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Prognostic value of lymphovascular invasion in women with lymph node negative invasive breast carcinoma

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ABSTRACT

This study aimed to test the hypothesis that lymphovascular invasion adds prognostic information to histological grade and tumour size in node-negative invasive carcinoma of the breast. Lymphovascular invasion was assessed in haematoxylin and eosin tumour sections from 2760 patients with node-negative invasive breast carcinoma treated with definitive surgery. Patients were divided into two groups: 990 in the no adjuvant therapy series (diagnosed in 1974–1988) with median follow-up of 13 years; and 1765 in the selective adjuvant therapy series (1988–2000) with median follow-up of 6.8 years. Lymphovascular invasion was identified in 19% of tumours and was associated with larger tumour size, higher histological grade and younger age. Overall, survival was associated on multivariate analysis with lymphovascular invasion, histological grade and tumour size in both patient series, and with histological type in the no adjuvant therapy series. In conclusion, lymphovascular invasion is an independent prognostic factor in node-negative breast cancer and should be considered in decisions about adjuvant treatment in this group of women.

1. Introduction

Axillary lymph node stage is an important prognostic factor in invasive carcinoma of the breast. The prognosis progressively worsens with increasing number of involved nodes. However, with long-term follow-up, at least 30% of node-negative patients develop distant metastases and die of breast cancer. This has prompted the search for prognostic factors in node-negative women. One approach has been to search for nodal metastases missed by conventional haematoxylin and eosin sections of the nodes; but such occult metastases do not appear to be an independent prognostic factor [1]. Furthermore, the frequency of lymph node positivity has declined following the introduction of mammographic screening for breast cancer and greater awareness leading to earlier presentation.

Histological grade and tumour size are the other pathological prognostic factors in invasive carcinoma of the breast with most evidence to support them; both of these factors are of independent prognostic value in women with node-negative tumours [2–4]. When used in combination, the three strongest prognostic factors in invasive breast cancer (nodal status, histological grade and tumour size) provide more powerful information than any individual factor used alone. The Nottingham Prognostic Index (NPI) [5] uses these three factors, with appropriate weighting for each factor, and has been externally validated by multiple studies [6–9]. The current factors that we use in guiding adjuvant systemic treatment in node-negative patients are the NPI (i.e., histological grade and tumour size) and oestrogen receptor status.

Lymphovascular invasion shows a clear relation with nodal status [2,10] and local recurrence [2,11–13]. It is also related to distant metastasis and overall survival in node-negative breast cancer [11,14,15], but most studies have been small or only used univariate analysis. This study aims to test the hypothesis that lymphovascular invasion adds prognostic

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information to histological grade and tumour size in node-negative invasive carcinoma of the breast.

2. Patients and methods

The study included patients with primary operable invasive breast carcinoma that was clinically less than 5 cm and treated with definitive surgery at Nottingham City Hospital between 1974 and 2000. All the patients were less than 71 years at the time of initial surgery. Some of these patients were included in a previous study of vascular invasion [2].

Tumours were received fresh in the pathology laboratory and incised immediately to ensure good fixation. From 1974 to 1991 the standard axillary procedure was triple node biopsy (sampling of low and high axillary and internal mammary nodes). From 1991, four node axillary sample was the standard procedure; this method has been validated by comparison with axillary clearance [16]. A small proportion of women had axillary clearance. Assessment of axillary nodal status was based on haematoxylin and eosin sections.

Lymphovascular invasion was assessed in the peritumoral tissue on haematoxylin and eosin sections. It was defined as carcinoma cells present within a definite endothelial lined space. Only definite lymphovascular invasion was regarded as positive. Possible lymphovascular invasion was scored as negative. No attempt was made to distinguish between blood vessels and lymphatics.

The Nottingham modification of the Scarff Bloom and Richardson method was used for histological grading [17]. Tumour size was based on macroscopic measurement in the early part of the study and microscopic measurement of the greatest diameter of the invasive carcinoma latterly. Histological type was categorised as described previously [18]. Mucinous [18–20] and tubular carcinoma [18,21] have the strongest evidence of good prognosis. Although the evidence is more limited, invasive cribriform carcinoma appears to have an excellent prognosis [21,22] like the histologically similar tubular carcinoma. These three histological types with a good prognosis were grouped together and compared with all other types. Oestrogen receptor status was assessed using the dextran coated charcoal method (cut-off 10 fmol/mg) or immunohistochemistry (cut-off H score of 10) [23].

