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ORIGINAL ARTICLE

A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival

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SUMMARY. The clinical and complete pathological response of a primary breast cancer to chemotherapy has been shown to be an important prognostic for survival. However, the majority of patients do not experience a complete pathological response to primary chemotherapy and the significance of lesser degrees of histological response is uncertain and the prognostic significance is unknown. The purpose of this study was to evaluate a new histological grading system to assess response of breast cancers to primary chemotherapy and to determine if such a system has prognostic value.

A consecutive series of 176 patients with large (≥ 4 cm) and locally advanced breast cancers were treated with multimodality therapy comprising primary chemotherapy, surgery, radiotherapy and tamoxifen. All underwent assessment of the primary breast tumour before and after completion of chemotherapy. Residual tumour was excised after completion of chemotherapy (mastectomy or wide local excision with axillary surgery). The removed tissue was assessed and response to chemotherapy graded using a five-point histological grading system based with the fundamental feature being a reduction in tumour cellularity; comparison being made with a pre-treatment core biopsy. All patients were followed up for 5 years or more. Pathological responses were compared to 5 year overall survival and disease-free survival using log rank tests.

The overall 5-year survival for all patients was 71%, and 5 year disease free interval was 60%. There was a significant correlation between pathological response using this new grading system and both overall survival ($P = 0.02$) and disease-free interval ($P = 0.04$). In a multivariate analysis of known prognostic factors, the Miller/Payne grading system was an independent predictor of overall patient survival.

This grading system, which assesses the histological response to primary chemotherapy, can predict overall survival and disease-free interval in patients with large and locally advanced breast cancers treated with such therapy. The relationship of degree of histological response to overall and disease-free survival has been shown in univariate and multivariate analyses and could potentially have an important role in the clinical management of patients with locally advanced breast cancer undergoing primary chemotherapy.

INTRODUCTION

Locally advanced breast cancer accounts for up to 15% of newly diagnosed cases in the UK.[1] Such disease presents two main clinical challenges. These are the control of local disease and the reduction or eradication of micrometastatic distant disease, which is frequently present at diagnosis and accounts for the poor survival of these patients.[2] It is not surprising, therefore, that primary or neo-adjuvant chemotherapy has been given to these patients in an attempt to downstage the primary tumour and also to reduce or eliminate micrometastatic disease.

Although primary chemotherapy does downstage the primary tumour and enables breast conservation surgery to be performed more frequently, a beneficial effect on

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survival has not yet been proven.[3–9] A complete clinical response with no residual detectable tumour occurs in up to one-quarter of these patients, with the remainder having a partial response, as assessed by standard UICC criteria.[10] However, when the residual breast tumour is examined histologically, then the responses are less marked and a complete pathological response occurs in only approximately 15–25% of cases at most.[11,12]

The clinical and complete pathological response of the primary tumour to chemotherapy has been shown previously to be an important prognostic indicator for disease-free and overall survival.[13–15] In particular, a complete pathological response after primary chemotherapy has been associated with 5 year survivals of up to 87%.[13] As the majority of patients do not experience a complete pathological response to primary chemotherapy, previous studies have attempted to classify the extent of residual tumour following chemotherapy but the implications of this for patient outcome subsequently are unclear.[16–19] Furthermore, in these other studies patients with either macroscopic or microscopic complete responses have often been grouped together for analysis,[16] or patients with less than a complete response to chemotherapy were all analysed together.[18]

It is clear from these studies that a complete histological response is a favourable prognostic indicator. However, the majority of patients fail to achieve such a response and it is unclear whether a less than complete histological response following chemotherapy has a prognostic significance. The aim of this study was to evaluate a new histological grading system used to assess the response of breast cancers to primary chemotherapy and to determine if such a system has prognostic value in patients receiving primary chemotherapy for breast cancer.

