Do patients whose tumor achieved a pathological response relapse at specific sites? A substudy of the EORTC 10994/BIG-1-00 trial

Do patients whose tumor achieved a pathological response relapse at specific sites? A substudy of the EORTC 10994/BIG-1-00 trial

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Abstract

Purpose: To determine the sites of first distant relapse in patients with or without pCR following neoadjuvant chemotherapy in breast cancer patients enrolled in the EORTC 10994/BIG-1-00 trial.

Methods: We included patients enrolled in the EORTC 10994/BIG-1-00 trial who received at least one chemotherapy cycle before surgery and who had been diagnosed with a distant relapse. pCR was defined as no evidence of residual invasive cancer in the primary tumor and axillary lymph nodes with or without residual ductal carcinoma in situ (DCIS). Site of first distant relapse was categorized as 'soft tissue', 'visceral', 'skeletal', 'central nervous system (CNS)' and 'other'. The association between relapse site and achievement of pCR was assessed using multivariate logistic regression models for molecular subtypes classification and preceding locoregional recurrence.

Results: The study included 383 (21%) eligible patients out of the 1,856 randomized, of whom 28 (7%) had achieved pCR. Median follow-up was 5.4 years. Achievement of pCR was associated with a trend towards a decreased presentation of skeletal metastases (21% (pCR) vs. 50% (non-pCR), OR=0.32, adjusted p-value=0.071) and an increase in the proportion of patients with CNS metastases as first distant relapse site (21% vs 9%, OR 2.39, adjusted p-value=0.183). Patients with pCR were more likely to present with only one relapse location category when compared to non-pCR (86% vs 69%).

Conclusion: Patients that achieved a pCR appeared less likely to present with skeletal metastases and more frequently presented with CNS metastases as first site of distant relapse, even after adjustment for molecular subtypes.

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Introduction

Neoadjuvant systemic therapy is a well-established strategy for locally advanced disease with the aim of down staging the tumor to enable more conservative surgery. Additionally, over the last few years it is also increasingly applied in early-stage breast cancer patients requiring systemic treatment showing similar long-term outcome as compared to adjuvant administration[1–4]. The early administration of systemic therapy also permits 'in-vivo' monitoring of the efficacy of administered systemic treatment[5].

The achievement of a pathologic complete response (pCR) after neoadjuvant treatment is associated with improved long-term survival and a decrease in both loco-regional and distant metastasis [5]. The pCR rate varies according to molecular subtype as does the association between pCR and long-term outcome, with the strongest correlation for the more aggressive subtypes [5–7].

The widely accepted explanation for this association is that the biology of the primary tumor and the micro metastatic disease are similar, and respond equally to the systemic neoadjuvant therapy. However, at least 10% of patients whose tumor achieved a pCR develop a recurrence within 5 years and more than two thirds of patients whose tumor did not achieve a pCR will not relapse [5]. In patients with triple negative tumors, in whom neither adjuvant hormonal nor trastuzumab therapies are going to interfere with the association between pCR and outcome, 15 to 20% of patients whose tumor achieved a pCR develop a recurrence within 5 years and 50% of patients whose tumor did not achieve a pCR will not relapse[5, 6, 8]. Thus, although pCR is a good prognosticator for survival it is not perfect. Several series have reported differences in estrogen receptor (ER) or human epidermal growth receptor 2 (HER2) status between the primary tumor and distant metastases in up to 32% and 14.5%, respectively[9, 10]. The biology of the micrometastatic disease in distant sites is certainly more complex than the biology of the primary tumor[11]. One could hypothesize that the correlation between pCR and survival is excellent in some specific sites while it remains poor in other sites. The first obvious example would be central nervous system metastasis. To our knowledge this question has never been addressed.

The aim of this study was to evaluate whether the sites of first distant relapse differed between patients whose tumor achieved a pCR after neoadjuvant chemotherapy versus those who did not in the EORTC 10994/BIG-1-00 trial[12].

Methods

Study design, eligibility and treatment

The EORTC 10994/BIG 1-00 trial enrolled patients aged ≤70 years with large operable or locally advanced/inflammatory breast cancer without evidence of distant metastases, who were candidates for neoadjuvant treatment. Patients were randomly assigned to receive either six cycles of anthracycline-based chemotherapy (FEC) or a taxane-based regimen, docetaxel for three cycles followed by epirubicin + docetaxel for three cycles (T-ET), all given prior to primary surgery. Subsequent locoregional treatment was determined according to guidelines described in the study protocol. Women with hormone receptor positive tumors were recommended to receive adjuvant endocrine therapy for 5 years. Patients with HER2 positive tumors were allowed to enter adjuvant clinical trials assessing trastuzumab or to receive this treatment in the adjuvant setting when it became standard practice[12].

