1023
686
424
158
32

**Table 1: Patients and tumours characteristics**

| Characteristics | Patients with LRR as first event | | |
|---|---|---|---|
| | No (N = 1477) N (%)* | Yes (N = 76) N (%)* | Total (N = 1553) N (%)* |
| **Age at diagnosis (years)** | | | |
| ≤ 40 | 292 (93.3) | 21 (6.7) | 313 (20.2) |
| 41 - 50 | 579 (95.2) | 29 (4.8) | 608 (39.2) |
| 51 – 70 | 606 (95.9) | 26 (4.1) | 632 (40.7) |
| **Clinical tumour status (cT)** | | | |
| cT1 – 2 | 837 (96.5) | 30 (3.5) | 867 (55.8) |
| cT3 | 487 (94.0) | 31 (6.0) | 518 (33.4) |
| cT4 | 152 (91.0) | 15 (9.0) | 167 (10.8) |
| cTx | 1 (100.0) | 0 (0.0) | 1 (0.1) |
| **Clinical nodal status (cN)** | | | |
| cN0 | 675 (96.7) | 23 (3.3) | 698 (44.9) |
| cN+ | 800 (93.8) | 53 (6.2) | 853 (54.9) |
| cNx | 2 (100.0) | 0 (0.0) | 2 (0.1) |
| **Type of surgery** | | | |
| Lumpectomy or quadrantectomy | 690 (95.4) | 33 (4.6) | 723 (46.6) |
| Mastectomy | 787 (94.8) | 43 (5.2) | 830 (53.4) |
| **Histological type** | | | |
| Ductal | 1218 (94.7) | 68 (5.3) | 1286 (82.8) |
| Lobular | 172 (96.6) | 6 (3.4) | 178 (11.5) |
| Other | 75 (97.4) | 2 (2.6) | 77 (5.0) |
| Unknown | 12 (100.0) | 0 (0.0) | 12 (0.8) |
| **Histological grade** | | | |
| 1 | 109 (97.3) | 3 (2.7) | 112 (7.2) |
| 2 | 703 (95.8) | 31 (4.2) | 734 (47.3) |
| 3 | 457 (93.3) | 33 (6.7) | 490 (31.6) |
| Not known or not assessable | 208 (95.9) | 9 (4.1) | 217 (14.0) |
| **Breast cancer subtype/trastuzumab** | | | |
| Luminal A-like | 489 (98.4) | 8 (1.6) | 497 (32.0) |
| Luminal B-like (HER2-) | 142 (96.6) | 5 (3.4) | 147 (9.5) |
| HER2+ Trastu- | 225 (89.6) | 26 (10.4) | 251 (16.2) |

| | | | |
|---|---|---|---|
| HER2+ Trastu+ | 105 (94.6) | 6 (5.4) | 111 (7.1) |
| Triple negative | 204 (91.1) | 20 (8.9) | 224 (14.4) |
| Unknown | 312 (96.6) | 11 (3.4) | 323 (20.8) |
| **Pathological response** | | | |
| ypT0/is ypN0 | 267 (94.3) | 16 (5.7) | 283 (18.2) |
| ypT+ ypN0 | 416 (97.7) | 10 (2.3) | 426 (27.4) |
| ypTx ypN+ 1-3 nodes | 446 (97.0) | 14 (3.0) | 460 (29.6) |
| ypTx ypN+ ≥4 nodes | 332 (90.5) | 35 (9.5) | 367 (23.6) |
| Unknown | 16 (94.1) | 1 (5.9) | 17 (1.1) |
| **Surgical margins** | | | |
| R0 | 1360 (95.4) | 66 (4.6) | 1426 (91.8) |
| R1 | 100 (91.7) | 9 (8.3) | 109 (7.0) |
| Unknown | 17 (94.4) | 1 (5.6) | 18 (1.2) |
| **Adjuvant hormonotherapy** | | | |
| ER+ and/or PR+ without hormonotherapy | 22 (84.6) | 4 (15.4) | 26 (1.7) |
| ER+ and/or PR+ with hormonotherapy | 1020 (97.1) | 30 (2.9) | 1050 (67.6) |
| ER- and PR- | 339 (90.2) | 37 (9.8) | 376 (24.2) |
| Unknown | 96 (95.0) | 5 (5.0) | 101 (6.5) |

Abbreviations:

ER: oestrogen receptor; PR: progesterone receptor; HER2: Human Epidermal growth factor Receptor 2; Trastu-: without adjuvant trastuzumab; Trastu+: with adjuvant trastuzumab; LRR: Locoregional recurrence; R0: negative surgical margins; R1: positive surgical margins.

