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Impact of age, tumor characteristics, and treatment on local control and disease outcome in early stage breat cancer : an EORTC translational research project

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CHAPTER 2

Improved survival after one course of perioperative chemotherapy in early breast cancer patients: long-term results from the European Organization for Research and Treatment of Cancer (EORTC) Trial 10854

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Abstract

The aim of this study was to examine whether one course of perioperative polychemotherapy yields better results in terms of survival, progression-free survival (PFS) and locoregional control than surgery alone in early stage breast cancer. From 1986 to 1991, 2795 patients with stage I/II breast cancer were randomised to receive either one perioperative course of an anthracycline containing chemotherapeutic regimen within 36 hrs after surgery or surgery alone. Patients were followed-up for overall survival, PFS and locoregional recurrence. The median follow-up period at time of the analysis was 11 years. PFS and locoregional control were significantly better (P=0.025 and P=0.004, respectively) in the perioperative chemotherapy arm. Node-negative patients seemed to benefit most from the perioperative FAC. Patients who received perioperative chemotherapy and locoregional therapy alone had significantly better overall survival rates than patients who received locoregional therapy alone (P=0.004). Patients who received additional systemic therapy did not seem to benefit from one course of perioperative chemotherapy (P=0.65). One course of perioperative polychemotherapy does improve PFS and locoregional control in early stage breast cancers. This effect is still present after 11 years of follow-up.

Introduction

Systemic adjuvant therapy has been shown to improve both disease-free survival and overall survival in breast cancer patients [1]. Over the past three decades, many investigators have studied the benefits of adjuvant chemotherapy in breast cancer. However, the significance of the timing of administration of chemotherapy in relation to locoregional treatment is still a matter of debate. Experimental studies, as well as mathematical hypotheses [2–6], have demonstrated that early timing of chemotherapy may be more effective than standard postoperative administration of chemotherapy.
Several randomised trials studying the effect of the administration of one dose of chemotherapy immediately after surgery with or without subsequent prolonged chemotherapy demonstrated better disease-free or relapse-free survival rates using this therapeutic regimen [7–9].
In the European Organization for Research and Treatment of Cancer (EORTC) trial 10854, of which preliminary results have been published previously, a similar effect was observed at a median follow-up time of 41months [10]. In this report, we will focus on the effect of perioperative chemotherapy after long-term follow-up.

Patients and methods

Patient characteristics
Eligibility requirements, randomisation procedures, surgical and radiation techniques used, characteristics of patients and tumours, and the distribution of patients among the treatment groups have been published previously [10]. In brief, eligible patients had primary operable breast cancer, T1-3, N0-2, M0, and had to be younger than 70 years of age at the time of randomisation.

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	Perioperative chemotherapy $n=1398$	Control $n=1395$
	n (%)	*n* (%)
Age (years)		
≤50	557 (40)	560 (40)
>50	841 (60)	835 (60)
Nodal status (pathological)		
Negative	741 (53)	728 (52)
Positive	644 (46)	661 (47)
Missing data	13 (1)	6 (0.5)
Tumour size (clinical)		
≤2 cm	407 (29)	416 (30)
>2 cm	969 (69)	954 (68)
Missing data	22 (2)	25 (2)
ER status		
ER+	910 (65)	909 (65)
ER−	324 (23)	347 (25)
Missing data	164 (12)	139 (10)
Type of surgery		
BCS[a]	773 (55)	770 (55)
Mastectomy	616 (44)	618 (44)
Missing data	9 (1)	7 (1)
Radiotherapy		
Yes	1082 (77)	1063 (76)
No	316 (23)	332 (24)
Additional systemic therapy		
Yes	606 (43)	592 (42)
No	756 (54)	776 (56)
Missing data	36 (3)	27 (2)

[a] Breast-conserving surgery. ER, oestrogen receptor.

