

Preoperative assessment of prognostic factors in breast cancer

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Abstract

The adoption of preoperative diagnostic strategies involving fine needle aspiration cytology (FNAC) or core biopsy is well established, allowing the planning of operating lists and bed occupancy and patient involvement in therapeutic management. In addition to diagnosis, however, pathologists are increasingly being asked to provide pathological prognostic information from preoperative samples. This leader describes techniques for predicting prognosis and response to treatment on these specimens and some of the problems inherent in the determination of prognosis on small samples. For example, although histological grade can be assessed relatively reliably on either core or FNAC samples, the evaluation of tumour type (which includes an overall assessment of the architecture of a given tumour) may be less reliable on small preoperative samples. Other well recognised histological prognostic factors, such as vascular channel invasion or tumour size, cannot be determined accurately on small preoperative samples. For those patients who might benefit from neoadjuvant treatment, predicting the response to such treatments—for example, by the assessment of oestrogen receptor status—can readily be performed on either core biopsy or FNAC. In the future, other molecular markers such as C-erbB-2 might also prove beneficial in predicting response to newly developed treatments.

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Any case of suspected carcinoma of the breast should be evaluated initially with a triple assessment comprising clinical, radiological, and pathological review.^{1–3} Pathological assessment will involve the evaluation of either a fine needle aspiration cytology (FNAC) sample or needle core biopsy (NCB) specimen. The relative frequency of utilisation of these procedures has varied over the past three decades and, in part, depends on local and personal preferences.

FNAC is a technique that has been used for over a century.^{4–5} It is relatively inexpensive and can be performed either freehand or with image guidance (ultrasound or stereotactic). However, it requires regular practice to ensure the maintenance of aspirator skill^{6–7} and may cause difficulty in interpretation for the less experienced pathologist. Thus, training and

experience are required in both the aspirator and the pathologist. Air dried or fixed smears, cytospin, or cytoblock preparations can be used. In addition, a variety of staining methods can be used, including Giemsa, haematoxylin and eosin (H and E), Papanicolaou, Diff-Quick, and periodic acid Schiff (PAS). In the right hands, the procedure is both sensitive (range, 74–96%) and specific (with most series approaching 100%),^{8–10} thereby fulfilling the minimum requirements of the National Health Service Breast Screening Programme (NHS-BSP).¹¹ The main drawback with FNAC, however, is the inability to provide morphological information, making the distinction between in situ and invasive carcinoma impossible at the preoperative stage. Therefore, it may not help in the assessment of the requirement for axillary lymph node dissection (unless a corresponding FNAC of an axillary lymph node reveals metastatic carcinoma).

NCB can also be performed either freehand or with image guidance. The technique can be undertaken by surgeons or radiologists and has more reliable and reproducible results.¹² NCB specimens can also be evaluated easily by histopathologists to whom H and E stained sections are familiar.¹³ However, the patient needs to be given a local anaesthetic, because the needle is larger than that used in FNAC, although the procedure is less traumatic with the newer automated “gun” devices. Even with little experience, good adequacy rates can be achieved, although this does, in part, depend on the number of cores taken.¹⁴ It has been shown to be more sensitive (97%) and specific (100%) than FNAC,¹⁵ and provides useful morphological information, particularly with respect to the presence of invasion in the sample. The presence of screen detected microcalcification may be confirmed and assessed in NCB samples and, in some instances, this can obviate the need for unnecessary surgery when a benign diagnosis is made. For these reasons, many centres have now switched from FNAC to NCB. However, it has been shown that the use of both techniques together provides the best results.^{16–17} The ultimate choice of method used varies according to local and personal preference.

Pathological prognostic factors are used in clinical practice for a variety of reasons. They provide detailed information on the prognosis of an individual patient as a basis for counselling and treatment and may allow stratification of patients according to the treatment regimens that can be used.¹⁸ They allow the comparison of treatments between groups of patients with similar prognoses and help to

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develop our understanding of breast cancer biology, which may permit the development of new treatment modalities. Predictive, as opposed to prognostic, factors can be identified that assist in the identification of an individual or group of patients who would respond to a particular treatment modality (for example, oestrogen receptor positive tumours).