Legend:

* Percentages are displayed as row percentages in the LRR as first events columns (no/yes) and as column percentages in the total column.

**Table 2: Patterns of locoregional recurrences as first event, number of involved sites per patient and time to LRR from date of surgery by site of relapse.**

| Site of LRR as first event | Total number of involved sites | Number of involved sites per patient | | Time to LRR from date of surgery (years) | |
|---|---|---|---|---|---|
| | N (%) | 1 site (N = 65) N (%) | ≥ 2 sites (N = 11) N (%) | Median in years (95% CI) | Min – Max (years) |
| **Local** | 31 (40.8) | 27 (41.5) | 4 (36.4) | 1.72 (1.16- 2.35) | 0.44-7.13 |
| **Chest wall** | 28 (36.8) | 23 (35.4) | 5 (45.5) | 0.98 (0.53-1.10) | 0.12-6.90 |
| **Axillary nodes** | 11 (14.5) | 4 (6.2) | 7 (63.6) | 2.44 (0.26- 4.17) | 0.25-6.46 |
| **Internal mammary nodes** | 3 (3.9) | 1 (1.5) | 2 (18.2) | 1.15 (0.88- 2.27) | 0.88-2.27 |
| **Infraclavicular nodes** | 6 (7.9) | 4 (6.2) | 2 (18.2) | 2.00 (0.65- 4.30) | 0.64-4.31 |
| **Supraclavicular nodes** | 8 (10.5) | 6 (9.2) | 2 (18.2) | 1.72 (0.06- 4.12) | 0.06-4.31 |

Abbreviations:
LRR: Locoregional recurrence; CI: confidence interval; Min: minimum; Max: maximum.

