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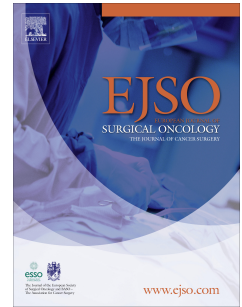
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Ductal Carcinoma In Situ of the breast in younger women: a subgroup of patients at high risk

Running head: DCIS in women under forty

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Abstract

Background: After breast conserving treatment, young age is a predictive factor for recurrence in patients with Ductal Carcinoma In Situ (DCIS) of the breast. The purpose of this study was to evaluate predictive factors for recurrence and outcomes in these younger women (under 40 years) treated for pure DCIS.

Methods: From 1974 to 2003, 207 cases were collected in 12 French Cancer Centers. Median age was 36.3 years and median follow-up 160 months. Seventy four (35.8%) underwent mastectomy, 67 (32.4%) lumpectomy alone and 66 (31.9%) lumpectomy plus radiotherapy.

Results: 37 recurrences occurred (17.8%): 14 (38%) were in situ and 23 (62%) invasive. After breast conservative treatment (BCT), the overall rate of recurrence was 27% (33% in the lumpectomy plus radiotherapy group vs. 21% in the lumpectomy alone group). Comedocarcinoma subtype ($p = 0.004$), histological size more than 10 mm ($p = 0.011$), necrosis ($p = 0.022$) and positive margin status ($p = 0.019$) were statistically significant predictive factors for recurrence. The actuarial 15-year rates of local recurrence were 29%, 42% and 37% in the lumpectomy alone, lumpectomy and whole breast radiotherapy and lumpectomy + whole breast radiotherapy with additional boost groups respectively. After recurrence, the 10-year overall survival rate was 67.2%.

Conclusion: High recurrence rates (mainly invasive) after BCT in young women with DCIS are confirmed. BCT in this subgroup of patients is possible if clear and large margins are obtained, tumor size is under 11mm and necrosis- and/or comedocarcinoma-free.

Keywords: comedocarcinoma; ductal carcinoma in situ; margin status; radiation therapy; local recurrence; relapse; surgery; young age; breast; and cancer survival

Introduction

Ductal carcinoma in situ (DCIS) of the breast is a relatively rare disease in women under 40 years of age (approximately 4% of a total 7000 breast cancers per year in France) [1], which tends to be diagnosed by clinical findings, incidentally, or after plastic surgery. However, DCIS is generally recognized as a precursor for invasive breast cancer [2, 3] and recurrence rates for younger women are high when compared to rates for women over 40 years [4-7]. Among patients with DCIS, mastectomy remains the treatment providing the optimal control rate but breast-conserving surgery has been progressively used for several years, owing to a better knowledge of the disease's natural history and an increasing use of screening mammography, allowing the detection of smaller lesions [8]. However, for women under 50 who are not part of French national screening programs and are diagnosed with more advanced tumor stages at diagnosis, greater analysis of predictive factors for recurrence is needed [4].

In invasive cancer, breast carcinoma is recognized as more aggressive and associated with higher mortality and recurrence in young patients [9] and our aim was to investigate whether this was the case for younger women with DCIS. To do this, we analyzed predictive factors for recurrence in these young patients, comparing observed rates with rates reported in the previous mentioned comparative study and in the literature as per Schmidt [10]. The current series represents to our knowledge the largest series of young women with DCIS. This work was motivated by the comparative study undertaken at Institut Bergonié between 731 DCIS patients over 40 and 81 DCIS patients 40 and under. The differences in treatment and prognosis between these two groups motivated us to

look more closely at this relatively poorly understood subgroup of younger patients, using a larger multi-institutional series.

