Histopathology 1992, 20, 479–489

Pathological prognostic factors in breast cancer. II. Histological type. Relationship with survival in a large study with long-term follow-up

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Date of submission 6 September 1991
Accepted for publication 9 December 1991

ELLIS I.O., GALEA M., BROUGHTON N., LOCKER A., BLAMEY R.W. & ELSTON C.W.
(1992) *Histopathology* 20, 479–489

Pathological prognostic factors in breast cancer. II. Histological type. Relationship with survival in a large study with long-term follow-up

The histological tumour type determined by current criteria has been investigated in a consecutive series of 1621 women with primary operable breast carcinoma, presenting between 1973 and 1987. All women underwent definitive surgery with node biopsy and none received adjuvant systemic therapy. Special types, tubular, invasive cribriform and mucinous, with a very favourable prognosis can be identified. A common type of tumour recognized by our group and designated tubular mixed carcinoma is shown to be prognostically distinct from carcinomas of no special type; it has a characteristic histological appearance and is the third most common type in this series. Analysis of subtypes of lobular carcinoma confirms differing prognoses. The classical, tubulo-lobular and lobular mixed types are associated with a better prognosis than carcinomas of no special type; this is not so for the solid variant. Tubulo-lobular carcinoma in particular has an extremely good prognosis similar to tumours included in the 'special type' category above. Neither medullary carcinoma nor atypical medullary carcinoma are found to carry a survival advantage over carcinomas of no special type. The results confirm that histological typing of human breast carcinoma can provide useful prognostic information.

Keywords: breast cancer, histological types, prognostic factors

Introduction

The favourable prognosis of certain histological types of invasive carcinoma of the breast is well recognized. Mucinous carcinoma of the breast was the first type identified to have a good prognosis in its pure form[1] and this has been confirmed by other studies[2]. Tubular carcinoma[3,4], invasive cribriform carcinoma[5], medullary carcinoma[6,7], infiltrating lobular carcinoma[8] and tubulo-lobular carcinoma[9] have all been shown subsequently to carry a better prognosis than invasive carcinomas of no special type (ductal NST). Lobular carcinoma has been further sub-categorized into classical, alveolar, mixed and solid subtypes of which classical has the best prognosis and solid lobular the worst[10]. In this study we review histological type according to strictly defined current criteria in a single consecutive series of patients with primary operable breast cancer.

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Materials and methods

SAMPLE POPULATION

The patients in this study presented consecutively with primary operable breast cancer to a single surgical team, under Professor R.W.Blamey, at the City Hospital, Nottingham between 1974 and 1987; a total of 1621 women were included. All women underwent simple mastectomy or lumpectomy with irradiation; adjuvant therapy was not given. A triple lymph node biopsy was also performed on each woman[11] to determine the

lymph node stage. Following primary treatment patients were reviewed at 3-monthly intervals to 18 months, 6-monthly intervals to 5 years and yearly thereafter. Follow-up ranged from a minimum of 3 years to a maximum of 16 years.

DETERMINATION OF HISTOLOGICAL TYPE

For each case a minimum of three sections of carcinoma stained with haematoxylin and eosin (H & E) were examined to determine the histological type. Only the first breast neoplasm of any particular patient was considered (a small number of patients presented at a later date with a second primary tumour of a different histological type). Typing was assessed independently by three observers (I.O.E., N.B. and C.W.E.). Any points of disagreement were resolved by discussion at a conference microscope until all parties were in agreement.

The criteria used to define each histological type are described briefly below.

Invasive carcinoma of no special type (ductal NST group)
This is a group containing those carcinomas which do not satisfy the criteria to be entered into other categories. This is the most common 'type' of invasive breast carcinoma comprising between 50% and 70% of the cancers in previous published series. These tumours are referred to variously as ductal carcinoma, carcinoma of no special type and carcinoma not otherwise specified. The term ductal carcinoma perpetuates the traditional concept that these tumours develop exclusively from mammary duct epithelium and not the intralobular epithelium; this is a view which is no longer so rigidly held. However, the term is commonly used and has been adopted by the W.H.O. For the purposes of this paper we will refer to this tumour group as 'ductal no special type' (ductal NST). The histological variation within the ductal NST group is considerable. The cells may be diffusely arranged or in syncytial sheets; nuclei range from highly pleomorphic to regular; there may be much glandular formation or none at all. For a tumour to be typed as ductal NST it must show that type in over 90% of its mass as judged by examination of representative sections of the tumour. If the ductal NST pattern should comprise between 10% and 90% of the tumour (the rest being of a recognized special type) then it will fall into one of the mixed groups—tubular mixed, mixed lobular and ductal or mixed ductal and special type (see below).

Lobular carcinoma
The classical form of infiltrating lobular carcinoma was first recognized by Foote & Stewart[12] and the definition reviewed by Wheeler & Enterline[13]. Other variants have since been recognized[10]. These are solid lobular carcinoma and mixed lobular carcinoma which were described by Fechner[14], alveolar lobular by Martinez & Azzopardi[15], and tubulo-lobular carcinoma which was first recognized by Fisher and co-workers[9]. The term lobular has been used for these carcinomas since in approximately 60% of cases adjacent lobular carcinoma *in situ* is also present. Whether all such carcinomas are derived directly from the lobular epithelial cells is unproven. Grossly infiltrating lobular carcinoma can vary from being a well-circumscribed scirrhous mass to a poorly defined area of induration.

