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Ductal carcinoma *in situ* of the breast results of conservative and radical treatments in 716 patients☆

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Abstract

Until now, less than 5% of the patients with breast ductal carcinoma *in situ* (DCIS) have been enrolled in clinical trials. Consequently, we have analysed the results of 'current practice' among 716 women treated in eight French Cancer Centres from 1985 to 1992: 441 cases (61.6%) corresponded to impalpable lesions, 92 had a clinical size of less than or equal to 2 cm and 70 from 2 to 5 cm; in 113 cases, the size was unspecified. Median age was 53.2 years (range: 21–87 years). 145 patients underwent mastectomy (RS) and 571 conservative surgery (CS) without (136) or with (435) radiotherapy (CS + RT). The mean histological tumour sizes in these three groups were 25.6, 8.2, 14.8 mm, respectively ($P < 0.0001$). After a 91-month median follow-up, local recurrence (LR) rates were 2.1, 30.1 and 13.8% in the RS, CS and CS + RT groups, respectively ($P = 0.001$); LR were invasive in 59 and 60% in the CS and CS + RT groups, respectively. In these groups, the 8-year LR rates were 31.3 and 13.9%, respectively ($P = 0.0001$). Nodal recurrence occurred in 3.7 and 1.8% in the CS and CS + RT groups. Metastases rates were 1.4, 4.4 and 1.4% in the RS, CS and CS + RT groups. Among the 60 cases of invasive LR, in CS and CS + RT groups 19% developed metastases. After multivariate analysis, we did not identify any significant LR risk factor in the CS group, whereas young age (< 40years) and incomplete excision were significant in the CS + RT group ($P = 0.012$ and $P = 0.02$, respectively).

Keywords: Ductal carcinoma *in situ*; Breast; Treatment; Conservative surgery; Radiotherapy; Local recurrence; Young age; Excision margins

1. Introduction

With the increasing use of mammography, ductal carcinoma *in situ* (DCIS) has become a more common diagnosis. Estimates for the next decade are that DCIS will form approximately 20% of all breast cancers [1,2]. For years, mastectomy was the standard treatment with an almost 100% cure rate.

Many centres now use breast conserving surgery, alone (CS) or with radiotherapy (CS + RT), for selected cases of DCIS [3–5] but results in term of local recurrence (LR) vary widely. This may be explained by heterogeneity in the inclusion criteria, therapeutic modalities, histological procedures, methods of detection and follow-up duration.

Until now, two randomised trials have confirmed that radiation therapy (RT) decreases the rates of LR of invasive and non-invasive disease in DCIS treated conservatively [6–9]. However, the patients included in

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these trials form less than 5% of all DCIS treated in the same period and it is still doubtful whether to use RT in all cases, such as those particularly outlined in the Van Nuys team's paper [10].

We describe herein a retrospective analysis of the treatments used and outcomes in DCIS in eight French Cancer Centres between January 1985 and December 1992.

2. Patients and methods

DCIS treated in eight cancer centres were listed by Enquête Permanente Cancer ((E.P.C.) = continuous cancer inquiry) and collected after confirmation of absence of microinvasion and axillary nodal involvement. For each case, a complete histological report was attached to the collecting form.

There was no age or size limitations. All patients underwent initial surgery by lumpectomy, quadrantectomy or mastectomy. Radical surgery (with or without reconstruction) was generally used for lesions larger than 3 cm or those that were multicentric, and often in cases of comedo carcinoma or involved margins. When the margin status was reported, it was considered free (>1 mm), close ($\leqslant 1$ mm) or involved when the margin edge transected a DCIS duct. Margin status was considered unknown especially in cases of fragmented specimen and/or in cases of re-excision without clear orientation. During the whole period of the study, the use of RT after CS became more common, but varied between the centres. When breast irradiation was carried out, treatment was classical with two opposite tangential fields (by cobalt photons). There were no limitations on the interval between the beginning of the RT and surgery, but in a large majority of cases external-beam irradiation began within 8 weeks after surgery.