For this sub-study we selected a subgroup of patients based on the following criteria: (i) Patients eligible in the EORTC 10994/BIG 1-00 trial, (ii) patients who received at least one cycle of neoadjuvant chemotherapy and who underwent surgery, (iii) patients who had a known pathological response status, and (iii) patients diagnosed with a distant relapse after surgery of which the site was specified. Patients with T4d tumors or who received radiotherapy before surgery were excluded from the analysis.

Pathologic complete response was defined in this sub-study as no evidence of residual invasive cancer (or very few scattered tumor cells) in the primary tumor and axillary lymph nodes with or without residual ductal carcinoma in situ (DCIS). Information on Ki-67 was not collected within the main study. Therefore,

tumor subtype classification was performed according to the simplified approach as proposed in the 2011 St. Gallen consensus, where Ki-67 is replaced by tumor grade [13] (Supplement A). Tumour histology, grade, ER, progesterone receptor (PgR) and HER2 status were based on local pathology assessment of the diagnostic biopsy.

Objectives and end-points

The primary objective of this study was to assess whether there are differences in the sites of first distant relapse between patients who achieved a pCR after neoadjuvant chemotherapy versus those who did not (non-pCR). Secondary objectives included 1) describing the differences in site of first distant relapse in the pCR and non-pCR groups by breast cancer subtype, 2) describing the clinicopathological characteristics of patients according to site of first distant relapse, 3) evaluating the effect of a preceding or concomitant locoregional recurrence (LR) on the occurrence of a specific site as first distant relapse, 4) studying the association between concomitant sites of first distant relapse.

We evaluated the first site of distant relapse as reported in the case report forms, i.e. 'soft tissue', 'visceral', 'skeletal', 'CNS' or 'other'. In case of multiple lesions, all concomitant lesions at first presentation were included. As part of the secondary objectives, invasive locoregional recurrences were considered if they occurred before or at the same time of the first distant relapse. Locoregional recurrences were ipsilateral invasive breast recurrences and regional recurrences (chest wall and regional lymph nodes: axillary, internal mammary, infra and supraclavicular).

Statistical analysis

A statistical analysis plan was prospectively developed. The association between the occurrence of a specific site of first distant relapse and pCR status was evaluated using four multivariate logistic regression models, one for each site ('soft tissue', 'visceral', 'skeletal', 'CNS') except 'other', adjusting for intrinsic subtype and preceding locoregional recurrence (yes/no). Sites of first distant relapse classified as 'other' were not evaluated because the obtained estimation would have not been interpretable due to the

heterogeneity of the corresponding sites. The association with pCR was assessed using the Wald chi-square test with adjusted p-values for multiple testing (Benjamini-Hochberg correction). A p-value <0.05 was considered statistically significant. Sensitivity analyses were subsequently performed, with univariate and multivariate models adjusting for age, clinical tumor and nodal status, histologic tumor type, subtype and allocated chemotherapy regimen. Differences in site of first distant relapse between the molecular subtypes according to pCR-status, patient and tumor characteristics, and the presence of preceding locoregional recurrence per relapse site, and the occurrence of concomitant sites of first distant relapse were tabulated (no formal statistical testing was done due to the limited number of patients in the subgroups).

All statistical analyses were performed using SAS software version 9.4 (SAS Institute).

Results

Of the 1,856 patients randomized in the trial, 383 patients diagnosed with a distant relapse were eligible for this substudy, of whom 28 (7%) were in the pCR-group and 355 (93%) in the non-pCR group. Reasons for ineligibility are shown in the consort diagram (Supplement B). The median follow-up was 5.4 years from date of randomization. Baseline patient and tumor characteristics according to pCR status are presented in Table 1. Median age of included patients was 49 years and most patients had clinically node positive disease (271/383; 71%). Overall, visceral (197/383; 51%) and skeletal metastases (185/383; 48%) were the most common sites of first distant relapse (Table 2).

