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Clinical Investigation: Breast Cancer

Sequence of Radiotherapy and Chemotherapy in Breast Cancer After Breast-Conserving Surgery

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Summary

The optimal sequence of radiotherapy and chemotherapy in breast-conserving therapy (BCT) is unknown. An analysis was done on 641 patients all treated with radiotherapy and adjuvant chemotherapy. In addition to the available literature (e.g., four trials and three review papers) our analysis showed that radiotherapy as an integral part of the primary treatment of BCT should be administered first, followed by adjuvant chemotherapy.

Purpose: The optimal sequence of radiotherapy and chemotherapy in breast-conserving therapy is unknown.

Methods and Materials: From 1983 through 2007, a total of 641 patients with 653 instances of breast-conserving therapy (BCT), received both chemotherapy and radiotherapy and are the basis of this analysis. Patients were divided into three groups. Groups A and B comprised patients treated before 2005, Group A radiotherapy first and Group B chemotherapy first. Group C consisted of patients treated from 2005 onward, when we had a fixed sequence of radiotherapy first, followed by chemotherapy.

Results: Local control did not show any differences among the three groups. For distant metastasis, no difference was shown between Groups A and B. Group C, when compared with Group A, showed, on univariate and multivariate analyses, a significantly better distant metastasis−free survival. The same was noted for disease-free survival. With respect to disease-specific survival, no differences were shown on multivariate analysis among the three groups.

Conclusion: Radiotherapy, as an integral part of the primary treatment of BCT, should be administered first, followed by adjuvant chemotherapy.

Keywords: Breast-conserving therapy, Chemotherapy, Radiotherapy, Sequence

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Introduction

Breast-conserving therapy (BCT) is the treatment of choice for early-stage invasive breast cancer and consists of lumpectomy followed by radiotherapy of the breast with or without a boost (1–4). In this respect, radiotherapy can be regarded as an integral part of the primary treatment, implicating that adjuvant systemic therapy should follow the primary treatment. Currently, women with early-stage breast cancer are increasingly being treated postoperatively with both radiotherapy and chemotherapy. The optimal sequence of radiotherapy and chemotherapy in the treatment of breast cancer has been and is still a matter of debate. Four randomized studies have been done so far, but no definitive conclusions could be drawn (5–8).

In our region, the sequence has also been a matter of debate until the end of 2004. We thereafter agreed on a fixed sequence of radiotherapy and chemotherapy. Up to that time, this decision depended on preference of the referring physician or hospital.

Since 1983, we have entered all BCT cases in our cohort on women with BCT, and have also included information on the sequence of chemotherapy and radiotherapy.

In this study, we used this database and focused on the effects of the sequence of chemotherapy and radiotherapy in BCT on local control, distant metastasis, and survival.

Methods and Materials

We used information from our prospective cohort of all patients diagnosed with invasive breast cancer in the Twente-Achterhoek region from 1983 through 2007 and treated with BCT. All received their radiotherapy at the Radiotherapy Department of the Medisch Spectrum Twente. A total of 3,372 BCT were registered in 3,265 patients with invasive breast cancer. All patient data, including demographics, pathology, staging information, treatment, and outcome were recorded and updated regularly. Patients were classified according to the TNM classification (4th edition, 1997). The cut-off for analysis of this study was February 2011.

Histological examination of all BCT was done in the Pathology Laboratory Oost Nederland according to standard procedures. The malignancy grading was performed according to the Bloom and Richardson grading system. In the early years, grading was not always performed routinely, so the pathologist did this retrospectively. Presence of lymph vascular space invasion (LVSI) was also recorded. Involvement of the margins of the lumpectomy specimen was defined as the presence of microscopic involvement of invasive carcinoma (IC), or ductal carcinoma *in situ* (DCIS) in the inked resection margin. Close margins were recorded as negative.