Table 1
Characteristics of the patients according to treatment subgroups

	RS (145)	CS (136)	CS + RT (435)
Median age (years)	53.3	53.1	53.4
< 40 years	17 (11.7%)	11 (8.1%)	35 (8.0%)
40–60 years	88 (60.7%)	83 (61.9%)	279 (64.1%)
> 60 years	40 (27.6%)	42 (30.9)	121 (27.8%)
Median F.U. (months)	75	102	91
Impalpable lesions	45 (31.3%)	86 (63.2%)	310 (71.3%)
Mean histological size (mm)	25.6	8.2	14.8
Architectural subtype			
Cribriform	18 (12.4%)	18 (13.2%)	50 (11.5%)
Papillary	7 (4.8%)	6 (4.4%)	33 (7.6%)
Cribriform + Papillary	35 (24.1%)	60 (44.1%)	141 (32.4%)
Solid	7 (4.8%)	4 (2.9%)	35 (8%)
Clinging	2 (1.4%)	2 (1.5%)	12 (2.8%)
Comedo	68 (46.9%)	11 (8.1%)	142 (32.6%)
Not specified	8 (5.5%)	35 (25.7%)	22 (5.1%)

RS, radical surgery; CS, conservative surgery; CS + RT, conservative surgery + radiotherapy; FU, follow-up.

The median prescribed dose was 50 Gy in 25 fractions (2 Gy per fraction) delivered in 5 weeks; 231 out of 435 (53%) patients received an 8–14 Gy boost, generally by electrons.

The primary endpoint of the study was LR in the treated breast. Secondary endpoints included nodal recurrence, metastases, recurrence-free, overall survival and contralateral breast cancer.

The time-to-recurrence curves were analysed by the Kaplan–Meier method and compared by the log-rank test in the Statistical Analysis Software (SAS) program (SAS Institute, Cary NC, USA). Adjusted relative risks were calculated by Mantel–Haenszel method. The groups were compared by the Fisher's Exact test and Mann–Whitney test for discrete and continuous variables, respectively.

3. Results

Our results are based on 'clinical practice' in a large experience in specialised centres using regularly a multidisciplinary approach in breast diseases.

3.1. Demography

Between January 1985 and December 1992, 716 women were treated: 145 (20.3%) by radical surgery (RS), 136 (19.0%) by CS alone and 435 (60.8%) by CS + RT. Axillary dissection was performed in 312 cases (43.6%): 6.6, 47.9 and 66% in the CS, CS + RT and RS groups, respectively. All were negative.

Median age was 53.2 years (range: 21–87 years). The median follow-up for the entire cohort was 91 months (75, 102 and 91 months for the RS, CS and CS + RT groups, respectively).

In 23.6% of the patients, a family history of breast cancer (at first and/or second degree) was found, and 15% of the women had previously undergone surgery for a benign lesion of the breast, such as fibroadenoma, cyst and/or dystrophic mastopathy.

Table 1 shows the main clinical and histological features according to treatment subgroups. We observed a total of 441 (61.6%) impalpable lesions with a significant predominance in the CS (63.2%) and the CS + RT (71.3%) groups ($P<0.001$). The mean histological sizes of the tumours were 8.2, 14.8 and 25.6 mm in the CS, CS + RT and RS groups, respectively ($P<0.0001$).

3.2. Local recurrence (Table 2)

We observed local recurrences (LR) in 104 out of 716 (14.5%): 41 were *in situ* and 63 were invasive. Three occurred after RS (2.1%), all invasive, 41 after CS (30.1%), with 17 *in situ* and 24 invasive, and 60 after CS + RT (13.8%) with 24 *in situ* and 36 invasive

($P < 0.0001$). The LR rates at 5 and 8 years were 23.6 and 31.3% in the CS group, and 9 and 13.9% in the CS + RT group (Fig. 1). The median time to local recurrence was 40 and 53 months in the CS and CS + RT groups, respectively.

Salvage treatment after LR in women treated by CS consisted of simple mastectomy in four cases, and modified radical mastectomy in 19 cases. Eighteen women underwent a second conservative treatment, 4 and 14 cases without and with radiotherapy, respectively.

In the four women who underwent a second conservative surgery alone and in one of the 14 women who underwent conservative surgery and radiotherapy, a second local recurrence occurred.