Patients, material and methods

Patients

Institutional review board approval was obtained prior to the commencement of this retrospective study. Written informed consent of patients was not required. This study combines the results of two previously published series of patients with DCIS [11, 12]. These series describe clinical, demographic and pathologic data for 1558 patients treated for DCIS across 12 Comprehensive Cancer Centers in France from January 1971 to December 1995. All patients with pure DCIS, with no invasion (American Joint Committee on Cancer clinical stage 0: TisN0M0), who were under 40 at the time of diagnosis were included in this study, including type 1 [13]. Patients with synchronous or previous contra-lateral invasive carcinoma were excluded.

Pathology

Whole lumpectomy specimens were analyzed from 2-mm thick slices. Surgical margins and quality of excision were routinely evaluated in each centre. Histopathology information was retrieved from pathology reports. For each patient we determined pattern, necrosis, margins, tumor size and grade as per Cutuli's recommendations [14].

Treatment

Patients underwent either lumpectomy or mastectomy according to disease stage. Non-palpable lesions underwent preoperative procedure using mammographic or ultrasonographic guidance. Excised specimens were submitted to radiography to confirm that the non-palpable lesion had been fully removed. Axillary lymph node dissection (ALND) was performed in some cases, but no sentinel node biopsies

were performed during this period. Lumpectomy patients underwent 50 Grays whole breast irradiation (WBR) in 25 fractions, 5 to 6 weeks after surgery, with an optional additional external or interstitial 10 Gray boost.

Follow-up data was reported yearly for all patients. To determine margin status, surgeons inked the external faces of samples and margins were judged to be free if carcinoma were either not present or were more than 3mm from the inked face.

Recurrences

Ipsilateral local recurrence (LR) was defined as the recurrence of an in situ or invasive cancer in the treated breast. Contra-lateral breast cancer (CBC) was defined as the subsequent development of breast cancer in the opposite, untreated breast (in situ or invasive). Regional recurrence was defined as the occurrence of axillary, supraclavicular or internal mammary chain recurrence and metastatic recurrence was defined as all other events at distance (bone, liver, lung, brain). Local recurrences were detected during clinical examinations or follow-up mammographies. Regional or metastatic recurrences were detected on symptomatic anomalies confirmed by supplementary examinations (such as imaging and pathology where applicable).

Statistical analysis

Overall survival (OS) and disease-free survival (DFS) rates were calculated from time of diagnosis until date of death, recurrence, or last follow-up if appropriate. The probability of survival or recurrence was calculated using the Kaplan-Meier method. Kaplan-Meier curves were compared using the log-rank procedure. Predictive factors of recurrence were analyzed by univariate analysis. All statistical tests were conducted using SPSS software (version 14.0) Chicago. The chosen significant level was $p < 0.05$.

Results

Patients, diagnosis and treatment

A total of 224 patients aged <40 years with pure DCIS were included. A subsequent 17 patients were excluded due to synchronous or previous contralateral invasive carcinoma, leaving 207 patients for analysis. Median age at diagnosis was 36.3 years (range: 18-40). DCIS was detected by clinical examination in 104 patients (50%) (palpable mass n=62, nipple discharge n=39 or Paget's disease n=3), by mammographic abnormality for 88 patients (42.8%) and incidentally in 15 (7.2%). Palpable masses were >2cm for 32 patients, between 1-2cm (n=17) and <1cm (n=8) (unknown in 5).

Among these 207 patients, 74 (35.8%) underwent mastectomy (M), 67 (32.4%) lumpectomy alone (LA), 66 (31.9%) lumpectomy followed by 50 Grays WBRT and 30 received a 10 Gray additional boost delivered by electrons (n=24), reduced photon fields (n=4) or interstitial implant (n=2). ALND was performed in 82 patients; (respectively 70% and 22% of mastectomy and lumpectomy patients). All excised lymph nodes were free of metastasis (pN0). There were 38 immediate (51%) and 16 delayed (22%) breast reconstructions. Two patients were prescribed tamoxifen.