Estrogen and progesterone receptors were considered positive when nuclear expression was present in more than 10% of the tumor cells. The mitotic activity index (MAI) was defined by the number of mitotic figures in an area of 2 mm^2 according to protocol (9).

The family history was registered according to first-degree relative.

Treatment

BCT consisted of lumpectomy with axillary clearance of Levels I to III, followed by whole- breast radiotherapy followed by a boost aimed at the lumpectomy cavity. After 2001, axillary staging was done by sentinel lymph node procedures, axillary dissection followed only in cases with proven axillary lymph node metastases or when sentinel node biopsy failed. Radiotherapy consisted of 50 Gy to the whole breast, followed by a boost of 14 Gy to the lumpectomy cavity. Adjuvant systemic and regional radiotherapy was given according to existing treatment guidelines. Regional radiotherapy was indicated for patients with either four or more axillary lymph node metastasis or presence of extranodal disease.

In the late 1980s, adjuvant systemic therapy was given for patients with histological proven axillary lymph node metastasis. From 1992 on, all premenopausal patients with histological proven axillary lymph node metastasis received chemotherapy. For postmenopausal patients adjuvant hormonal therapy was given in case of tumor-positive axillary lymph nodes. Since 1999, indications for adjuvant systemic therapy depended not only on lymph node status but also on the MAI, histological grade, and tumor size. Premenopausal women received chemotherapy and hormonal therapy when the estrogen receptor status was positive.

Through 2007, a total of 641 patients with 653 BCT received both chemotherapy and radiotherapy and are the basis of this analysis. In late 2004 treatment with trastuzumab was introduced in our region. Until the end of 2007, 24 patients had been treated with trastuzumab. To prevent any bias those were excluded from analysis, leaving 617 patients with 629 BCT. Patients were divided into three groups. Group A and B comprised patients treated before 2005, Group A radiotherapy first, and Group B chemotherapy first. Group C consisted of patients treated from 2005 onward when we had a fixed sequence of radiotherapy first followed by chemotherapy.

Statistical methods

Time to recurrence and length of follow-up were calculated from the date of the lumpectomy. To test between-group differences for categorical data Chi-square tests were used, and these analyses with regard to local recurrences were performed in relation to the number of BCT. For all survival analyses, patients were censored if they had not experienced an event (local recurrence, distant metastasis) at the date of last follow-up or at the date of death. Local recurrence–free survival (LRFS) is defined by survival time without local recurrent disease, and an event was defined by the occurrence of recurrent disease in the treated breast.

Statistics for distant metastasis and disease-specific survival (DSS), corrected for intercurrent death, were performed in relation to the number of patients and calculated by the method of Kaplan and Meier. This means that for the DSS analysis, data for patients who died of causes other than breast cancer were regarded as censored data. An event was defined as death due to breast cancer. Distant metastasis–free survival (DMFS) was defined as survival without distant metastasis in patients. An event was defined as the occurrence of a distant metastasis in the patient. Disease-free survival (DFS) is defined by survival without any recurrence.

For comparison of survival distributions the log-rank test was used. Variables that were univariate related to the outcomes of interest ($p < 0.05$) were entered in the multivariate analyses. Because of the median follow-up of those after 2004, we executed 5-year rates for univariate and multivariate analysis.

Analyses were performed using STATA (10).

From 2005 onward, we fixed the sequence of the two postoperative treatment modalities in radiotherapy first, followed by

chemotherapy. The latter gave us the opportunity to investigate the phenomenon of "confounding by indication" by comparing results from 2005 onward with those before 2005. When treatment before 2005 with the "freely chosen" sequence radiotherapy → chemotherapy showed better results compared with those from 2005 onward with the "compulsory" sequence radiotherapy → chemotherapy, then this would be indicative of "confounding by indication."