Table 2
Results according to treatment subgroups (91-months follow-up)

	RS (145)	CS (136)	CS + RT (435)	*P* value
LR (total)	3 (2.1%)	41 (30.1%)	60 (13.8%)	<0.0001
Non-invasive	0	17 (12.5%)	24 (5.5%)	<0.0001
Invasive	3 (2.1%)	24 (17.6%)	36 (8.3%)	<0.0001
NR	0	5 (3.7%)	8[a] (1.8%)	NS
M	2 (1.4%)	6[b] (4.4%)	6[b] (1.4%)	NS

LR, local recurrence; NR, nodal recurrence; M, metastases; RS, radical surgery; CS, conservative surgery alone; CS + RT, conservative surgery + radiotherapy; NS, non significant.

[a] 6 out of 8 cases associated with invasive local recurrence.

[b] 1 out of 6 cases associated with contralateral metachronous invasive breast cancer.

3.3. Regional recurrence

We observed 13 out of 716 nodal recurrences (1.8%) with 5 (3.7%) and 8 (1.8%) cases after CS and CS + RT, respectively.

3.4. Distant metastases

We observed two metastases in the RS group (1.4%), whereas 6 cases occurred in both the CS group (4.4%) and CS + RT group (1.4%). All distant metastases occurred after previous invasive LR. Thus, there was a 22% rate of distant metastases after invasive LR (14/63), but none in the 653 cases without invasive LR.

3.5. Contralateral breast cancer

40 patients (5.6%) with previous or simultaneous infiltrating breast cancer were included in the study, but only in the analysis on LR. Excluding these 40 cases from the analysis, the rates of subsequent contralateral BC were 7.3% (9/123), 7.1% (30/420) and 6.0% (8/133) in the CS, CS + RT and RS groups, respectively.

3.6. Analysis of factors influencing local recurrence

Among patients treated by CS or CS + RT, the two main factors influencing the LR rate were the excision quality and age.

Among women treated by CS, the 8-year LR rates were 36.4, 28.6 and 31.7% in women younger than 40

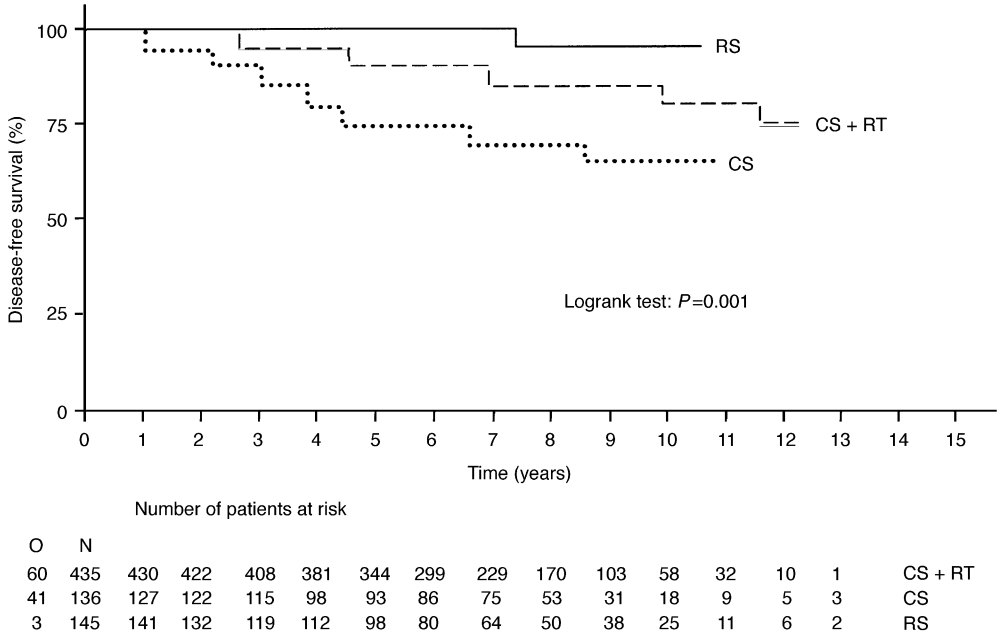
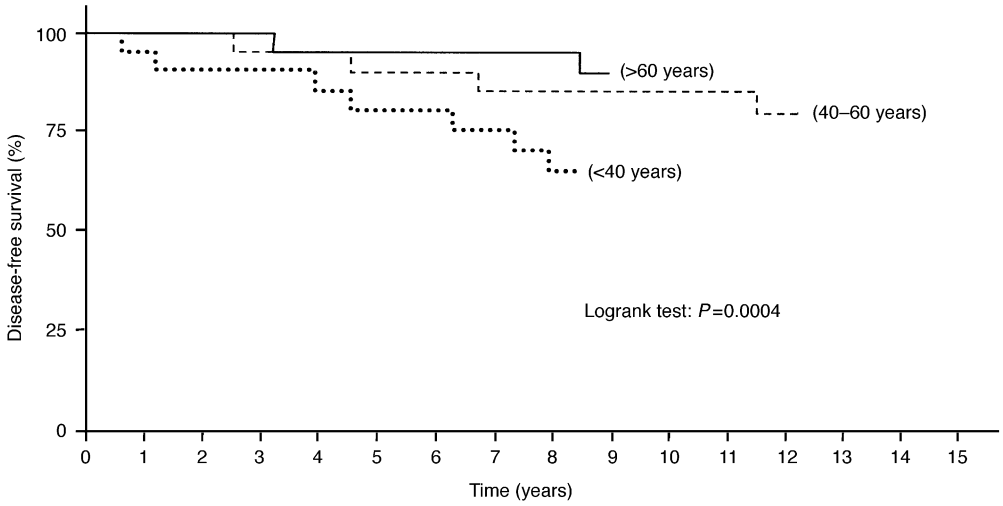