**Table 3: Multivariate analysis for predictive factors of locoregional recurrence as first event at 5 years**

| **Potential predictive factors** | | | | **Full Multivariate Fine and Gray model** | **Backward procedure selection** | **Final Multivariate Fine and Gray model** | |
|---|---|---|---|---|---|---|---|
| | Patients (N (%)) (N = 1505) | LRR as first event (N (%)) (N = 74) | Competing events (N (%)) (N = 341) | HR (95% CI) | (Yes/No) | HR (95% CI) | 2-sided p-Value (Gray test) |
| **Age at diagnosis (years)** | | | | | | | |
| **≤ 40** | 303 (20.1) | 21 (28.4) | 82 (24.0) | 1.00 | No | | |
| **41-50** | 592 (39.3) | 28 (37.8) | 116 (34.0) | 0.83 (0.45-1.54) | | | |
| **51-70** | 610 (40 .5) | 25 (33.8) | 143 (41.9) | 0.61 (0.34-1.12) | | | |
| **Clinical tumour status (cT)** | | | | | | | |
| **cT1-2** | 838 (55.7) | 30 (40.5) | 128 (37.5) | 1.00 | No | | |
| **cT3** | 507 (33.7) | 29 (39.2) | 153 (44.9) | 1.50 (0.80-2.78) | | | |
| **cT4** | 160 (10.6) | 15 (20.3) | 60 (17.6) | 2.16 (1.01-4.61) | | | |
| **Clinical nodal status (cN)** | | | | | | | |
| **cN0** | 674 (44.8) | 23 (31.1) | 101 (29.6) | 1.00 | No | | |
| **cN+** | 831 (55.2) | 51 (68.9) | 240 (70.4) | 1.27 (0.75-2.13) | | | |
| **Type of surgery** | | | | | | | |
| **Lumpectomy or quadrantectomy** | 702 (46.6) | 33 (44.6) | 106 (31.1) | 1.00 | No | | |
| **Mastectomy** | 803 (53.4) | 41 (55.4) | 235 (68.9) | 0.71 (0.39-1.28) | | | |
| **Histological type** | | | | | | | |
| **Ductal** | 1256 (83.5) | 66 (89.2) | 282 (82.7) | 1.00 | No | | |
| **Lobular** | 176 (11.7) | 6 (8.1) | 41 (12.0) | 0.79 (0.34-1.86) | | | |
| **Other** | 73 (4.9) | 2 (2.7) | 18 (5.3) | 0.39 (0.10-1.63) | | | |
| **Breast cancer subtype / trastuzumab** | | | | | | | |
| **Luminal A** | 491 (32.6) | 8 (10.8) | 83 (24.3) | 1.00 | **Yes** | 1.00 | **< 0.0001** |
| **Luminal B (HER2-)** | 143 (9.5) | 5 (6.8) | 37 (10.9) | 1.99 (0.64-6.17) | | 2.29 (0.76-6.97) | |
| **HER2+ Trastu-** | 245 (16.3) | 25 (33.8) | 84 (24.6) | **5.70 (2.57-12.67)** | | **6.26 (2.81-13.93)** | |
| **HER2+ Trastu+** | 105 (7.0) | 5 (6.8) | 18 (5.3) | **3.15 (1.03-9.62)** | | **3.37 (1.10-10.34)** | |
| **Triple negative** | 219 (14.6) | 20 (27.0) | 50 (14.7) | **6.12 (2.67-14.01)** | | **6.44 (2.83-14.69)** | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Unknown** | 302 (20.1) | 11 (14.9) | 69 (20.2) | 2.20 (0.88-5.47) | | 2.28 (0.93-5.63) | |
| **Pathological response** | | | | | | | |
| **ypT0/is ypN0** | 278 (18.5) | 16 (21.6) | 24 (7.0) | 1.00 | **Yes** | 1.00 | **< 0.0001** |
| **ypT+ ypN0** | 420 (27.9) | 10 (13.5) | 42 (12.3) | 0.60 (0.26-1.37) | | 0.58 (0.26-1.28) | |
| **ypT+ ypN+ 1-3 nodes** | 450 (29.9) | 14 (18.9) | 121 (35.5) | 0.68 (0.33-1.39) | | 0.74 (0.36-1.52) | |
| **ypT+ ypN+ ≥4 nodes** | 357 (23.7) | 34 (45.9) | 154 (45.2) | **2.16 (1.11-4.02)** | | **2.43 (1.34-4.40)** | |
| **Surgical margins** | | | | | | | |
| **R0** | 1398 (92.9) | 65 (87.8) | 309 (90.6) | 1.00 | No | | |
| **R1** | 107 (7.1) | 9 (12.2) | 32 (9.4) | 1.68 (0.75-3.75) | | | |

Abbreviations: HR: Hazard ratio, LRR: Locoregional recurrence, HER2: Human Epidermal

**Supplementary material**

Supplementary file: EORTC 10994/BIG 1-00, Protocol Guidelines for Radiotherapy

### 5.2.2. GUIDELINES FOR RADIOTHERAPY

**5.2.2.1 Radiotherapy equipment** should in all cases furnish megavoltage beams, namely telecobalt, high energy x-rays, and electron beams. Interstitial brachytherapy may be used for localised small-volume « boost » treatment. The use of modern treatment planning techniques, including simulation (either conventional simulator or CT-based simulation) and computer-assisted dosimetric calculations, is required.