Association between pCR status and site of first distant relapse

Patients whose tumor achieved pCR were less likely to present with skeletal metastases as compared to non-pCR patients (6/28 (21%) vs. 179/355 (50%) patients; OR 0.32, 95% CI 0.12-0.82; P=0.071, Table 2). A

similar trend was observed in all subtypes apart from Luminal A-like, though the numbers are very small (Table 3).

Conversely, the proportion of patients with CNS metastasis as first metastatic site was numerically higher in the pCR-group as compared to in the non-pCR group (6/28 (21%) vs. 32/355 (9%) patients; OR 2.39, 95% CI 0.87-6.58; *P*=0.183, Table 2). This difference was greatest in the HER2+ Luminal B-like subtype (Table 3). These differences in the incidence of skeletal and CNS metastases between patients whose tumor did or did not achieve pCR remained after further adjustment for age, histologic type, clinical node and tumor status, subtype and received chemotherapy regimen (data not shown).

For the remaining sites (soft tissue and visceral) we did not observe an association with pCR status (Tables 2).

Clinicopathological characteristics of patients according to site of first distant relapse

Patients with soft tissue and CNS metastases were older and had higher grade tumors as compared to patients with visceral and skeletal metastases (Table 4). Patients presenting with skeletal metastasis more frequently had tumors with a lobular histology, a lower-grade (I and II), and a luminal-like subtype (17%, 54%, and 59% respectively). Patients presenting with CNS metastases were predominantly clinically node positive (84% N+ vs. 16% N0, Table 4). Furthermore, in these patients we observed a higher rate of HER2+/non-luminal and TN breast cancer.

Preceding locoregional recurrence

In 68 patients, the first distant relapse was preceded by or occurred concomitantly with a locoregional recurrence (Table 1). The proportion of patients with a prior LR was highest in those presenting with soft tissue metastases (18/47 (38%) versus 13% (CNS) to 19% (visceral) in the other groups (Table 4)). We did not observe differences in site of first distant relapse according to pCR status for patients that did or did not have a preceding LR event (results not shown).

Association between pCR status and extent of metastatic disease

The proportion of patients who presented with more than one site of metastatic spread was numerically lower in the group of patients whose tumor achieved a pCR as compared to patients in the non-pCR group (4/28 (14%) vs. 112/355 (32%) patients with >1 relapse site, Table 5). Patients with soft tissue as first site of distant relapse most frequently presented with at least one other metastatic site (32/47 patients (68%)). In 60% of patients with CNS as first site of distant relapse, the CNS was the only site of metastatic disease. Skeletal and visceral metastases were the most common combination in case of more than one site of relapse (70 out of 116 patients (60%) with >1 metastatic site, Table 5).

Discussion

In this study, there was a numerical difference in presentation with CNS metastasis, with a higher incidence in the pCR group (Odds Ratio 2.39). Of note, CNS metastasis accounted for one fifth of all first distant metastasis in the pCR group. This finding supports the concept of the brain being a sanctuary site where malignant cells are protected from anti-cancer therapeutics by the blood-brain barrier[14]. Patients with a non-luminal HER2+ or TN subtype have higher pCR rates as compared to patient with luminal subtypes[5] and have been shown to more frequently metastasize to the brain and viscera[15, 16]. Thus, an excess of CNS metastases in the pCR group might be expected in the non-luminal HER2+ and TN subtypes.

Furthermore, patients whose tumor achieved a pCR had a lower rate of skeletal metastasis as first site of distant relapse as compared to patients whose tumor did not achieve pCR (Odds Ratio 0.32). This observed difference could perhaps have been explained by a molecular subtype bias. Patients with a luminal subtype are less likely to achieve a pCR and are known to more frequently metastasize to skeletal tissue[17, 18].

We also evaluated the influence of a preceding LR, since such an event could have an influence on the subsequent distant metastatic spread as these patients might receive additional systemic treatment. Furthermore, the local recurrence itself could give rise to metastatic spread. We did not observe a statistically significant association between a prior LR and any site of first distant relapse after adjustment for pCR status and subtype. These results should be interpreted with caution since the number of LRs preceding distant relapses was relatively low.

The median follow-up of patients included in this study was 5.4 years. This time-frame will have an influence on the distribution of relapse sites we observed. Previous studies have shown that patients with a shorter disease-free survival (DFS) more often present with visceral and CNS metastases[19]. The incidence of these metastatic sites reaches its peak in the second year of follow-up after which the incidence declines, whereas bone metastases can even occur later on. Furthermore, patients with a shorter DFS are more often of the TN subtype which is known to metastasize frequently to the visceral tissue as is also demonstrated in this study[8, 20, 21]. Longer follow-up is needed.