Results

Of all 629 patients with BCT, we distinguished three groups. Group A, patients who had radiotherapy first and were treated before 2005, comprised 62.6% (394/629); Group B, patients who had chemotherapy first and were treated before 2005, comprised 15.4% (97/629); and Group C, patients who were treated from 2005 onward with a fixed sequence of radiotherapy and chemotherapy and administering radiotherapy first, comprised 21.9% (138/629). Patients and tumor characteristics of the three groups are presented in Table 1, showing a significant difference for age, MAI, and lymph node status. Patients in Group C were significantly older than patients in the Groups A and B and had a more favorable MAI ($\leq$12 mitoses in 2 mm^2). Group B showed significantly more involvement, of more than three positive lymph nodes.

Table 2 shows the characteristics for the adjuvant regional radiotherapy and hormonal therapy. Those having chemotherapy after radiotherapy before 2005 received significantly less regional radiotherapy. From 2005 onward, this difference was even more pronounced, because of the extended indications for adjuvant systemic therapy. Adjuvant hormonal therapy was given significantly more frequently in those with chemotherapy before the radiotherapy. All patients with adjuvant regional radiotherapy received adjuvant hormonal therapy.

The length of the follow-up ranged from 5 to 285 months, with a median of 87 months. This was 104.5 months for Group A, 95 months for Group B, and 46 months for Group C.

Local control

The 5- and 7-year LRFS for the three groups was 96.2% and 93.9% for Group A, 99.0% and 97.3% for Group B, and 99.7% and 99.7% for Group C (log rank, $p = 0.2121$).

In univariate analyses, young age, presence of LVSI, positive margin status, and hormonal therapy showed significance.

Distant metastasis

Of all 617 patients, 19.8% (122/617) developed distant metastasis during follow-up. The 5- and 7-year DMFS probabilities for the three groups were 85.1% and 80.4% for Group A, 78.0% and 75.5% for Group B, and 97.8% and 97.8% for Group C (log rank $p = 0.0013$) (Fig. 1).

On univariate analysis, compared with group A no difference in distant metastasis was seen for Group B (hazard ratio [HR] = 1.3; 95% confidence interval [CI] = 0.8−2.0; $p = 0.329$), but for Group C significant less distant metastasis were seen (HR = 0.2; 95% CI = 0.05−0.55; $p = 0.003$). Also the number of lymph node metastasis, presence of LVSI, young age, positive margin status, and adjuvant regional radiotherapy showed significance for distant metastases. In a multivariate Cox regression corrected for the above-mentioned variables, administering chemotherapy after radiotherapy from 2005 onward (Group C), compared with Group A showed a significant better DMFS (HR = 0.2; 95% CI = 0.07−0.72; $p = 0.0012$).

Disease-free survival

The 5- and 7-year DFS probabilities for the three groups were 82.8% and 76.9% for Group A, 78.0% and 74.2% for Group B, and 98% and 98% for Group C (log rank $p < 0.001$) (Fig. 2).

In univariate analyses, besides sequence of radiotherapy and chemotherapy, the following variables showed significance for recurrences: presence of LVSI, number of positive lymph nodes, positive margin status, young age, presence of carcinoma *in situ*, adjuvant radiotherapy, and hormonal therapy. In multivariate analyses corrected for the above-mentioned variables, Group C showed significantly fewer recurrences compared with Group A (HR = 0.2; 95% CI = 0.06−0.61; $p = 0.005$).

Disease-specific survival

The 5- and 7-year DSS probabilities for the three groups were 91.8% and 86.7% for Group A, 87.1% and 82.3% for Group B, and 98.5% and 98.5% for Group C (log-rank $p = 0.0245$) (Fig. 3).

On univariate analysis, the number of lymph node metastasis, positive margin status, negative progesterone status, presence of LVSI, high MAI, adjuvant hormone therapy, and adjuvant regional radiotherapy showed significance for DSS. In a multivariate Cox regression analysis corrected for the above-mentioned variables, the sequence of chemotherapy and radiotherapy did not show significance.