The histological variants are identified as follows.

a *Classical lobular carcinoma* is composed of small round or ovoid regular cells with little cytoplasm which is often eccentrically placed in a plasmacytoid manner. Although intracytoplasmic lumina are seen in all types of breast carcinoma they are most frequent in invasive lobular carcinoma[16] and may be a prominent feature. These structures may be visible on H & E staining but are more easily visualized by immunocytochemical staining for epithelial membrane antigen or histochemical staining with periodic acid-Schiff and Alcian blue[16]. The tumour cells infiltrate in a diffuse manner and form characteristic cords between collagen bundles—so-called Indian filing. Such cords of tumour cells infiltrate around existing structures in a 'targetoid' pattern.

b The *alveolar variant* consists of cells of the same uniform appearance as the classical type but these are clustered in small aggregates of 20 or more cells.

c In the *solid variant* of lobular carcinoma the cells are of uniform lobular type but these infiltrate in diffuse sheets with little or no intervening stroma.

d *Tubulo-lobular carcinoma* is composed of cords of small neoplastic cells in between bands of collagen. The cells in some cords form distinct microtubules. These tubules are smaller than the tubules seen in tubular carcinoma but they also consist of a single layer of small uniform cells with little cytoplasm. It should be emphasized that the overall infiltrative pattern is highly reminiscent of classical lobular carcinoma. Elastosis and the presence of an intraduct papillary or cribriform element are common features; necrosis and the presence of a lymphoid infiltrate are rare occurrences. To be typed as tubulo-lobular a tumour must show that pattern in over 90% of its area.

e Some tumours show a *combination of the above patterns*. These are classified as *mixed lobular carcinomas*[14]. Alternatively a mixed lobular tumour may be one which has the infiltrative pattern of classical lobular but shows cellular atypia and pleomorphism. The cells

in this type may also be larger and contain more cytoplasm than in the classical type. If a tumour consists of mixtures of the lobular subtypes then 80% of it must be a single pattern in order for it to be typed as such. If such a tumour is composed of lobular and ductal NST elements more than 90% of the tumour must be lobular or a mixture of the above lobular types for that type to be allocated to the tumour. Those cases with a true biphasic pattern containing less than 90% lobular type should be classed as ductal and lobular mixed.

Tubular carcinoma

Two main morphological subtypes are now recognized; the 'pure' type in which there is a stellate structure with dense central fibrosis and elastosis, and the sclerosing type characterized by a more diffuse and haphazard infiltration of tubules into adjacent connective and adipose tissue[17,18]. The tubules have lumina which appear round or oval. There is only a single layer of cells forming each tubule (normal ductules and lobules are lined by both epithelial and myoepithelial cells and are thus two-layered). The neoplastic cells are small, have a uniform appearance and often show apical cytoplasmic snouting, the protrusion of a small pseudopodium of cytoplasm from each cell into the lumen of the tubule. Other features associated with this type include the presence of infiltrative tubules in adipose tissue without associated fibrous stroma and the presence of carcinoma *in situ* (frequently of the cribriform type, occasionally lobular). For a tumour to be classed as tubular it must contain over 90% tubular morphology[3,4,18,19]. If a cancer consists of less than 90% tubular carcinoma, it enters the tubular mixed, ductal and special type or miscellaneous categories. The only exception to this is the combination of tubular and cribriform elements; a tumour is typed as tubular if that pattern forms over 50% of the tumour.

Tubular mixed carcinoma

Since the original descriptions of pure tubular carcinoma it has been recognized that some breast carcinomas exhibit a mixture of tubular and other types, usually ductal NST. Unfortunately there has been a lack of agreement concerning the percentage of tubules required to fulfil the criteria for tubular carcinoma, some authors setting the cut-off at 75% rather than 90%[20–22]. Others have used the term tubular mixed[18] or tubular variant carcinoma[23,24] to describe those cases in which between 90% and 75% of the tumour consists of tubular structures. Such definitions exclude a significant proportion of tumours in which the tubular component amounts to less than 75% and which are therefore consigned to the general category of ductal NST. Since this may result in the loss of potentially useful prognostic information we have chosen a much broader definition for our category of tubular mixed carcinoma. We require there to be a stellate mass with an infiltrating border of variable thickness composed of cells typical of ductal NST carcinoma. Centrally the lesion contains tubules identical to those found in tubular carcinoma. These are usually embedded in a dense, fibrous often hyalinized stroma. Elastosis in the central area is common. The two types of carcinoma merge one into the other, there being a gradual progression from well-differentiated tubular or cribriform carcinoma to less well-differentiated ductal NST carcinoma. Necrosis and lymphoid infiltration are rare. Even if only a few well-formed tubules can be found in the centre of a lesion which shows the characteristic distribution of ductal NST and tubular elements then it is typed as tubular mixed carcinoma.

Invasive cribriform carcinoma

This type of carcinoma, which has similarities to tubular carcinoma, has been regarded as a special type[5,25] for its excellent prognosis. The tumour is arranged as invasive islands of small regular cells similar to those found in cribriform ductal carcinoma *in situ*. The nuclei are usually dense, small and regular. Within the invasive islands of cells are arches of cells which produce well-defined spaces. Apical snouting into these lumina is a regular feature. For a tumour to be typed as cribriform this pattern must form at least 90% of the lesion, although a tumour with over 50% cribriform pattern can be accepted provided that the rest of the lesion is composed of tubular carcinoma.