The NPI was calculated using the following formula [5]: NPI = histological grade + lymph node stage + (tumour size/cm × 0.2). All tumours in the present series were node-negative and therefore scored 1 for lymph node stage.

For survival analysis, the patients were divided into two series. The first was patients who presented in the period before either adjuvant chemotherapy or endocrine treatment was used in the Nottingham Breast Unit (1974–1988). In the second series, selected patients received adjuvant treatment (1988–2000). Univariate survival analysis was performed using Kaplan–Meier curves and log-rank significance testing. Multivariate analysis of breast cancer related survival and time to distant metastases was performed using Cox's proportional hazards method. The following variables were included in multivariate analysis: lymphovascular invasion, histological grade, tumour size, histological type (mucinous, tubular and cribriform versus other types), oestrogen receptor status, patient age, and whether the patient received adjuvant endocrine treatment or adjuvant chemotherapy. Time to local recurrence has been analysed in previous studies [2,24,25].

3. Results

There were 2760 node-negative patients treated between 1974 and 2000 that satisfied the inclusion criteria. In the no adjuvant therapy series there were 990 patients with median follow-up of 13.0 years (range 0.3–29.9) and 417 breast cancer related deaths. In the selective adjuvant therapy series there were 1765 patients with median follow-up of 6.8 years (range 0–15.4) and 189 breast cancer related deaths. There was a clear relationship between lymphovascular invasion and nodal status in the whole series of 5038 patients with invasive carcinoma treated between 1974 and 2000: lymphovascular invasion was present in 19% of the node-negative tumours and 47% of node-positive tumours. All subsequent results presented relate only to node-negative tumours.

Lymphovascular invasion was associated with increasing tumour size ($\chi^2 = 40$, $P < 0.0001$; Table 1), higher histological grade ($\chi^2 = 55$, $P < 0.0001$), less favourable Nottingham Prognostic Index group ($\chi^2 = 48$, $P < 0.0001$), younger age ($\chi^2 = 32$, $P < 0.0001$), and was less common in tubular, cribriform and mucinous type carcinomas ($\chi^2 = 23$, $P < 0.0001$).

On univariate analysis, lymphovascular invasion was associated with a worse survival in both series of patients (Fig. 1), but the survival was better for patients in the selective adjuvant therapy series. In the no adjuvant therapy series, the 10-year survival was 47.5% for patients with tumours with

Table 1 – Relation of lymphovascular invasion to pathological features and to patient age

Feature	Lymphovascular invasion	
	Absent	Present
Tumour size		
1–10 mm	474	57 (11%)
11–20 mm	1138	261 (19%)
21–30 mm	475	146 (24%)
31–40 mm	108	41 (28%)
>40 mm	45	13 (22%)
Histological grade		
1	583	62 (10%)
2	788	184 (19%)
3	865	271 (24%)
Nottingham Prognostic Index		
Good Prognostic Group (NPI ⩽ 3.40)	1079	173 (14%)
Moderate Prognostic Group 1 (NPI 3.41–4.40)	708	180 (20%)
Moderate Prognostic Group 2 (NPI 4.41–5.40)	447	164 (27%)
Histological type		
Tubular, cribriform, mucinous	213	16 (7%)
Other	2025	502 (20%)
Patient age		
<36 years	86	31 (26%)
36–49 years	626	201 (24%)
50–70 years	1530	286 (16%)