Discussion

In our study, we found no differences in outcomes between subjects given adjuvant chemotherapy before or after radiotherapy in BCT in patients treated before 2005. From 2005 onward, with radiotherapy administered before the chemotherapy, both DMFS and DFS were better when compared with the patients treated before 2005.

Radiotherapy and chemotherapy are increasingly being used in the treatment of breast cancer. For women with early-stage breast cancer, adjuvant radiotherapy has been shown to reduce considerably the risk of local recurrence and improves breast cancer−specific survival (11, 12). Adjuvant chemotherapy has also been shown to improve 15-year survival by about 10% for women less than 50 years of age and by about 3% for women 50 to 69 years of age. (13) Most clinicians are reluctant to delay the start of adjuvant chemotherapy. Their opinion about the estimated detrimental effect on survival is based on theoretical considerations, small cohort studies, and so-called expert opinion. Neither large randomized studies nor large cohort studies have ever confirmed this position. Current practices for the sequencing of radiotherapy and chemotherapy include chemotherapy before radiotherapy, concurrently, sandwiching, and after. It is not clear which of these sequences is the best.

Looking at the tumor characteristics among the three groups, specifically with respect to age, MAI, and the number of positive lymph nodes, one would expect a difference in DMFS and DSS.

Table 1 Patient and tumor characteristics in 617 breast cancer patients with 629 breast-conserving therapies according the three different groups

Characteristics	Before 2005 Group A (n = 394): First radiotherapy n (%)	Before 2005 Group B (n = 97): First chemotherapy n (%)	After 2004 Group C (n = 138): First radiotherapy n (%)	p value
Age category				
≤40 years	82 (20.8)	21 (21.6)	13 (9.4)	
41−50 years	190 (48.2)	35 (36.1)	55 (39.9)	<0.001
>50 years	122 (31.0)	41 (42.3)	70 (50.7)	
Family history				
Positive	76 (19.3)	21 (21.6)	26 (18.8)	NS
None	318 (80.7)	76 (78.4)	112 (81.2)	
Localization primary				
Lateral	273 (69.3)	64 (66.0)	102 (73.9)	NS
Medial/central	121 (30.7)	33 (34.0)	36 (26.1)	
Histology				
Ductal carcinoma	348 (88.3)	86 (88.7)	123 (89.1)	
Lobular carcinoma	23 (5.8)	8 (8.2)	9 (6.5)	
Tubular carcinoma	7 (1.8)	1 (1.0)	1 (0.7)	NS
Medullar carcinoma	15 (3.8)	2 (2.1)	3 (2.2)	
Rest	1 (0.3)	0	2 (1.4)	
Differentiation grade				
Grade 1	25 (6.4)	8 (8.2)	10 (7.3)	
Grade 2	147 (37.3)	44 (45.4)	50 (36.2)	NS
Grade 3	160 (40.6)	42 (43.3)	78 (56.5)	
Unknown	62 (15.7)	3 (3.2)	0	
Carcinoma *in situ*				
DCIS	107 (27.2)	26 (26.8)	52 (37.7)	
LCIS	18 (4.6)	4 (4.1)	6 (4.3)	NS
None	269 (68.3)	67 (69.1)	80 (58.0)	
Estrogen receptor status				
Positive	240 (60.9)	66 (68.0)	95 (68.8)	
Negative	137 (34.8)	30 (31.9)	43 (31.2)	NS
Unknown	17 (4.3)	1 (1.1)	0	
Progesterone receptor status				
Positive	232 (58.9)	59 (60.8)	88 (63.8)	
Negative	143 (36.3)	37 (38.1)	50 (36.2)	NS
Unknown	19 (4.8)	1 (1.1)	0	
Lymph-angio invasion				
Positive	69 (17.5)	20 (20.6)	27 (19.6)	
Negative	325 (82.5)	77 (79.4)	111 (80.4)	NS
Margin status				
Negative	324 (82.2)	85 (87.6)	124 (89.9)	
Positive IC	37 (9.4)	6 (6.4)	10 (7.2)	
Positive DCIS	24 (6.1)	5 (5.1)	4 (2.9)	NS
Positive IC + DCIS	9 (2.3)	1 (1.0)	0	
Re-excision				
Yes	33 (8.4)	10 (10.3)	14 (10.1)	
None	360 (91.4)	86 (88.7)	124 (89.7)	NS
Unknown	1 (0.2)	1 (1.0)	0	
MAI				
Low ≤12	87 (22.1)	37 (38.1)	58 (42.0)	
High >12	216 (54.8)	51 (52.6)	48 (34.8)	<0.001
Unknown	91 (23.1)	9 (9.3)	32 (23.2)	
Lymph node status				
Negative	132 (33.5)	21 (21.7)	60 (43.5)	
1−3 Positive	214 (54.3)	29 (29.9)	58 (42.0)	<0.001
>3 Positive	48 (12.2)	47 (48.4)	20 (14.5)	