Histological findings

The circumstances of diagnosis and findings on histological examination of the specimen are summarized in Table 1 according to treatment received. Median size was 11mm. Mastectomy was performed in statistically larger lesions, but diameters were statistically similar between the patients who receive exclusive surgery (LA) or surgery with additional radiotherapy (LRT) ($p=0.46$). The rate of involved margins was similar in the 2 lumpectomy groups (LA and LRT) with 14% on average.

Mastectomy patients presented a higher proportion of high-grade lesions. Comedocarcinomas accounted for 22% overall, but the proportion varied

significantly according to treatment, from 5% in lumpectomy to 38% in the mastectomy group ($p=0.05$). The rate of necrosis in lumpectomy patients was significantly higher in patients who received postoperative radiotherapy (LRT) than in the lumpectomy alone (LA) group (47% vs. 21% $p= 0.002$).

Recurrences

As shown in Table 2, with a median follow up of 160 months, 95%CI [148.96-172.69], 37 patients (17.8%) presented local recurrence (LR). Thirty six of them occurred in the breast-conserving treatment (BCT) group (local recurrence rate = 27%) and one occurred for a mastectomy patient. Recurrences were invasive in 7/14 LA patients and 15/22 LRT patients. For the 40 patients with recurrence, median time to recurrence was 56 months (min/max: 6.6 - 165.8 months).

Contra-lateral breast cancer

Overall, 18 patients (8.6%) subsequently developed a contralateral breast cancer (CBC), which was non-invasive in 9 patients and invasive in 8 patients. Information was missing for one patient.

Outcome after recurrences

Recurrence was treated by salvage mastectomy alone in 24 cases (11 LA and 13 LRT), by breast conservative surgery in 4 cases in the LA group and by a combination of surgery, radiotherapy, chemotherapy and/or hormonotherapy in the other 12 patients. Outcomes are given in Table 3.

The mastectomy patient who relapsed developed axillary node involvement two years later. Another mastectomy patient also developed an axillary node recurrence but without earlier LR. A third mastectomy patient developed metastases without either previous local or regional recurrence.

Of the 7 LA patients with invasive LR, 4 developed axillary node involvement (3 simultaneously) and one subsequently developed metastases. One further patient developed metastases without previous loco regional recurrence. Another patient

with local recurrence who refused treatment, developed invasive disease and died from metastases. Among the LRT patients, 1/7 with in situ LR and 2/14 with invasive LR developed axillary node involvement, 6/15 developed metastases after invasive LR.

Among the 37 loco-regional recurrences, 10 patients died from metastatic disease: 3/74 M patients, 1/67 LA patient and 6/66 LRT patients. In patients with relapses, the 10-year survival rate was 67.2% compared to 98% overall for patients with no recurrences. The 10-year global breast-specific survival rates after M, LA or LRT were 98.4%, 98.2% and 94.7% respectively.

Predictive factors of recurrence

The following were significant independent predictive factors of local recurrence: comedocarcinoma ($p=0.004$), histological size $>10\text{mm}$ ($p=0.011$), necrosis ($p=0.022$) and positive margins ($p=0.019$) (Figure 1). As necrosis was much higher in the LA group than in the LRT group, we also looked at actual rates of recurrence according to treatment group and presence of necrosis. There were more recurrences when necrosis was present for the LA group (61.5%) vs. when necrosis was not present in the same group (14%). There was no difference between recurrence rates according to presence of necrosis in the LRT group (32.1% recurrence with necrosis, 31.3% without).

The following factors were not predictive of local recurrence: age under 35 ($n=82$) ($p=0.32$), tumor grade ($p=0.19$) and radiotherapy with ($p=0.62$) or without boost ($p=0.33$) (Figure 2). We also tested for age-based recurrence rate differences with the log-rank test finding no differences between local recurrence rates for women <35 years ($n=82$) and women ≥ 35 years ($n=126$).