There is an exhaustive selection of putative prognostic factors available for assessment in breast cancer.^{19–20} Some of these may be classified as time dependent or chronological (for example, tumour size, stage, and vascular or lymphatic invasion), whereas the remainder are innate biological features of the tumour. The latter group is extensive and includes histological type and grade, markers of proliferation, tumour DNA content, hormone and growth factor receptors, oncogene/tumour suppressor gene expression, proteases, and second messenger system activity. There is no general consensus as to which of these features should routinely be reported in excision biopsies but tumour grade, lymph node stage, and tumour size have all been shown to be independent prognostic factors in multivariate analysis. These factors, therefore, have been combined to produce the Nottingham prognostic index score.^{21–23} Each patient's tumour has an individual value, which allows the prediction of individual prognosis and decisions can thus be made about appropriate treatment. Other prognostic factors that are routinely recorded within our own practice are tumour type, lymphovascular channel invasion, and oestrogen receptor status.

There are important potential benefits to the identification of prognostic and predictive factors preoperatively on NCB or FNAC. For example, prognostic factor assessment in NCB and FNAC would allow the identification of patients who would benefit from neoadjuvant treatment (predominantly patients with grade 3 tumours); those in whom conservation surgery is inadvisable (patients with definite vascular channel invasion); and those who may benefit from specific treatment modalities (for example, tamoxifen, herceptin). Preoperative assessment, particularly NCB, may be useful in establishing “baseline” information before treatment. In addition, sequential biopsy and radiological assessment may determine the baseline and subsequent response to non-operative management in those patients who are unfit for surgery.

The value of the assessment of prognostic factors in preoperative samples is in part compromised by problems of sampling error: only a small portion of what might be a heterogeneous tumour is obtained and this may not be representative of the tumour as a whole. This might be particularly true for NCB unless multiple samples are taken. Studies have nevertheless shown that grading and typing of invasive carcinoma on NCB and grading on FNAC correlate well with excision specimens (G McKee, *et al.* British Society of Clinical Cytology, 1991)^{24–32} and thus the assessment of

prognostic factors on preoperative samples might not be as unreliable as believed previously.

Evaluation of traditional prognostic factors

TUMOUR GRADE

The grade of an invasive carcinoma of the breast is calculated according to the Nottingham modification of the Bloom and Richardson method.^{33–34} Tubule formation, nuclear pleomorphism, and mitotic frequency are evaluated. Each variable is scored 1–3 and the cumulative score used to assign a numerical grade of 1, 2, or 3 (see UK NHSBSP reporting guidelines³⁴ for more information). The grade derived by this method has been shown in multivariate analysis to be an independent factor in predicting patient prognosis and correlates well with 10 year survival figures.³³ It has been shown in many series to be reproducible when strict criteria are applied to well fixed specimens.^{35–37}

The application of this method to NCB samples appears straightforward because formalin fixation is likely to be optimum. However, as mentioned previously, even if multiple cores are obtained, problems may arise with sampling only a small proportion of a heterogeneous tumour. Tubule formation may therefore be overestimated or underestimated and pleomorphism may be underscored. Mitotic counts might be inaccurate because in tumour grading the periphery of the tumour is assessed—the growing edge of the tumour—where mitotic figures are more frequent. In addition, the core might have an insufficient amount of tumour to allow 10 high power fields to be counted. As a result, the estimation of mitotic frequency might be inaccurate and is generally underscored in the core biopsy sample.^{24–26}

Studies have shown^{24–26–38} that when estimating histological grade, there is a tendency to underscore rather than overscore on core biopsy samples compared with excision specimens. This might result in some patients who would benefit from receiving neoadjuvant treatment (either chemotherapy or radiotherapy) for grade 3 tumours being excluded, but very few would be given unnecessary treatment. This tendency for undergrading has also been documented in prostatic carcinomas,^{39–40} although in these tumours grading is based mainly on architectural features, rather than nuclear pleomorphism and mitotic frequency.