Fig. 1. Disease-free survival (DFS) according to treatment. RS, radical surgery; CS, conservative surgery; CS + RT, conservative surgery and radiotherapy; O, observed; N, number; Time (years).

years, from 41 to 60 years and older than 60 years, respectively (P = non-significant (NS)). In the same subgroups treated by CS + RT, LR rates were 32.4, 13.7 and 8.3%, respectively ($P = 0.0004$) (Fig. 2).

Among women treated by CS, the 8-year LR rates were 34.1, 57 and 25.9% according to complete, unknown/doubtful and incomplete excision quality, respectively (P = NS). In the same subgroups treated by CS + RT, the LR rates were 11.5, 25 and 9.3%, respectively ($P = 0.013$) (Fig. 3). Finally, the actuarial disease-free survival (DFS) rates at 5 and 10 years were 94.3 and 83.7% in the CS + RT group versus 80.5 and 65.7% in the CS group ($P = 0.0001$) (Fig. 4).

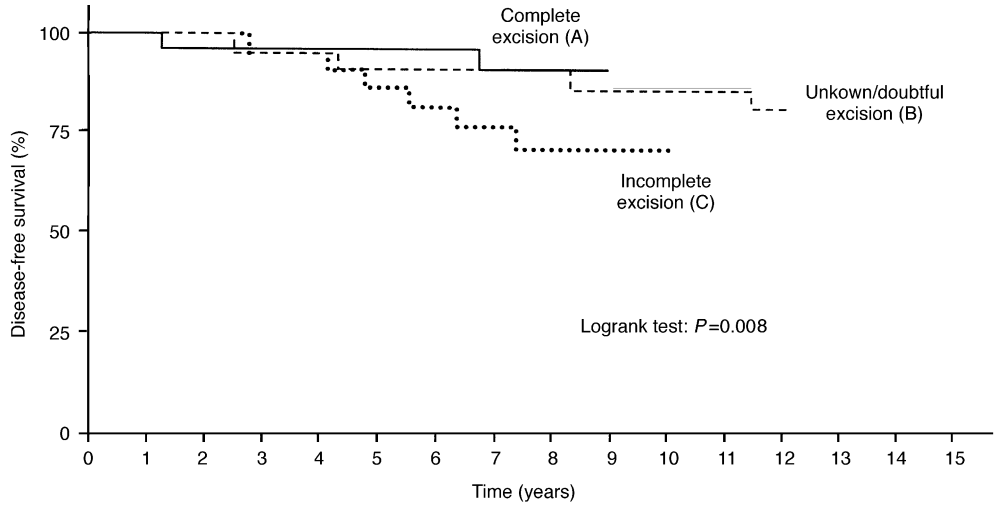
The influence of the lesion size on the LR rates is shown in Table 3. Among the CS and CS + RT groups, this parameter did not influence statistically the results,



