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REVIEW

259 Patients with DCIS of the breast applying USC/Van Nuys prognostic index: a retrospective review with long term follow up

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Abstract
Background The Van Nuys Prognostic Index (VNPI) is a simple score for predicting the risk of local recurrence (LR) in patients with Ductal Carcinoma In Situ (DCIS) conservatively treated. This score combines three independent predictors of Local Recurrence. The VNPI has recently been updated with the addition of age as a fourth parameter into the scoring system (University of Southern California/ VNPI).
Patients and methods Our database consisted of 408 women with DCIS. Applying the USC/VNPI we reviewed retrospectively 259 patients who were treated with breast conserving surgery with or without radiotherapy (RT). Of these patients 63.5% had a low VNPI score, 32% intermediate and 4.5% a high score. In the low score group, the majority of the patients underwent Conservative Surgery (CS) without RT while in the intermediate group, almost half of the patients received RT. Eighty-three percent (83%) of the patients with high VNPI were treated with Conservative Surgery plus RT. Nodal assessment by Sentinel Lymph Node Biopsy was obtained in 32 patients since 2002.
Results Twenty-one Local Recurrences were observed (8%) with a mean follow up of 130 months: sixteen were invasive. No statistically significant differences in Disease Free Survival were reached in all groups of VNPI score between patients treated with Conservative Surgery or Conservative Surgery plus RT. However it was noted that the higher the VNPI score, the lower was the risk of local recurrence in the group treated additionally with RT, even though it was not statistically significant. Further analysis included those patients treated with Conservative Surgery alone and followed up. Disease-free survival (DFS) at 10 years was 94% with low VNPI and 83% in both intermediate and high score ($P < 0.05$). No significant differences were observed in the subgroups of VNPI. The Local Relapse rate after Conservative Surgery alone, increased with tumor size, margin width, and pathology classification ($P < 0,05$), while age was not found to be a significant factor. Lesions with only mammographic appearances are associated with lower DFS but it did not reach significance (P = ns), while assumption of estrogenic hormones and familial history of breast cancer are significant factors associated with a higher risk of local recurrence. After multivariate analysis including seven clinical and pathological factors, the only significant

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predictors of local recurrence remained margin width of surgical excision, previous therapy with estrogens (contraceptives or Hormone Replacement Therapy) and the Van Nuys pathologic classification. The overall survival breast cancer specific was 99% and no differences were observed between groups (P = ns). The comparison of patients treated with a total mastectomy and those conservatively treated showed a significantly better local relapse free survival rate obtained with mastectomy (98.2% vs. 89.7% at 10 years $P = 0.02$). However, the overall cause-specific survival did not prove any better outcome (98.7% in both groups). Of the 32 patients who underwent a Sentinel Lymph Node Biopsy, four were found to have micrometastases and all of them had a previous Directional Vacuum Assisted Biopsy.

Conclusions Although in our series there is not a significant difference in LR rates by the parameter of age, the new USC/VNPI is still a simple and reliable scoring system for therapeutic management of DCIS. We did not find any statistically significant advantage in groups treated with the addition of RT. Obtaining wide surgical margins appears to be the strongest prognostic factor for local recurrence, regardless of other pathological factors or the addition of adjuvant radiation therapy. However, only prospective randomized studies can precisely predict the risk of LR of conservatively treated DCIS. The clinical significance of Sentinel Lymph Nodes micrometastases Immuno-Histo-Chemistry-detected found in DCIS patients remains uncertain. However, we hypothesize that the anatomical disruption after preoperative biopsy procedures increases the likelihood of epithelial cell displacement and the frequency of IHC-positive Sentinel Lymph Nodes, both of which are directly proportional to the degree of manipulation.

Keywords Breast cancer · Ductal carcinoma in situ · Prognosis · Treatment · Van Nuys prognostic index · Age · Margins · Sentinel lymph node biopsy

Background and aims

Ductal Carcinoma In Situ (DCIS) of the breast is a complex and heterogeneous spectrum of pathological lesions with a widely variable malignant potential and a not yet clearly understood natural history [1, 2]. Before the 1980's, the DCIS was a very rare entity (2–5% of all breast cancers), mostly treated by radical mastectomy [3]. In the last two decades the widespread use of screening mammography has increased the diagnosis of breast cancer in the non-palpable stage of DCIS. This currently represents approximately up to 20% of all new tumors [4, 5] and up to 30% of the screen-detected breast cancers [6]. The Van Nuys Prognostic Index (VNPI) is a score, developed on the basis of a multivariate retrospective analysis of some measurable prognostic factors in a large series of women [7]. It is useful in predicting the risk of local recurrence (LR) in patients with conservatively treated DCIS and is therefore an aid to the complex treatment decision-making process. This score combines three independent predictors of LR (tumor size, margin width and pathologic classification). The addition of scores (ranging from 1 to 3) from each of these three factors allows the identification of three major groups with low, intermediate and high recurrence risk. Several recent papers have shown patient age (Table 1) to be clinically significant [8–10]. The VNPI has recently been revised as the University of Southern California (USC)/VNPI with the addition of age as a fourth parameter into the scoring system [11] (Table 2). Each group of low (score 4–6), intermediate (score 7–9) or high risk for recurrence (score 10–12) is supposed to be best treated according to these guidelines. Lesions with a low score show a low rate of local recurrences, with no further decrease with adding of radiotherapy, and could be best treated by wide local excision alone [7]. The intermediate group benefits from a statistically significant reduction of local recurrence rate by adding adjuvant radiotherapy. Lesions with a high VNPI score showed a high recurrence rate regardless of whole breast irradiation. In these cases mastectomy should be considered as the best treatment