Mucinous carcinoma

This type has also been described under the titles of mucoid or colloid carcinoma. Histologically the tumour consists of small islands (10–20 cells) of uniform small cells in lakes of extracellular mucin. At the growing edge of the tumour these islands may be embedded in loose fibrous stroma. The stroma itself does not contain a lymphoid or histiocytic infiltrate: necrosis and vascular invasion are rare as is the presence of an *in situ* component. The presence of any ductal NST carcinoma within a tumour removes it from this category to that of mixed ductal and special type. We believe like others[19] that this definition, which is more restrictive than the Royal College of Pathologists Working Group definition[26] which allows 10% of no specific type, is more appropriate for this particular special type.

Medullary carcinoma

The criteria for medullary carcinoma have been

reviewed repeatedly[27]. Three diagnostic features are used[7,28]: (i) the tumour is composed of interconnecting sheets of large bizarre and pleomorphic carcinoma cells forming a syncytial network; (ii) the intervening stroma between these bands contains moderate or large numbers of lymphoid cells which do not intervene extensively between individual tumour cells; and (iii) the infiltrative margin of the tumour is pushing giving a sharply defined border. In addition there is usually little fibrous stroma and patchy necrosis is common. *In situ* elements and vascular invasion are not usually present. This pattern must be consistent throughout the entire tumour in order for it to be typed as medullary; a diagnosis of atypical medullary carcinoma should be considered if there is any deviation.

Atypical medullary carcinoma
Tumours bearing some but not all the features of medullary carcinoma have been described by both Fisher *et al.*[28] and Ridolfi *et al.*[7] as atypical medullary carcinoma. For a tumour to be defined as atypical medullary it may show a lesser degree of lymphoid infiltration, points of microscopic invasion beyond its border or dense areas of fibrosis, whilst still having the other features of a medullary carcinoma. A well-circumscribed tumour is also classified as atypical medullary if up to 25% of it is composed of ductal NST and the rest shows classical medullary features. Tumours composed of between 10% and 75% medullary carcinoma are classified as ductal NST.

Mixed ductal and lobular carcinoma
Tumours are entered into this category if they contain both distinct and separate ductal NST and lobular elements and the former forms between 10% and 90% of the carcinoma. These tumours can be regarded as biphasic and are distinct from mixed lobular carcinoma which has a relatively uniform appearance but a combination of a lobular infiltrative pattern and less specific cell type.

Mixed ductal and special type carcinomas
This category includes any mixtures of tubulo-lobular, tubular (tubular mixed carcinoma being morphologically distinctive is described separately above), cribriform or mucinous with ductal NST carcinoma where the latter forms over 10% of the tumour mass (or any part of a mucinous carcinoma).

Miscellaneous
Very rare tumour types, for example spindle cell carcinoma, metaplastic carcinoma, papillary carcinoma, secretory apocrine carcinoma, microinvasive or mixtures of special types of carcinomas (e.g. mucinous and tubular carcinomas) were allocated to this category. The prognosis of these very rare subtypes is probably different but the low numbers of each type identified precluded individual analysis.

Carcinoma in situ
As its name suggests, this is a non-invasive tumour contained within the duct or lobular basement membrane[29].

(a) *Ductal carcinoma* in situ. In ductal carcinoma *in situ*, instead of the normal bilayer of luminal epithelial cell and myoepithelial cell, the ducts are partly or completely filled with a proliferation of distinctive tumour cells. Should these cells penetrate beyond the basement membrane then the carcinoma is immediately entered into one of the invasive groups. Four common types of ductal carcinoma *in situ* are recognized—micropapillary, cribriform, solid and comedo[19] but for the purposes of this study they were not separately subclassified.

(b) *Lobular carcinoma* in situ. This entity is recognized by a proliferation of characteristic cells within the acini of mammary lobules. These cells, which fill and distort the lobules, are small and regular without nuclear atypia and have scanty cytoplasm. 'Pagetoid' spread into adjacent ductules is a common feature[19].

ADDITIONAL STUDIES

The first cohort of 141 tumours of tubular mixed type was given a score according to the proportion of tumour in which tubular structures were apparent:

Score	% tubules (approximate)
1	90–75
2	75–50
3	50–5

The score was determined initially by one observer (N.B.). All 141 cases were reviewed on a subsequent occasion by the same observer and all were given a grade identical to that given on the initial examination.

HISTOLOGICAL GRADE

In order to satisfy the criteria for the Nottingham Prognostic Index[30] all tumours, irrespective of histological type, were assigned an individual histological grade. Assessment was carried out according to the protocol described by Elston & Ellis[31]. Three grades of differentiation are used: I, well; II, moderate; III, poor.

STATISTICAL TESTS

Probability of survival curves were calculated for patients in each type category using the life table method[32]. Mantel's test[33] was utilized to assess the difference between various survival curves. The chi-squared test for trend[34] was also used.

Results

The frequency of each histological type and associated 10 year survival rate for the 1621 women is shown in Table 1 and the overall survival rate to 10 years is 54% (Figure 1).

As a single group, lobular carcinoma was the commonest specific type of invasive breast carcinoma (excluding ductal NST) and has been examined both as a single entity and as the subtypes previously defined. The frequency of these subgroups is shown in Table 2. Invasive lobular carcinomas as a group show a highly significant survival advantage compared with ductal NST carcinoma ($\chi^2=22.5$; $P<=0.0001$) (Figure 2). Figure 3 shows the survival curves for the lobular subgroups. There is a highly significant difference in the behaviour of these subtypes of lobular carcinoma ($\chi^2=14.6$; $P<0.006$). The classical, tubulo-lobular and lobular mixed subtypes have a significantly better prognosis than ductal NST carcinoma ($\chi^2=17.2$; $P<0.0001$; $\chi^2=8.6$; $P=0.003$; $\chi^2=8$; $P=0.005$, respectively). Solid lobular carcinoma shows a similar prognosis to that of ductal NST. Alveolar lobular cases appear to have a favourable prognosis; however, only nine cases were identified precluding statistical comparison with ductal NST.