A variety of techniques has been described for grading breast carcinomas in FNAC samples (G McKee, *et al.* British Society of Clinical Cytology, 1991).^{27–32–41} Some use fixed smear preparations,^{32–41} whereas others can be performed on air dried, Giemsa stained smears.²⁷ These methods assess a variety of cytological features, including cell dissociation, nuclear size, cell uniformity, nucleoli, nuclear margin, and nuclear chromatin pattern. Indeed, some groups have confirmed the value of these features individually by morphometry.⁴² Tumours can then be grouped into either high or low grades²⁷ or grades 1 to 3³² accordingly.

These values have been shown to correlate well with histological grade on excision specimens. In addition, with the McKee system⁵² of cytological grading, most lobular carcinomas (excluding pleomorphic lobular tumours) will be classified as grade 1, whereas on histology these are predominantly, although not invariably, grade 2 tumours, scoring 3 for tubules, 2 for pleomorphism, and 1 for mitotic counting. Although these results do compare with grade on histology, their routine use in preoperative FNAC specimens is not currently advocated in the UK NHSBSP.¹¹ It should also be noted that it is not possible to discriminate between in situ and invasive disease on cytology and the grade described may be given to a case of pure ductal carcinoma in situ.

TUMOUR TYPE

Invasive carcinomas are separated on morphological grounds into one of a variety of specialised types, mixed type, or ductal/no special type (NST).³⁵ Special types include tubular, cribriform, mucinous, lobular, and medullary. Further subtyping can be performed and infiltrating lobular carcinoma may be classified as being a classic, alveolar, solid, or tubulolobular variant. Mixed forms including tubular mixed, mixed lobular, NST, or special type plus NST can be identified. Tumour type has been shown to correlate with long term survival,⁴³⁻⁴⁵ but is of less prognostic importance than grade.⁴⁶ This may be because type and grade show complex inter-relations (for example, tubular carcinomas are by definition grade 1 and medullary carcinomas invariably grade 3).

Histological typing of invasive breast tumours is carried out on well fixed samples and involves the assessment of several blocks to determine all of the features present. The evaluation of a variety of features including the extent of tubule formation, the presence of lymphoid stroma, mucin production, syncytial or discohesive growth pattern, and "Indian file" formation allows tumours to be separated according to type. Some groups have suggested that the presence of an invasive lobular component might guide the surgeon to expand the area of excision, because the clinical assessment of the overall extent of tumour invasion is difficult and incomplete removal is more likely.⁴⁷

The evaluation of tumour type is fraught with the same difficulties as grade assessment on NCB. This again stems from the possible problem of obtaining a sample that is not representative of the tumour as a whole. However, certain types can be recognised on NCB (such as mucinous or lobular), although the possibility of a mixed tumour cannot be ruled out. A common problem with attempting to ascribe tumour type on NCB is the confusion between tubular mixed (or tubular variant) carcinomas and invasive NST carcinoma.²⁴ This is a result of sampling error and tumour heterogeneity, because tubular mixed carcinomas show a central elastotic area with tubule formation, surrounded by an area resembling invasive NST carcinoma.

It is not possible to confirm the presence of invasive carcinoma on FNAC, so the accurate classification of tumour type is also impossible. However, some information may be obtained to give an indication of type—for example, a mucinous background might suggest a mucinous phenotype, whereas intracytoplasmic mucin or lumina or Indian file rows of cells favour lobular carcinoma.²⁷

TUMOUR SIZE

This is a time dependent prognostic factor, with smaller predicting increased survival.^{21 48-51} Although on NCB an evaluation of the minimum size of the tumour may be made, neither FNAC nor NCB is of practical day to day use in the measurement of this parameter. Clinical preoperative assessment is also of limited value, with poor correlation between clinical assessment and the size of the excised tumour. If a preoperative estimate of size is required, this should be performed ultrasonographically.⁵²

VASCULAR CHANNEL INVASION

Vascular invasion can be assessed on NCB and may, in association with high grade, indicate patients who require postoperative adjuvant treatment. However, although the presence of definite or probable vascular channel invasion is specific (when identified on NCB, this is confirmed on excision sampling), it is not sensitive (not all cases with vascular invasion on histology are identified on NCB).^{24 38} The presence of histologically confirmed vascular channel invasion is associated with an increased risk of metastatic disease, increased risk of local recurrence, and reduced survival.⁵³ FNAC cannot be used to determine vascular invasion in invasive breast carcinoma.

