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Infiltrating Lobular Carcinoma of the Breast: Response to Endocrine Therapy and Survival

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Abstract—*The records of* 480 *patients who received systemic therapy for advanced breast cancer in the University Hospital of South Manchester from* 1975 *to* 1983 *were examined. There were* 264 *with infiltrating duct carcinomas (IDC) and* 33 *with infiltrating lobular carcinomas (ILC) for whom the response to endocrine therapy was known. There were* 92 *responses* (35%) *among the IDC patients and* 9 (27%) *among the ILC patients. Sixty-seven per cent of IDC patients tested had steroid hormone receptor positive tumours compared to* 90% *for ILC* ($P < 0.001$). *Comparison of survival from diagnosis, disease free interval and survival from relapse showed no significant differences between the two groups. Thus despite almost all ILC patients having hormone receptor positive tumours their survival was similar to that of IDC patients. This appears to be due to a lower than expected response rate to endocrine therapy. This is a further indication of the different biological characteristics of these two histological sub-types of breast carcinoma.*

INTRODUCTION

PATIENTS with carcinoma of the breast whose tumours are steroid hormone receptor positive have been shown to survive significantly longer than those whose tumours are receptor negative [1–3]. Moreover it appears that this improvement in survival is not due to a decreased probability of relapse but is a reflection of the greater chance of response to endocrine therapy following recurrence [4]. A higher proportion of infiltrating lobular carcinomas (ILC) are receptor positive compared to the commoner infiltrating duct carcinomas (IDC) [5–7] and might therefore be expected to have higher response rates to endocrine therapy and correspondingly improved survival. In this paper we compare the patient characteristics, response to endocrine therapy and survival for patients with ILC and IDC who have either relapsed following primary treatment or who presented with advanced disease.

PATIENTS AND METHODS

Four hundred and eighty patients who had received systemic therapy for advanced breast carcinoma were studied. These were all such patients with lobular or duct carcinomas seen at the University of South Manchester between December 1975 and December 1985. In 384 cases (80%) endocrine therapy was the initial systemic treatment used.

Seventy-five IDC patients (22%) and 12 ILC patients (26%) were not evaluable for response. The major reasons for this were insufficient data and disease that could not be measured accurately.

All local recurrences were confirmed histologically but dated from the time of first appearance. Bone disease was assessed by X-ray changes rather than isotope scan appearances and pleural effusions had to be cytologically confirmed. Abnormal LFTs had to be accompanied by characteristic isotope or ultrasound appearances to be accepted as evidence of liver disease. Isolated local recurrences were usually treated by excision or radiotherapy or both, with no systemic treatment until a second relapse occurred. Following relapse all patients had a trial of endocrine therapy regardless of receptor status unless life threatening disease dictated the urgent use of chemotherapy. First line endocrine therapy was either with tamoxifen or ovarian ablation by oophorectomy or radiotherapy (1000 rads). Response was assessed using standard U.I.C.C. criteria [8].

Steroid hormone reeptor assays were by the dextran-coated charcoal method as previously described [9]. The lower limits of receptor concentrations accepted as positive were 5 fmol/mg for oestrogen and 5 fmol/mg for progesterone.

Statistical analysis of survival was by the log-

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Table 1. Patient characteristics

Characteristics		IDC	ILC	P
Total		264 (89%)	33 (11%)	NS*
Post surgery XRT		31 (12%)	5 (15%)	NS
Menopausal status:	pre	50 (19%)	11 (33%)	NS
(at relapse)	peri	21 (8%)	2 (6%)	NS
	post	193 (73%)	20 (61%)	NS
Dominant site:	bone	150 (57%)	22 (67%)	NS
	soft tissue	50 (19%)	6 (18%)	NS
	lung/pleura	48 (18%)	4 (12%)	NS
	liver	16 (6%)	1 (3%)	NS
Patients with three or more metastatic sites		66 (25%)	14 (42%)	$P < 0.02$
Age at relapse (mean)		62.0	56.0	
Receptors:	ER+ PR+	62 (43%)	12 (60%)	
	ER+ PR−	31 (22%)	3 (15%)	
	ER− PR+	4 (3%)	3 (15%)	
	ER− PR−	47 (33%)	0 —	$P < 0.001$
Endocrine therapy:	tamoxifen	235 (89%)	25 (76%)	NS
	oophorectomy	18 (7%)	8 (24%)	$P < 0.01$
	X-ray menopause	11 (4%)	—	
		Median (range)	Median (range)	
Survival from diagnosis (months)		50 (2–247+)	46 (2–146)	NS
Disease free interval		16 (0–135)	10 (0–114)	NS
Survival from relapse		28 (2–141+)	25 (2–118)	NS

*NS = Not significant.

rank method [10] and comparison of patient subgroups by the chi-squared test for contingency tables or the Mann–Whitney U test depending on the skewness of the distribution.

RESULTS

There were 297 patients in whom the response to endocrine therapy was known, 264 with infiltrating duct carcinoma and 33 with infiltrating lobular carcinoma. Patient characteristics are shown in Table 1. The only significant differences between the two groups were the proportions with receptor positive tumours and the numbers with three or more sites of involvement at relapse.

Sixty-seven per cent of patients with IDC who had steroid hormone receptors measured were positive compared to 90% of ILC patients. This difference was statistically significant ($P < 0.001$). Among these patients there was a somewhat higher proportion of those with infiltrating lobular carcinoma who were pre-menopausal and this was reflected in a significantly higher rate of oophorectomy as the primary endocrine therapy.

The other major difference between the two groups was in the number of metastatic sites at the time of commencing endocrine therapy. In the IDC group 66 patients (25%) had three or more sites of disease compared to 14 (42%) in the ILC group, $P < 0.02$.