Tubular mixed carcinoma, the third largest group with 220 patients, shows a better survival (Figure 4) than ductal NST carcinoma ($\chi^2=38.3$; $P<0.0001$). In the subset study the frequency of tumours with different percentages of tubule formation is shown in Table 3. The percentage of tubular structures appeared to be unimportant in determining prognosis with no significant differences on life table analysis.

There were 38 cases of pure tubular carcinoma in the series; only three deaths have occurred to date giving a

Table 1. Frequency of each histological type in the series

Type of carcinoma	No. in study	Relative frequency (%)	10 year survival (%)
Ductal NST	760	47.0	47
Lobular	243	15.0	54
Tubular	38	2.3	90
Tubular mixed	220	13.6	69
Cribriform	13	0.8	91
Mucinous	14	0.9	80
Medullary	44	2.7	51
Atypical medullary	76	4.6	55
Mixed ductal and lobular	77	4.7	40
Mixed ductal and special type	40	2.5	64
Miscellaneous	21	1.3	60
In situ (DCIS)	73	4.5	92
LCIS	2	0.1	NA
Total	1621	100	54

DCIS = Ductal carcinoma *in situ*; LCIS = lobular carcinoma *in situ*; NA = not appropriate.

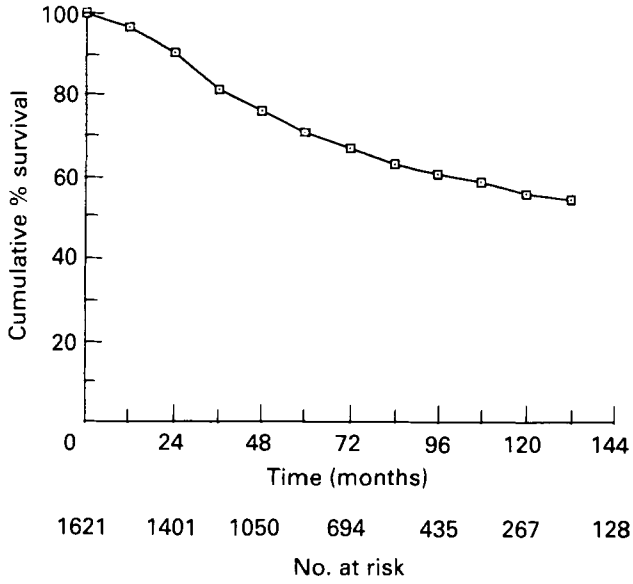

Figure 1. Survival curve for all 1621 patients.

Table 2. Frequency of subtypes of lobular carcinoma

Subtype	No. in type	Relative frequency in lobular subtype (%)
Classical	97	40
Alveolar	9	4
Solid	25	10
Tubulo-lobular	15	6
Mixed	97	40
Total	243	100

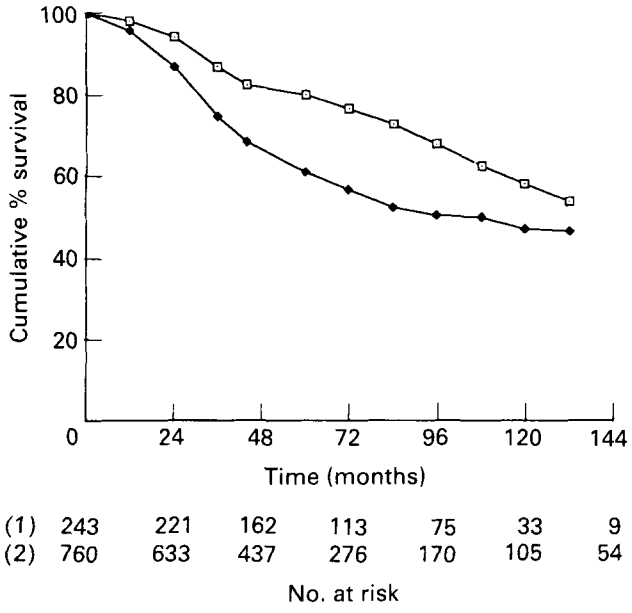

Figure 2. Survival curve for patients with ⊡, invasive lobular carcinoma (1) compared with that for ◆, ductal NST carcinoma (2). χ^2 (1 df) = 22.5; $P < 0.0001$.