PATIENTS AND METHODS

Patients

A consecutive series of 176 patients were prospectively included in this study and were treated in the Aberdeen Breast Unit, Aberdeen Royal Infirmary between 1990 and 1998. Patients had been diagnosed as having large breast cancers (>4 cm) or locally advanced breast cancers (T3,T4 or any T stage but with N2 nodal stage). All patients had histologically proven invasive carcinoma (core biopsy, $n = 159$, or open surgical biopsy, $n = 17$) prior to commencing primary chemotherapy. Staging of the patient's tumours was performed by chest radiography, isotope bone scan, liver function tests and an abdominal ultrasound scan if liver function tests were abnormal. No patient had detectable metastatic disease before primary chemotherapy was instituted.

Primary chemotherapy

All these patients were treated with primary chemotherapy according to standard protocols within the Aberdeen Breast Unit. Patients received between 4 and 6 pulses of primary chemotherapy given at 3 weekly intervals comprising cyclophosphamide (1000 mg/m^2), doxorubicin (50 mg/m^2), vincristine (1.5 mg/m^2) all given by intravenous bolus injection followed by oral prednisolone (40 mg/day) for 5 days.

Surgery

Following completion of primary chemotherapy, all patients responses were assessed clinically using UICC criteria (complete, partial, stasis and progression),[10] and by mammography and breast ultrasonography. Patients underwent surgical resection of the residual tumour mass by either breast conservation surgery or mastectomy. The type of surgical procedure depended on residual tumour size and patient preference and was carried out between 4 and 6 weeks following completion of chemotherapy. In those patients where no residual mass was palpable (complete clinical response) following primary chemotherapy, and who had requested breast conservation surgery, the original tumour was subjected to a needle localisation (either mammographically or ultrasonically) prior to surgery being undertaken. Axillary surgery (either sample or clearance at the discretion of the surgeon) was performed in all patients. Radiotherapy was given to patients post-operatively according to standard unit protocols with no patient in this study receiving radiotherapy pre-operatively.

Pathological examination

The surgically removed breast tissue or mastectomy was sent fresh for pathological examination, thinly sliced and promptly fixed in neutral buffered formalin. If tumour was detectable macroscopically, its size was measured and at least four paraffin-embedded sections were stained with haematoxylin and eosin for histological evaluation. If no gross disease was found, widespread sampling of the involved quadrant was undertaken and was guided by pre-operative radiological siting of the tumour.

The histological response to chemotherapy was assessed using a new grading system devised by two of the authors (IDM and SP). This is a five-point scale, which focuses on the principal manifestation of che-

motherapeutic effect being a reduction in tumour cellularity. Often residual tumour cells show specific morphological effects (gross nuclear pleomorphism and cytoplasmic enlargement, cytoplasmic vacuolation). However, this did not influence grading which hinged upon the loss of tumour burden compared with the diagnostic pre-treatment core biopsy (Fig. 1). Immunocytochemistry for cytokeratins was used if necessary to assist in the identification of malignant cells. The tumours were scored blindly by each pathologist and agreement by consensus if necessary was achieved.

Histological grading system ('Miller and Payne system')

Grade 1: No change or some alteration to individual malignant cells but no reduction in overall cellularity.
Grade 2: A minor loss of tumour cells but overall cellularity still high; up to 30% loss.
Grade 3: Between an estimated 30% and 90% reduction in tumour cells.
Grade 4: A marked disappearance of tumour cells such that only small clusters or widely dispersed individual cells remain; more than 90% loss of tumour cells.
Grade 5: No malignant cells identifiable in sections from the site of the tumour; only vascular fibroelastotic stroma remains often containing macrophages. However, ductal carcinoma in situ (DCIS) may be present.

Grades 1–4 are categorised as a partial pathological response (pPR) and grade 5 was a complete pathological response (cPR). Residual ductal carcinoma in situ only was classified as a complete response. Examples of these different categories of response are shown in Figs. 1–6.