Table 1. Patient characteristics; all patients (N = 2793)

Exclusion criteria were bilateral breast cancer, previous treatment for breast cancer and previous systemic treatment for other cancers, distant metastases, and a poor World Health Organization (WHO) performance (>2). Patients were randomised to either receive one course of perioperative chemotherapy within 36 hrs after surgery or surgery alone. Patient characteristics are shown in Table 1. Patients who were younger than or equal to 50 years of age at the time of diagnosis were classified as premenopausal. Patients older than 50 years were considered postmenopausal. Tumour oestrogen receptor status (ER) was measured using a biochemical assay according to the best method locally available at every institution. A value of 510 fmol ER per mg protein was considered positive and a value of 0–9 fmol ER per mg protein was considered negative [11]. No information on the progesterone receptor status was collected. In the subgroup of node-negative premenopausal patients, ER status was also measured by immunohisto-chemistry in a central pathology review.

Treatment

Patients were treated with either (modified) radical mastectomy or breast-conserving surgery. Perioperative chemotherapy consisted of one single course of 50 mg/m^2 doxorubicin, 600 mg/m^2 5-fluorouracil, and 600 mg/m^2 cyclophosphamide (FAC), administered intravenously (i.v.) within 36 h after surgery. Axillary lymph node-positive premenopausal patients in the perioperative chemotherapy group were recommended to receive an extra five cycles of cyclophosphamide, methotrexate and 5-fluorouracil (CMF). Node-positive patients, younger than 50 years, who did not receive perioperative chemotherapy, were advised to have one conventional course of FAC followed by five cycles of CMF after surgery. Adjuvant hormonal therapy at the time was not routinely given in the management of breast cancer and the decision to give tamoxifen was therefore left to the discretion of the respective investigators. Radiotherapy was given in both arms. Postoperative radiation had to be started 6 weeks after surgery and was given in all cases in which surgery was considered not to be radical. A detailed description concerning the administration of radiotherapy was given previously [10].

Statistical considerations

The primary endpoint of the EORTC 10854 trial is overall survival. Secondary

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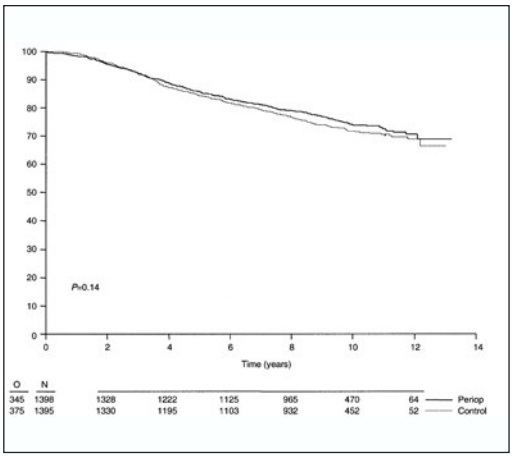