Number of patients at risk

O	N													
12	35	33	32	30	28	25	24	17	10	6	3	2	1	<40 years
38	279	276	271	264	247	220	193	152	119	77	45	24	9	40–60 years
10	121	119	119	114	106	99	82	60	41	20	10	6	2	>60 years

Fig. 2. Disease-free survival (DFS) according to age in CS + RT group (conservative surgery and radiotherapy). y, years; O, observed; N, number; Time (years).



Number of patients at risk

O	N														
36	312	309	304	292	273	250	219	165	123	68	40	23	8	1	A
4	43	42	40	39	38	32	28	22	18	14	4	1			B
20	80	79	78	76	70	62	52	42	29	21	14	8	3	1	C

Fig. 3. Disease-free survival (DFS) according to excision quality in the CS + RT (conservative surgery and radiotherapy) group. Time (years); O, observed; N, number.

Table 3
Local recurrence (LR) rates according to tumour size and treatment subtype

Tumour size	CS	CS + RT
	LR	LR
< 1 cm	10/29 (34%)	15/114 (13%)
1–2 cm	4/10 (40%)	8/82 (10%)
2.1–4 cm	1/5 (20%)	11/65 (17%)
> 4 cm	–	2/16 (13%)
Unknown	26/92 (28%)	24/158 (15%)
Total	41/136 (30%)	60/435 (14%)

CS, conservative surgery; CS + RT, conservative surgery + radiotherapy. NB. The relative risk of LR adjusted to tumour size was 2.64 in the CS group versus the CS + RT group (95% confidence interval (CI): 1.53–4.56) ($P < 0.001$).

Table 4
Local recurrence (LR) rates according to architectural subtype in the CS and CS + RT groups

Architectural subtype	CS	CS + RT
	LR	LR
Cribriform (c)	2/18 (11%)	4/50 (8%)
Papillary (p)	1/6 (17%)	3/33 (9%)
Mixed (c + p)	18/60 (30%)	13/141 (9%)
Solid + clinging	3/6 (50%)	8/47 (17%)
Comedo carcinoma	9/11 (82%)	27/142 (19%)
Not specified	8/35 (23%)	5/22 (23%)
Total	41/136 (30%)	60/435 (14%)

CS, conservative surgery; CS + RT, conservative surgery and radiotherapy. NB. The relative risk adjusted to histological subtype was 2.86 in the CS group versus the CS + RT group (95% CI: 1.98–4.12) ($P = 0.001$).

but the RT benefit on local control was confirmed for all tumour sizes. The relative risk adjusted to tumour size was 2.64 in CS versus CS + RT group (95% confidence interval (CI): 1.53–4.56] ($P < 0.001$).

Table 4 shows the influence of the architectural subtype on the LR rates in both conservative treatment subgroups. Radiotherapy increased local control in each category, but its benefit was only significant in the mixed (cribriform + papillary) and comedo carcinoma subtypes. The relative risk adjusted to histological subtype

Table 5
Multivariate analysis of risk factors for the LR in the CS and CS + RT groups

Variable	Hazard ratio	95% CI	*P* value
Treatment group			
CS + RT	1.00		
CS	2.25	1.51–3.36	< 0.0001
Age			
⩾ 60 years	1.00		
40–59 years	1.50	1.06–2.13	
< 40 years	2.25	1.12–4.53	0.023
Tumour			
Non palpable	1.00		
Palpable	1.06	0.70–1.61	0.78
Excision quality			
Complete	1.00		
Unknown/doubtful	1.35	1.05–1.75	
Incomplete	1.83	1.10–3.05	0.020
Family history of breast cancer			
Presence	1.00		
Absence	1.19	0.73–1.95	0.49

CS, conservative surgery alone; CS + RT, conservative surgery and radiotherapy; LR, local recurrence.

