

RISK FACTORS FOR IPISILATERAL BREAST TUMOR RECURRENCE IN PATIENTS WITH DUCTAL CARCINOMA IN SITU UNDERGOING WIDE EXCISION ALONE

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Purpose : We review our experience of treating ductal carcinoma in situ (DCIS) patients with wide excision alone and examine risk factors that are associated with ipsilateral breast tumor recurrence (IBTR).

Materials and Methods : Between January 1990 and December 2002, 47 out of 257 DCIS patients who were treated with wide excision alone were included in this study. The primary end point of this study was IBTR. Local control rate was calculated by Kaplan-Meier method. Variables including tumor size, nuclear grade, margin status, necrosis, mitosis, multifocal disease, ER/PR status, patient's age, microcalcification, re-excision, contralateral invasive carcinoma, and Van Nuys prognostic index (VNPI) were enrolled for analysis

Result : With a median follow-up interval of 5.94 years, IBTR developed in 6 patients (12.5%), with 3 invasive carcinomas, and 3 DCIS. Necrosis was the only significant prognostic factor for IBTR ($p = 0.0249$) by Fisher's exact test. Nuclear grade, VNPI ≥ 6 , and mitosis were marginal significant ($p = 0.0586$, $p = 0.0718$, and $p = 0.0684$, respectively). Multivariate analysis failed to identify any significant risk factors.

Conclusion : Necrosis is a significant risk factor for IBTR in patients with DCIS undergoing wide excision alone.

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Key words: Ipsilateral breast tumor recurrence, Ductal carcinoma in situ,
Wide excision

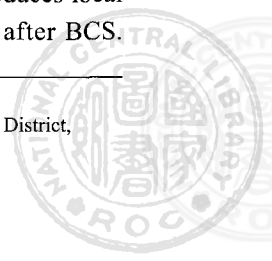
INTRODUCTION

Conventionally, mastectomy is the treatment of choice, which achieves nearly 100% cure rate for patients with ductal carcinoma in situ (DCIS) [11, 16, 18]. However, the success of breast conserving surgery (BCS)

plus radiotherapy (RT) for invasive breast carcinoma also makes it feasible for non-invasive DCIS. Data from three randomized controlled trials, including NSABP B-17 [2, 3, 5], EORTC 10853 [1, 10], and a UK [8] trial, have shown that radiation therapy reduces local recurrence for patients with DCIS after BCS.

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In these trials, adjuvant RT reduces the relative and absolute risk of ipsilateral breast tumor recurrence (IBTR) by 35- 65%, and 5-10% respectively. Patients treated with wide excision alone experienced 22%-32% of IBTR after follow-up interval of 5-12 years, which means majority of them had undergone unnecessary RT and raises the question that can we identify low-risk patients who could be treated with surgery alone.

Silverstein et al. analyzed a retrospective cohort data and proposed a Van Nuys prognostic index (VNPI) to predict local recurrence after wide excision. They assigned score 1 for age > 60 years, tumor size < 15mm, surgical margins > 10mm, nuclear grade 1 or 2 without comedonecrosis, score 2 for age 40-60 years, tumor size 16-40 mm, surgical margins 1-9 mm, nuclear grade 1 or 2 with comedonecrosis, and score 3 for age < 40 years, tumor size \geq 41 mm, surgical margins < 1 mm, nuclear grade 3, and suggested that wide excision alone was safe for patients with score of 4 to 6. The 10-year local recurrence-free survival of this group was greater than 95% [12, 13, 14, 15]. A prospective phase II study tried to validate this concept. The definition of low-risk patients in this series was as follows: grade 1 or 2 DCIS, tumor size \leq 2.5 cm, and wide excision with a minimum of 1 cm resection margin. The IBTR after wide excision alone was 12% at 5 years. The authors concluded that DCIS could not be treated with wide excision alone [9]. Therefore, we review our experience of treating DCIS patients with wide excision alone and examine risk factors associated with IBTR.