Table 1 Studies investigating the influence of the age on LR rate of DCIS after CS + RT Modified from Vicini and Recht [45]

Author	LR rate (%)	P
Fourquet et al. [41]	29−14	ns
Fowble et al. [37]	13−2	ns
Bijker et al. [48]	23−12	s
Vicini et al. [8]	23−9	s
Fisher et al. [67]	13−5	s
Solin et al. [27]	32−13−8−6	s
Van Zee et al. [36]	40−18−8	s
Hiramatsu et al. [68]	10−8	s
Fisher et al. [69]	15−10−9	s
Szelei-Stevens et al. [70]	9−2	s
Harris et al. [71]	8−13−9	s
Vicini et al. [45]	26−9	s
Cutuli et al. [29]	29−13−8	s
Anuja Jhingran et al. [10]	5−3	ns
Boland et al. [16]	8−15−13	ns
Rodrigues et al. [22]	0−7−7	ns
Solin et al. [21]	18−15−8−5	s
Silverstein et al. (660 pts) [28]	∼84/∼70/∼54	s $P < 0.01$
Silverstein et al. (706 pts) [11]		s $P = 0.02$

Table 2 The USC/VNPI scoring system

Van Nuys Prognostic Index			
Parameter	Score 1	Score 2	Score 3
Van Nuys Classification	Group 1	Group 2	Group 3
	Non-high nuclear grade without necrosis	Non-high nuclear grade with necrosis	High nuclear grade with or without necrosis
Margins	$\geq$10 mm	1–9 mm	<1 mm
Size	$\leq$15 mm	16–40 mm	>40 mm
Age	>60	40–60	<40

Modified from Silverstein MJ; Ductal Carcinoma in Situ of the breast 2nd ed. 2002

option, eventually followed by immediate reconstruction [12, 13].

In this paper, we retrospectively applied the new USC/VNPI to our series of DCIS patients treated with conservative surgery, in conjunction with an evaluation of the prognostic significance of seven clinical-pathological factors including those factors forming the Van Nuys Prognostic Index. Particular focus was placed on the role of age, the margins of excision, and the effect of adding adjuvant radiotherapy on disease-free survival. A comparison was also carried out between the outcomes of those patients treated with breast conserving therapy with or without adjuvant Radiotherapy and those underwent mastectomy. Furthermore we described our experience and findings with Sentinel Lymph Node Biopsy in DCIS in an attempt to evaluate the prognostic value of micrometastatic involvement of the Sentinel Node in pure DCIS.

Patients and methods

In the breast disease database from the Breast Unit of the Department of Surgery, S. Orsola Malpighi University Hospital in Bologna, Italy, there are 408 women recorded with a final diagnosis of DCIS (accordingly to the criteria of the American Joint Committee on Cancer) who have undergone surgical treatment from 1976 to 2006. Out of these patients 149 underwent a mastectomy (65% of cases had a size greater then 40 mm, 55% were lesion of high nuclear grade). Nodal assessment by Sentinel Lymph Node Biopsy was obtained in 32 patients since 2002. We reviewed retrospectively 259 patients treated with breast conserving surgery with, or without, radiotherapy (RT). 186 of these patients were treated with conservative surgery alone and 73 received adjuvant Radiotherapy. Applying USC/VNPI, 164 (63.5%) of these had a low VNPI (4–5–6), 83 (32%) intermediate (7–8–9), and 12 (4.5%) had a high score (10–11–12). The clinical-pathological features of the series are listed in the Tables 3 and 4. In the first group the majority of patients underwent

Table 3 Clinico-pathological features of the patients population and VNPI score distribution

	Low VNPI n (%)	Interm VNPI n (%)	High VNPI n (%)
Age			
<40 yrs	7 (32%)	13 (59%)	2 (9%)
40–60 yrs	105 (59%)	63 (36%)	8 (5%)
>60 yrs	52 (85%)	7 (11%)	2 (3%)
Pathological Tumor Size			
$\leq$15 mm	130 (83.5%)	23 (15%)	1 (0.5%)
16–40 mm	34 (34%)	57 (58%)	8 (8%)
>40 mm	–	3 (50%)	3 (50%)
Margin width of excision			
<1 mm	3 (11%)	16 (57%)	9 (32%)
1–9 mm	18 (39%)	25 (55%)	3 (6%)
$\geq$10 mm	143 (77%)	42 (23%)	–
Van Nuys Pathologic Classification			
Group 1	136 (85.5%)	22 (14%)	1 (0.5%)
Group 2	22 (46%)	24 (50%)	2 (4%)
Group 3	6 (11.5%)	37 (71%)	9 (17.5%)
Clinical appearance (palpable lesion or nipple discharge)			
Yes	73 (66%)	32 (29%)	5 (5%)
No	91 (61%)	51 (34%)	7 (5%)
Familial History of Breast carcinoma			
Yes	36 (60%)	18 (30%)	6 (10%)
No	128 (65%)	65 (32%)	6 (3%)
Contraceptives or HRT			
Yes	22 (55%)	14 (35%)	4 (10%)
No	142 (65%)	69 (31%)	8 (4%)
Treatment			
CS	144 (77.5%)	40 (21.5%)	2(1%)
CS + RT	20 (27.5%)	43 (59%)	10 (13.5%)
Local Recurrences	7 (4%)	11 (13%)	3 (25%)
LR Invasives	7 (100%)	8 (73%)	1 (34%)
LR In Situ (% of total LR)	0	3 (27%)	2 (66%)
Deaths	9	5	2
Breast Cancer	1	1	1
Other causes	8	4	1
Total	164 (63.5%)	83 (32%)	12 (4.5%)

Table 4 Clinico-pathological features of the patients population and distinction by treatment option