Figure 1. Overall survival

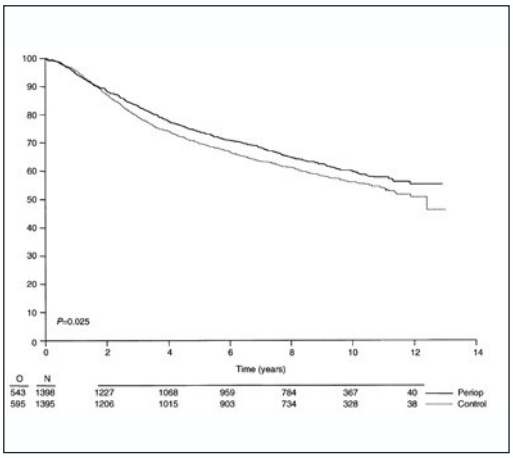

Figure 2. Progression-free survival

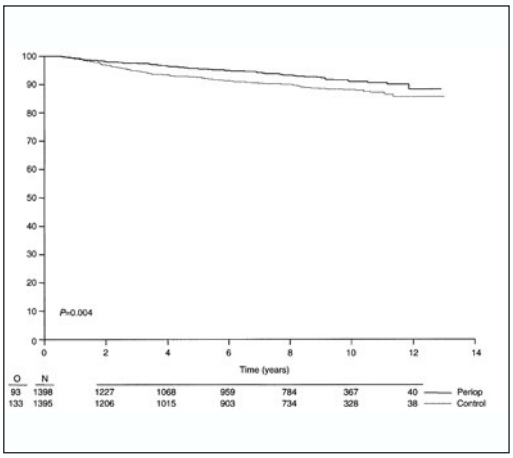

Figure 3. Locoregional recurrence as first event

endpoints are progression-free survival (PFS) and locoregional recurrence as the first event. PFS was defined as the time between the date of randomisation and the date of relapse (including secondary primary tumours and contralateral breast cancers) or death, whichever came first. A locoregional recurrence was defined as any recurrence in the breast or axilla. Only recurrences which occurred before the diagnosis of a distant metastasis and/or a new primary tumour were regarded as a locoregional recurrence as the first event and added to the analysis. Statistical calculations were performed using the 'intent-to-treat principle'. This means that all data are used in the statistical calculations, regardless of the fact whether a patient was eligible or not. PFS and overall survival curves, as well as locoregional recurrence rates, were estimated using the Kaplan–Meier method [12] and log-rank tests for the comparison of treatment effects were also used [13]. Cox proportional-hazard regression models [14] were used to estimate hazard ratios (HR) with their 95% confidence interval (CI). All tests were two-sided.

Results

Main analysis

From May 1986 to March 1991, 2795 patients were enrolled from 16 institutions from nine different countries onto this trial (Appendix). 41patien ts were ineligible. 2793 patients were included in the analysis. 2 patients, of whom information concerning randomisation was missing, were excluded from the analysis. After a median follow-up of 11 years, overall survival (71% versus 74%) was not significantly different between the two treatment groups (HR=0.9; 95% CI:

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0.78–1.37; P = 0.14) (Fig. 1). However, PFS rates (53% versus 59%) are significantly different in favour of the perioperative chemotherapy group (HR=0.88; 95% CI: 0.78–0.98; P = 0.025) (Fig. 2). In line with the PFS results, locoregional control (86% versus 91%) was significantly different also in favour of the study-arm; (HR=0.69; 95% CI: 0.54–0.89; P = 0.004) (Fig. 3).

Subgroup analyses
To study the effect of perioperative chemotherapy in the specified groups of patients, subgroup analyses were carried out. However, one must interpret the outcome of these analyses with caution, as these were not preplanned analyses and are therefore only to be regarded as exploratory analyses.

Node-negative patients
1467 patients without axillary lymph node metastases were included in the trial. Node-negative patients in the study-arm did not have a significant better overall survival (HR=0.89; 95% CI: 0.70–1.13; P = 0.33) after perioperative FAC. However, a significant effect of perioperative FAC was observed on the PFS rate (HR=0.83; 95% CI: 0.70–0.99; P = 0.035). In addition, perioperative chemotherapy did have a profound effect on locoregional control in this subgroup, resulting in a significant difference in the locoregional control rates (HR=0.67; 95% CI: 0.48–0.93; P = 0.018) in favour of the study-arm.

Patients with T1 tumours
Patients with small tumours who received perioperative FAC did not benefit significantly in terms of overall survival (HR=0.86; 95% CI: 0.62–1.18; P = 0.34) and PFS (HR=0.92; 95% CI: 0.73–1.17; P = 0.50). However, perioperative chemotherapy had a marginally favourable effect on locoregional control (HR=0.64; 95% CI: 0.42–0.99; P = 0.047).

Premenopausal patients
Premenopausal patients have been established as the patients that benefit the most from adjuvant chemotherapy for breast cancer. Patients younger than or equal to 50 years of age at the time of diagnosis were deemed to be premenopausal patients in this study. Perioperative chemotherapy did not yield better overall survival rates (HR=0.91; 95% CI: 0.72–1.15; P = 0.43) or PFS rates (HR=0.87; 95% CI: 0.73–1.05; P = 0.15) in this subgroup. Moreover, the administration of one course of perioperative FAC did not result in better locoregional control rates (HR=0.75; 95% CI: 0.53–1.05; P = 0.096).

Timing of administration
We presumed that if timing influences treatment efficiency, this effect could only be demonstrated in patients who received extra adjuvant systemic therapy. To study the 'timing-effect' of one course of perioperative FAC, we therefore selected all patients who received prolonged adjuvant systemic treatment. In total, 1198 patients were included in the 'timing' analysis, but no effect of timing was found on overall survival (HR=0.65; 95% CI: 0.78–1.17; P = 0.65) or PFS (HR=0.94; 95% CI: 0.80–1.12; P = 0.50), respectively. In addition, no effect of timing was found on locoregional control (HR=0.88; 95% CI: 0.59–1.31; P = 0.52).