Discussion

Despite the fact that our series is a retrospective, multicentre series, this ensured that we had a large enough sample to make statistical comparisons. To our knowledge, this study is the largest series of patients with DCIS aged under 40 published in the literature. Based on an incidence rate of 4% of DCIS patients aged younger than 40, our series of 207 patients under 40 years of age represents in theory a sample of over 5000 women with DCIS. These results can be directly compared to other studies comparing outcomes for older vs. younger DCIS patients. These results coming from a large series are important as they strictly defined inclusion and tested for age under 35 as a predictive factor in an attempt to identify an appropriate cut-off age.

Survival

The 10-year OS rate after a diagnosis of DCIS and salvage therapy after breast failure has frequently been reported at 94% or more[12, 15-17]. In our series, patients with recurrence had worse prognosis than patients without recurrence. The 10-year actuarial OS rate after recurrence was much lower at 67.2% (compared to 98% for recurrence-free patients). For older women this difference between survival rates is not generally observed with overall rates around 96-98% for recurrence and recurrence-free [2]. In our series of young patients, we observed an increase of breast cancer death when local recurrence occurred. Young patients often had symptomatically-detected lesions. However, young patients did not have higher grade DCIS compared to older patients, which is in concordance with two other reports [15, 18].

Diagnosis and recurrence

In our study, diagnosis was performed on clinical findings in 50% of patients. This rate is comparable to Bijker et al's [4, 15] findings that younger women have a

higher rate of symptomatically-detected lesions (66% vs. 25% of women older than 40) because they do not undergo routine mammograms. Patients underwent the 3 classical treatment modalities in approximately the same percentages compared to rates reported in the literature of up to 50% for mastectomies [19].

The rate of CBC observed (8.6%) in our sample is similar to rates described in the literature (3-9%) [12, 15, 16, 20, 21]. No positive lymph nodes were found in this series, confirming that ALND is not a suitable treatment for young patients with pure DCIS. The 10-year actuarial recurrence rates were 3.3% (M), 23% (LA), 35.6% (LRT) and 29.9% (LRT and boost). These are similar to rates reported in the EORTC trial for younger women (34% at 10 years overall) [15].

Predictive factors for recurrence

Four predictive factors for recurrence were identified in our series of women <40 years with DCIS. According to previously published studies, margin status appears to be the most constant predictive factor of recurrence[7, 8, 12, 22-24]. Indeed, free margins appear difficult to obtain. Bijker et al described in an international randomized trial 27% (11/41) of involved margin status in young patients compared to 22% (157/700) in women older than 40 years of age [15]. Vicini [17, 24] explained the higher rate of recurrences in young women by a total volume of re-excision less than 60 ml. Wazer et al showed in their series a greater likelihood of having a tumor on re-excision in young patients as compared with patients older than 45 years of age [25]. It is likely in our series that a breast-conserving treatment was proposed more frequently to young patients whatever the size and margin status of DCIS and the size of the breast. Only 14.2% of patients had positive margins, and they were consistently distributed among the LA (8 cases, 12%) and LRT (11 cases, 16%) groups. Despite the small number of patients with positive margins, this factor is one of the most important predictive factors of recurrence and the only one that can

be controlled by clinicians. Clearly, radiotherapy does not compensate for surgical margins which are not free of cancer. In the MD Anderson study, Jhingran et al concluded that patient age does not affect outcome, if the margins were free [16]. More research is required here; and particularly in the definition of 'free margins' [26]. Recent French guidelines recommend 2mm [27] based on the meta-analysis by Dunne [28] indicating that outcomes with 2mm surgical margins were comparable to outcomes with wider margins.

Comedocarcinoma was also found to be a predictive factor for recurrence, but this was also associated with high grade and necrosis which may partially account for this higher rate of recurrence. In agreement with Rogrigues et al's [29] findings, the multivariate analysis showed the presence of necrosis to be a significant predictor for local recurrence. Finally, tumor size >10mm was found to be a predictive factor for local recurrence in our series, in contrast to Vicini et al. [17] who noted more tumors >10mm in patients younger than 45 years but that this factor did not increase risk of local recurrence. The small number of patients (31) could explain the lack of difference observed in their series.