This study has strengths and limitations. A major strength of the study is that the population consists of patients from a large randomized trial with a total of 383 patients with events of interest. The main limitation is the small number of patients in the pCR group, which prohibits drawing firm conclusions from this study. This limitation is even more important when trying to analyze the results by molecular subtypes. It is well known that the metastatic behavior and prognosis of breast cancer is dependent on tumor biology of the different intrinsic subtypes[22]. We attempted to adjust for possible molecular subtype bias by performing multivariate analyses.

In conclusion, there appear to be differences in the occurrence of tissue-specific sites of first distant relapse between patients that achieved pCR after neoadjuvant chemotherapy when compared to those that did not, even after adjustment for molecular subtypes. The trends observed in the present study

need to be confirmed in a meta-analysis as well to establish the clinical implication on long-term prognosis.

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Reference list

1. Mauri D, Pavlidis N, Ioannidis JPA (2005) Neoadjuvant versus adjuvant systemic treatment in breast cancer: A meta-analysis. J Natl Cancer Inst 97:188–194. doi: 10.1093/jnci/dji021

2. Tryfonidis K, Senkus E, Cardoso MJ, Cardoso F (2015) Management of locally advanced breast cancer perspectives and future directions. Nat Rev Clin Oncol 12:147–162.

3. Wolmark N, Wang J, Mamounas E, et al (2001) Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr 15212:96–102.

4. van der Hage JA, van de Velde CJ, Julien JP, et al (2001) Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 19:4224–37. doi: 10.1200/JCO.2001.19.22.4224

5. Cortazar P, Zhang L, Untch M, et al (2014) Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. Lancet 384:164–172. doi: 10.1016/S0140-6736(13)62422-8

6. von Minckwitz G, Untch M, Blohmer J-U, et al (2012) Definition and Impact of Pathologic Complete Response on Prognosis After Neoadjuvant Chemotherapy in Various Intrinsic Breast Cancer Subtypes. J Clin Oncol 30:1796–1804. doi: 10.1200/JCO.2011.38.8595

7. Bonnefoi H, Litiere S, Piccart M, et al (2014) Pathological complete response after neoadjuvant chemotherapy is an independent predictive factor irrespective of simplified breast cancer intrinsic subtypes: a landmark and two-step approach analyses from the EORTC 10994/BIG 1-00 phase III trial. Ann Oncol 25:1128–1136. doi: 10.1093/annonc/mdu118

8. Liedtke C, Mazouni C, Hess KR, et al (2008) Response to Neoadjuvant Therapy and Long-Term Survival in Patients With Triple-Negative Breast Cancer. J Clin Oncol 26:1275–1281. doi: 10.1200/JCO.2007.14.4147

9. Dieci M V., Barbieri E, Piacentini F, et al (2013) Discordance in receptor status between primary and recurrent breast cancer has a prognostic impact: A single-institution analysis. Ann Oncol 24:101–108. doi:

10.1093/annonc/mds248

10. Lindström LS, Karlsson E, Wilking UM, et al (2012) Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. J Clin Oncol 30:2601–2608. doi: 10.1200/JCO.2011.37.2482

11. Cejalvo JM, Martínez de Dueñas E, Galván P, et al (2017) Intrinsic Subtypes and Gene Expression Profiles in Primary and Metastatic Breast Cancer. Cancer Res 77:2213–2221. doi: 10.1158/0008-5472.CAN-16-2717

12. Bonnefoi HR, Piccart-Gebhart MJ, Bogaerts J, et al (2011) TP53 status for prediction of sensitivity to taxane versus non-taxane neoadjuvant chemotherapy in breast cancer (EORTC 10994/BIG 1-00): a randomised phase 3 trial. Lancet Oncol 12:527–539. doi: 10.1016/S1470-2045(11)70094-8

13. Goldhirsch A, Wood WC, Coates AS, et al (2011) Strategies for subtypes-dealing with the diversity of breast cancer: Highlights of the St Gallen international expert consensus on the primary therapy of early breast cancer 2011. Ann Oncol 22:1736–1747. doi: 10.1093/annonc/mdr304

