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CLASSICAL PROGNOSTIC FACTORS FOR SURVIVAL AND LOCO-REGIONAL CONTROL IN BREAST CANCER PATIENTS TREATED WITH RADICAL MASTECTOMY ALONE

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A retrospective analysis of clinical and pathological prognostic factors was performed in 1 068 breast cancer patients treated with radical mastectomy alone in 1952–1980. Three endpoints were considered: 10-year survival, 10-year disease-free survival and 10-year loco-regional relapse-free survival. Both univariate and multivariate analyses confirmed the prognostic significance of tumour size, histological type and grade (Bloom classification) and involvement of axillary nodes for all three endpoints. Additionally, young age appeared to be a significant risk factor for loco-regional disease-free survival. Prognostic subgroups were defined by the use of 3 main indicators. In node negative patients with T1 tumours the prognosis seemed to be good regardless of histological grade (80–90% 10-year disease-free survival), in T2 tumours the survival was significantly dependent on histological type and grade. In node positive patients increasing number of involved nodes and higher histological grade had an independent adverse effect on all three endpoints. The study demonstrates that classical, commonly available prognostic factors clearly distinguish subgroups with different prognosis, which may be helpful when deciding on the use of adjuvant local and/or systemic therapies.

The purpose of studying prognostic factors in breast cancer is to identify patients who are at high risk of relapse and should be offered adjuvant loco-regional and/or systemic therapy. The classical prognostic factors in breast cancer are: tumour size, involvement of axillary lymph nodes and histological type and grade. In recent literature there is an abundance of reports discussing the significance of new prognostic indicators (DNA content, S-phase fraction, oncogen amplification or overexpression, cathepsin D, etc.) and their value in addition to the classical ones. Some of these new indicators are very promising, but they are not likely to come soon into routine use, least of all in developing countries. Efforts are therefore continuing to find the best way of using the classical prognostic factors and their combination in management of breast cancer patients.

The aim of the present study was to assess the value of clinical and histological variables for predicting survival and risk of loco-regional recurrence in a large group of patients with operable breast cancer treated in one institution with radical mastectomy alone and followed up for at least 10 years.

Material and Methods

The retrospective analysis was performed in the group of consecutive 1 068 patients with operable breast cancer treated with radical mastectomy between 1952–1980. The mean age of the patients was 54.7 years, with a range from 22 to 82 years. The group included 104 clinical stage I patients, 804 stage II and 160 patients were classified as stage III (UICC TNM 1968). Until 1973, all patients were treated with Halsted mastectomy, but later Patey operation was applied in stage I and II patients. Neither postoperative radiotherapy nor adjuvant systemic treatment was used in these patients. Follow-up examinations were car-

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ried out regularly every 3 months during the first 5 years postoperatively, every 6 months up to 10 years and once a year thereafter. Only 5.5% of patients were lost to follow-up during the 10-year period. For statistical analysis the SAS (Statistical Analysis System) package was used in an IBM computer. For all analyses three endpoints were considered: 10-year survival rate (S), 10-year disease-free survival rate (DFS), and 10-year loco-regional relapse-free survival rate (LRRFS). For S the cancer death was considered as an event, patients known to die from other causes were censored as well as those lost to follow-up who were disease-free at last examination. In DFS either loco-regional failure or distant metastases, whichever appeared first, were taken as an event. In LRRFS analysis all relapses in chest wall and/or regional lymph nodes were taken into account regardless of whether they occurred before, concomitantly with or after distant dissemination.

In univariate analysis these rates were calculated with life-table methods, and compared by the log-rank test. The variables under consideration were: age, menopausal status, localization of primary tumour within the breast, clinical size of tumour, histological type (WHO) and grade (Bloom & Richardson) in ductal cancer, as well as results of histological examination of axillary lymph nodes (number of nodes involved and number of nodes examined). Subsequently multivariate analysis for the same endpoints was carried out with Cox's regression model (1–3).

Additional analysis was performed to demonstrate the influence of prognostic factors on risk of recurrence in the chest wall (local relapse) and in 3 regional localisations (supraclavicular nodes, axilla, parasternal recurrence). To show the interactions between variables, 10-year S, DFS and LRRFS rates were calculated for 8 (T1 and T2) prognostic subgroups in node negative patients, and in 5 subgroups, each with a number of patients exceeding 30, in node positive patients.