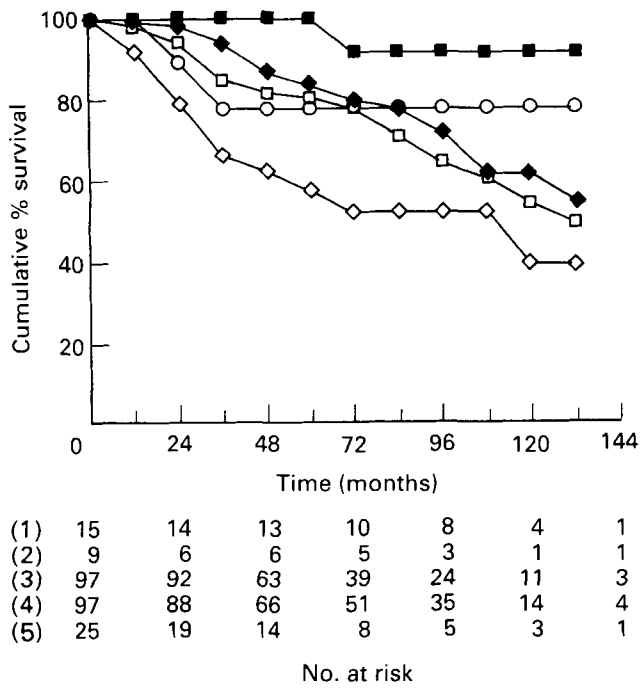

Figure 3. Survival curves for patient with subtypes of invasive lobular carcinoma. ■, tubulo-lobular (1); ○, alveolar (2); ◆, classical (3); □, mixed (4); ◇, solid (5). χ^2 (4 df) = 14.6; $P = 0.006$.

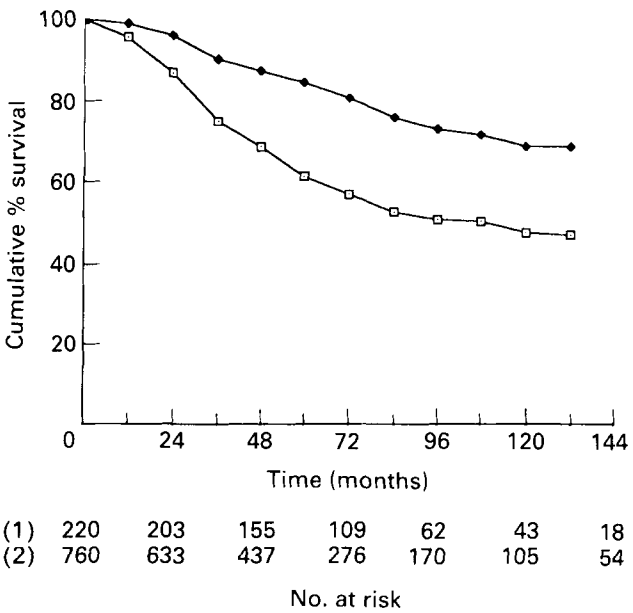

Figure 4. Survival curve for patients with ◆, tubular mixed carcinoma (1) compared with that for ⊡, ductal NST carcinoma (2). χ^2 (1 df) = 38.3; $P < 0.0001$.

Table 3. Frequency of subtypes of tubular mixed carcinoma

Subtype	No. in type	Relative frequency (%)
1	34	24.1
2	40	28.4
3	67	47.5
Total	141	100.0

highly significant survival advantage over ductal NST carcinoma ($\chi^2 = 18$; $P = < 0.0001$). The 13 cases of invasive cribriform carcinoma showed a similar significant survival advantage over ductal NST carcinoma ($\chi^2 = 7.5$; $P = 0.006$) as did the 14 cases of pure mucinous carcinoma. The survival curves for these special types of tumour are shown in Figure 5.

These rare so-called 'special types' of breast cancer which show an extremely good prognosis (tubulo-lobular, tubular, invasive cribriform and mucinous) when grouped together (80 cases) have a frequency of 5% and a highly significant survival advantage (Figure 6) over ductal NST carcinoma ($\chi^2 = 39.0$; $P < 0.0001$).

No significant difference was found between the survival curves of medullary and atypical medullary carcinomas nor between these types and ductal NST

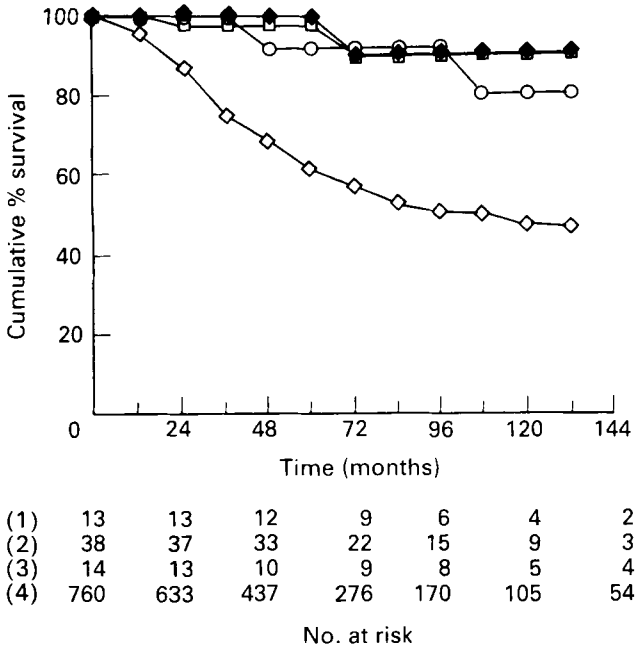

Figure 5. Survival curves for patients with □, tubular (2), ◆, invasive cribriform (1) and ○, mucinous (3) carcinoma compared with that for ◇, ductal NST carcinoma (4). (1) *v* (4) χ^2 (1 df) = 7.5; $P < 0.006$; (2) *v* (4) χ^2 (1 df) = 18; $P < 0.0001$; (3) *v* (4) χ^2 (1 df); $P = 0.02$.