14. Palmieri D, Chambers AF, Felding-Habermann B, et al (2007) The biology of metastasis to a sanctuary site. Clin Cancer Res 13:1656–1662. doi: 10.1158/1078-0432.CCR-06-2659

15. Pogoda K, Niwińska A, Murawska M, Pieńkowski T (2013) Analysis of pattern, time and risk factors influencing recurrence in triple-negative breast cancer patients. Med Oncol. doi: 10.1007/s12032-012-0388-4

16. Lin NU, Claus E, Sohl J, et al (2008) Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer. Cancer 113:2638–2645. doi: 10.1002/cncr.23930

17. James JJ, Evans a J, Pinder SE, et al (2003) Bone metastases from breast carcinoma: histopathological - radiological correlations and prognostic features. Br J Cancer 89:660–665. doi: 10.1038/sj.bjc.6601198

18. Kast K, Link T, Friedrich K, et al (2015) Impact of breast cancer subtypes and patterns of metastasis on outcome. Breast Cancer Res Treat 150:621–629. doi: 10.1007/s10549-015-3341-3

19. Park, Y., Chang, M., Lee, S., Kim, S., Cho, E., Choi, Y., Ok, O., Baek, H., Lee, J., Nam, S. and Yang J (2009) Heterogeneity of Triple Negative Breast Cancer (TNBC): TNBC Might Be Divided into Two or More Subgroups by Clinicopathologic Findings. Cancer Res 69:6032.

20. Metzger-Filho O, Sun Z, Viale G, et al (2013) Patterns of recurrence and outcome according to breast cancer subtypes in lymph node-negative disease: Results from international breast cancer study group trials VIII and IX. J Clin Oncol 31:3083–3090. doi: 10.1200/JCO.2012.46.1574

21. Lee Y, Kang E, Lee AS, et al (2015) Outcomes and recurrence patterns according to breast cancer subtypes in Korean women. Breast Cancer Res Treat 151:183–190. doi: 10.1007/s10549-015-3390-7

22. Kennecke H, Yerushalmi R, Woods R, et al (2010) Metastatic behavior of breast cancer subtypes. J Clin Oncol 28:3271–3277. doi: 10.1200/JCO.2009.25.9820

Table 1. Baseline characteristics of 383 included patients

	pCR N= 28		non-pCR N= 355		Total N= 383	
	N	%	N	%	N	%
Median age at diagnosis	48		49		49	
Age at diagnosis						
≤40	7	25.0	83	23.4	90	23.5
41-50	9	32.1	123	34.6	132	34.5
51-70	12	42.9	149	42.0	161	42.0
Menopausal status						
Premenopausal	15	53.6	207	58.3	222	58.0
Postmenopausal	13	46.4	148	41.7	161	42.0
cT stage						
T1-2	11	39.3	126	35.5	137	35.8
T3	15	53.6	160	45.1	175	45.7
T4	2	7.1	69	19.4	71	18.5
cN stage						
N0	13	46.4	97	27.3	110	28.7
N1	13	46.4	224	63.1	237	61.9
N>1	2	7.1	32	9.0	34	8.9
Unknown	0	0.0	2	0.6	2	0.5
Tumor histology						
Ductal	26	92.9	291	82.0	317	82.8
Lobular	2	7.1	43	12.1	45	11.7
Other	0	0.0	18	5.1	18	4.7
Missing	0	0.0	3	0.8	3	0.8
Tumor grade						
I	0	0.0	14	3.9	14	3.7
II	12	42.9	153	43.1	165	43.1
III	16	57.1	130	36.6	146	38.1
Not assessed/Unknown	0	0.0	58	16.4	58	15.1
Subtype						
Luminal A-like	3	10.7	82	23.1	85	22.2
Luminal B-like (HER2-negative)	1	3.6	42	11.8	43	11.2
Luminal B-like (HER2-positive)	6	21.4	64	18.0	70	18.3
HER2+, non luminal-like	6	21.4	34	9.6	40	10.4
Triple negative	6	21.4	55	15.5	61	15.9
Unknown	6	21.4	78	22.0	84	21.9
Neoadjuvant chemotherapy regimen						
FEC	17	60.7	193	54.4	210	54.8
T-ET	11	39.3	162	45.6	173	45.2
Number of cycles						
1	0	0.0	1	0.3	1	0.3
2	0	0.0	3	0.8	3	0.8
3	0	0.0	5	1.4	5	1.3
4	0	0.0	5	1.4	5	1.3
5	1	3.6	4	1.1	5	1.3
6	27	96.4	337	94.9	364	95.0
Type of surgery						
BCS	15	53.6	100	28.2	115	30.0
Mastectomy	13	46.4	254	71.5	267	69.7
Unknown	0	0.0	1	0.3	1	0.3
Preceding locoregional recurrence						
No	21	75.0	294	82.8	315	82.2
Yes	7	25.0	61	17.2	68	17.8