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Before 2005 Group A (n = 394): First radiotherapy n (%)	Before 2005 Group B (n = 97): First chemotherapy n (%)	After 2004 Group C (n = 138): First radiotherapy n (%)	p value
Tumor size				
pT1	227 (57.6)	45 (46.4)	70 (50.7)	
pT2	167 (42.4)	52 (53.6)	68 (49.3)	NS

Abbreviations: DCIS = ductal carcinoma *in situ*; IC = invasive carcinoma; LCIS = lobular carcinoma *in situ*; MAI = mitotic activity index; NS = not significant.
p Value has been calculated on known components of variables.

Group C showed more favorable characteristics compared with the other two. The MAI was significantly worse for Group A and B, with more than 50% cases with a high MAI. The number of positive lymph nodes was significantly higher for Group B. With respect to positive lymph nodes irrespective of the number, Group B showed 78.3% compared with 66.5% for the other two groups. This might result in a worse outcome for Group B compared with the other two groups On the other hand, this is reflected in the adjuvant regional radiotherapy and hormonal therapy for Group C, which is higher compared with the other two. Adjuvant hormonal therapy is applied in significantly more cases when compared with those having chemotherapy after the radiotherapy. Overall, one would expect, together with the extension of the indications during the years for adjuvant systemic therapy, a better outcome for Group C.

Decisions on whether giving chemotherapy before or after the radiotherapy were before 2005 mainly based on the fact that clinicians were convinced that administering chemotherapy first would enable a better survival probability. From 2005 onward, when agreement was reached on administering radiotherapy first, one might expect that results would be worse for those receiving radiotherapy before chemotherapy, compared with those patients who received the same treatment sequence prior to 2004. This would be indicative of confounding by indication in the period before 2004, when patients could be offered the sequence chemotherapy → radiotherapy when this was deemed more appropriate. That we do not see this hypothesis confirmed is probably partly the result of the extending indications for adjuvant systemic therapy in the last decade. The latter might explain the improved results of after 2004 compared with the results from the period before 2005. Nonetheless, confounding by indication does not seem to be playing a substantial role before fixing the sequence to radiotherapy → chemotherapy.

Most adjuvant chemotherapy trials defined a particular time from surgery to start of chemotherapy beyond which patients were not longer eligible to participate. Strictly speaking, the benefits of treatment described by a clinical trial are applicable only to patients treated within the same time frame as in the trial. Whether equivalent benefit can be ascribed when chemotherapy is started beyond the time specified is not known.

Besides local control, cosmetic outcome is an important item with BCT. Radiotherapy preceded or followed by chemotherapy after surgery might have a negative impact on cosmesis. Most of the literature involves concomitant radiotherapy and chemotherapy (14). We have not scored this item because scoring cosmetic outcome is dependent on many factors such as patient, physician, time, type of surgery, and type of chemotherapy. It is our impression that, on the cosmetic outcomes of the breast, the effect was limited.