	CS n (%)	CS + RT n (%)	Total n. tot.
Age			
<40 yrs	11 (50%)	11 (50%)	22
40–60 yrs	124 (70%)	52 (30%)	176
>60 yrs	51 (84%)	10 (16%)	61
Pathological Tumor Size			
$\leq$ 15 mm	130 (83.5%)	24 (16.5%)	154
16–40 mm	55 (56%)	44 (44%)	99
>40 mm	1 (17%)	5 (83%)	6
Margin width of excision			
<1 mm	7 (25%)	21 (75%)	28
1–9 mm	32 (69%)	14 (31%)	46
$\geq$ 10 mm	147 (79%)	38 (21%)	185
Van Nuys pathologic classification			
Group 1	137 (86%)	22 (14%)	159
Group 2	28 (58%)	20 (42%)	48
Group 3	21 (40%)	31 (60%)	52
VNPI score			
Low (4–5–6)	144 (88%)	20 (12%)	164 (63.5%)
Intermediate (7–8–9)	40 (48%)	43 (52%)	83 (32%)
High (10–11–12)	2 (17%)	10 (83%)	12 (4.5%)
Clinical appearance (palpable lesion or nipple discharge)			
Yes	76 (69%)	34 (31%)	110
No	110 (74%)	39 (26%)	149
Familial history of breast carcinoma			
Yes	43 (72%)	17 (28%)	60
No	143 (72%)	56 (28%)	199
Contraceptives or HRT			
Yes	29 (72%)	11 (28%)	40
No	157 (72%)	62 (28%)	219
Local Recurrences	14 (7.5%)	7 (9.5%)	21
LR invasives	11 (79%)	5 (71%)	16 (76%)
LR In Situ (% of total LR)	3 (21%)	2 (29%)	5 (24%)
Deaths	9	7	16
Breast cancer	1	2	3
Other causes	8	5	13
Total	186	73	259

conservative surgery (CS) without RT (88%); in the intermediate group about half (52%) of patients received RT; whereas 83% of patients with high VNPI were treated with Conservative Surgery plus RT. Specimens were measured in their three dimensions, formalin fixed and serially sectioned in slices every 2–3 mm. The specimens were always completely sampled and a median number of blocks was 15. The distance used to define the margin width was the narrowest distance between the tumour and any inked margin. The distance of tumour to the specimens edge was reported for every marking margins and measured using a micrometer. Since 2002 the presence of foci of microinvasion was excluded by examination with Immuno-Histo-Chemistry anticytokeratin. Each case was classified in groups based on the size of the lesion, surgical margin width, age and pathology classification [14] and was scored accordingly to the new USC/Van Nuys Prognostic Index proposed by M.J. Silverstein in 2003 [11]. In order to obtain a reliable pathology assessment of the surgical margins, the use of the cautery during intraoperative dissection was avoided. Clear margins were obtained and ensured with shavings of resection cavity based on radiographic intra-operative evidence of margin status [15, 16]. Negative margins were defined as a width of at least 10 mm [17]. The Van Nuys pathology classification is based on nuclear grade and presence or absence of comedo-type necrosis [18, 19]. The Adjuvant radiotherapy in the pre-VNPI period was prescribed based on surgical margins status (involved or close margins), size of the lesion (diffuse, multicentric DCIS) and grade of the lesion (high nuclear grade). Adjuvant RT was administered by whole breast external beam irradiation (40–50 Gy). Some patients received a boost to the tumour bed. The Adjuvant Hormonal therapy was prescribed for the patients with ER positive lesions, since and when this status information was available. The sentinel lymph nodes were analyzed by serial sections stained with hematoxylin and eosin and Immuno-Histo-Chemistry anticytokeratin. The sentinel lymph nodes were classified as negative, H&E positive (macrometastases > 2 mm or micrometastases 0.2–2 mm), IHC positive (micrometasases <0.2 mm or isolated tumor cells). The sentinel lymph nodes were identified by gamma probe using an isotope mapping technique after an intradermal injection of 99 mTc labeled albumin. The patients were distinguished by groups of VNPI score. The patients treated by conservative surgery alone were retrospectively reviewed after a long term follow up and the prognostic value of all the clinico-pathological characteristics was analyzed. A statistical analysis of disease-free survival and breast cancer-specific survival for each group (obtained by Kaplan-Meier curves for univariate analysis and Cox regression for multivariate analysis and compared for statistically significant differences between each curve with the log rank test) was conducted using the software SPSS 11.5®. The differences were considered statistically significant for $P < 0.05$.

Results

The comparison for the presence or absence of factors, such as, clinical evidence, familial history of breast cancer, and previous therapy with estrogens, revealed no

significant differences between the groups of VNPI score. Twenty-one Local Recurrences (LR) were observed (8%), out of which sixteen were invasive after a mean follow up period of 130 months. The greater proportion of the invasive recurrences occurred in the intermediate and high score VNPI group, resulting in a significantly higher incidence (9.6% and 8.3% respectively vs. 4.2% in the low score group). The higher the final VNPI score and the score of each prognostic parameter, the more likely the patients received adjuvant therapy, accordingly to the literature experience [11]. No statistically significant differences in Disease Free Survival were reached in all groups of VNPI between patients treated with Conservative Surgery or Conservative Surgery plus RT but we did note that the higher the VNPI score was, the lower the risk of local recurrence was in the group treated by adding RT, even if not to a statistically significant degree (Table 5). It has to be noted that in the groups with a higher VNPI score, where the benefit from adjuvant RT in avoiding local recurrence after Conservative Surgery could be greater, the differences in DFS between the two treatment groups did not reach a significant degree because of the small number of cases. Of the patients conservatively treated with surgery alone, disease-free survival at 10 years was 94% with low VNPI, and 83% in both intermediate and high score ($P < 0.05$ between low and intermediate/high score) (Fig. 1). No significant differences were observed in analyzing the differences between the subgroups within low, intermediate or high VNPI score (Table 6). The LR rate