BCS= Breast-conserving surgery; pCR= pathological Complete Response; cT= clinical Tumor; cN= clinical lymph Nodes, FEC= 5-fluorouracil, epirubicin and cyclophosphamide, T-ET= docetaxel x3 → epirubicin + docetaxel x3
Percentages may not add up to 100% due to rounding

Table 2. Association between site of first distant relapse and pCR status after neoadjuvant chemotherapy

	pCR N=28	non-pCR N=355	Total N=383	Univariate pCR vs. non-pCR	Multivariate[a] pCR vs. non-pCR	
	N (%)	N (%)	N (%)	OR (95% CI)	OR (95% CI)	*Adj. P*-value
Soft tissue						
No	24 (86%)	312 (88%)	336 (88%)			
Yes	4 (14%)	43 (12%)	47 (12%)	1.21 (0.40-3.65)	0.94 (0.30-2.95)	.909
Visceral						
No	14 (50%)	172 (48%)	186 (49%)			
Yes	14 (50%)	183 (52%)	197 (51%)	0.94 (0.44-2.03)	0.80 (0.36-1.74)	.756
Skeletal						
No	22 (79%)	176 (50%)	198 (52%)			
Yes	6 (21%)	179 (50%)	185 (48%)	0.27 (0.11-0.68)	0.32 (0.12-0.82)	.071
CNS						
No	22 (79%)	323 (91%)	345 (90%)			
Yes	6 (21%)	32 (9%)	38 (10%)	2.75 (1.04-7.29)	2.39 (0.87-6.58)	.183
Other						
No	24 (86%)	292 (82%)	316 (83%)			NA[b]
Yes	4 (14%)	63 (18%)	67 (17%)	0.77 (0.26-2.31)	0.73 (0.24-2.22)	

pCR= pathological Complete Response, CNS=Central Nervous System

[a]Adjusted for subtype and preceding locoregional relapse (yes/no)

[b]The odds-ratio for the 'other' category is displayed without the corresponding *P*-value, bringing the number of *P*-values included in the Benjamini-Hochberg correction to 4-tested values.

Table 3. Site of first distant relapse according to pCR status per tumor subtype

	Lum-A		Lum-B (HER2-)		Lum-B (HER2+)		HER2+		Triple Negative		Unknown	
	pCR N=3	non-pCR N=82	pCR N=1	non-pCR N=42	pCR N=6	non-pCR N=64	pCR N=6	non-pCR N=34	pCR N=6	non-pCR N=55	pCR N=6	non-pCR N=78
Soft tissue												
N	0	4	0	4	1	10	1	6	1	8	1	11
%	0%	5%	0%	10%	17%	16%	17%	18%	17%	15%	17%	14%
Visceral												
N	1	36	1	14	3	38	4	19	4	33	1	43
%	33%	44%	100%	33%	50%	59%	67%	56%	66%	60%	17%	55%
Skeletal												
N	2	50	0	26	1	31	1	12	1	17	1	43
%	67%	61%	0%	62%	17%	48%	17%	35%	17%	31%	17%	55%
CNS												
N	0	2	0	2	2	3	1	5	1	8	2	12
%	0%	2%	0%	5%	33%	5%	17%	15%	17%	15%	33%	15%
Other												
N	0	12	0	7	1	10	0	7	1	9	2	18
%	0%	15%	0%	17%	17%	16%	0%	21%	17%	16%	33%	23%

CNS=Central Nervous System
Percentages displayed for column
Patients could have presented with multiple sites of relapse then percentages are not cumulative

Table 4. Patient, tumor and treatment characteristics according to site of first distant relapse

