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Patient, tumor and therapeutic features related to recurrence of ductal carcinoma *in situ* (DCIS)

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Abstract

To evaluate the correlations between patient, tumor and therapeutic features and DCIS recurrence after primary treatment, a cohort of 132 cases of DCISs, treated at "Prof. Dr. Ion Chiricuţă" Oncology Institute, Cluj-Napoca, Romania, between 1999 and 2010, were studied. Present study showed that age <45 years at diagnosis and presence of the necrosis were significantly correlated with recurrence, meanwhile nuclear grade is significantly correlated with quicker relapse meaning that for high-grade lesions recurrence occurs usually during the first 36 months of follow-up, meanwhile for non-high-grade lesions recurrence usually occurs after 36 months of follow-up. Also, the study showed that a important factor correlated with recurrence (both local and overall) for patients treated with breast conservative surgery (BCS) was the status of the resection margins as well as the association of adjuvant radiotherapy. Overall recurrence rate was 9.(84)% and during a mean follow-up of 62.99 months with limits between 24 (imposed by study) and 153 months, standard deviation 29.28.

***Keywords*:** ductal carcinoma in situ (DCIS), breast conservative surgery (BCS), resection margins status, necrosis, nuclear grade, recurrence.

Abbreviations: DCIS – Ductal carcinoma *in situ*; IBC – Invasive breast cancer; BCS – Breast conservative surgery; RT – Radiotherapy; IOCN – "Prof. Dr. Ion Chiricuţă" Oncology Institute, Cluj-Napoca; VNPI – Van Nuys Prognostic Index.

Introduction

The most common disease-related event a DCIS patient can experience is recurrence [1]. DCIS recurrence occurs as DCIS or IBC, with half of them being IBCs and those can be life-threatening [2].

Although many authors have paid attention to this issue we are still not able to precisely define the risk factors for DCIS recurrence [1, 2] although important advances of the field have been done [3].

Tumor and patient characteristics related to DCIS recurrence were intensive studied but still no Romanian study was published to date (to my knowledge).

The main goal of the present paper was to study tumor and patient characteristics possible related to recurrence, which was this study's end-point.

Absence of a screening program not only makes DCIS much less frequent than in countries with screening programs but also presentation of DCIS at diagnosis is different (palpable mass as the most common presentation followed by bloody nipple discharge instead of asymptomatic mammographic detected microcalcifications).

Yet there is a group of patients, not very large nor in Romania neither in countries with screening programs, for which these differences may be not so evident. This is the group of young patients, meaning patients under the age of the mammographic screening start. Because some mammographic screening programs begin at 40 years (and even the Van Nuys Prognostic Index [4] and Rudloff's nomogram [3] include age <40 years at diagnosis as risk factor), but other mammographic screening programs begin at 50 years, I choose the age of 45 years as a cut-off for this study, trying to find out if on our experience age <45 years at diagnosis is a risk factor for recurrence.

Materials and Methods

This retrospective monoinstitutional study uses data from patient files, and from the electronic database of Pathology and Surgery Departments of IOCN (FileMaker® format). All cases were diagnosed between 1999 and 2010 in our institution, having a minimum of 24 months follow-up period. Surgical treatment and pathologic report were done in IOCN. Some of the RT or hormonal treatments were done outside IOCN but were selected only cases with treatment history available. Also, only cases with IOCN diagnosed recurrences were included in study.

Patient selection

Inclusion criteria:

- DCIS diagnosis established in IOCN and first treatment in IOCN between 1999–2010;
- Absence of any previous oncological treatment.

Exclusion criteria:

- Absence of a minimal 24 months follow-up period.

The study included 132 cases diagnosed and treated in IOCN between 1999 and 2010. All cases had a minimum of 24 months period of follow-up.

Studied parameters

Age at diagnosis, nuclear grade, histological grade, architectural type, microinvasion, necrosis, estrogen and progesterone receptor status, type of definitive surgical procedure, resection margins status, fulfill of RT and hormonal treatments where necessary, existence (and date of diagnosis) of a recurrence, type of recurrence, disease free survival period and follow-up period were studied for each case.

For some of the missing results for the estrogen and progesterone receptors tests were done where sufficient tumor sample was available. Unfortunately, for 25 cases there was no sufficient material for tests, so only 107 cases have complete estrogen and progesterone receptors reports and analyses of data regarding them were reported to 107 cases.

There were five cases with no specification of initial resection margins status because these cases were primary mastectomies after diagnosis (core or surgical incision biopsy).