Table 5 DFS at 10 years and differences between groups by treatment (CS plus or not RT)

VNPI score	CS (%)	CS + RT (%)	*P*
Low VNPI (4–5–6)	94.7	92.3	0.71
Intermediate VNPI (5–6–7)	78.5	86.8	0.38
High VNPI (10–11–12)	50	100	0.23

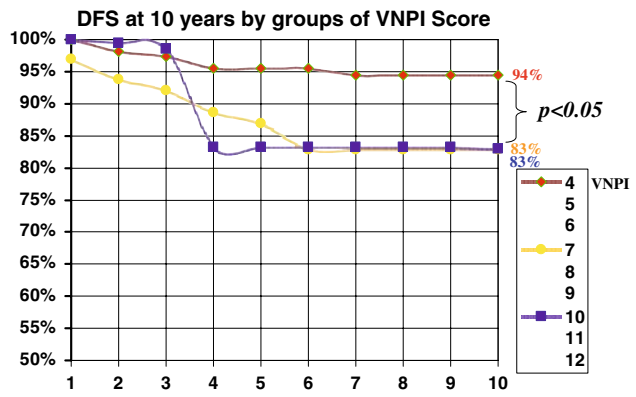

Fig. 1 DFS at 10 years by groups of VNPI score

Table 6 DFS in the subgroups of VNPI

VNPI score	No. of events/Total	DFS (%)	*P*
4	1/26	94.7	4 vs. 5 P = ns
5	2/82	96.6	4 vs. 6 P = ns
6	4/56	91.5	5 vs. 6 P = ns
7	1/38	97	7 vs. 8 P = ns
8	4/27	83.4	7 vs. 9 $P < 0.01$
9	6/18	57.2	8 vs. 9 $P < 0.05$
10	2/9	78	
11	0/1	–	10 vs. 12 P = ns
12	1/2	50	

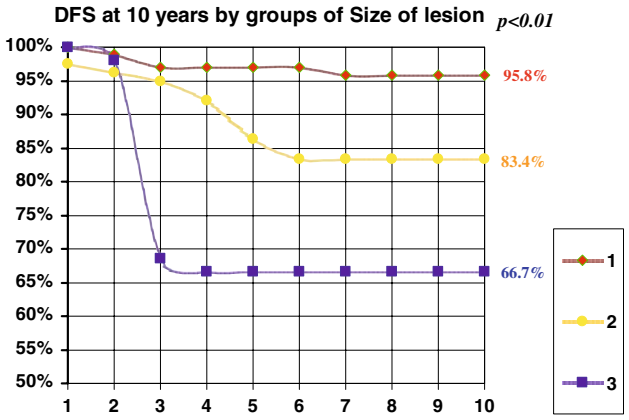

Fig. 2 DFS at 10 years by groups of size of lesion

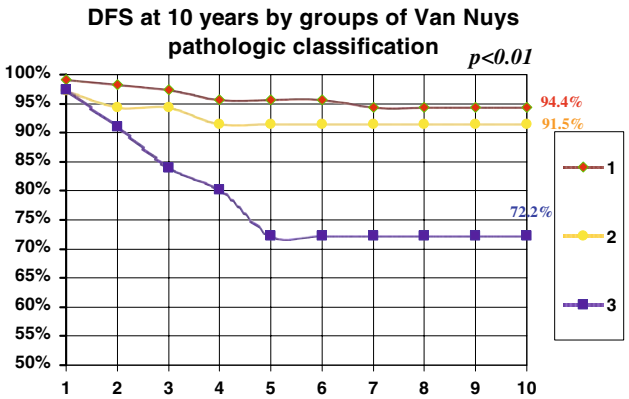

Fig. 3 DFS at 10 years by groups of Van Nuys pathologic classification

increased with tumor size, margin width and pathologic classification ($P < 0.05$) (Figs. 2–4), but age was not a significant factor (Fig. 5). Lesions with only mammographic appearance were associated with lower DFS than the patients with lesions clinically evident as palpable mass or nipple discharging (P = ns). The use of estrogenic