So far, four randomized trials of two different comparisons of sequencing have been published (5–8). The comparisons were concurrent versus sequential in three and radiotherapy followed by chemotherapy versus chemotherapy followed by radiotherapy in one trial (6). Bellon *et al.* presented, in 2005, the long-term results from the only trial comparing chemotherapy first vs. radiotherapy first. However, this trial was small (n = 244) and underpowered. The investigators found no advantage to giving radiotherapy before adjuvant chemotherapy in patients treated with breast-conserving surgery. Interpreting their results properly, their conclusion should be that no difference was found in giving either radiotherapy or chemotherapy first. Despite the fact that our study is not randomized, but with more power, we confirm their findings. Three trials included one arm with concomitant chemo-radiotherapy vs. chemotherapy followed by radiotherapy (5, 7, 8). Those trials do not give an answer as to whether one should give radiotherapy before or after chemotherapy.

A Cochrane review on sequencing of radiotherapy and chemotherapy including the trials mentioned above, suggested that the different methods of sequencing chemotherapy and radiotherapy do not appear to have a major effect on survival or recurrence for women with breast cancer if radiation is started within 7 months after surgery (15). Also Bowden *et al.*, in their review, could not come to any conclusion about the optimal sequence of radiotherapy and chemotherapy (16).

Recently Balduzzi *et al.*, in a review summarizes the data available on the effects of interaction between systemic therapy

Table 2 Adjuvant therapy characteristics of hormonal therapy and or regional radiotherapy of 629 breast-conserving therapies according to timing of chemotherapy in relation to radiotherapy

Characteristic	Before 2005 Group A (n = 394): First radiotherapy n (%)	Before 2005 Group B (n = 97): First chemotherapy n (%)	After 2004 Group C (n = 138): First radiotherapy n (%)	p value
Regional radiotherapy				
Yes	138 (35.0)	48 (49.5)	22 (15.9)	
No	256 (65.0)	49 (50.5)	116 (84.1)	<0.001
Hormonal therapy				
Yes	164 (41.6)	73 (75.3)	95 (68.8)	
No	230 (58.4)	24 (24.7)	43 (31.2)	<0.001

Those receiving adjuvant regional radiotherapy also received adjuvant hormonal therapy.

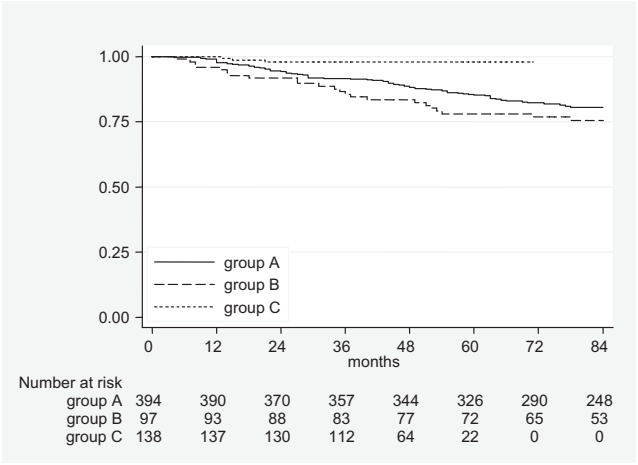

Fig. 1. Distant metastasis−free survival of 617 patients treated with breast-conserving therapy according to sequence of radiotherapy and chemotherapy. Group A, first radiotherapy; Group B, first chemotherapy; and Group C, from 2005 onward with fixed sequence of radiotherapy first, followed by chemotherapy.