Results

In the whole group of 1 068 patients 10-year S was 64.5%, 10-year DFS 53%, and 10-year LRRFS 73.5%. Table 1 shows 10-year S, DFS and LRRFS rates in relation to prognostic variables, and demonstrates the prognostic significance of tumour size, histological type and grade and extent of nodal involvement for all endpoints. Lower DFS and LRRFS rates were found in 15 node positive patients in whom a small number of nodes were examined. Additionally, age appeared to be a significant factor for LRRFS. Table 2 presents results of the multivariate analysis. These results confirmed independent prognostic significance of tumour size, nodal involvement, histological type and grade for all endpoints, and in case of LRRFS the importance of age was also confirmed. More detailed analysis of risk of recurrence, in particular loco-regional areas is presented in Table 3. The incidence of chest wall recurrence was particularly high (26%) in patients with locally advanced T4 tumour, was significantly higher in node positive than in node negative patients and increased by grade. Risk of relapse in supraclavicular nodes was highest (24%) when 4 or more axillary nodes were involved. It also depended on tumour size and grade, and was higher (18%) in women under 35 years of age. Recurrence in the axilla was very rare ($< 1\%$). Significantly higher risk of axillary recurrence was found in patients with T3 tumour (3%) and with 4 or more nodes involved (6%). The incidence of parasternal recurrence was also low, correlated with nodal involvement and was higher in medial/central localization of the tumour. Multiple recurrences (chest wall + regional or multiple regional) occurred more frequently in patients with massive ($\geqslant 4$) nodal involvement (14%) and in patients with high grade tumour.

Table 4 shows the correlation between tumour size and grade in node negative patients. In patients with small tumour (T1) the prognosis remained favourable (80–90% 10-year DFS) irrespective of histology, although one should notice that high grade tumours (Bloom III) were infrequent in the T1 category. However, in patients with T2 tumours survival was significantly decreased in subgroups with higher grades (Bloom II & III) in comparison with low grade (Bloom I) and non-ductal histology. Table 5 shows an example of the interrelations between prognostic variables in node positive patients. Only subgroups with at least 30 patients were taken into account, for which reason only T2 tumours were included. Decreasing survival rates for all endpoints with increasing nodal involvement and grade were demonstrated.

Discussion

Our data confirm the prognostic significance of tumour size, degree of nodal involvement, and tumour grade in breast cancer. The number of metastatic axillary nodes is widely recognized to be the most powerful independent determinant of DFS and S, and has influenced decisions on adjuvant therapies (4–6). It has also been suggested that the number of removed nodes could be of prognostic importance. Mouridsen et al. (7) found that increased number of excised nodes correlated with improved survival in node negative patients treated within the DBCG trials. Wilking et al. (8) have found that, after adjustment for the number of involved nodes, the risk of recurrence and death decreased with an increasing number of nodes removed. Our data in general did not support these findings with exception of the poor survival in a small subgroup (15 patients) of node positive patients in whom no more than 6 nodes were removed.

Compared to survival data, the risk factors for loco-regional failure have been somewhat less well documented in the literature. Data from large clinical trials have pro-

Table 1

10-year survival (S), disease-free survival (DFS) and loco-regional relapse-free survival (LRRFS) in relation to age, menopausal status, localization of primary tumour, tumour size, histological type and grade, number of axillary nodes examined and involved

Variable	Number of patients	10-yr S		10-yr DFS		10-yr LRRFS	
		%	p-value	%	p-value	%	p-value
Age							
≤35	51	55		46		62	
36–50	365	66		57.5		72	
51–65	431	63		63		72.5	
>65	225	65		47		81.5	
			0.47		0.307		0.015
Menopause							
pre	457	66		56		70	
post	593	63		50		76	
			0.56		0.336		0.027
Localisation**							
outer	531	64		52		75.5	
inner/central	535	65		54		72	
			0.21		0.6		0.38
Tumour size							
T1	155	80		77		87.5	
T2	778	63		50.5		72	
T3	63	56		42		74.5	
T4	72	47		30		49.5	
			<0.0001		<0.0001		<0.0001
Histology							
ductal B I	195	81		68.5		85.5	
B II	443	59		45		70	
B III	248	49.5		39.5		61.5	
nonductal	182	80		73.5		84	
			<0.0001		<0.0001		<0.0001
Number of involved nodes****							
0 (negative)	626	77		68		85	
1–3 (positive)	265	54		40		65	
>4 (positive)	173	33		16		40.5	
			<0.0001		<0.0001		<0.0001
Number of examined nodes***							
Histologically negative							
<6	46	76		72		88	
7–12	255	79		67		86	
>13	316	79		68		84	
			0.92		0.79		0.63
Histologically positive							
>6	15	29		6.5		23	
7–12	144	49		31		58	
<13	278	45		32		57	
			0.42		0.003		0.006