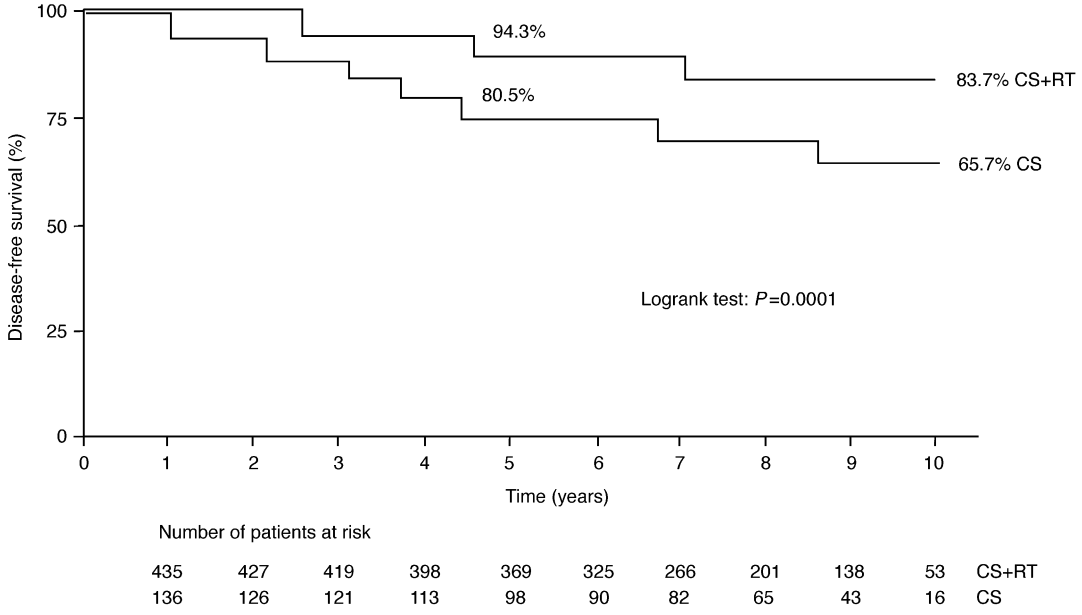


Fig. 4. Actuarial disease-free survival (DFS) in CS (conservative surgery) and CS + RT (conservative surgery and radiotherapy) groups. Time (years).

Table 6
Comparison of the results in randomised trials and our series concerning conservative surgery alone (CS) or with radiotherapy (CS + RT)

	Follow-up (months)	NSABP B-17		EORTC 10853		Present series	
		CS (403)	CS + RT (411)	CS (500)	CS + RT (502)	CS (136)	CS + RT (435)
LR	51			16%	9%	18.4%	4.8%
(Total)	91[a]	26.8%	12.1%			30.1%	13.8%
LR (*in situ*)		13.4%	8.2%	8%	5%	12.5%	5.5%
LR (invasive)		13.4%	3.9%	8%	4%	17.6%	8.3%

LR, local recurrence; NSABP, National Surgical Adjuvant Breast and Bowel Project; EORTC, European Organization for Research and Treatment of Cancer.

[a] Among 623 patients (77%) who underwent central pathology review and with a 102 months median follow-up, the rates of LR in the NSABP B-17 trial were 31 and 13% in CS and CS + RT groups, respectively ($P = 0.0001$).

was 2.86 in the CS group versus the CS + RT group (95% CI: 1.98–4.12) ($P = 0.001$). The presence of necrosis, atypical hyperplasia, mastosis or associated lobular carcinoma *in situ* had no influence on the LR rates both in the CS and CS + RT groups.

A Cox proportional hazard regression model was fitted for the multivariate analysis, using five variables: treatment group (CS versus CS + RT), age (subdivided into three categories), method of DCIS detection (palpable versus non-palpable), family history of breast cancer (present or absent) and excision quality (complete, doubtful/not specified or incomplete) (Table 5).

The absence of RT was the overwhelming factor for LR in the CS group with no other risk factor for LR achieving independent significance. Age and excision quality were significant in the CS + RT group ($P = 0.002$ and $P = 0.04$, respectively).