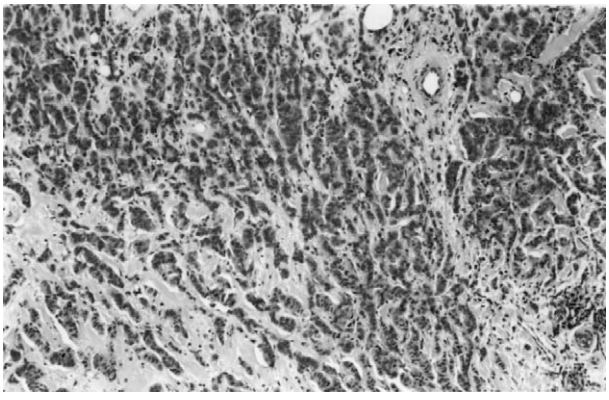

Fig. 1 Example of pre-treatment core biopsy – a high cellularity tumour (H&E × 230).

Statistics

Overall survival and disease-free survival were compared to both clinical and histological response (using

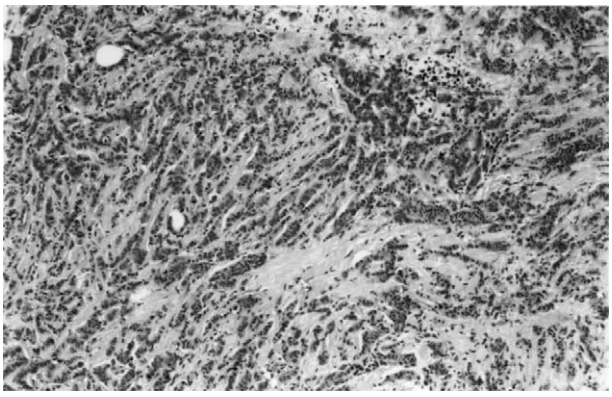

Fig. 2 Example of Miller/Payne grade 1 response – demonstrates no reduction in tumour cellularity (H&E × 230).

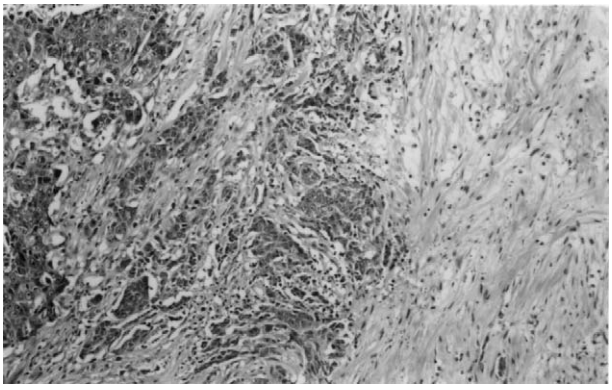

Fig. 3 Example of Miller/Payne grade 2 response – a slight reduction in the number of tumour cells (H&E × 230).

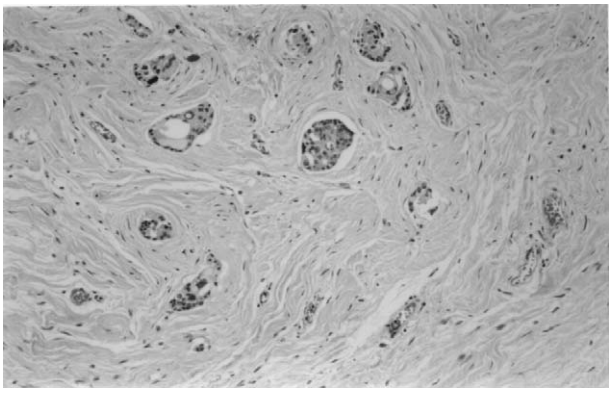

Fig. 4 Example of Miller/Payne grade 3 response – demonstrates a significant loss of tumour cells after completion of chemotherapy (H&E × 230).