	Soft tissue N=47		Visceral N=197		Skeletal N=185		CNS N=38		Other N=67	
	N	%	N	%	N	%	N	%	N	%
Median age at diagnosis	50 yrs		48 yrs		48 yrs		53 yrs		49 yrs	
Age at diagnosis										
≤40	8	17.0	43	21.8	54	29.2	7	18.4	16	23.9
41-50	16	34.0	80	40.6	59	31.9	10	26.3	27	40.3
51-70	23	48.9	74	37.6	72	38.9	21	55.3	24	35.8
Menopausal status										
Premenopausal	24	51.1	121	61.4	112	60.5	19	50.0	39	58.2
Postmenopausal	23	48.9	76	38.6	73	39.5	19	50.0	28	41.8
cT stage										
T1-2	13	27.7	69	35.0	66	35.7	14	36.8	23	34.3
T3	18	38.3	93	47.2	85	45.9	16	42.1	33	49.3
T4	16	34.0	35	17.8	34	18.4	8	21.1	11	16.4
cN stage										
N0	17	36.2	64	32.5	50	27.0	6	15.8	18	26.9
N1	19	40.4	118	59.9	123	66.5	25	65.8	42	62.7
N>1	10	21.3	14	7.1	12	6.5	7	18.4	7	10.4
Unknown	1	2.1	1	0.5	0	0.0	0	0.0	0	0
Tumor histology										
Ductal	39	83.0	169	85.8	145	78.4	32	84.2	52	77.6
Lobular	3	6.4	16	8.1	32	17.3	4	10.5	12	17.9
Other	5	10.6	11	5.6	7	3.8	1	2.6	2	3.0
Missing	0	0.0	1	0.5	1	0.5	1	2.6	1	1.5
Tumor grade										
I	0	0.0	6	3.0	8	4.3	0	0.0	0	0.0
II	13	27.7	85	43.1	92	49.7	14	36.8	30	44.8
III	24	51.1	74	37.6	59	31.9	18	47.4	25	37.3
Not assessed/Unknown	10	21.3	32	16.2	26	14.1	6	15.8	12	17.9
Subtype										
Luminal-A	4	8.5	37	18.8	52	28.1	2	5.3	12	17.9
Luminal-B (HER2-negative)	4	8.5	15	7.6	26	14.1	2	5.3	7	10.4
Luminal-B (HER2-positive)	11	23.4	41	20.8	32	17.3	5	13.2	11	16.4
HER2+, non-luminal	7	14.9	23	11.7	13	7.0	6	15.8	7	10.4
Triple negative	9	19.1	37	18.8	18	9.7	9	23.7	10	14.9
Unknown	12	25.5	44	22.3	44	23.8	14	36.8	20	29.9
Neoadjuvant regimen										
FEC	28	59.6	101	51.3	112	60.5	21	55.3	34	50.7
T-ET	19	40.4	96	48.7	73	39.5	17	44.7	33	49.3
Type of surgery										
BCS	10	21.3	59	29.9	51	27.6	11	28.9	22	32.8
Mastectomy	37	78.7	137	69.5	133	71.9	27	71.1	45	67.2
Unknown	0	0.0	1	0.5	1	0.5	0	0.0	0	0.0
Preceding locoregional recurrence										
No	29	61.7	159	80.7	158	85.4	33	86.8	52	77.6
Yes	18	38.3	38	19.3	27	14.6	5	13.2	15	22.4

BCS= breast-conserving surgery; pCR= pathological Complete Response; cT= clinical Tumor; cN= clinical lymph Nodes; CNS= Central Nervous System, FEC= 5-fluorouracil, epirubicin and cyclophosphamide, T-ET= docetaxel x3 → epirubicin + docetaxel x3

Percentages are displayed for columns. Percentages may not add up to 100% due to rounding.

Table 5. Occurrence of concomitant sites of first distant relapse

5A. Number of concomitant sites of first distant relapse

	Number of concomitant sites of first distant relapse			
	One single site N= 267		More than 1 site N= 116	
	N	%	N	%
pCR status				
pCR	24	*85.7*	4	*14.3*
Non-pCR	243	*68.5*	112	*31.5*
Site of relapse				
Soft tissue	15	*31.9*	32	*68.1*
Visceral	103	*52.3*	94	*47.7*
Skeletal	96	*51.9*	89	*48.1*
CNS	23	*60.5*	15	*39.5*
Other	30	*44.8*	37	*55.2*

pCR= pathological Complete Response;
Percentages are displayed for rows. Number of patients by site of relapse for those with more than one sites of relapse are not cumulative.