* menopausal status unknown in 18 patients,
** localisation unknown in 2 patients,
*** number of nodes examined unknown in 14 patients,
**** number of nodes involved unknown in 4 patients.

vided evidence that status of axillary nodes is the strongest factor influencing the risk of loco-regional recurrence. In patients treated with mastectomy alone within the Manchester trial, the 10-year rates of loco-regional failure were 16% for node negative and 41.5% for node positive patients (9); the respective rates in the Stockholm trial were 23% and 48% (10). The influence of nodal involvement, tumour size and skin infiltration on the risk of chest wall recurrence has also been reported in retrospective studies (11–15). Data on importance of histologic type or

Table 2

Multivariate analysis for survival (S), disease-free survival (DFS) and loco-regional relpase-free survival (LRRFS) in 1 068 patients treated with mastectomy alone

Variable	S		DFS		LRRFS	
	p-value	RR	p-value	RR	p-value	RR
Age, years						
36–35	0.17	0.72	0.14	0.73	0.17	0.7
51–65	0.30	0.78	0.34	0.82	0.09	0.65
>65	0.12	0.66	0.19	0.74	0.0005	0.36
Tumour size						
T2	0.15	1.34	0.0026	1.75	0.02	1.71
T3	0.006	2.19	0.0004	2.46	0.04	2.07
T4	0.0005	2.68	0.0001	3.70	0.0003	3.27
Nodal involvement						
N positive 1–3	<0.0001	2.15	<0.0001	2.21	<0.0001	2.69
N positive ⩾4	<0.0001	4.26	<0.0001	4.29	<0.0001	5.27
Histology						
Bloom II	<0.0001	2.32	<0.0001	1.89	0.001	2.00
Bloom III	<0.0001	4.26	<0.0001	2.81	<0.0001	3.18
nonductal	0.14	1.48	0.33	1.23	0.028	1.83

RR (relative risk) = 1 for age ⩽35, T1, N negative, histology Bloom I.

Table 3

Relapse-free survival in local and regional localization in relation to age, menopausal status, primary tumour localization, tumour size, nodal involvement and histology

Variable	No. of patients	Chest wall		Supraclavicular		Axillary		Parasternal		Multiple	
		%RFS	p-value	%RFS	p-value	%RFS	p-value	%RFS	p-value	%RFS	p-value
Age											
⩽35	51	88		82		100		92		96	
36–50	361	90		90		99.6		96		94	
51–65	431	87		92		99		97		96	
>65	225	92	0.35	95	0.014	99	0.62	97	0.39	98	0.18
Menopause											
No	457	89		89		99.5		97		94	
Yes	593	89	0.55	94	0.001	99	0.53	96	0.89	97	0.015
Localization											
outer	531	89		91		99.5		98		97	
inner	535	89	0.89	92	0.46	99	0.44	95	0.009	95	0.24
Tumour											
T1	155	94		98		99		99.9		97	
T2	778	89		91		99		96		96	
T3	63	92		87		97		98		98	
T4	72	74	0.0014	87	0.018	100	0.15	89	0.43	96	0.87
Axillary nodes											
N negative	626	93		96		99.7		97		99	
N positive 1–3	265	83		91		100		95		95	
N positive ⩾4	173	81	<0.0001	76	<0.0001	94	0.004	95	0.015	86	<0.0001
Histology											
Bloom I	195	93		96		99.7		97		99.9	
Bloom II	443	88		90		99		97		95	
Bloom III	248	86		88		99		92		93	
nonductal	182	92	0.044	95	0.013	100	0.64	98	0.077	98	0.003

Table 4

Prognostic subgroups in node negative patients

Prognostic subgroup	Number of patients	10-yr S %	10-yr DFS %	10-yr LRRFS %
T1				
Bloom I	30	96	89	93
Bloom II	42	86	82	95
Bloom III	8	87	87	87
nonductal	41	90	90	96
		$p = 0.6$	$p = 0.8$	$p = 0.6$
T2				
Bloom I	80	92	84	92
Bloom II	164	72	58	79
Bloom III	110	65	53	77
nonductal	86	86	76	89
		$p < 0.0001$	$p < 0.0001$	$p = 0.018$