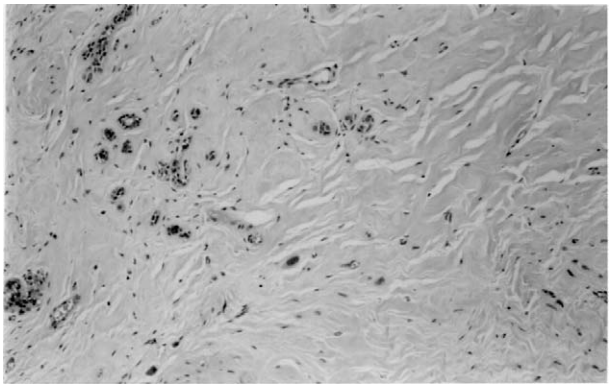

Fig. 5 Example of Miller/Payne grade 4 response – demonstrates a very good response with very few tumour cells remaining (H&E × 230).

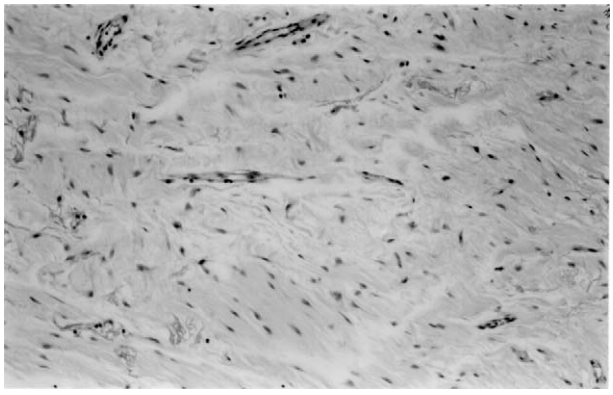

Fig. 6 Example of Miller/Payne grade 5 response – a complete histological response with no residual tumour cells (H&E × 230).

the Miller and Payne grading system) using Kaplan–Meir survival curves and log rank tests. A multivariate analysis to determine independent predictors of survival (overall and disease-free) was undertaken using a Cox proportional hazard model, with $P<0.05$ accepted for each additional variable to enter. All statistical analyses were performed using SPSS version 9.0 for Microsoft Windows 98.

RESULTS

Patients

A total of 170 of the 176 patients recruited were available for analysis in this study. Of the six patients unavailable, three patients died while receiving chemotherapy (myocardial infarction in two, and neutropaenic sepsis in one) and, therefore, no pathological material was available for examination. A further three patients had disease progression and received radiotherapy prior to surgery and were not included in the analysis. The patient's ages ranged from 29 to 74 years (mean 51 years). In terms of menopausal status, 90 (51%) patients were pre-menopausal and 86 (49%) were post-menopausal. The staging of their tumours as assessed clinically is shown in Table 1.

Table 1 Clincial TNM stage at diagnosis

	Node status		
Tumour stage	NO	N1	N2
Tx	0	0	3
T2	36	12	0
T3	52	28	4
T4	13	15	13

Clinical responses to primary chemotherapy

Clinical responses to primary chemotherapy as assessed by the UICC criteria are summarised in Table 2. A total of 33 patients (19%) had a complete clinical response, 98 (58%) a partial response, 35 (21%) had stasis of disease and in 4 (2%) there was disease progression.

Pathological responses

Pathological responses to primary chemotherapy as assessed by the Miller and Payne grading system criteria are summarised in Table 3. Twenty-six patients (15%) had a Grade 1 response, 41 patients (24%) a Grade 2 response, 46 patients (27%) a Grade 3 response, 34 patients (20%) a Grade 4 response and 23 patients

Table 2 Clinical responses to primary chemotherapy

Clinical response (UICC)	Number of patients
Complete response	33
Partial response	98
Static disease	35
Disease progression	4

Table 3 Response to primary chemotherapy according to Miller/Payne grading system

Grade	Number of patients (%)
1	26 (15)
2	41 (24)
3	46 (27)
4	34 (20)
5	23 (14)

(14%) a Grade 5 response. There was no interaction between tumour grade and the degree of response as assessed by our new classification.

Survival

The overall 5-year survival for all patients was 71% and 5-year disease-free survival was 60%. Kaplan–Meier survival curves comparing clinical responses and overall 5-year survival and 5-year disease-free interval were plotted. There was a significant correlation between clinical responses to primary chemotherapy and overall survival ($P = 0.01$) and disease-free survival ($P = 0.02$) in these patients.