**5.2.2.2 Choice of target volumes** depend upon the clinical presentation and the extent of surgery, if any:

- In the event of breast preservation (either with or without surgery), the **entire breast and underlying chest wall** must be irradiated.
- After mastectomy, **chest wall** irradiation will be given to all patients with locally advanced cancers; for « large operable » lesions, the indication for chest wall irradiation will be assessed on a case-by-case basis by the treating radiation oncologist.
- After axillary clearance (at least level I-II), **axillary irradiation** may be omitted if adequate control is expected without radiotherapy. Its use is optional at the discretion of the treating radiation oncologist. In the event of more limited axillary surgery, axillary irradiation is generally recommended, especially if nodal positivity is demonstrated. If axillary surgery is not performed, the axilla must be irradiated.
- **Supra- and infraclavicular irradiation** is generally recommended for the patient population in this study. Irradiation of the ipsilateral **internal mammary nodes** (IMN) is optional, but should not unduly compromise the homogeneity of radiotherapy given to the breast and chest wall, and must be planned in such a way as to minimize radiation exposure to lung and heart. Internal mammary irradiation may be reasonable in patients with locally advanced disease, or those having clinical or histological axillary nodal involvement, particularly in the event of central or medial tumor location.

**5.2.2.3 Beam arrangements and dose specification**

- The **breast and underlying chest wall** are treated with two tangential photon beams, whose deep edges may be opposed to minimize lung irradiation. Both fields are to be treated daily. A half-beam technique is permissible. Breast dose should be prescribed at the intersection of the beam axes (ICRU 29). If this point is judged to be too close to the skin, or if a half-beam technique is used, the dose may be prescribed at a point in the center of the breast. Homogeneity guidelines recommend that dose within the target volume be within +10% and -5% of the prescribed dose. Wedge filters may be needed to achieve this goal. A computer-generated dose distribution is required in the central plane, and dose distribution calculations in two off-axis planes are recommended (but not required). Appropriate bolus should be used in cases with skin involvement.
- For **chest wall irradiation after mastectomy** tangential beams can be used, as described above, or electron beams of appropriate energy may be employed. The target volume should encompass the surgical scar and the skin flaps delimiting the implantation site of the amputated breast, with adequate margins. Bolus should be used as clinically indicated. If electron beams are used, dose prescriptions should follow recommendations of ICRU 54.

Electron energy should be chosen so that the 85% isodose corresponds to the mid-point of the ribs.

- Axillary **irradiation** is generally accomplished with the same anterior photon beam used for **supra/infraclavicular irradiation**, but will usually require an additional posterior beam to bring the dose at axillary mid-plane to the level of the prescribed dose. The supraclavicular dose is prescribed at a depth of 3 cm. Angling of the supraclavicular field to minimize esophageal and spinal cord irradiation is allowed.
- **Internal mammary irradiation** aims to treat the IMN in the first 4 ipsilateral interspaces, which are assumed to be situated at 3 cm from the midline, and at 3 cm depth. Use of an 5-cm-wide anterior field of appropriate length (bordering medially on the midline) is acceptable, but the IMN may also be included in the tangential beams used to irradiate the breast/chest wall. Other techniques are also acceptable if they conform to the guidelines of EORTC Protocol 22922/10925. Actual depth and location of the nodes may vary considerably, especially if the breast is in place. Use of imaging techniques for treatment planning is recommended. If a direct IM field is used, an appropriate mixture of photon and electron beams should be used to minimize cardiac irradiation.
- **Boost irradiation** includes the breast tumor bed in patients having had conservation surgery, and all sites of gross initial disease (prior to chemotherapy) that had not been excised. Boost irradiation can be given with localised megavoltage beams (preferably electrons, if feasible) or with interstitial brachytherapy. Boost volumes should include suspected residual disease with 2 cm circumferential margins (for the breast boost deep and superficial margins will be narrower).

#### 5.2.2.4 Prescribed doses

- The **recommended** dose to the prescription point in all treatment volumes (breast/chest wall, axilla, infra/supraclavicular, IMN) is 50 Gy, given in 25 daily fractions of 2 Gy, five times weekly. Alternative dose prescriptions include 50.4 Gy (28 x 1.8 Gy, 5 times weekly), or 45 Gy (18 x 2.5 Gy, 4 times weekly). Other fractionation schedules can be considered by a study investigator. After conservation surgery, breast boost dose should be 16 Gy (8 x 2 Gy) for external beam and 16 Gy (Paris system) for low-dose interstitial boost. An equivalent dose for high-dose-rate brachytherapy will be established.