5B. Distribution of concomitant sites of first distant relapse

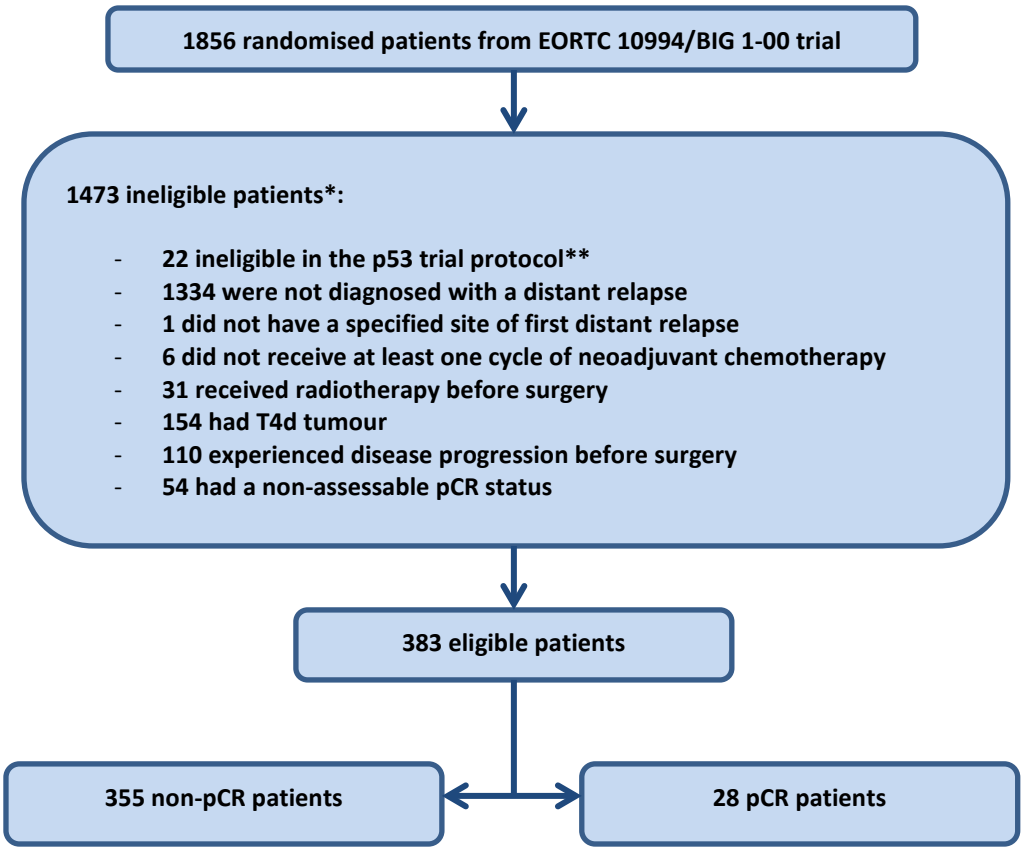
Sites of first distant relapse		Patients with more than one relapse site category (N=116)									
		Soft tissue		Visceral		Skeletal		CNS		Other	
		Yes N=32	No N=84	Yes N=94	No N=22	Yes N=89	No N=27	Yes N=15	No N=101	Yes N=37	No N=79
Soft tissue	*N*			21	11	20	12	4	28	11	21
	%			*22.3%*	*50%*	*22.5%*	*44.4%*	*26.7%*	*27.7%*	*29.7%*	*26.6%*
Visceral	*N*					70	24	10	84	26	68
	%					*78.7%*	*88.9%*	*66.7%*	*83.2%*	*70.3%*	*86.1%*
Skeletal	*N*							7	82	21	68
	%							*46.7%*	*81.2%*	*56.8%*	*86.1%*
CNS	*N*									1	14
	%									*2.7%*	*17.7%*
Other	*N*										
	%										

Percentages displayed for column and are not cumulative.

Supplement A: Simplified breast cancer subtype classification proposed by the 2011 St. Gallen consensus

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
Luminal-B like (HER2+)	ER+	*and/or*	PgR+	Her2+	Any
HER2+, non-luminal	ER-		PgR-	Her2+	Any
Triple Negative	ER-		PgR-	Her2-	Any

Supplement B: Consort diagram



* Patients can be ineligible for more than one reason.

** Reasons for ineligibility are listed in the original 10994 trial publication[12]