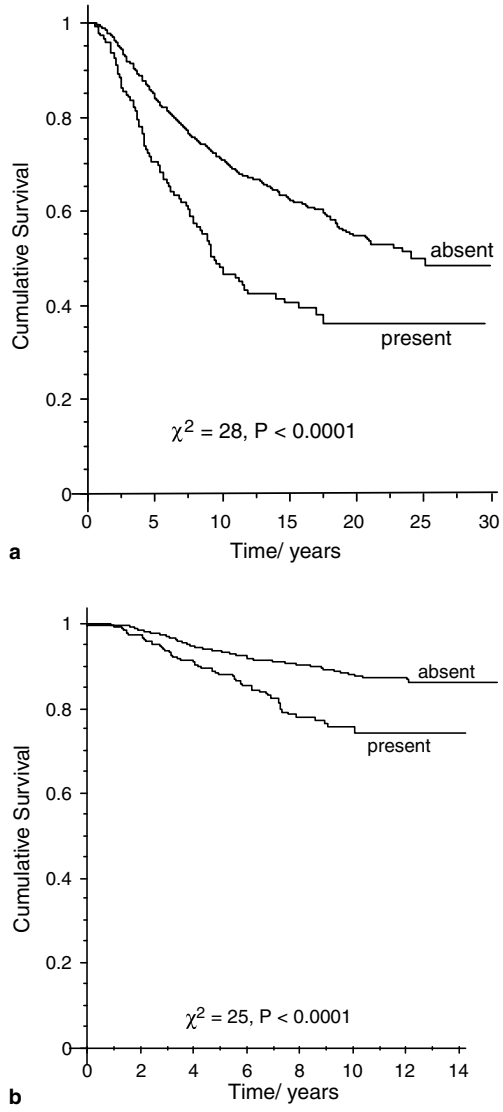

Fig. 1 – Lymphovascular invasion and breast cancer specific survival of women with node-negative operable invasive carcinoma of the breast: (a) no adjuvant therapy group; (b) selective adjuvant therapy group.

lymphovascular invasion and 71.2% for patients with tumours without lymphovascular invasion; the equivalent figures for the selective adjuvant therapy series were 75.8% and 88.0%. Tumours of patients from the selective adjuvant therapy group tended to be smaller ($P < 0.0001$, Mann–Whitney U) and of lower grade ($\chi^2 = 5.6$, $P = 0.06$) and were more often oestrogen receptor positive ($\chi^2 = 81$, $P < 0.0001$), of tubular, cribriform or mucinous histological type ($\chi^2 = 10$, $P = 0.002$) and in the good prognostic group of the Nottingham Prognostic Index ($\chi^2 = 19$, $P < 0.0001$).

In the no adjuvant therapy series, multivariate analysis showed that worse overall survival was associated with larger tumour size, higher histological grade, presence of lymphovascular invasion and histological type other than tubular, cribriform or mucinous (Table 2a). Similar results were obtained for all three methods of entering variables: all included, stepwise forward and stepwise backwards.

Table 2 – Multivariate analysis of breast cancer-related survival in the series of patients with no adjuvant systemic therapy

Factor	Relative risk	(95% Confidence interval)	P value
(a) All survival data included			
Tumour size/cm	1.35	(1.24–1.47)	<0.0001
Histological grade	1.22	(1.06–1.40)	0.004
Lymphovascular invasion	1.64	(1.28–2.09)	<0.0001
Histological type	0.37	(0.19–0.73)	0.004
(b) Only including first 5 years of follow-up			
Tumour size/cm	1.36	(1.20–1.54)	<0.0001
Histological grade	1.80	(1.40–2.30)	<0.0001
Lymphovascular invasion	1.79	(1.27–2.52)	0.001
Histological type	0.24	(0.03–1.49)	0.12

Table 3 – Multivariate analysis of breast cancer-related survival in the series of patients with selective adjuvant systemic therapy (all variables included)

Factor	Relative risk	(95% Confidence interval)	P value
Tumour size/cm	1.46	(1.21–1.77)	<0.0001
Histological grade	2.31	(1.64–3.26)	<0.0001
Lymphovascular invasion	1.66	(1.17–2.35)	0.004
Adjuvant chemotherapy	0.45	(0.25–0.82)	0.009
Adjuvant endocrine treatment	0.65	(0.43–0.98)	0.04
Oestrogen receptor status	0.69	(0.47–1.02)	0.06
Patient age	1.02	(0.998–1.03)	0.07
Histological type	0.56	(0.16–1.87)	0.34

In the selective adjuvant therapy series, multivariate analysis showed a consistent association of overall survival with tumour size, histological grade, vascular invasion and receipt of adjuvant chemotherapy for all three methods of entering variables. Oestrogen receptor status, receipt of adjuvant endocrine treatment and patient age just reached statistical significance in some analyses (Table 3).