Statistical data analyses were done using SPSS® software. Statistics tests (frequency for ordinal variables, descriptive – minimum, maximum, mean, standard deviation) for scale variables and cross tabs with Pearson's *chi*-square test and Fisher's exact test to analyze the correlations between variables were done. Correlations were considered statistical significant (S) for p-value <0.05.

Results

The mean follow-up period was 62.99 months with limits between 24 and 153 months, standard deviation 29.285.

There were 13 recurrences in the 132 cases series with which occurred after disease-free survival intervals ranging from 13 to 96 months with a mean value of 39.38 months and standard deviation of 23.01 months.

Recurrences trend to group in two patterns. Eight of the 13 recurrences occurred in the first 36 months (three years) of follow-up. On the other hand, the remaining five recurrences occurred distributed at 39, 56, 60, 60 and 96 months of follow-up rising the question if there is a factor which stratifies them.

There were eight local recurrences (ipsilateral breast recurrences) and five contralateral breast recurrences. Eight of the recurrences were IBCs (five ipsilateral and three contralateral breast) and five were DCISs (three ipsilateral and two contralateral breast).

First, the age at diagnosis and the pathologic tumor features were tested for correlation with either local or overall recurrence.

Table 1 shows the cross tabs of the variables studied and the results of Pearson's *chi*-square test and Fisher's exact test for the overall recurrence and Table 2 presents the same characteristics for the local recurrence.

The Fisher's exact t-test was computed only for 2×2 tables; where the tested variable had more than two categories only Pearson's *chi*-square test was computed.

Than for the group of BCS, resection margins status was tested for correlation with either local or overall recurrence also showed (individualized) at the end of Tables 1 and 2.

Given the strong correlation found between age at diagnosis and overall-recurrence, tries were carried out to find if there are statistic significant differences in distribution of pathological features of the tumors for under and over 45-year-old women. No statistical significant difference was observed.

Table 1 – ***Overall recurrence correlations***

		Overall recurrence			Pearson's *chi*-square / Fisher's test significance Two-sided / One-sided
		No	*Yes*	*Total*	
Age [years]	*<45*	32	8	40	.01 (S)
	>45	87	5	92	.021 (S)
	Total	119	13	132	.014 (S)
Nuclear grade	*Non-high*	78	7	85	.403
	High	41	6	47	.543
	Total	119	13	132	.292
Histological grade	*G1*	45	4	49	.556
	G2	28	2	30	–
	G3	46	7	53	–
	Total	119	13	132	
Architectural type	*Non-comedo*	78	6	84	.168
	Comedo	41	7	48	.225
	Total	119	13	132	.141
Micro-invasion	*Absent*	89	10	99	.866
	Present	30	3	33	1.000
	Total	119	13	132	.584
Necrosis	*Absent*	58	2	60	.022 (S)
	Present	61	11	72	.037 (S)
	Total	119	13	132	.020 (S)
ER	*Absent*	32	2	34	.176
	Present	62	11	73	.219
	Total	94	13	107	.149
PR	*Absent*	41	3	44	.158
	Present	53	10	63	.231
	Total	94	13	107	.133
Surgical procedure	*BCS*	44	8	52	.085
	Mastectomy	75	5	83	.133
	Total	119	13	132	.079
	Only for BCS				
Resection margins status [mm]	*<2*	9	6	15	.005 (S)
	2–10	17	2	19	–
	>10	18	0	18	–
	Total	44	8	52	
Resection margins status 1 [mm]	*0–2*	9	6	15	.002 (S)
	≥2	35	2	37	.005 (S)
	Total	44	8	52	.005 (S)

Finally, starting from the observation that recurrences trend to group in two distinctive patterns based on the disease-free survival period, the recurrences were split in two groups: recurrence in the first 36 months of follow-up or recurrences at more than 36 months of follow-up. Just looking at the table it was obvious that nuclear grade is the factor which stratifies them but tests were done for all pathologic features of the tumor. Only the nuclear grade had statistic significance. Table 3

presents these results for nuclear grade correlation with recurrence pattern.