Likewise Kaplan–Meier survival curves comparing histological response, assessed using the Miller and Payne grading system and overall 5-year survival and 5-year disease-free interval were plotted. There was a significant correlation between the Miller/Payne grade of response and disease-free survival ($P = 0.04$) and overall survival ($P = 0.02$) (Figs. 7 and 8).

A further analysis was carried out comparing those patients who had undergone a complete histological response (Miller/Payne grade 5 response) with all other patients. This revealed a highly significant survival advantage in those patients undergoing a complete histological response for both disease-free survival ($P < 0.001$) and overall survival ($P < 0.001$). The 5-year overall survival of these patients was 100%.

Multivariate analysis for overall survival

A multivariate analysis was undertaken to determine which factors including the Miller/Payne grading system were independent predictors of patient's survival using the Cox proportional hazards model. The factors entered into the statistical analysis were as follows: T stage of the tumour, N stage of the tumour, menopausal status, clinical response to chemotherapy (those who responded versus patients who had no response), oestrogen receptor status (positive or negative), the presence or absence of any residual tumour in lymph nodes after chemotherapy and the degree of histological response in the residual primary tumour, as assessed using the Miller/Payne system.

The results of this analysis are shown in Table 4. It can be seen that an increasing grade of pathological response (Miller and Payne classification) as well as a negative oestrogen receptor status and absence of histologically detected residual tumour in the axillary nodes after chemotherapy were independent predictors

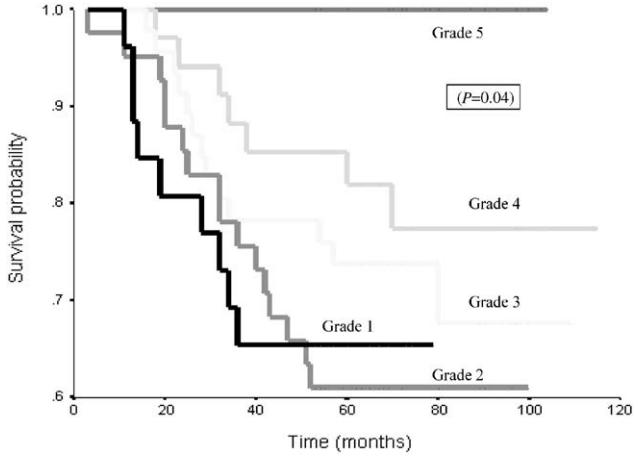

Fig. 7 Overall survival compared with histological response to chemotherapy.

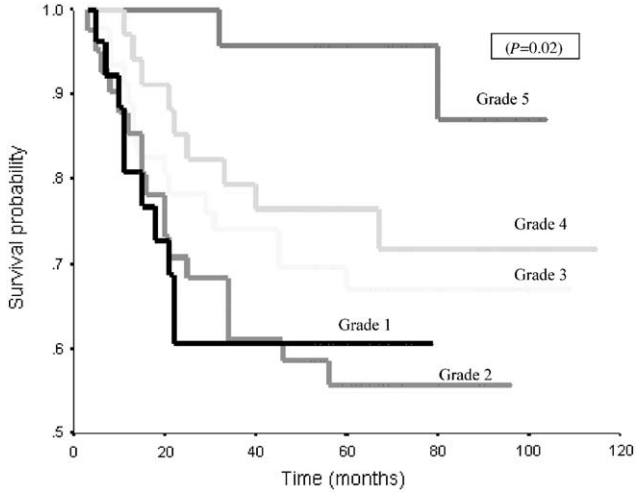

Fig. 8 Disease free survival compared with histological response to chemotherapy.