METHODS AND MATERIALS

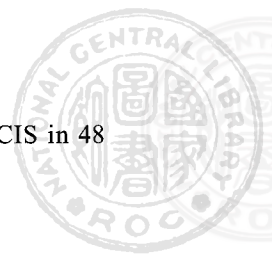
Between January 1990 and December 2002, 257 breast cancer patients with stage 0 (TisN0M0) were treated at Koo Foundation Sun Yat-Sen Cancer Center. Selection criteria for this study included (1) DCIS, (2) treatment with

wide excision. Exclusion criteria were (1) any evidence of micro-invasion, (2) breast irradiation and (3) ipsilateral mastectomy. However, patients with simultaneous contralateral DCIS (n= 2), and previous (n= 1) or simultaneous (n= 5) contralateral invasive breast cancers were included. The patient with previous contralateral invasive cancer received adjuvant cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) for 6 cycles, and had DCIS 19 months after the previous surgery. Four patients with simultaneous contralateral invasive cancer had chemotherapy, including CAF for 6 cycles in 2, doxorubicin and cyclophosphamide for 4 cycles in 1, and doxorubicin for 3 cycles followed by cyclophosphamide, methotrexate, and 5-fluorouracil for 6 cycles in 1 case. Besides, all these 6 patients with contralateral breast cancer took tamoxifen for 5 years or until recurrence. One of the patients with simultaneous bilateral DCIS underwent radiation to one side of her breast, and we included the other side of breast without radiation. Totally, 47 patients with 48 breasts with DCIS were enrolled in this study.

The primary study end point is IBTR. Local control duration was defined from the day of surgery to the day of histology confirmation of local recurrence. If patients did not have histology confirmation, the day of recurrence was based on the image confirmation. Local control rate was calculated by Kaplan-Meier method. Variables including tumor size, nuclear grade, margin status, necrosis, mitosis, multifocal disease, ER/PR status, patient's age, microcalcification, re-excision, contralateral invasive carcinoma, and Van Nuys prognostic index were enrolled for analysis by univariate analysis, and multivariate analysis, with Fisher's exact test, Chi-square test, and Cox proportional hazard regression model.

RESULTS

There were 47 patients with DCIS in 48



breasts undergoing wide excision alone enrolled in this study. Patients' characteristics and IBTR were shown in Table 1. More than half of the

patients were 40-60 years old. Majority of them had small tumor size (<16 mm, 77%) and surgical margin more than 1 cm (88%). Around

Table 1. Univariate analysis for risk factors (N= 48)

Factors	No. of Breasts (%)	No. of IBTR (%)	Fisher's Exact Test p-value
Necrosis			0.0249
Absent	29(60)	1(3)	
Present	18(38)	5(28)	
Unknown	1(2)		
Nuclear grade			0.0586
Grade 1	30(63)	2(7)	
Grade 2	14(29)	2(14)	
Grade 3	4(8)	2(50)	
Mitosis			0.0718
Absent	16(33)	0(0)	
Present	28(58)	6(21)	
Unknown	4(9)		
Multifocal disease			0.1300
No	39(81)	4(10)	
Yes	5(10)	2(40)	
Unknown	4(9)		
VNPI			0.0856
4-6	32(67)	2(6)	
7-9	16(33)	4(25)	
VNPI			0.0684
4-5	19(40)	0(0)	
6-9	29(60)	6(21)	
Margin			0.2259
>10mm	42(88)	4(10)	
1-9mm	5(10)	2(40)	
<1mm	1(2)	0(0)	
Age			0.1867
>60	10(21)	1(11)	
40-60	24(50)	5(21)	
<40	14(29)	0(0)	
Microcalcification			0.2948
Absent	15(31)	3(20)	
Minimal (< 3 ducts/10 tumor ducts)	18(38)	3(17)	
Extensive (> 3 ducts/10 tumor ducts)	12(25)	0(0)	



Table 1. Continued

Factors	No. of Breasts (%)	No. of IBTR (%)	Fisher's Exact Test p-value
Unknown	3(6)		
ER			0.4899
-,+	9(19)	1(11)	
++,+++	23(48)	1(4)	
Unknown	16(33)		
PR			1
-,+	13(27)	1(8)	
++,+++	18(38)	1(6)	
Unknown	17(35)		
Contralateral invasive			0.5032
No	43(90)	5(12)	
Yes	5(10)	1(20)	
Re-excision			1
No	43(90)	6(14)	
Yes	5(10)	0(0)	
Tumor size			1
<15mm	37(77)	5(14)	
>15mm	11(23)	1(9)	

Abbreviations: VNPI, Van Nuys prognostic index; IBTR, ipsilateral breast tumor recurrence; ER, estrogen receptor; PR, progesterone receptor.