In both the no adjuvant therapy and selective adjuvant therapy series the presence of vascular invasion was associated with a relative risk of death of about 1.7 in all three NPI subsets (Table 4). In the selective adjuvant series the proportion of patients receiving adjuvant chemotherapy was 0.1% in the Good Prognostic Group, 11% in Moderate Prognostic Group 1 and 30% in Moderate Prognostic Group 2. The equivalent figures for adjuvant hormone therapy in the three Prognostic Groups are 4%, 55% and 53%.

The relative risk for histological grade was higher in the selective adjuvant therapy series (2.31) than in the no adjuvant therapy series (1.22). Also histological type was an independent prognostic factor in the adjuvant series, but not in the no adjuvant therapy series. A potential explanation of these discrepancies is the longer follow-up and greater statistical power in the no adjuvant therapy series. This hypothesis was tested by analysing only the first 10 years of follow-up (312 deaths) in the no adjuvant therapy series; all follow-up

Table 4 – Overall survival in Nottingham Prognostic Index subsets according to the presence or absence of lymphovascular invasion

Nottingham Prognostic Index Group	5-year survival			10-year survival			Relative risk[a] for LVI positive (95% CI)	Number of deaths
	Whole group (%)	LVI negative (%)	LVI positive (%)	Whole group (%)	LVI negative (%)	LVI positive (%)		
No adjuvant therapy series								
Good Prognostic Group	92.1	93.5	80.0	80.7	82.9	62.4	1.83 (1.07–3.11) P = 0.03	108
Moderate Prognostic Group 1	83.3	84.7	75.1	67.1	69.5	52.8	1.73 (1.15–2.59) P = 0.008	156
Moderate Prognostic Group 2	68.8	71.3	58.6	50.1	54.6	34.4	1.63 (1.13–2.35) P = 0.009	150
Selective adjuvant therapy series								
Good Prognostic Group	97.6	97.8	96.0	92.4	93.2	87.9	1.73 (0.82–3.65) P = 0.15	39
Moderate Prognostic Group 1	90.0	90.6	88.4	78.8	82.8	66.3	1.92 (1.22–3.02) P = 0.004	82
Moderate Prognostic Group 2	82.0	84.0	77.6	73.4	76.0	68.5	1.45 (0.89–2.36) P = 0.14	68

LVI, lymphovascular invasion.
a Based on whole survival curves.

Table 5 – Multivariate analysis of distant metastasis free survival

Factor	Relative risk	(95% Confidence interval)	P value
(a) No adjuvant therapy series			
Tumour size/cm	1.36	(1.25–1.49)	<0.0001
Histological grade	1.26	(1.09–1.47)	0.002
Lymphovascular invasion	1.51	(1.16–1.96)	0.002
Histological type	0.58	(0.31–1.08)	0.08
(b) Selective adjuvant therapy series			
Tumour size/cm	1.42	(1.18–1.70)	0.0002
Histological grade	1.75	(1.34–2.28)	<0.0001
Lymphovascular invasion	2.01	(1.43–2.82)	<0.0001
Adjuvant chemotherapy	0.47	(0.27–0.82)	0.007
Oestrogen receptor status	0.61	(0.42–0.89)	0.01

after 10 years was censored. A similar analysis with a 5 year cut-off was also performed (173 deaths). These analyses showed a higher relative risk for histological grade of 1.53 with only 10 years follow-up and of 1.80 with only 5 years follow-up (see Table 2b). The relative risk for histological type was approximately constant, but it was an independent prognostic factor in the 10 year analysis and not in the 5 year analysis.

There was a consistent relationship between distant metastasis free survival and tumour size, histological grade and vascular invasion in both the no adjuvant therapy and selective adjuvant therapy series (Table 5).

4. Discussion

Lymphovascular invasion was associated with a worse overall survival on univariate analysis consistent with previous studies [10,11,15]. The survival was better in the selective adjuvant therapy series than in the no adjuvant therapy series. Adjuvant systemic treatment was one factor contributing to improved survival. Also the differences in tumour size, grade, histological type and oestrogen receptor status all favoured better prognosis in the selective adjuvant therapy series. Finally, there is a risk of under staging with the triple node sample, which was the standard procedure during the time of the no adjuvant series.