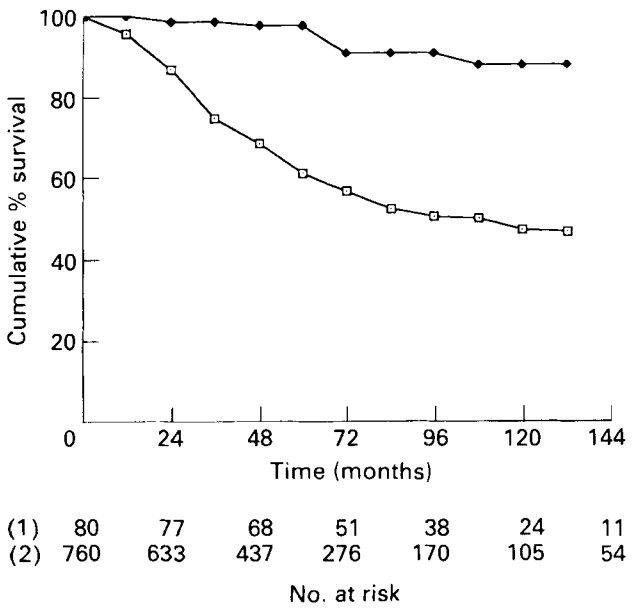

Figure 6. Survival curve for patients with ◆, special types (1) combined into one group compared with that for □, ductal NST carcinoma (2). χ^2 (1 df) = 39.0; $P < 0.0001$.

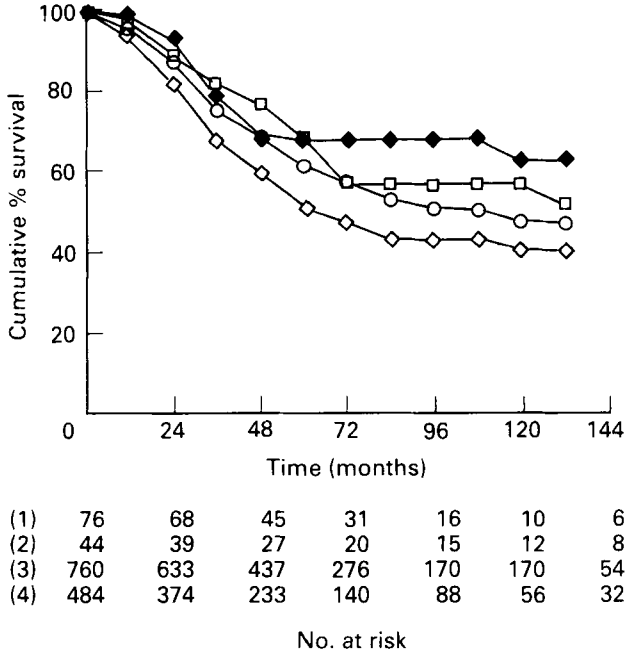

Figure 7. Survival curves for patients with □, medullary (2) and ◆, atypical medullary (1) compared with those for ○, ductal NST carcinoma (3) and ◇, ductal NST grade III carcinoma (4). (1) *v* (3) χ^2 (1 df) = 2.3; $P = 0.1$; (1) *v* (2) χ^2 (1 df) = 0.1; $P = 0.7$; (2) *v* (3) χ^2 (1 df) = 0.9; $P = 0.3$; (1) *v* (4) χ^2 (1 df) = 8.9; $P = 0.003$; (2) *v* (4) χ^2 (1 df) = 4.8; $P = 0.03$.

carcinoma (Figure 7). Medullary and atypical medullary carcinomas by definition have a poor histological grade. It is more appropriate to compare medullary and atypical medullary carcinoma with ductal NST grade III tumours, when a significant difference in survival is found ($\chi^2 = 4.8$; $P = 0.03$ and $\chi^2 = 8.9$; $P = 0.003$, respectively).

Analysis of the mixed types of tumour showed no survival difference between mixed ductal and lobular carcinomas and ductal NST carcinomas. However, tumours of mixed ductal and special type had a significantly improved survival compared with ductal NST carcinomas which was comparable to tubular mixed carcinomas (Figure 8).

The miscellaneous group of tumours is heterogeneous and was not analysed separately. Of interest, however, are the eight cases of invasive papillary carcinoma which were included in this group. These women had a 10 year survival of 60% but because of the low frequency (0.5%) further analysis was not performed.

The frequency of ductal carcinoma *in situ* and lobular carcinoma *in situ* is included in Table 1. A variety of different treatment regimes have been used for ductal carcinoma *in situ*. For these reasons these cases have not been analysed further in this study. The frequency of

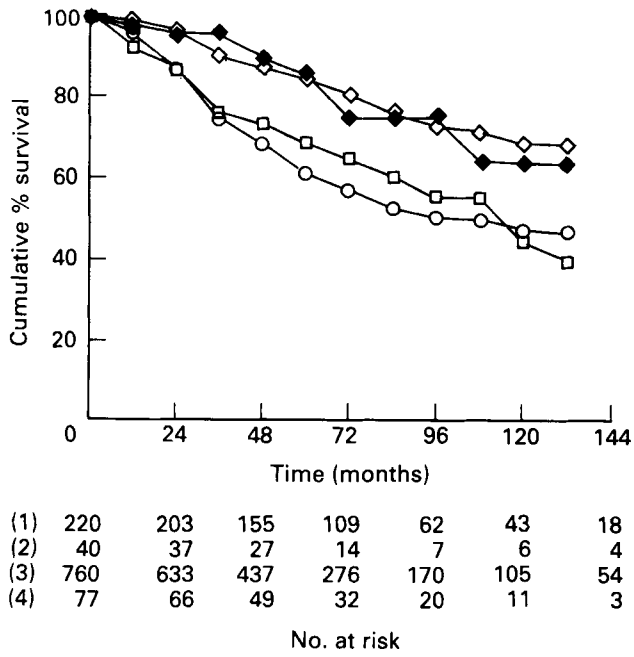

Figure 8. Survival curves for patients with mixed tumours (◆, mixed ductal and special type (2); □, mixed ductal and lobular (4)) compared with those for ○, ductal NST (3) and ◇, tubular mixed carcinoma (1). (1) *v* (2) χ^2 (1 df)=0.001: P=0.9; (2) *v* (3) χ^2 (1 df)=7.2: P=0.007; (3) *v* (4) χ^2 (1 df)=0.3: P=0.6.

lobular carcinoma *in situ* was too low for any further analysis.