60 percent of the DCIS specimen showed nuclear grade 1, and two third of the patients fall into the group with VNPI of 4-6.

With a median follow-up interval of 5.94 years (ranging from 1.44 to 15.89 years), IBTR developed in 6 patients (12.5%, 6/48 breasts), with 3 invasive carcinomas, and 3 DCIS. The Kaplan-Meier curve for IBTR was shown in Fig. 1. All IBTR were located within or immediately adjacent to the previous tumor site, as a true recurrence. All events occurred within 2 years after treatment. Three-year local control rate was 87.5%.

Patients' characteristic with IBTR and their subsequent treatment were shown in Table 2. They all underwent modified radical mastectomy, and the 3 patients with invasive cancer all had pathological stage of T1N0.

Distribution of Van Nuys prognostic index

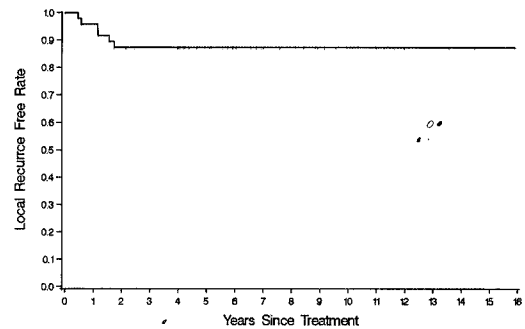


Fig 1. Local recurrence-free survival.

for IBTR was shown in Table 3. Most patients had VNPI 5 (n= 15), VNPI 6 (n= 13), and VNPI 7 (n= 13). All IBTR developed in patients with VNPI 6, with 2 in VNPI = 6 (15.4%, 2/13) and 4 in VNPI = 7 (30.8%, 4/13).

Univariate analysis of risk factors for IBTR in all patients treated with wide excision alone

Table 2. Characteristics of patients with IBTR

Patients with IBTR	Age	Time to recurrence (year)	Recurrent tumor	Initial site	Recurrent site	Treatment
1	44	0.57	T1N0	Rt 9' /0.5 cm	Beneath scar	MRM
2	50	1.16	DCIS	Lt 9'	Lt 9.5' /2 cm	MRM
3	44	1.73	DCIS	Rt 3.5' /3 cm	Rt 4-6' /2 cm	MRM
4	42	0.46	T1N0	Rt 3' /6 cm	Beneath scar	MRM
5	63	1.15	T1N0	UOQ	Beneath scar	MRM
6	46	1.56	DCIS	Rt 12' /2 cm	Rt 12' subareolar	MRM

Abbreviations: IBTR, ipsilateral breast tumor recurrence; DCIS, ductal carcinoma in situ; UOQ, upper outer quadrant; MRM, modified radical mastectomy; Rt, right; Lt, left.

Table 3. Distribution of VNPI

VNPI	No. of breasts	No. of IBTR (%)
4	4	0
5	15	0
6	13	2 (15)
7	13	4 (31)
8	2	0
9	1	0

Abbreviations: VNPI, Van Nuys prognostic index; IBTR, ipsilateral breast tumor recurrence.

were seen in Table 1. Necrosis was the only significant prognostic factor for IBTR ($p = 0.0249$) by Fisher's exact test. Nuclear grade, VNPI ≥ 6 , and mitosis were marginal significant ($p = 0.0586$, $p = 0.0718$, and $p = 0.0684$, respectively). VNPI ≥ 7 was also marginal significant ($p = 0.0856$). Multivariate analysis and Cox proportional hazard regression model failed to identify any risk factor that is associated with IBTR.