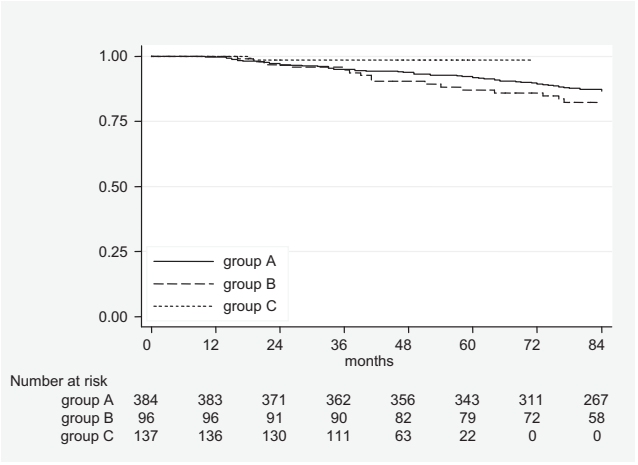

Fig. 3. Disease-specific survival of 617 patients treated with breast-conserving therapy according to sequence of radiotherapy and chemotherapy. Group A, first radiotherapy; Group B, first chemotherapy; and Group C from 2005 onward, with fixed sequence of radiotherapy first, followed by chemotherapy.

and radiotherapy on the risks of local and distant relapse in operable breast cancer patients (17). Their conclusions were that the optimal sequence of systemic therapy and radiotherapy remains still uncertain due to many variables such as the limited available studies carried out in patients with different characteristics, treated with different adjuvant treatments and different radiotherapy methodologies. They also stated that "although available results on timing of chemotherapy are conflicting, early delivery of adjuvant chemotherapy might be important for selected subgroups of patients." This not only conflicts with their overall conclusion but is also not based on any study, Phase III study, or large cohort study.

Numerous retrospective studies have been conducted looking at the sequence or timing of chemotherapy or radiotherapy. Lohrisch *et al.*, in a retrospective review of 2,594 patients, showed that adjuvant chemotherapy is equally effective up to 12 weeks after definitive surgery. (18) Sanchez *et al.*, in a large retrospective study of 2,782 patients on timing of initiation of adjuvant chemotherapy, concluded that the optimum timing of initiation of chemotherapy is unknown, and that delay in the initiation has no influence over survival even more than 9 weeks after surgery (19).

Nowadays, the duration of the radiotherapy treatment can be limited significantly due to the implementation of hypofractionation schemes, whereas recent developments in adjuvant systemic therapy result in a longer time span, potentially resulting in an increased delay of the radiotherapy. Studies conducted so far have not taken into account this shorter duration of radiotherapy and longer duration of chemotherapy.

We therefore suggest that radiotherapy of BCT, as an integral part of the primary treatment, should be administered first, followed by adjuvant chemotherapy.

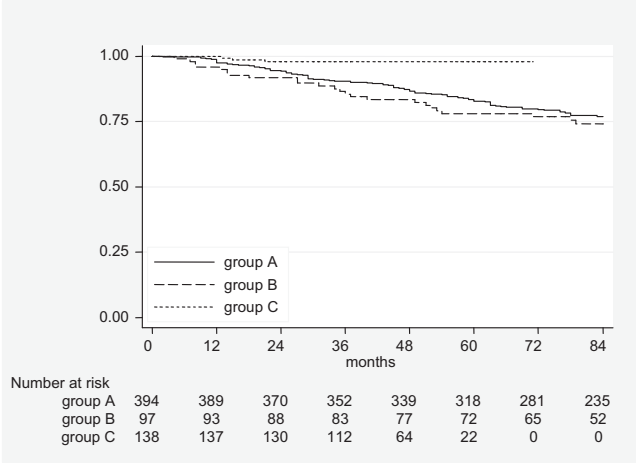

Fig. 2. Disease-free survival of 629 breast-conserving treatments with 617 patients according to sequence of radiotherapy and chemotherapy. Group A, first radiotherapy; Group B, first chemotherapy; and Group C from 2005 onward, with fixed sequence of radiotherapy first, followed by chemotherapy.

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