Discussion

This study confirms that histological tumour type can provide useful prognostic information in patients with primary operable breast cancer. The data presented support the view that histological type is important in determining treatment in modern practice and also in allaying the fears of those women whose life is unlikely to be threatened in the short or medium term by the disease.

The relative frequency of ductal NST carcinoma in this study is at the lower end of the range described in previous large studies[28,35]. This is not surprising because ductal NST carcinoma is essentially a diagnosis of exclusion, and the increased recognition of specific subtypes will naturally reduce the number of cases placed in that category. An additional factor is the separation of mixed types such as tubular mixed carcinoma, mixed ductal NST and special type and mixed ductal NST and infiltrating lobular. In fact if the number of cases in these (mixed) groups is combined with the number in the ductal NST group the overall total forms 74% of cases in the series, similar to the findings of others[28,35]. It is also important to note that because of the better prognosis of many of these mixed categories the overall survival for the ductal NST category is poorer than in previous studies, 47% at 10 years compared with 50–60%[19].

In this series a survival advantage is confirmed for patients with invasive lobular carcinoma when compared with ductal NST. The value of subtyping lobular carcinoma is also illustrated by our results (Figure 3). There are significant differences in survival between classical lobular carcinoma (good prognosis), mixed lobular (average prognosis) and solid lobular (poor prognosis). These results largely confirm the finding of Dixon and co-workers[10]. It is also notable that the proportions of each subtype recorded in this study are similar to those presented by Dixon *et al.* who reported equal numbers of classical and mixed lobular carcinomas (classical, 97; mixed, 97). Lobular carcinoma accounts for a greater percentage of cases (15%) in our series than in many others. This is probably a result of a broad definition of mixed lobular being accepted in this study although there was no deliberate policy to do this. Thus, a proportion of carcinomas which others would have regarded as ductal NST were here entered into the mixed lobular group. Survival rates in this large mixed group were no worse than in the study of Dixon and co-workers[10].

For the purpose of this discussion we regard tubulo-lobular carcinoma as a distinct and separate entity, because there is still a lack of agreement concerning its assignment as a variant of tubular or infiltrating lobular carcinoma[19]. Tubulo-lobular carcinoma was described by Fisher *et al.*[9] who emphasized its lobular origin. They recorded a frequency of 1.5% and our own frequency of 1% is in close agreement with this. The clinical details in Fisher's study are rather scanty and they simply state that 'treatment failure' was intermediate between that for tubular carcinoma and that for ductal NST carcinoma. A similar outcome is reported by Page & Anderson[19]. Although numbers in our series are small only one of these 15 patients with tubulo-lobular carcinoma has died after 10 years of follow-up, which tends to confirm the relatively favourable prognosis of this type. It is clear that further studies are required to establish the precise status of tubulo-lobular carcinoma, but whether the prognosis is excellent or good it is certainly worthy of separate consideration from other types.

The frequency of tubular carcinoma in this series of symptomatic cases (2.3%) is very similar to that found in other studies[19], although it is interesting that significantly higher frequencies are found in mammographic screening[24,36,37]. We have confirmed the excellent prognosis noted in previous studies[3,18,21,22,24] (Figure 5) with

a survival at 10 years of 90%, significantly better than that for ductal NST carcinoma. Our results also confirm the excellent prognosis found for invasive cribriform carcinomas by Page and co-workers[5]. The 13 cases reviewed over 10 years of follow-up showed a 91% survival rate. This is an important type of carcinoma since it can readily be recognized and offers an excellent prognosis, similar to that for tubular carcinoma, despite the fact that these lesions are usually larger[5] at presentation.

Tubular mixed carcinoma, as defined in this study, is the third commonest group, forming 14% of the cases in the series. It is clear from the significantly better survival compared with ductal NST carcinoma (Figure 4) that identification of cases as tubular mixed provides clinically useful prognostic information. Whilst it has been accepted that carcinomas with 75% or more tubular formation (designated as either pure tubular or tubular variant) have an excellent prognosis[3,18,21,22,24], previous studies have shown that carcinomas with less than 75% of tubules have no better survival than ductal NST carcinoma[4]. We investigated the influence on prognosis of the percentage of tubule formation in a cohort of 141 cases of tubular mixed carcinoma, using cut-off points of 90–75% (group 1), 75–50% (group 2) and 50–5% (group 3). No significant difference was found between the survival curves of these groups, and we also found a significant survival advantage for groups 2 and 3 combined (<75% tubule formation) compared with ductal NST carcinoma. Since tubular mixed carcinoma implies a good prognosis (69% 10 year survival) intermediate between that of pure tubular carcinoma and ductal NST carcinoma we believe that use of our broad definition is justified, particularly as it identifies a significant proportion of cases that would otherwise be lost within the ductal NST cases. In our definition tubular mixed carcinomas must have a sclerotic centre, usually with elastosis, containing definite tubular structures, but with a less differentiated ductal NST pattern at the periphery. Although based on circumstantial evidence, mainly the greater average tumour size, Linell *et al.*[20] have proposed that tubular carcinomas may progress into less differentiated carcinomas with time if left untreated. The survival data presented here lend some support to that contention.