- Areas of unexcised initial gross disease in the breast/chest wall should receive boosts of 20-26 Gy. Boosts to unexcised initial gross disease in nodal areas should be limited (e.g. to 10-16 Gy) according to considerations of normal tissue tolerance (plexus).

Supplementary table 1: Simplified breast cancer subtype classification

| **Breast cancer subtype** | **ER status** | **PgR status** | **Her2 status** | **Tumor grade** |
|---|---|---|---|---|
| **Luminal-A like** | ER+ *and/or* | PgR+ | Her2- | Grade 1 or 2 |
| **Luminal-B like HER2-** | ER+ *and/or* | PgR+ | Her2- | Grade 3 |
| **HER2+** | Any* ER *and/or* | PgR | Her2+ (IHC3+ or amplified) | Any or unknown |
| **Triple Negative** | ER- | PgR- | Her2- | Any or unknown |

Abbreviations:

ER: oestrogen receptor; PR: progesterone receptor; HER2: Human Epidermal growth factor Receptor 2; Trastu-: without adjuvant trastuzumab; Trastu+: with adjuvant trastuzumab; LRR: Locoregional recurrence; R0: negative surgical margins; R1: positive surgical margins.

Legend:

* Positive, negative or unknown.

Supplementary table 2: patients whose tumour achieved a pCR (ypT0/is ypN0) and presented with a locoregional relapse as first event

| | | | |
|---|---|---|---|
| | **One site only (N=14)** | **More than one site (N=2)** | **Total (N=16)** |
| | **N (%)** | **N (%)** | **N (%)** |
| **Local** | | | |
| **no** | 4 (28.6) | 0 (0.0) | 4 (25.0) |
| **yes** | 10 (71.4) | 2 (100.0) | 12 (75.0) |
| **Chest wall** | | | |
| **no** | 14 (100.0) | 2 (100.0) | 16 (100.0) |
| **Axillary nodes** | | | |
| **no** | 13 (92.9) | 0 (0.0) | 13 (81.3) |
| **yes** | 1 (7.1) | 2 (100.0) | 3 (18.8) |
| **Internal mammary nodes** | | | |
| **no** | 14 (100.0) | 2 (100.0) | 16 (100.0) |
| **Infraclavicular nodes** | | | |
| **no** | 12 (85.7) | 2 (100.0) | 14 (87.5) |
| **yes** | 2 (14.3) | 0 (0.0) | 2 (12.5) |
| **Supraclavicular nodes** | | | |
| **no** | 13 (92.9) | 2 (100.0) | 15 (93.8) |
| **yes** | 1 (7.1) | 0 (0.0) | 1 (6.3) |

Supplementary table 3: Validity of the primary results: multivariate Fine and Gray model, Cox model and bootstrap process based on Cox model analysis

| | **Multivariate Fine and Gray model*** | | **Multivariate Cox model**** | | **Cox model Bootstrap** |
|---|---|---|---|---|---|
| | **Backward procedure selection (Yes/No)** | **Final 2-sided p-value (Gray test)** | **Backward procedure selection (Yes/No)** | **Final 2-sided p-value (Gray test)** | **(% of inclusion) (N = 5000)** |
| **Age at diagnosis** | No | | No | | 44.2 |
| **Clinical tumour status** | No | | No | | 58.3 |
| **Nodal tumour status** | No | | No | | 20.7 |
| **Histological type** | No | | No | | 8.8 |
| **Type of surgery** | No | | No | | 24.8 |
| **Breast cancer subtype/trastuzumab** | Yes | < 0,0001 | Yes | < 0,0001 | **99.9** |
| **Pathological response** | Yes | < 0,0001 | Yes | < 0,0001 | **98.5** |
| **Surgical margins** | No | | No | | 39.8 |

Legend:

* with distant relapse as first relapse/death as event of interest and locoregional relapse as first relapse as competing risk

** with locoregional as first relapse as first relapse as event of interest and where distant relapse as first relapse/deaths are censored