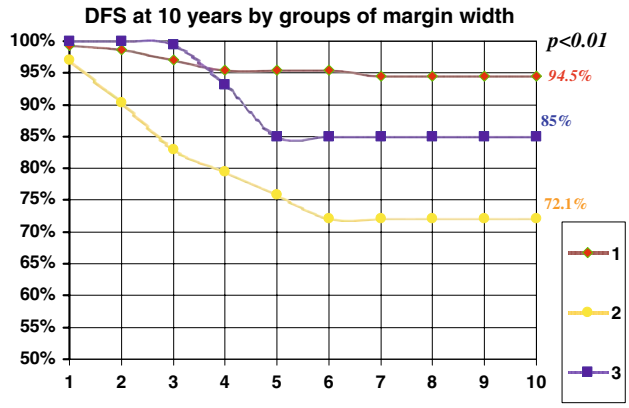

Fig. 4 DFS at 10 years by groups of margin width

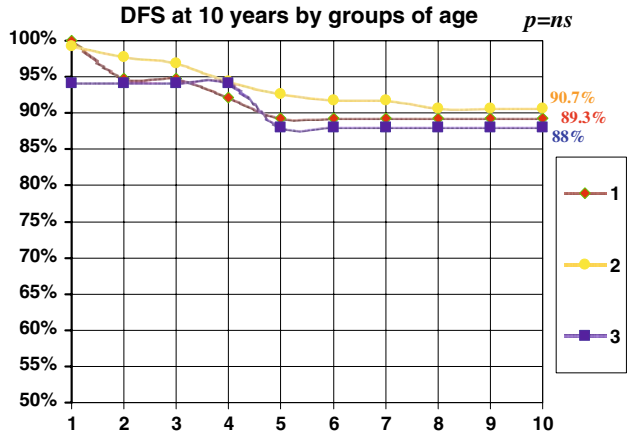

Fig. 5 DFS at 10 years by groups of age

hormones (for birth control or hormones replacement therapy) and a family history of breast cancer were found to be significant factors associated with higher LR risk. After multivariate analysis including these seven factors: pathological size of the primary lesion, margins of excision, pathology classification including nuclear grading and presence or absence of comedonecrosis, age, clinical appearance, the use of hormones, and a familial history of breast cancer, the only significant predictors of local recurrence remained margin width of surgical excision, the use of estrogenic therapy (contraceptives or Hormone Replacement Therapy) and pathology classification (Table 7). The overall survival breast cancer specific was 99% and no differences were observed between the main groups of VNPI score (P = ns). Finally we compared the patients treated with total mastectomy with those conservatively treated. The comparison showed a significant better local relapse free survival obtained with mastectomy (98.2% vs. 89.7% at 10 years $P = 0.02$) but the overall cause specific survival did not prove any advantage between the two different treatment groups (98.7% in both) (Figs. 6 and 7).

Out of the 32 patients who sustained a Sentinel Lymph Node Biopsy, four were found to have micrometastases, three of whom had a "high risk" DCIS but the fourth had a low score VNPI lesion. Surprisingly all of these patients underwent a previous Directional Vacuum Assisted Biopsy and a strong tissue manipulation, and the nodal positivity was only detected by IHC with a similar morphologic pattern in each different patient (Figs. 8–13). In all of these patients the final extensive histopathologic assessment of the lesion was negative for finding invasive or microinvasive foci.

Discussion

Several papers have analyzed series of patients with DCIS trying to retrospectively evaluate the criteria included by Silverstein in his Van Nuys Prognostic Index as well as other clinical and pathological features, to confirm his value and identify other significant relapse-predictive factors [16, 20–23]. It is notable in our series that the presence of close margins width was the strongest predictive factor of local relapse, even if the closer the margin the greater was the proportion of patients treated adding adjuvant radiotherapy (75% of patients if the margins were less than 1 mm from tumour foci). This finding, together with the lack of significant disease free survival advantages in all VNPI groups irradiated in comparison with those not

Table 7 The prognostic significance for local recurrences of 7 clinical and pathological factors in the patients treated by conservative surgery

Factor	DFS at 10 years	Univariate analysis	Multivariate analysis
Tumor size (1–2–3)	95.8%–83.4%–66.7%	$P < 0.01$	$P = 0.228$
Margin width (1–2–3)	94.5%–72.1%–85%	$P < 0.01$	$P = 0.002$
Pathologic classification (1–2–3)	94.4%–91.5%–72.2%	$P < 0.01$	$P = 0.024$
Age (1–2–3)	89.3%–90.7%–88%	P = ns	P = ns
Clinical appearance (yes/no)	90.9%–89.3%	P = ns	
Birth Control Pill – HRT (yes/no)	92.3%–70.1%	$P < 0.01$	$P = 0.009$
Familial history of breast cancer (yes/no)	93.2%–80.9%	$P < 0.01$	$P = 0.897$

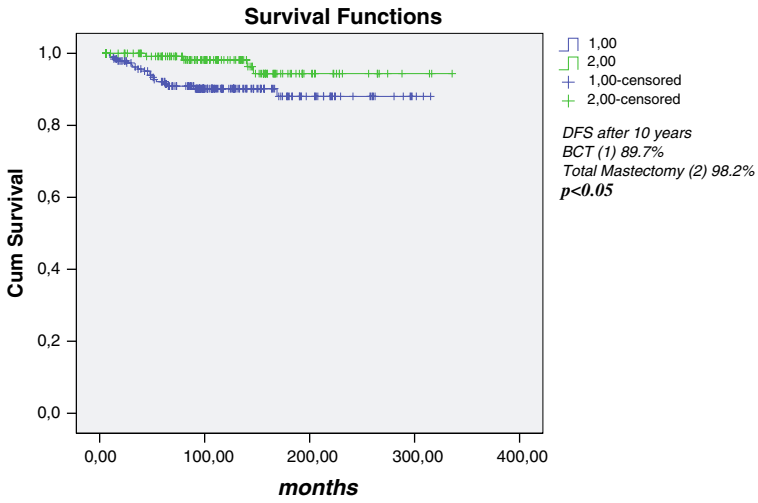

Fig. 6 Comparison of disease free survival after breast conserving treatment (1) and total mastectomy (2)