Impact of radiotherapy

Unlike in other series [6, 11, 15, 18, 21, 30], radiation therapy with or without boost did not reduce the incidence of local recurrences. In the EORTC trial, radiotherapy reduced the risk of local recurrences, but this decrease was less important in young patients than in older patients [15]. In a recent retrospective study, Omlin et al. [30] described a potential link between the radiotherapy dose and the local recurrence rate in women 45 years or younger with DCIS. These results have to be confirmed with on-going phase III prospective trials evaluating potential benefits of additional boost and stratified by age. Rudloff et al. [31] recently reported that recurrence risk

remains substantial even with free margins and that radiotherapy reduced the risk of recurrence particularly for patients in at risk subgroups, including younger women.

Conclusions

Patients under 40 with DCIS constitute a particularly poor prognosis group with a higher risk of recurrence and poorer survival. We describe a lower 10-year survival rate after local relapse than those previously reported in the literature. Our data provide further supporting evidence that younger women are at higher risk of local recurrence of DCIS than older women, as has been suggested in previous series. Age appears to be one more parameter that should be considered in the complex decision-making process if we want to reduce local recurrence risks, thus improving chances for survival.

We recommend to limit the use of a safe conservative surgery to tumors with margins $\geq 2\text{mm}$, DCIS size $\leq 11\text{mm}$ or smaller and free of necrosis and comedocarcinoma. Mastectomy ought to be proposed in cases of multifocal DCIS, tumors larger than 10mm , positive margins after re-excision, DCIS with necrosis or comedocarcinoma or small breasts (ruling out efficient surgery).

Mastectomy and immediate breast reconstruction should be proposed for patients with all poor predictive factors. Oncoplastic surgery techniques may offer promising alternatives to mastectomy to obtain large free margins. In all cases, the treatment procedure should be explained to the patient and the treatment should be chosen by the patient in consultation with the medical team (radiologist, surgeon, pathologist and oncologist).

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Table 1. Patient characteristics

		M	LA	LRT	Total	
		N=74	N=67	N=66	N=207	(%)
Diagnosis	Mammogram	31	22	35	88	(42.5)
	Clinical	37	38	29	104	(50.2)
	Incidental	6	7	2	15	(7.3)
Architectural Subtype	Comedo	28	3	15	46	(22.2)
	No comedo	46	64	51	161	(77.8)
Grade (n=108)	Low	17	30	18	65	(31.4)
	Intermediate	8	4	2	14	(6.8)
	High	19	5	5	29	(14.0)
	Unknown	-	-	-	99	(48.3)
Histological size (n=117)	<10mm	8	25	25	58	(28.0)
	> 10mm	30	12	17	59	(28.5)
	Unknown	-	-	-	190	(43.5)
Necrosis (n=192)	Yes	38	13	28	72	(34.8)
	No	31	50	32	120	(58.0)
	Unknown	-	-	-	15	(7.3)
Margins status (n=133)	Free	-	59	55	114	(55.1)
	Positive	-	8	11	19	(9.2)
	Unknown	-	-	-	74	(35.8)

M=mastectomy, LA=lumpectomy alone, LRT= lumpectomy and radiotherapy.