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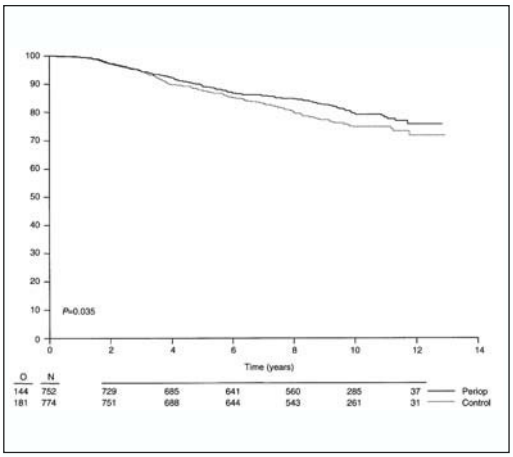

Figure 4. Overall survival in patients with 1 course of peri-operative FAC and no further systemic therapie versus patients treated with locoregional therapie alone.

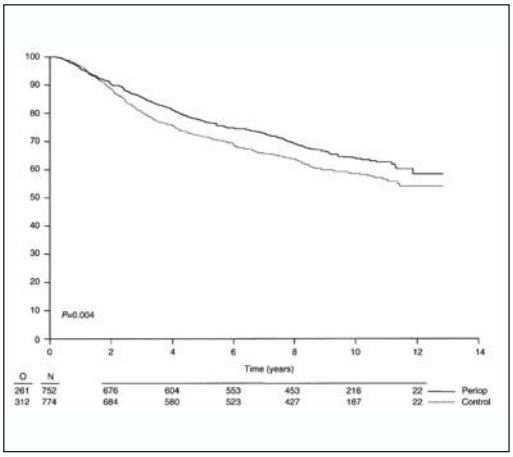

Figure 5. Progression-free survival in patients with 1 course of peri-operative FAC and no further systemic therapie versus patients treated with locoregional therapie alone.

Perioperative FAC as the sole systemic therapy

To test the absolute effect of one perioperative course of FAC, we compared the data of the patients in the control group who did not receive adjuvant systemic treatment with the patients who received perioperative chemotherapy alone in the study-arm. Patient characteristics are listed in Table 2. In this subset, which consisted of 1532 patients, a significant difference in favour of the perioperative chemotherapy group was shown in terms of overall survival (HR=0.80; 95% CI: 0.64–0.98; P = 0.035) and PFS (HR=0.79; 95% CI: 0.67–0.93; P = 0.004) (Figs. 4 and 5). Locoregional control was also significantly better in the study-arm (HR=0.60; 95% CI: 0.43–0.83; P = 0.0023) (Fig. 6).

Type of surgery

Perioperative chemotherapy did not have a significant effect on overall survival when patients were compared according to type of surgery (data not shown). Interestingly, perioperative chemotherapy has a significant impact on PFS (HR=0.84; 95% CI: 0.72–0.98; P = 0.031) and locoregional control (HR=0.71; 95% CI: 0.52–0.97; P = 0.029) in patients who underwent breast-conserving surgery, but not in patients who underwent mastectomy (HR=0.92; 95% CI: 0.78–1.08; P = 0.30 and HR=0.67; 95% CI: 0.43–1.04; P = 0.074, respectively).

ER-status

ER-status was known in 89% of the patients. 65% was ER-positive, 24% were ER-negative. In the ER-positive population, patients who received perioperative chemotherapy had a marginally significant better locoregional control rates (HR=0.71; 95% CI: 0.52–0.98; P = 0.04). Perioperative chemotherapy did not have a significant effect on overall survival and PFS in ER-positive patients. In ER-negative patients, locoregional control as well as PFS or overall survival rates were not significantly altered by perioperative chemotherapy.