The frequency of mucinous carcinoma found in this series (0.9%) is at the lower end of the range described by other workers[28,38,39]. This may be due to the strict application of the exclusion criterion that the presence of any ductal NST element precludes a tumour from being termed mucinous. Because of the small number of cases in this group statistical data must be interpreted with caution but the 10 year survival rate of 80% compared with the 47% for ductal NST carcinoma supports previous reports that pure mucinous carcinoma has a very good overall prognosis[2,38,39]. There are too few cases of mixed mucinous and ductal NST carcinoma in our study to confirm directly the view that the mixed type of mucinous carcinoma has a prognosis intermediate between pure mucinous carcinoma and ductal NST[2,38,39], although this is true for the mixed ductal and special type group of which mucinous/ductal NST forms a part.

The combination of tubular, invasive cribriform, mucinous and tubulo-lobular carcinomas into a special type category emphasizes the difference in prognosis from ductal NST carcinoma (Figure 6), but this grouping must remain provisional. The inclusion of tubular and cribriform carcinoma is valid as both have an excellent prognosis. The addition of mucinous and tubulo-lobular is, however, more dubious; the prognosis for mucinous is very good but not excellent, and the excellent prognosis for tubulo-lobular carcinoma reported here requires confirmation in other studies.

It has become widely accepted that medullary carcinoma of the breast carries a good prognosis. This perception has been based on a number of reports in the past[6,40,41], but the most widely quoted and influential study is that of Ridolfi and co-workers[7]. They found an 84% 10 year survival for medullary carcinoma compared with 58% for ductal NST carcinoma with atypical medullary carcinoma having an intermediate prognosis. It must be pointed out that both these survival rates are higher than would normally be expected, raising the possibility of selection bias in the construction of the study. Other studies have not demonstrated a survival advantage for medullary carcinoma[42,43] and it is possible that this may be related in part to a lack of agreement on the appropriateness of the histological diagnostic criteria. Indeed, Gallager[44] has claimed that a good prognosis is only found if the definition is followed rigorously. Interestingly, Pedersen *et al.*[45] have recently shown unacceptable inter- and intra-observer variability using the criteria proposed by Fisher *et al.*[28] and Ridolfi[7]. In our own study, applying these criteria as strictly as possible, we have found no difference in survival between medullary and atypical medullary carcinoma nor between these two groups and ductal NST carcinoma (Figure 7). The results support the view that medullary carcinoma should not be placed in a 'good' prognostic category, although there is a significant improvement in survival compared with ductal NST carcinomas of histological grade III (Figure 8). Recently Fisher *et al.*[27] have reached a similar conclusion based on their finding of only a small survival advantage in node negative patients with typical medullary carcinoma compared with atypical

medullary and ductal NST carcinoma, following adjuvant chemotherapy. From their studies on intra-observer variation Pedersen *et al.*[46] have now proposed a simplified histopathological definition of medullary carcinoma based only on two criteria, a syncytial growth pattern and diffuse moderate or marked mononuclear infiltrate. They suggest that these criteria are reproducible with consistency and claim that medullary carcinoma defined in this way has a significantly better prognosis than ductal NST carcinomas, grades II or III. Further studies are required to test these proposals, but in the meantime we believe that medullary carcinoma should be regarded as having a moderate rather than a good prognosis.

The separate analysis of mixed tumours other than tubular mixed has proved of interest. Tumours which showed any of the distinct patterns of lobular carcinoma in combination with ductal NST were typed as ductal and lobular mixed. The vast majority of ductal and lobular mixed carcinomas showed over 50% lobular features and in contrast to the tubular mixed group no significant improvement in prognosis could be identified over ductal NST carcinoma. Mixed tumours with distinct ductal and special type components (other than tubular) did, however, show a better prognosis statistically than ductal NST; although the group is relatively small (2.5% of the total) it carries a closely similar survival to tubular mixed carcinoma. We believe therefore that this type merits greater recognition as an important tumour with a good prognosis.

Our results have demonstrated clearly that identification of the histological type of breast carcinoma can provide highly significant prognostic information. To summarize, the special types (tubular, invasive cribriform, mucinous) and tubulo-lobular carcinoma carry an excellent prognosis, tubular mixed and mixed ductal and special types have a good prognosis, classical lobular, medullary and atypical medullary carcinoma have an average prognosis and the solid lobular and ductal NST types are of relatively poor prognosis. It is likely that even more precise prognostic subdivisions may be obtained from a combination of histological type and grade and this will be the subject of a future study.

The frequency of the various histological types presented in this study of symptomatic patients is different from that observed in cases of breast carcinoma detected by mammographic screening[24,37] where much higher frequencies of excellent and good prognostic type are found. Accurate identification of histological type will become increasingly important as screening becomes more widely established, not only because of the prognostic and therapeutic implications but also as a quality assurance performance indicator[31]. The requirements for typing are relatively simple; good specimen fixation and preparation combined with strict application of the appropriate diagnostic criteria. We would encourage all pathologists involved in the diagnosis and management of breast disease to recognize and report the various histological subtypes of breast carcinoma routinely.

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