Table 4 Independent predictors of survival in patients undergoing primary chemotherapy

Factor	*b*	Exp(*b*)	95% CI Exp(*b*)	*P*
Tumour (T) stage	0.1362	1.1459	0.9032–1.4550	0.2621
Nodal (N) stage	0.1303	1.1392	0.7142–1.8169	0.5844
Menopausal status	−0.1585	0.8534	0.4616–1.5780	0.6133
Oestrogen receptor status	−0.8288	0.4366	0.2318–0.8228	0.0103
Pathological node status	0.8846	2.4221	1.1826–4.9607	0.0156
Clinical response	0.5704	1.7689	0.9250–3.3826	0.0846
Pathological response (Miller and Payne)	−0.2885	0.7494	0.5725–0.9810	0.0358

Key: clinical tumour stage = T1–T4; clinical node stage = 0–2; pathological nodal status = presence or absence of tumour metastases; pathological response = Miller–Payne grades 1–5.

of a better overall survival in patients undergoing primary chemotherapy.

DISCUSSION

There is no standard method of assessing pathological response to primary chemotherapy in patients with breast cancer. Previously, other pathological grading systems have used a variety of methods to assess response to primary chemotherapy. These include microscopic or macroscopic evaluation or microscopic assessment alone. For example, the Chevallier classification[16] categorises a complete response as the disappearance of macroscopic or microscopic tumour, whilst the presence of residual DCIS with no invasive disease constitutes a lesser degree of response. The presence of residual invasive disease is divided into residual disease with some stromal alteration and disease with no obvious response. The Sataloff classification (purely microscopic) has four categories of response – a total or near total therapeutic effect, greater than 50% therapeutic effect but less than near total, therapeutic effect evident but less than 50%, or no effect.[20]

Another system, the Honkoop classification,[19] describes two categories of response – minimal residual disease with either no residual tumour or scattered foci of tumour microscopically and gross residual disease with either macroscopic tumour or diffuse infiltration microscopically. The Kuerer[17] classification describes three categories of response – no evidence of residual tumour, $<1\,cm^3$ of residual tumour macroscopically (only residual microscopic foci of tumour cells placed in this group) and $>1\,cm^3$ of residual tumour macroscopically. The classification used in the NSABP B-18 trial[18] divides patients into two groups – those with a complete histological response (but including residual in situ disease) and patients in whom there was any evidence of residual invasive carcinoma histologically.

The new histological grading system for assessing the response to primary chemotherapy described in our study is based on the degree of tumour cell loss, which occurs within the tumour during primary chemotherapy. It does not take into account the residual macroscopic or microscopic tumour size. Whereas residual tumour cells often show morphological changes (which are not chemotherapeutic-agent specific, including cytoplasmic swelling, nuclear hyperchromasia and apoptosis), the key feature of cellular damage in tumours responding to chemotherapy is an overall loss of tumour cellularity.

The initial assessment of tumour cellularity is based on an assessment of a core biopsy of the tumour. The problems of tumour heterogeneity are well recognised and, therefore, at least three core biopsies (and up to 5 with larger tumours) were taken from different areas of the tumour. Thus, the assessment of pre-chemotherapy cellularity was based on as wide a sampling of the tumour as possible with this technique. Clearly an open (surgical) tumour biopsy would allow more tissue to be removed for histological examination but we had avoided the need for an additional surgical procedure unless this was necessary because a definitive histological diagnosis on core biopsy has not been obtained.

We emphasise that to constitute a grade 5 response (pCR) the site of the previous tumour (now a fibroelastotic scar) should be identified. It was considered inadequate to equate the absence of histological disease with a pCR as this may have just reflected inadequate tissue sampling. Occasionally large segments of breast parenchyma had to be embedded to reveal the defining scar. We recommend embedding the whole of the tumour face of the residual scar and unless this scar is clearly identified, a complete pathological response (Miller/Payne Grade 5) is not accepted in our system.