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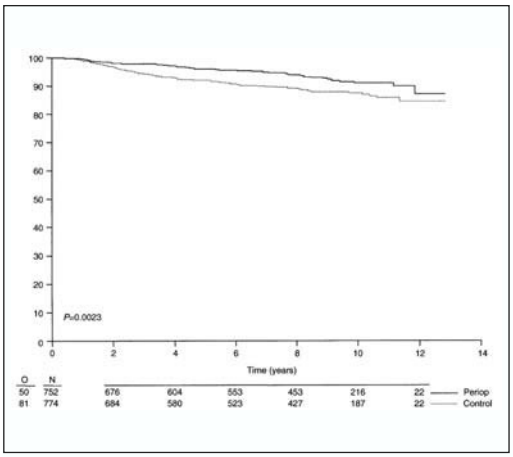

Figure 6. Locoregional recurrence in patients with 1 course of peri-operative FAC and no further systemic therapie versus patients treated with locoregional therapie alone

Discussion

This trial was set up primarily to study whether one course of chemotherapy given directly after surgery would yield better results in terms of prognosis than surgery alone in early stage breast cancer patients. As demonstrated in the main analyses, our results firmly demonstrate that perioperative chemotherapy after surgery leads to better locoregional control than surgery alone. We also showed that one course of perioperative FAC significantly improves progression-free survival rates.
Moreover, in a subset of patients who received locoregional treatment alone, one course perioperative FAC resulted in significant higher survival rates for those given perioperative chemotherapy. However, when patients who also received prolonged courses of chemotherapy or patients who received hormonal therapy were studied, no significant effect of perioperative administration of FAC could be shown.
Ever since chemotherapy became part of the therapeutic strategy against breast cancer, timing has been a matter of discussion. Several trials have studied early administration of (poly) chemotherapy after surgery [7–9,15–17]. These trials and their overall results are listed in Table 3. To date, however, no evidence of a significant effect of early timing of chemotherapy after primary tumour removal on treatment outcome has been demonstrated.
Since EORTC trial 10854 was initiated in 1986, the indication guidelines of adjuvant chemotherapy have shifted substantially. In the 1980s, chemotherapy was given on the basis of nodal- and menopausal status. At present, the decision to administrate chemotherapy is based on a combined evaluation of tumour stage, tumour grade and menopausal status in order to pursue a 10% disease-free survival gain after 10 years [19]. This shift has

	1× perioperative FAC $n=756$	Control $n=776$
	n (%)	*n* (%)
Age (years)		
⩽50	319 (42)	329 (42)
>50	437 (58)	447 (58)
Nodal status (pathological)		
Negative	666 (90)	651 (86)
Positive	71 (10)	104 (14)
Missing data	19 (3)	21 (3)
Tumour size (clinical)		
<2 cm	266 (36)	274 (36)
>2 cm	480 (64)	488 (64)
Missing data	10 (1.5)	14 (2)
ER status		
ER+	477 (63)	478 (62)
ER−	188 (25)	207 (27)
Missing data	91 (12)	91 (12)
Type of surgery		
BCS	494 (65)	490 (63)
Mastectomy	259 (34)	283 (36)
Missing data	3 (0.5)	3 (0.5)

BCS, breast conserving surgery; ER, oestrogen receptor; FAC, doxorubicin, 5-fluorouracil and cyclophosphamide.

Table 2. Patient characteristics; patients treated with 1 course of peri-operative FAC and no further systemic therapy versus patients treated with locoregional therapy alone