Table 2 – ***Local recurrence correlations***

		Local recurrence			Pearson's *chi*-square / Fisher's test significance Two-sided / One-sided
		No	*Yes*	*Total*	
Age [years]	*<45*	36	4	40	.211
	>45	88	4	92	.244
	Total	124	8	132	.193
Nuclear grade	*Non-high*	80	5	85	.908
	High	44	3	47	1.00
	Total	124	8	132	.591
Histological grade	*G1*	46	3	49	.742
	G2	29	1	30	–
	G3	49	4	53	–
	Total	124	8	132	
Architectural type	*Non-comedo*	80	4	84	.408
	Comedo	44	4	48	.461
	Total	124	8	132	.319
Micro-invasion	*Absent*	92	7	99	.400
	Present	32	1	33	.679
	Total	124	8	132	.360
Necrosis	*Absent*	59	0	59	.009 (S)
	Present	65	8	73	.007 (S)
	Total	124	13	132	.007 (S)
ER	*Absent*	33	1	34	.223
	Present	66	7	73	.43
	Total	99	8	107	.211
PR	*Absent*	42	2	44	.335
	Present	57	6	63	.466
	Total	99	8	107	.284
Surgical procedure	*BCS*	45	7	52	.004 (S)
	Mastectomy	75	1	83	.006 (S)
	Total	119	8	132	.006 (S)
	Only for BCS				
Resection margins status [mm]	*<2*	10	5	15	.018 (S)
	2–10	17	2	19	–
	>10	18	0	18	–
	Total	44	8	52	
Resection margins status 1 [mm]	*0–2*	10	5	15	.008 (S)
	≥2	35	2	37	.016 (S)
	Total	45	7	52	.016 (S)

Table 3 – ***Recurrence pattern (<36 months or >36 months) in correlation with pathologic features of the tumor***

		Recurrence pattern			Pearson's *chi*-square / Fisher's test significance Two-sided / One-sided
		<36 months	*>36 months*	*Total*	
Nuclear grade	*Non-high*	2	5	7	.008
	High	6	0	6	.021
	Total	8	5	13	.016
All other variables tests showed no significant correlation.					

Discussion

Age

Younger age at diagnosis is known to be an adverse prognostic factor for DCIS recurrence although diverse studies use different age grouping schedules. Perhaps the most known is the VNPI [4], which stratifies patients in three groups, <40 years, 40–60 years and >60 years with worsening prognostic in this order. The much newer nomogram published by Rudloff R *et al.* [3] also considers age in assessing recurrence risk after DCIS treatment. Cutuli B *et al.* [5] also finds, on French centers experience, age <40 years at diagnosis as being a risk factor for recurrence for patients treated with BCS and RT. Meijnen P *et al.* also finds on a Dutch survey that age <40 years at diagnosis is a risk factor for DCIS recurrence [6]. Other studies use 50 years as cut-off age [2]. There are also three studies, one of Vargas C *et al.* [7] and two of Vicini FA *et al.* [8, 9] who have found age <45 years at diagnosis as being risk factor for DCIS recurrence. The *EORTC Breast Cancer Cooperative Group* also found young age at diagnosis as being a risk factor for DCIS recurrence [10].

In the present study, age proved to be correlated with overall recurrences, age <45 years at diagnosis being a risk factor for overall recurrence. It is very possible that on larger series, it may be correlated even with local recurrence but in present series, there are only 52 BCSs. Even so, local recurrence was 2.(4) folds more frequent in <45-year-old women than in >45-year-old women.

On the other side, in the present study, local recurrence had similar rate to the opposite breast recurrence (four cases each) in <45-year-old group, recurrences which occurred at more than 12 months and not to six months after the initial treatment and which were diagnosed as new clinical and imagistic lesions not preexisting ones. This raises the question if young age at diagnosis correlates with other patient features (genetic) the risk for DCIS being in fact for both breasts especially since no tumor feature was found to be statistical significant correlate with age at diagnosis.

Such a conclusion may have important therapeutic implications because if larger studies can prove it, this means that for <45-year-old patients, mastectomy (which in Europe is in trend to be indicated in such cases [5, 6]) may be to much or worse not enough, requiring bilateral mastectomy for selected patients.

Necrosis

The only tumor feature that showed statistical significant correlation with both local and overall recurrence was the presence of the necrosis. It has to be mentioned that all types of necrosis were counted not only comedo-necrosis. These findings are concurrent with literature data. One of the newest meta-analysis, that one of Wang SY *et al.* (2011) showed necrosis to be highly correlated with recurrence of DCIS [11]. Also, other studies, both on American [12] or European series, showed this association [13, 14].

Nuclear grade

In the present study, the nuclear grade of the tumor did not correlate neither with overall recurrence nor with local recurrence. Even the literature data is inconsistent on this aspect. According to Virnig BA *et al.* (2010) meta-analysis [2], only one study showed statistical significant correlation between nuclear grade and any (overall) recurrence [15] meanwhile other studies failed to show

this correlation [16, 17] or correlation between contralateral recurrence and nuclear grade [18, 19].