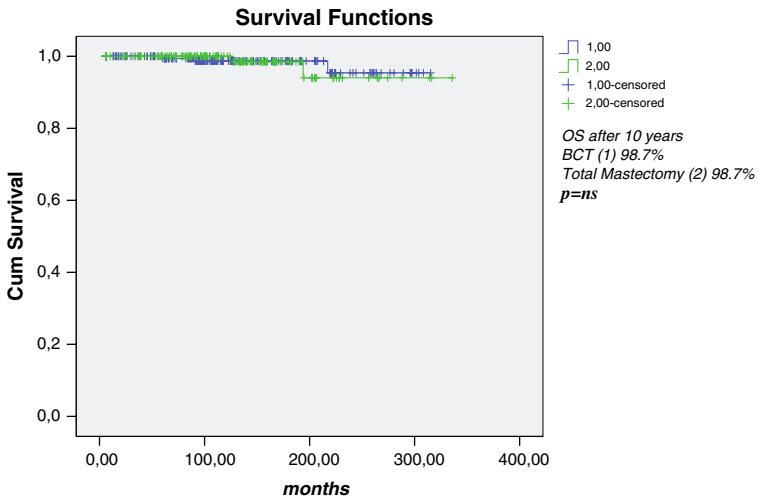

Fig. 7 Comparison of overall survival breast cancer specific after breast conserving treatment (1) and total mastectomy (2)

irradiated, could suggest the hypothesis that performing a wide surgical excision and making sure to obtain free wide margins would guarantee better local control of disease than irradiating the whole breast and the tumour bed. Several studies have confirmed an association between positive or close resection margins and local outcome of DCIS lesions even in patients treated with CS and adjuvant Radiotherapy, including the NSABP B-17 findings from Fisher [8, 24–27]. Silverstein underlined the importance of achieving free and wide excisional margins, confirming the lack of benefit from the addition of postexcisional radiation therapy if wide margins (more than 10 mm) are achieved. The benefit of adding RT is more significant if the margins are close or involved [28]. Poor excision quality was confirmed in a large series from Cutuli et al. [29] as a significant predictor of relapse, even in the group of patients treated with CS + RT. The addition of RT reduced significantly the local recurrence rate in all subgroups. Furthermore, Kestin found the proportion of DCIS present in proximity to the surgical margin as a more reliable predictor of residual disease than the margin status [30].

Compared with the rate of approximately 50% invasive relapses after conservative treatment of DCIS reported in the literature [20, 31–35], Silverstein observed in the large Van Nuys series an overall relapse rate of 17% with a 41% rate of invasive recurrences [11]. Rodrigues reported 18% of invasive relapses, 29% including patients with mixed microinvasive component [22]. Also Boland observed a rate of 25% of invasive recurrences [16]. In the NSABP reports the proportion of invasive recurrences in irradiated patients was 28% while this rate was higher, 45%, in the EORTC group. The proportion of invasive local recurrences in our series was slightly higher than in these previous series (16 out of 21, 76%), but similar percentages are reported by Solin who reports a 60% of invasive relapses out of any histologic type of recurrence from a large multicenter series of 1003 patients [21]. In our study the invasive recurrences in the subgroup of CS were 79%;

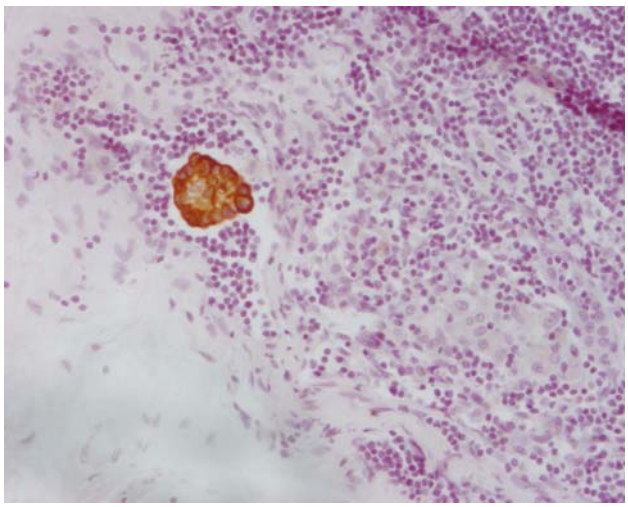

Fig. 8 *Pt #1* sentinel node (IHC); micrometastatic cell cluster

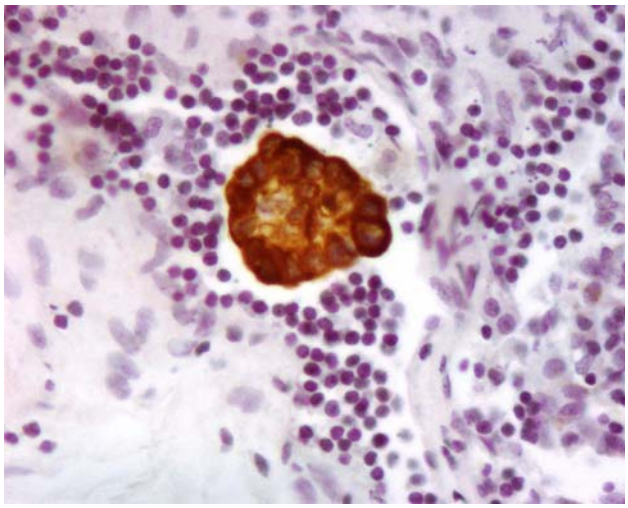

Fig. 9 *Pt #1* sentinel node (IHC); micrometastatic cell cluster (magnification)