The overall loss of cellularity after chemotherapy is not always reflected by a decrease in tumour size, either macroscopically or microscopically, as although tumour cells are destroyed, the fibrous stroma remains. Indeed there are several examples of patients exhibiting a complete histological response to chemotherapy, with no residual tumour cells remaining, still having residual palpable disease and macroscopic signs of residual tumour on pathological examination. This is important to note and may help to explain why in previous studies, such as the NSABP B18, the degree of clinical response was not a predictor of survival as patients with residual 'tumours' clinically were actually composed of scar tissue and not malignant cells. Our new classification is only based on histological appearances and thus avoids this difficulty.

Some of the previously reported grading systems have correlated their differing degrees of response with survival. The Kuerer classification[17] has also shown that patients with no evidence of residual tumour have a significantly better 5-year survival (89% vs 64%) and disease-free interval (87% vs 58%). The NSABP B-18 trial[18,21] has shown that patients with a pCR had a 5-year survival of 85.7% vs 76.9% in the pPR group. The Honkoop classification[19] has reported that in a multivariate analysis an improved pathological response to chemotherapy was correlated to both disease-free interval ($P=0.04$) and survival ($P=0.04$). In the Sataloff classification a total or near total therapeutic effect was associated with a significantly increased 5-year survival.[20]

Pathological complete responders account for only 14% of patients in our study. However, there is no consensus on how to grade the different degrees of partial pathological response in the majority of patients. Analysis of the differing degrees of histological response using our novel grading system demonstrated that patients with a grade 5 (pCR) response had a 100% 5 year survival, those with a grade 4 response a 81% 5-year survival and a grade 3 response had a 74% 5-year survival. In contrast those with a grade 2 response had a 60% 5-year survival and if the response was categorised as grade 1 then 63% of patients survived for 5 years.

Further examining our data revels that three distinct groups of histological responses can be identified. Complete histological responders (grade 5) have a significantly better survival than other patients (100%). A second group comprising those with a Grade 3 and 4 responses have a significantly better survival of 74–81%, and patients within a third group with poorer Grade 1 and 2 responses whose survival range from 60% to 63%. There is a similar finding when comparing histological response with disease-free survival in these groups of patients.

A multivariate analysis, examining established key factors, has shown that the histological response, as assessed by our grading system, is an independent prognostic variable for survival. This demonstrates that the degree of histological response to primary chemotherapy does allow identification of those patients with a better prognosis subsequently. In addition, the absence of oestrogen receptors and the absence of residual tumour in the axillary lymph nodes were also independent predictors of a better survival in this group of patients. However, this means that irrespective of the oestrogen receptor status and the lymph node status in a patient, our histological grading system shows that for each incremental increase in having a better histological response, there is a 25% reduction in the risk of the patient dying.

An important area of concern when applying grading systems is their degree of reproducibility in the hands of other pathologists. However, by introducing 'tighter' definitions for the different categories of response we anticipate that this will reduce inter-observer variability. Our grading system has accurately predicted diseased-free survival and overall survival in patients who have received primary chemotherapy for locally advanced breast cancer. Furthermore, our classification is the only one that determines prognosis in those patients who have experienced a non-complete response. This classification expands upon the NSABP-B18 study that considered all patients in the non-complete categories together.

A major implication of our new classification is that as we may now be able to identify a patient's prognosis after completion of primary chemotherapy subsequent treatments can be 'targeted' to individual patients. For example, in patients who fall into the poorer prognosis categories, there is a possibility that further adjuvant chemotherapy with non-cross resistant chemotherapeutic agents could be offered whilst patients in the good prognosis categories require no further chemotherapy. For example, after doxorubicin-based therapy a further schedule with a taxane may be offered to those patients in poor prognosis categories. However, it is recognised that results from randomised trials are required to provide an evidence base for such an approach. Nevertheless, our classification provides the basis for such an approach to be considered.

In summary, therefore, our new grading system, which assesses the main manifestation of pathological response to chemotherapy (reduction in tumour cellularity detected histologically) can identify patients with a better prognosis. The relationship of degree of histological response to overall and disease-free survival has been shown in univariate and multivariate analyses and could potentially have an important role in the clinical management of patients with locally advanced breast cancer undergoing primary chemotherapy.

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