The most important finding of the present study in what regards the nuclear grade is that it is not a risk factor for recurrence but it stratifies the recurrences by the disease free survival. As shown in Table 3, high-grade lesions recur quicker than non-high grade lesions. This may be an explanation for inconsistency of the data regarding the relation between nuclear grade and recurrence. As closer the mean follow-up period of a study will be to 36 months as bigger the influence of high nuclear grade on recurrence will be. Practically, in this study, six of the eight recurrences in the first 36 months were from high nuclear grade lesions meanwhile after 36 months of follow-up all five recurrences were from non-high-grade lesions.

To validate this finding on multivariate analysis, there is a need for much larger study but if this finding is true it may also have importance in decision making of the treatment especially for younger women for which even delayed DCIS-related events are likely to validate and in whom differences between normal resting mammary tissue and DCIS seems to be greater [23] but not only for them [20, 21].

No other tumor pathologic feature showed significant correlation with recurrence.

Resection margins status

Initially, the 52 cases treated with BCS were grouped in two subgroups: positive or <2 mm margins and >2 mm margins. Then, the 52 cases were grouped in three subgroups according to the resection margin status, as follows:

- Margin positive or <2 mm;
- Margin between 2 and 10 mm;
- Margin >10 mm.

For both variants, the positive or <2 mm margin status showed significant higher overall and local recurrence rates over than 2 mm margins (Tables 1 and 2). In the last variant no recurrence occurred for the 20 cases with margins larger than 10 mm even with six cases which had no adjuvant RT (no indication for RT according to VNPI) [22].

Intensively studied in the literature, the only one surgeon-dependent risk factor proven to correlate with DCIS recurrence in BCS treated patients [2, 3, 21] also showed significant in this study.

Surgical treatment

In this study were included 80 cases of mastectomies (60.606% from the 132 cases of the series) and 52 cases of BCS 39.393% from the 132 cases of the series). Although the percent of mastectomies may be seeming high (and it is) the trend of the last years was to favor the BCS. Besides, there are two important objective reasons for which the rate of mastectomies is still high:

- There were only a few mammographic detected lesions and the big majority of the cases were symptomatic at diagnosis – palpable breast mass or bloody nipple discharge;
- Part of mastectomies were patient's choice. The patients were well informed but they asked for mastectomy (cancerophobia seems pandemic not only "west-emic"; but certainly there is also a role of the surgeon's belief and communication method.

The VNPI [22] was used in the studied period and mentioned on pathologic reports. Unfortunately, the attempt to find out if it is validated by the outcomes failed due to the "on demand" mastectomies.

Under these circumstances of course the mastectomy highly correlated with a reduced risk of local recurrence (seven of the 52 BCS recurred meanwhile only one of the 80 mastectomies recurred, Pearson's *chi*-square test significance two-sided = 0.004; Fisher's exact test significance two-sided = 0.06), maybe also because of avoidance of residual tumor [24]. Even in these circumstances, the overall recurrence rate did not statistical significant differ between BCS and mastectomy (it was on trend but not significant; Pearson's *chi*-square test significance 0.08; Fisher's exact test significance 0.133, both two-sided).

More important is the influence of RT on recurrence in the BCS group. Thirty-five of the 52 patients have had adjuvant RT. As expected [10, 21] the rate of recurrences was significantly higher for the remaining 17 patients who have not had adjuvant RT (Table 4).

Table 4 – ***Overall recurrence and local recurrence correlation with RT in the BCS group***

		Overall recurrence			Pearson's *chi*-square / Fisher's test significance Two-sided / One-sided
		No	*Yes*	*Total*	
RT	*No*	11	6	17	.006
	Yes	33	2	35	.011
	Total	44	8	52	.011
		Local recurrence			
RT	*No*	12	5	17	.019
	Yes	33	2	35	.031
	Total	45	7	52	.031

Conclusions

According to this study, age <45 years at diagnosis and necrosis correlate with overall recurrence. Necrosis also correlates with local recurrence. Resection margins status correlates with both overall and local recurrence (positive or <2 mm margins having higher rates of recurrence). Nuclear grade stratifies the disease-free survival period, high-grade DCISs recurring quicker than non-high-grade DCISs. Adjuvant RT for BCS treated patients significantly reduces the risk of both overall and local recurrence. Future studies are needed to address possible therapeutic implications of higher non-ipsilateral recurrence rate in <45 years at diagnosis age group.

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