Table 5

Prognostic subgroups in node positive patients

Prognostic subgroup	Number of patients	10-yr S %	10-yr DFS %	10-yr LRRFS %
T2, N positive 1–3 Bloom I	39	73	57	73
T2, N positive 1–3 Bloom II	104	50	36	71
T2, N positive 1–3 Bloom III	52	42	33	49
T2, N positive $\geqslant 4$ Bloom II	63	41.5	15	37
T2, N positive $\geqslant 4$ Bloom III	37	24	8	30

grade are scarce, but increased incidence of loco-regional relapses in patients with undifferentiated cancer or high grade was reported by Donegan et al. (16) and Tubiana & Sarrazin (17). Our study provided more detailed analysis of risk factors for local and regional recurrences. The most significant factor appeared to be the status of axillary nodes, which strongly influenced failure risk in chest wall and all regional sites. Tumour size was particularly important in relation to chest wall relapses, and histological grade was associated with increased risk of both chest wall and supraclavicular recurrences (Table 3). LRRFS was significantly lower in young patients, which was related to an excess of supraclavicular node metastases (Tables 1 and 3). The higher incidence of parasternal recurrences in inner or central tumours was probably consistent with the higher risk of internal mammary node involvement in this localisation.

Our results show that in patients with a combination of high risk factors the incidence of loco-regional failure may indeed be very high (Table 5). Postoperative radiotherapy is probably indicated in these patients, since results of recent trials have shown that adjuvant systemic treatment does not satisfactorily reduce the rate of LR relapse (18–21). The present study, as well as many others, confirms the independent prognostic significance of tumour size, histologic grade and status of axillary nodes.

Many attempts have been made to assess simultaneous influence of three main prognostic indicators in order to estimate as precisely as possible the risk of relapse in individual patients. Well known is a prognostic index worked out in Nottingham, which makes it possible to separate several subgroups of patients with distinctly different survival rates (22, 23). The Nottingham model includes 'stage', (level of nodal involvement) instead of number of nodes involved, in addition to tumour size and grade (Bloom classification). This index may therefore underestimate the prognostic significance of number of nodes involved and also, in view of Scandinavian reports, the number of resected nodes (7, 8).

Joensuu & Toikkanen (24) identified subgroups with favourable prognosis among 311 breast cancer patients. Although they analysed 16 variables and many of them

were significant in univariate analysis (including S-phase fraction, progesterone receptor, DNA index and ploidy, tumour necrosis) only 3 classical factors (size, grade, nodal status) appeared to be significant in multivariate analysis. In our analysis, the simultaneous use of 3 prognostic factors made it possible to define many subgroups with distinctly different prognosis (Table 5).

Special attention has been paid to node negative breast cancer in recent years due to controversy regarding the use of systemic adjuvant therapy. Although many newly developed prognostic indicators have been investigated, only the relative influence of tumour grade and size will be discussed here. As far as tumour size is concerned, Rosen et al. (25) found excellent prognosis (89% 20-year DFS) in node negative patients with tumours of 1 cm or less (T1a, b); for tumours between 1 and 2 cm (T1c) the rate was 77% and for T2 tumour only 68%. Joensuu & Toikkanen (26) reported 98% 5-year survival rate in pT1a and b breast cancer. On the other hand Fisher et al. did not observe a prognostic significance of tumour size (0–2 cm vs. 2.1–4 cm) in node negative patients treated within the NSABP B-06 protocol. In their experience histological and nuclear grade as well as histological type were the most significant prognostic indicators (27, 28). The prognostic importance of histological and nuclear grading has been confirmed by many other authors but also criticized as being subjective and not reproducible (29–31). Our results have confirmed the prognostic importance of tumour size and histological type and grade in both node negative and node positive patients. Data from Table 4 suggest that the grade is of significant prognostic importance in node negative patients with T2 tumours whereas in T1 tumours the prognosis seems to be good regardless of histological grade. Data in Table 5 show that in node positive, T2 patients increasing number of involved nodes and higher histological grade bore an independent adverse relation to the prognosis. In patients with 4 or more nodes involved and grade III the survival was extremely poor.

In conclusion, our results confirm the great clinical value of classical prognostic factors in breast cancer. The multivariate analysis was useful in defining prognostic subgroups with different risk of death and loco-regional failure. This can be of help when deciding on the use of adjuvant loco-regional and/or systemic therapy.

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