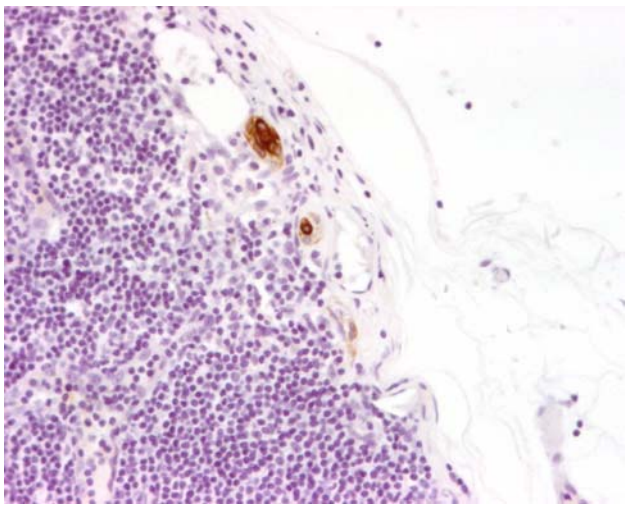

Fig. 10 *Pt #1* sentinel node (IHC); single tumor cells, IHC-positive

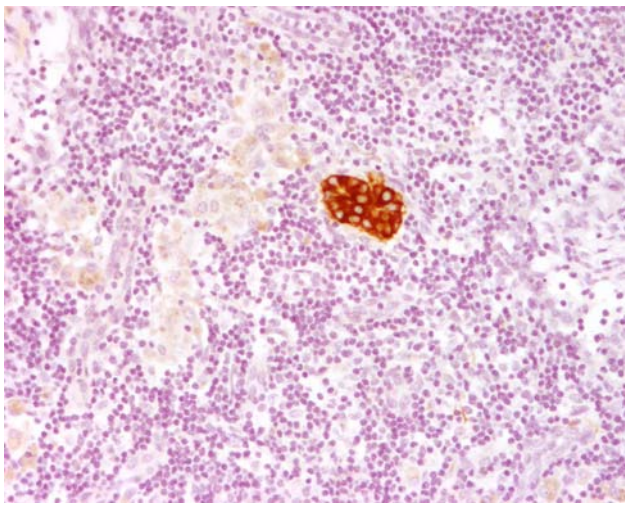

Fig. 11 *Pt #2* sentinel node (IHC); micrometastatic cell cluster

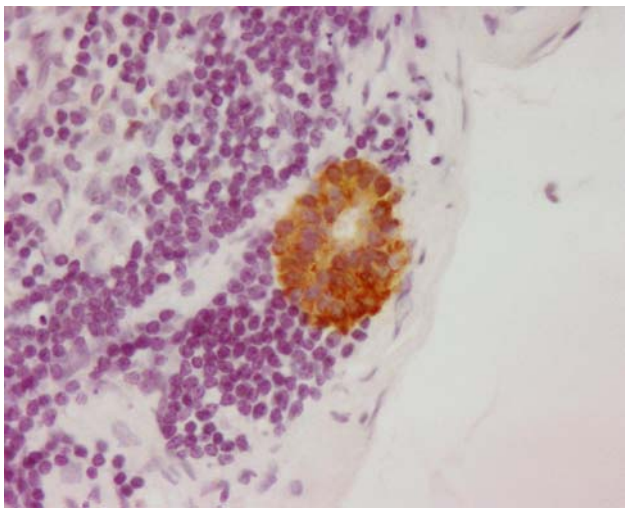

Fig. 12 *Pt #2* Sentinel Node (IHC); micrometastatic cell cluster (magnification)

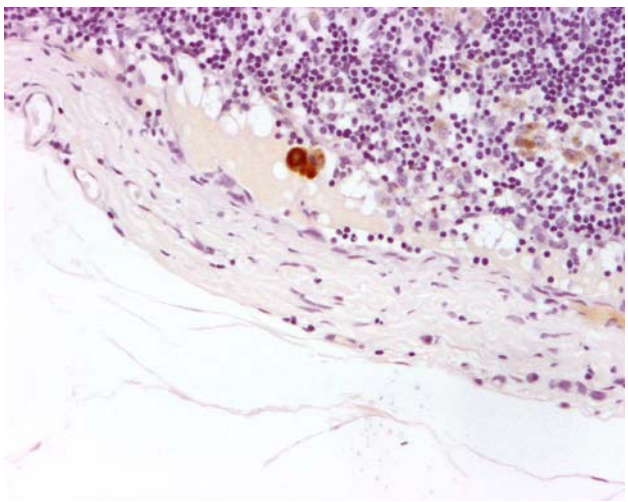

Fig. 13 *Pt #2* sentinel node (IHC); single tumor cells, IHC-positive

the percentage in the CS + RT group was slightly lower (71%). Moreover the majority of the recurrences, in situ and invasives, occurred in the intermediate or high VNPI score (in patients with high score and conservatively treated the overall rate of relapse was 25% with one invasive recurrence out of three). Similar findings are described by De Mascarel et al. [20] with 2 invasives recurrences out of 4 cases of relapse in the high VNPI group and three of them relapsed even if irradiated.

In the past years there has been an increasing amount of evidence of the prognostic value of age for DCIS and several studies reported results of variable statistical significance with different ages investigated. In our analysis the age did not show prognostic significance either in univariate analysis or in the multivariate. Some authors have demonstrated higher local recurrence rates in younger patients [8, 27, 36–41] but other studies failed to confirm these findings (Table 1) [10, 26, 42–44]. Although the prognostic role of the age resulted statistically significant in several studies, associated variables may interact and confuse the impact of the patient age. The younger age seems to be associated with larger lesions and worse histologic characteristics and nuclear grade [45], but paradoxically younger patients have historically been treated with more conservative resections than older patients for better cosmetic results, therefore they have a higher risk of residual tumor burden. However the presence of negative and wide surgical margins could guarantee low relapse rates even in younger patients [27] regardless of their age. Silverstein [11] in 2001 showed the results of multivariate analysis of the large series of patients from the University of Southern California, demonstrating age as an independent significant prognostic factor in conservatively treated DCIS, with the most appropriate breaking points at the ages of 40 and 60 years.