Table 2. First recurrence for DCIS patients under 40 years of age according to treatment

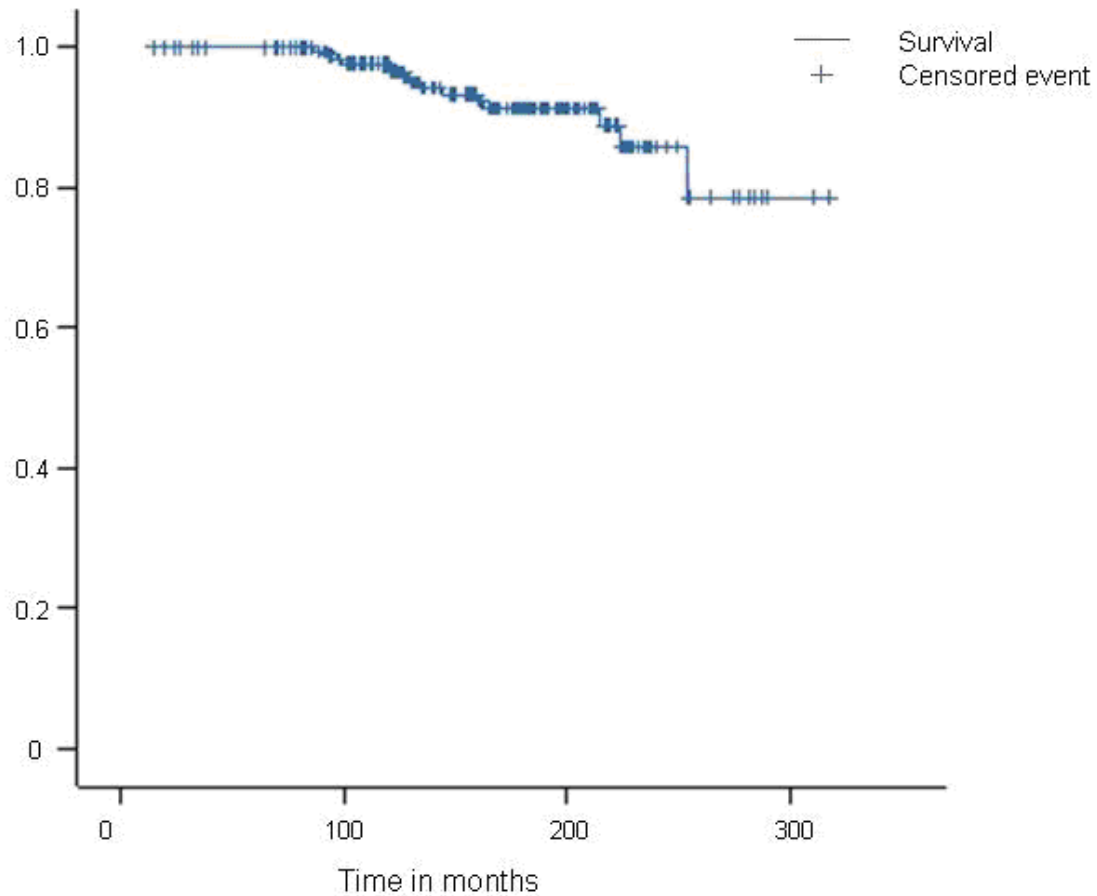
	M	LA	LRT	All
	(N=74)	(N=67)	(N=66)	(N=207)
LR alone	1	11	21	33
– In situ	0	7	7	14
– Invasive	1	4	14	19
LR+Nodal recurrence	0	3	1	4
Nodal recurrence alone	1	0	0	1
Metastasis	1	1	0	2

M=mastectomy, LA=lumpectomy alone, LRT= lumpectomy and radiotherapy, LR= local recurrence

Table 3. Outcomes for DCIS patients under 40 years of age
at median follow-up of 160 months and recurrence rate according to outcomes

Outcome	Alive (n=162)	Alive with breast cancer (n=3)	Alive with other cancer (n=2)	Death from breast cancer (n=10)	Death other cause (n=4)	Lost to follow up (n=26)	Total (n=207)
Treatment Group							
- Mastectomy (M)	67	0	0	3	0	4	74
- Lumpectomy alone (LA)	48	1	1	1	3	13	67
- Lumpectomy with radiotherapy (LRT)	47	2	1	6	1	9	66
Recurrence (%)	(14.2)	(66.7)	(0)	(100)	(50)	(11.5)	(19.3)