DISCUSSION

In our study, all IBTR locating in the previous tumor bed, and developing within 2 years in our study, both suggested that IBTR was truly a primary recurrence. If we could identify these high-risk patients, they might benefit most from adjuvant RT. We found 4 potential risk factors for IBTR, i.e. necrosis,

nuclear grade 2-3, mitosis and VNPI ≥ 6 . This observation suggests that high grade DCIS is more susceptible to local recurrence.

IBTR at 3 years in our study was 12.5%. It is comparable to that in the prospective phase II studies reported by Julia S.W., 12% at 5 years [9], and EORTC 10853 trial, 16% at 4 years [10]. The risk of invasive carcinoma in IBTR was 50% in our series, which is also comparable to the reports of most series, around 40-50% [1, 5, 10].

EORTC 10853 trial reported age < 40 , detection by clinical symptoms, positive surgical margin, cribriform and solid/comedo subtype, and no addition of radiation to wide excision as significant risk factors for local recurrence in multivariate analysis. Multivariate analysis from a retrospective study [9] identified younger age, electron boost energy ≤ 9 MeV, and margin ≤ 2 mm were associated with IBTR. Young age has been found to be an independent risk factor for local recurrence in several studies [17], as well as the impact of surgical margin on IBTR reported in EORTC 10853 and NSAPB B-24 [4]. In the clinical practice, the only risk factor that we could make difference is negative surgical margin, and we usually achieve it as possible as we can. Thus, in a group whose age is similar and surgical margins are negative, histological features that indicate high grade, might become the most important factors to

predict local recurrence, as the result seen in our study, and NSABP B-17 [6,7], that comedo necrosis is a significant predictors of IBTR.

The limitation of our study is small patient number. It made us unable to get significant results from multivariate analysis. The marginal significant factors we identified in univariate analysis might become significant if we have enough patients. Besides, our study is a retrospective review. The reasons why these patients didn't receive post-operative radiation might be individual choice, or the influence of modified VNPI (VNPI was modified in 2001 by adding age as 4th risk factor [13, 15]). Non-uniform criteria to decide who needs post-operative radiation result in the bias of patient selection.

VNPI prospectively validated by Julia S.W. lead to a negative conclusion. Our findings suggest selecting patients with VNPI 4-5 might be more appropriate to get positive results. A new phase II study to validate the criteria might be necessary.

CONCLUSION

Necrosis is a significant risk factor for IBTR in patients with DCIS undergoing wide excision alone. Patients with VNPI 6 and 7 treated with BCS alone might not be as safe as BCS plus radiotherapy.

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乳管原位癌接受乳房保留手術後之局部復發相關危險因子

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目的：我們回顧本院乳管原位癌以乳房保留手術治療的病人，並分析其同側乳房腫瘤復發相關的危險因子。

材料與方法：自 1990 年 1 月至 2002 年 12 月間，於和信治癌中心醫院治療的 257 位乳管原位癌病人中，有 47 位只接受乳房保留手術且無術後放射線治療的病人列入分析。我們探討下列危險因子，包括腫瘤大小、細胞核分化、病灶切除周邊安全距離、病灶組織壞死、細胞核的有絲分裂、多發性腫瘤、賀爾蒙受體、年齡、鈣化點、再次切除、對側侵犯性癌症、奈氏指數等等，與同側乳房腫瘤復發的關係。

結果：於中位數 5.94 年的追蹤時間，同側乳房腫瘤復發發生於 6 位病人，其中有 3 位是侵犯性癌症，3 位仍是乳管原位癌單。單變項分析中，病灶組織壞死是唯一統計學上有意義的危險因子，而細胞核分化、細胞核的有絲分裂、奈氏指數 ≥ 6 ，則是接近有統計學上的意義。至於多變項分析則未得到有意義的危險因子。

結論：病灶組織壞死是和同側乳房腫瘤復發相關的危險因子。

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關鍵詞：同側乳房腫瘤復發、乳管原位癌、乳房保留手術