Radiation therapy in an adjuvant setting has become routinely used in the treatment of DCIS based on the findings of the prospective randomized study from NSABP B-17 [24], although the first report from Fisher did not define which subset of patients might benefit from adjuvant RT [46]. Two other randomized trials, the EORTC trial [47, 48] and the United Kingdom, Australia and New Zealand DCIS trial [49], confirmed that the addition of radiation therapy after breast conserving surgery reduces the rate of omolateral local recurrence by about half. Similar results were shown from retrospective series analysis [29, 50]. Successive studies recognized that postoperative RT may not significantly improve the local outcome in all types of DCIS [7, 51, 52]. Silverstein [11] noted that DCIS is a heterogeneous group of lesions, so a uniform treatment policy is not appropriate: "Some patients require no treatment other than excision alone, others benefit from complete excision plus RT and some others will require mastectomy". The survival curves from the Van Nuys series showed that, regardless of the presence of high nuclear grade, comedonecrosis, large tumor size, or young age, the risk of local relapse remains slight if wide margins of resection are achieved. In such cases the addition of RT do not add statistically significant benefit in terms of disease free survival [11, 28], while RT markedly improves the outcome of patients with close or involved margins (less than 1 mm) and, to a lesser degree, with intermediate (1–9 mm) margins. Our series (Table 5) confirmed these findings of the different benefits of adding RT for different subset of patients. There was no advantage in the low VNPI score subgroup. The DFS benefit was higher in the intermediate group and in the high score group but did not reach statistical significance. No definitive conclusion could be made from this survival analysis due to the small number of cases in the samples. Other authors have noted a markably high local recurrence rate of 12% at 5 years even for small low grade DCIS lesions widely excised, raising the debate about this questioned issue [53]. This study from Wong et al. suffer limitations due to be a single arm prospective trial and to have a short follow up because of forced interruption of the study due to the high recurrence rate. Moreover this trial included lesions with clinical extent up to 2.5 cm, lesions with grade 3 nuclei and presence of necrosis, as well as some patients with margins closer than 10 mm. Thereby the recurrence rate resulted significantly higher in these subset of patients with worse pathological features, who avoided adjuvant Radiotherapy even though they were likely to have Intermediate-High risk for recurrence if scored accordingly to VNPI. The results of further prospective randomized trials are needed to better identify which subset of DCIS patients could safely avoid RT and integrate the role of adjuvant Hormonal therapy.

The total mastectomy treatment guarantee significantly lower local failure rate in our experience. This finding is confirmed by Cutuli et al. In their series local recurrence rates were 2.1%, 30.1% and 13.8% in the Mastectomy, CS and CS + RT groups, respectively ($P = 0.001$) [54]. Also Ciatto et al. in a previous review reported the same result [55]. Nevertheless the treatment option does not affect the long term overall survival as noted in the Silverstein series [28].

The DCIS is a non-obligate precursor of invasive breast carcinoma lacking the ability to metastatize while in the In situ phase; thus is not indicated any formal axillary dissection or Sentinel Lymph Node Biopsy. Lagios and Silverstein noted that SLNB is not useful in predicting which DCIS patients will develop invasive recurrence because it does not reflect the status of margins. Therefore, "patients with DCIS will be better served by more thorough pathologic evaluation and more careful surgical

attention to margins than by a questionable value of a sentinel lymph node procedure, particularly one that employs Immuno-Histo-Chemistry" [56]. Usually the low rate (0.8–2%) of axillary lymph node involvement reported in literature [57–61] for DCIS lesions is attributed to undetected invasive or microinvasive foci or to the histologically subtle loss of a restricting basement membrane, often associated with high grade intraductal lesions [62]. In our policy we usually consider SLNB for those patients with "high risk" DCIS lesions to be candidates for mastectomy. High risk features include wide extent of microcalcifications on the mammography, multicentric lesions, clinically relevant (palpable mass or presence of nipple discharge) tumors, high nuclear grade and/or presence of comedonecrosis on the preoperative biopsy specimen. In each of our four patients with micrometastatic involvement of SLN, all of whom underwent a preoperative Vacuum Assisted biopsy with a strong tissue manipulation, the micrometastatic cell cluster presented exactly the same morphologic pattern and it was evident only by Immuno-Histo-Chemistry. This finding seems to confirm the hypothesis already given by some authors that the anatomic disruption of the basement membrane subsequent to invasive preoperative bioptic procedures could displace the malignant epithelial cells and produce an iatrogenic tumor embolization to the SLN. It would induce not true biologic micrometastases but rather a benign transport of breast epithelium, lacking in clinical significance [63–66].

Conclusions

In our series we did not find a significant difference in Local Recurrence rates by the parameter of age. Nevertheless the new USC/VNPI is a score easy to calculate and reliable to apply in a clinical setting for predicting the outcome and planning of the therapeutic management of DCIS. We also did not find any statistically significant advantage in groups treated by adding Radiotherapy, especially in those with a low prognostic score. Furthermore, the aim of obtaining free wide surgical margins seems to be of better prognostic value than irradiating the breast in an adjuvant setting. However, we do note several limitations to our retrospective study and only prospective randomized studies and a longer follow up period can precisely predict the risk of Local Recurrence of DCIS conservatively treated and to determine which factors are strongly associated, as well as, the role of Radiotherapy in maintaining local control of disease and therefore in which subset of patients with different prognostic scores it could be recommended. A clinical prospective randomized trial, planned within a Breast Screening Program could provide enough cases to evaluate in a large and robust database the prognostic factors and identify the best treatment options in each subset of patients with DCIS. The clinical significance of Sentinel Lymph Node IHC-detected micrometastases remains uncertain. We confirm the hypothesis that the anatomic disruption of basement membrane after preoperative bioptic procedures increases the likelihood of epithelial cell displacement and the frequency of IHC-positive Sentinel Lymph Node, of which, both are directly proportional to the degree of manipulation [63]. Therefore, in those patients, this kind of micrometastases could be lacking in biologic and prognostic value.

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