Among the patients with receptor positive tumours there was no statistical difference in the absolute level of oestrogen or progesterone receptor between the ILC and IDC patients.

Table 2. Response to endocrine therapy

	IDC	ILC
CR	38 (14%)	4 (12%)
PR	54 (20%)	5 (15%)
Static (6 months+)	45 (17%)	7 (21%)
Progression	127 (48%)	17 (51%)

The overall response rate to endocrine therapy was 34%. There were 92 responses (CR + PR) among the IDC patients and 9 in the ILC group giving response rates of 35 and 27%, respectively (Table 2). This difference was not statistically significant. The median duration of response was 19 months (range 4–75) for IDC and 12.5 months (range 6–26) for ILC ($P > 0.05$).

Comparison of the disease free survival, time to progression and overall survival showed no difference between the IDC and ILC patients (Fig. 1).

DISCUSSION

Several studies have demonstrated an overall survival advantage for patients with oestrogen receptor (ERP) positive tumours [1–3] and in some cases this has been shown to be due to improved survival after relapse [3, 11, 12]. Moreover it appears that this survival advantage following

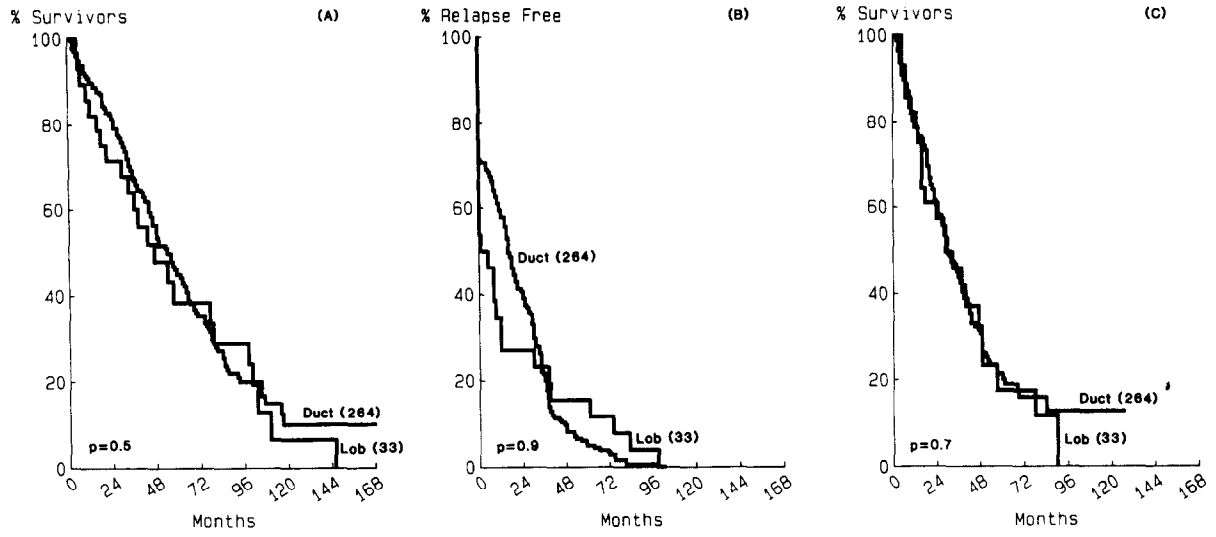

Fig. 1. Comparison of survival from diagnosis (A), disease free interval (B) and survival from relapse (C) for patients with infiltrating lobular carcinoma (Lob) and infiltrating duct carcinoma (Duct) for whom response to endocrine therapy is known.

relapse is related to response to endocrine therapy [4].

In unselected patients a response rate of the order of 30% can be expected to endocrine therapy [13–16] but the presence of ERP predicts for a response in up to 50% of cases [13–21]. In most series 60–70% of IDC carcinomas are ERP positive while approx. 90% of ILC tumours are ERP positive [2–4].

In the present study 67% of IDC and 90% of ILC tumours were receptor positive and the overall response rate to endocrine therapy was 34%. Among the 264 IDC patients there were 101 responses (35%) indicating a response rate of 50–60% in receptor positive tumours results in keeping with previous reports [13, 17–21]. However a different picture emerges with ILC. Despite over 90% of tumours being receptor positive the response rate to endocrine therapy was only 27%. In addition there was a trend for the duration of response to endocrine therapy to be shorter for patients with ILC. Thus it appears that the survival of ILC patients is not superior to that of IDC patients because of a lower than expected response rate to endocrine therapy and a short duration of response.

Why do patients with ILC have such a poor response rate to endocrine therapy? It is recognized that the level of hormone receptor can influence response to therapy [22] but in this series there was no difference in the levels between the ILC and IDC tumours (Table 1). Moreover there was no increase in the ILC patients of unfavourable visceral sites of disease which are known to have low levels of receptors and therefore a poor response rate to endocrine treatment [23]. The only difference between the two groups at the start of endocrine therapy that may account for the poor response rate is the extent of disease. Significantly more ILC patients had three or more sites of involvement at this time indicating a greater tumour burden with consequently increased chance of primary resistance [24]. The more rapid overgrowth of these resistant lines would also explain the shorter duration of response in these patients.

It has been shown that although the primary presentation and 'surgical curability' of IDC and ILC are similar [1], their behaviour following relapse is markedly different. ILC shows a particular propensity to infiltrate diffusely through skin and along serosal surfaces notably the peritoneum and meninges [25, 26] while IDC remains confined to the classical metastatic sites of bone, lung, skin, liver and brain. It is likely that this unusual metastatic pattern and the relative insensitivity to endocrine therapy are due to differences in cell surface structure and function in this type of tumour.

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