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Study	*n* patients	Median follow-up (months)	TNM	Study design	RFS	OS
Nissen–Meyer The Scandinavian Adjuvant Chemotherapy Study 1 1965–1975	1026	205	T1-3, N0-2, M0 T1-2 80%	I: Mast→1×C→RT vs	I 52% (17 years FU)	I 36%
			N0 60%	II: Mast→RT	II 40% $P<0.001$	II 31% NS
Cancer Research Campaign 2 Trial [18] 1980–1985	2230	48	T1-2, N0-1, M0	I: Mast/BCT→1×C±RT & Tam	I ±67% (4 years FU)	NS
			T1 28% N0 49%	Vs. II: Mast/BCT→±RT & Tam	11 ±67%	NS
IBCSG (Trial V)[a] 1981–1985	2628	42	T1-3a, N0-1, M0	Ia: N0: Mast→1×CMFL (<36 h)	N0: Ia 77%	N0: Ia 90%
			N0 51%→(T1 41%)	Ib: N+: Mast→1×CMFL (<36 h) ±vs IIa: N0: Mast IIb: N+: 5×CMFLP±Tam IIc: N+: 6×CMFLP±Tam	(3.5 years FU) IIa 73% $P=0.04$ N+: Ib 40% IIb 60% IIc 62% $P<0.0001$	IIa 86% NS N+: Ib 69% IIb 74% IIc 80% $P=0.011$
Sertoli 1985–1992	600	68	T1-3a, N0-2, M0	I: Mast/BCT→1×FEC (<72 h), if N+: 5×FEC & 6×CMF±RT & Tam	I 76%	I 88%
			T1 53% T2 39% N0 53%	vs II: Mast/BCT→RT, if N+: 6× FEC and 6× CMF & Tam	(5.7 years FU) II 70% $P=0.053$	II 84% NS
EORTC 10854 1986–1991	2795	132	T1-3, N0-1, M0	I: Mast/BCT→1×FAC±RT & Tam	I 65% (11 years FU)	I 74%
			T1 30% N0 53%	vs II: Mast/BCT→±RT & Tam	II 60% $P=0.025$	II 71% NS

Mast, mastectomy; C, cyclophosphamide; RT, radiotherapy; BCT, breast-conserving therapy; FEC, 5-fluorouracil epirubicin cyclophosphamide; CMF, cyclophosphamide methotrexate 5-fluorouracil; Tam, tamoxifen; CMFL, cyclophosphamide methothrexate 5-fluorouracil leucovorin; CMFLP, cyclophosphamide methothrexate 5-fluorouracil leucovorin prednisone; FAC, 5-fluorouracil doxorubicin cyclophosphamide; RFS, relapse-free survival; OS, overall survival; NS, not significant.

[a] The International (Ludwig) Breast Cancer Study Group (trial V).

Table 3. Perioperative chemotherapy trials

led to a higher fraction of early stage breast cancer patients receiving chemotherapy nowadays compared with two decades ago. If this trial was to be executed now, the subgroup of patients who would not receive additional systemic therapy would be much smaller. The question therefore is whether patients in which additional systemic therapy is not indicated nowadays (i.e. node-negative patients with small tumours and favourable histological parameters) would benefit from one course of chemotherapy.

Based upon our results, this question is difficult to answer. However, the presented results can be of use in designing future clinical trials.

However, the outcome that one course of chemotherapy as a sole systemic therapy is able to induce a modest, but significant increase in overall survival and better locoregional control rates in a subset of low-risk breast cancer patients regardless of the tumour stage and menopausal status, is an important finding. One could advocate on the basis of this finding that all patients with early stage breast cancer should at least receive some form of chemotherapy. Arguments against this policy have always been based on treatment-related toxicities and the long-term risks of

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developing haematological malignancies after chemotherapy that would not be counterbalanced by the merits of systemic cytotoxic therapy in node-negative breast cancer patients. This group of patients, however, is known to have a 70–80% long-term survival rate after locoregional therapy alone, meaning that 20–30% of these patients will eventually develop distant metastases and subsequently die of breast cancer. The argument concerning toxicity may be real in a setting where adjuvant chemotherapy consists of prolonged schemes like in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-13 trial [20]. This trial investigated whether 12 cycles of methotrexate and 5-fluorouracil followed by leucovorin after surgery would yield better results than surgery alone in premenopausal, node-negative, ER-negative patients. In accordance with our results, this trial demonstrated a significant better disease-free survival rates and better locoregional control in favour of the adjuvant chemotherapy group. A comparable study conducted by Amadori and colleagues [21] using CMF showed similar data. In the EORTC trial 10854, only one course of an anthracycline-containing chemotherapeutic regimen was given. This type of adjuvant treatment induced a significant improvement in progression-free survival and locoregional control in the overall analysis, as well as overall survival in a large subset of patients without intolerable mortality and morbidity [22].
Therefore, one should be aware of these data when developing a treatment strategy for patients with early stage node-negative breast cancer.

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