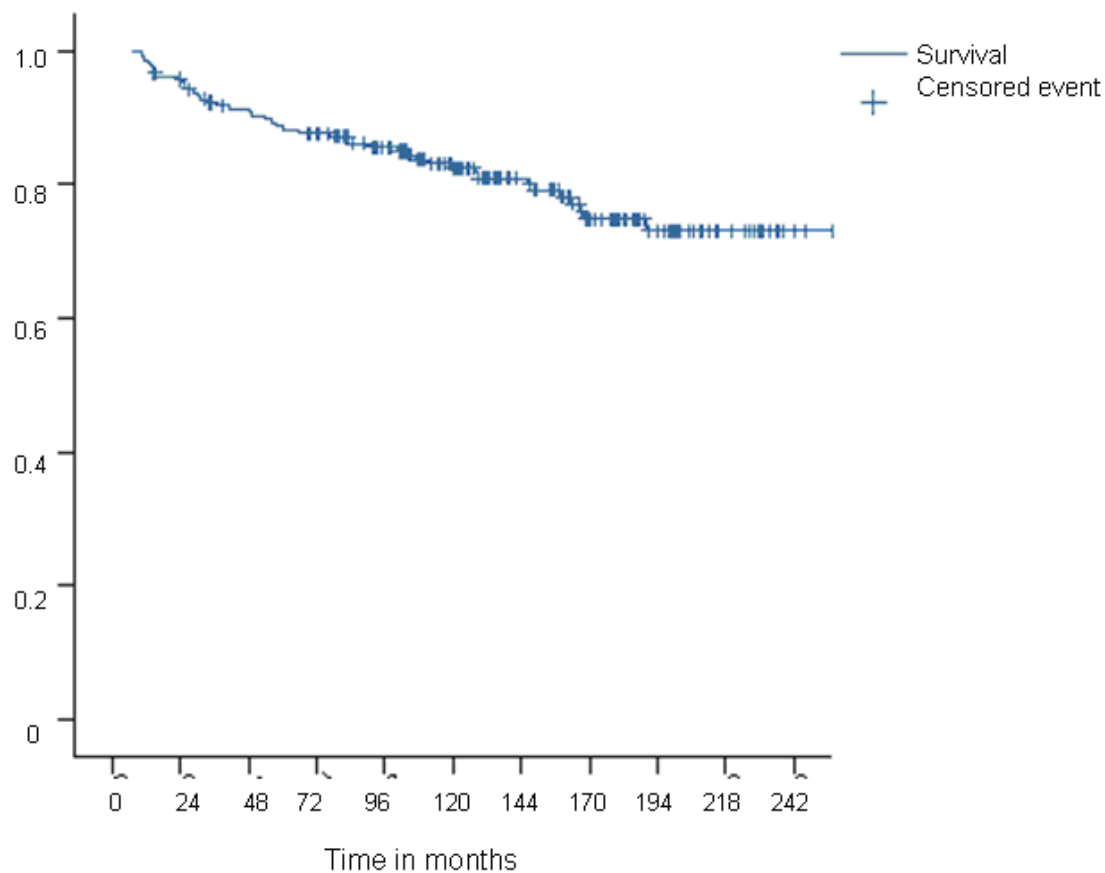
Figure 1. Overall survival for women ≤ 40 years with ductal carcinoma in situ (DCIS) over full follow-up.



Mean survival in months 290.54 [95%CI 276.8 – 304.3]

	Months						
	0	50	100	150	200	250	310
At risk	207	198	172	105	49	12	1
Cumul. events	0	0	4	10	12	14	15

Figure 2. Probability of non-recurrence for women ≤ 40 years with ductal carcinoma in situ (DCIS)



Mean survival 250.43 [95%CI 234.6 – 266.2]

	Months						
	0	50	100	150	200	250	310
At risk	208	179	148	83	32	9	2
Cumul. events	0	20	29	38	43	43	43