4. Discussion

Mastectomy remains the safest treatment for women with DCIS and our results confirm a 98% local control rate as reported by other series [1,2].

Two large randomised trials showed that RT statistically increases local control following local excision of DCIS [6–9] and the multivariate analysis in this study points to a similar finding.

Several papers have tried to identify the pathological features that are predictive for LR, but the majority have failed [1]. The analysis of the histological characteristics in the DCIS series is complicated for several reasons: lesions are heterogeneous with two or three architectural components present in various proportions in approximately one third of cases; it is often difficult to quantify the presence of necrosis and grade is also not easily reproducible. This point is illustrated by the numerous pathological classifications used [11–15], and the discordance observed in the central pathology reviews by expert panellists on DCIS [16,17]. Furthermore, the size of the lesions may also be difficult to assess.

In the literature, the most important histological parameter which allows the LR rate to be predicted is the margin status [1,8–10]. As in invasive cancer [18,19], young age is now considered as a supplementary LR risk factor [4,6,8,9]. In the latest report by Vicini and colleagues [20], 31 women younger than 45 years old showed a 26.1% 10-year rate of ipsilateral failure after CS + RT, versus 8.6% in the older patients ($P = 0.03$). In Solin's multicentric study on mammographically-detected DCIS [21], the 10-year rates of local failure were 31% for patients under 40 years, 13% between 40 and 49 years, 8% between 50 and 59 years and 6% above 60 years ($P = 0.0001$). In these studies, young age at diagnosis was also found as an independent risk factor for LR.

In another two series [22,23], young age was also found as a LR risk factor, with a 10-year failure rate of 30 and 33%, respectively. Indeed, LR rates are approximately 3-fold higher in women under 40 years of age. The updated results of the 10853 European Organization for Research and Treatment of Cancer (EORTC) trial confirm these results [9] with a 2.14 LR hazard ratio in women younger than 40 years ($P = 0.02$). Our data are consistent with these results: we observed 27, 15 and 9 of LR rates in women under 40, 41–60 and older than 60 years, respectively with a 2.25 LR hazard ratio in women younger than 40 years ($P = 0.023$). For young patients, it is likely that mastectomy should be more frequently proposed. However, the role of boost (14–16 Gy) RT could also be discussed following the recent results of this technique in invasive breast carcinoma [24].

In this study, the majority of LR occurred within 5 years. This suggests that during this period close clinical and mammographic follow-up should be performed. Several studies have shown a better prognosis for infraclinically discovered LR, which most frequently corresponded to new foci of DCIS [25].

According to Silverstein and colleagues [26], invasive local failure after CS or CS + RT is a serious event that may convert patients with previous stage 0 disease to patients with disease that ranges from stage I to IV.

Among our 101 patients with LR after CS (41) or CS + RT (60), 13 had simultaneous or metachronous axillary recurrence, and 12 developed metastases. Thus, after invasive LR, 6 out of 24 (25%) and 6 out of 36 (17%) patients in the CS and CS + RT groups, respectively, developed metastases. Our global rate of metastases after invasive LR (20%) is exactly the same as in the Van Nuys team. These results emphasise the importance of early diagnosis of LR. In another Solin's series [27], the 5-year actuarial rates of overall and cause-specific survival after salvage treatment were 78 and 84%, respectively.

However, despite these considerations, DCIS remains a favourable disease. The great majority are now discovered by mammography [25,28]. We confirm the importance of case selection for mastectomy (such as the negative influence of age less than 40 years and of incomplete excision on the LR rate), the addition of RT to CS and of the quality of margin excision in CS. A comparison of our results in comparative treatment group with those of randomised trials in the literature is shown in Table 6. Until now, there have been no recognised criteria to select patients for treatment by local excision alone [29–32]. The Van Nuys team initially used grade and the width of margin excision for selection [33] and have more recently stated that an adequate width of margin excision (minimum 10 mm on careful pathological inspection) is the most important factor in this respect. The role of tamoxifen in DCIS treatment is currently under investigation. A trial (National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24) shows a modest benefit in the short-term rate of LR with the use of this drug after wide local excision and RT [34].

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