The association of lymphovascular invasion with tumour size, histological grade, histological type and patient age is consistent with previous studies [2,10]. These associations emphasise the importance of multivariate analysis in prognostic studies of lymphovascular invasion.

In multivariate analysis of the no adjuvant therapy series overall survival was associated with tumour size, histological grade, lymphovascular invasion and histological type. In the selective adjuvant therapy series multivariate analysis showed a consistent association of overall survival with tumour size, histological grade, vascular invasion and receipt of adjuvant chemotherapy. Patients in the no adjuvant therapy series received homogeneous treatment. However in the selective adjuvant therapy series there was increasing use of adjuvant chemotherapy, and to a lesser extent of adjuvant endocrine treatment with time. Also with the shorter follow-up and better survival there were fewer deaths in this group and therefore less statistical power. Despite these reservations, lymphovascular invasion was consistently associated with worse survival independent of tumour size and histological grade. Also the relative risk of death associated with lymphovascular invasion was similar in the different NPI groups. The effect of lymphovascular invasion was significant in all the NPI groups in the no adjuvant therapy series, but not in all the groups in the selective adjuvant series. The major reason for this is statistical power: the number of deaths in the selective adjuvant series is less than half that of the no adjuvant therapy series (the relationship of survival with lymphovascular invasion is significant in all groups with at least 80 deaths; Table 4).

Most of the larger studies have shown that vascular invasion is an independent prognostic factor in node-negative breast cancer (Table 6). Some of these studies only included invasive carcinomas of no special type and some distinguished lymphatic and blood vessel invasion. Only one large study (by Fisher and colleagues of 950 patients) has not found

Table 6 – Studies of the relation of lymphovascular invasion and other pathological factors with overall survival on multivariate analysis

Study [Ref.]	Number of patients	Number of deaths	Overall survival multivariate analysis		
			Association	No association	RR for LVI/LI
Clayton (1991)[a][26]	378	111	Size, mitoses, LI, skin/deep fixation		1.7
Lauria (1995)[a] [10]	377	55	Size, LI	Grade	2.26
de Mascarel (1998)[a] [15]	1320	129	Size, grade, LVI	ER	1.65
Millis et al. (2002) [1]	477	153	Size, grade	LVI ($P = 0.07$)	1.5
Present study	990[b]	417	Size, grade, LVI, type	ER	1.6
	1765[c]	189	Size, grade, LVI	Type, ER	1.7

LVI, lymphovascular invasion; LI, lymphatic invasion; ER, oestrogen receptor status, RR, relative risk.
a All tumours of no special type.
b No adjuvant systemic treatment.
c Selective adjuvant systemic treatment.

an association between survival and lymphatic or blood vessel invasion on univariate analysis [27]. In our previous study of 776 patients, lymphovascular invasion was associated with survival on univariate, but not on multivariate analysis; a reflection of the smaller number of patients and shorter follow-up compared with the present study.

A great advantage of lymphovascular invasion as a prognostic factor is that it can be assessed in routinely processed paraffin embedded haematoxylin and eosin sections. Good fixation is essential to avoid retraction artefact, which hampers interpretation. In this study, we incised breast carcinomas immediately on receipt in the laboratory to ensure good fixation. With clear criteria it is possible to achieve good concordance in the diagnosis of lymphovascular invasion [2,28]. We do not believe it is appropriate to try to distinguish lymphatics and blood vessels, but rather to classify the process as lymphovascular invasion, in agreement with UK and USA guidelines [29,30].

In conclusion, this study supports our hypothesis that lymphovascular invasion adds prognostic information to histological grade and tumour size in women with node-negative invasive carcinoma of the breast. It is simple and cheap to determine. We suggest that lymphovascular invasion should be considered in decisions about potential adjuvant treatment in this group of women. Lymphovascular invasion should also be included in addition to histological grade and tumour size in studies of new prognostic factors in node-negative breast cancer.

Conflict of interest statement

None declared.

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