LYMPH NODE STAGE

Unless samples (either NCB or FNAC) are also taken from axillary lymph nodes at the time of preoperative assessment, the presence of nodal metastases cannot be predicted preoperatively.

HORMONE RECEPTORS

Oestrogen receptors (ER) and progesterone receptors (PR) are nuclear steroid hormone receptors. Their activation is linked with the regulation of certain genes, particularly those controlling cell growth. The ER status of a tumour correlates well with patient response to antioestrogen treatments, particularly tamoxifen, but also to gonadotrophin releasing hormone analogues.⁵⁴⁻⁵⁶ Therefore, it can be used to identify those patients who might benefit from neoadjuvant endocrine treatment. The combination of the assessment of ER and PR may further refine the prediction of the response to endocrine treatment. However, the ER status does not have independent prognostic value because of its close relation with tumour grade. Thus, ER is best considered as a "predictive" rather than prognostic factor.

On excision samples, ER status is now routinely calculated after immunohistochemical labelling of the receptor. This may be

performed on formalin fixed, paraffin wax embedded tissue, using an avidin-biotin complex-peroxidase labelling technique. Numerical scores can be obtained by assessment of the intensity of staining and the percentage of tumour cells stained,⁵⁷ or by a semiquantitative estimate of only the proportion of nuclei expressing the receptor.⁵⁸ The same technique can be applied to NCB specimens and may also be used for PR status. However, it is important to remember that these are labile soluble antigens and appropriate specimen preparation is vital. The main drawback with their evaluation on preoperative samples is again that of tumour heterogeneity.

ER status assessment of FNAC samples can be carried out using a similar technique to that described for NCB, although different antibodies might be required. However, it is important to be certain that only tumour nuclei are scored, because some normal breast epithelial cells are ER and PR positive, whereas other stromal cells are negative. The inadvertent inclusion of these nuclei in scoring methods will falsely affect the overall score. The assessment of hormone receptors on cytology also requires an additional slide or a cytoblock to be prepared in advance.

MOLECULAR MARKERS

Apart from the hormone receptors outlined above, a wide range of other molecular markers has been identified in breast cancer. Many of these are of disputed independent prognostic relevance and the list is too exhaustive to make the assessment of these practicable in everyday reporting. Most are associated with mechanisms of differentiation, cell growth, and replication or with vascular invasion and metastatic potential. These markers include epithelial mucins (MUC1/EMA),⁵⁹⁻⁶⁰ tumour suppressor genes (p53, retinoblastoma gene),⁶¹⁻⁶³ oncogenes (c-myc, c-erbB-2, ras),⁶⁴⁻⁶⁶ proteases (cathepsin D),⁶⁷⁻⁶⁸ growth factor receptors (epidermal growth factor receptor),⁶¹⁻⁶⁹ proliferation markers (ki-67/Mib1),⁶⁸⁻⁷⁰ adhesion molecules (E-cadherin, integrins, catenins),⁷¹ and tumour DNA ploidy and S-phase fraction.⁷²⁻⁷³ Many can be assessed by immunohistochemical methods, but the amount of tumour sample required makes their evaluation on small preoperative samples impractical. In addition, although many are of confirmed prognostic value in univariate analysis, their main role is to add information to those factors that reach independent significance (see above), or as research tools in the attempt to understand tumour biology and the development of new treatments.

Early results of antimono-clonal antibody treatments with the novel agent Herceptin show promising results. Therefore, the assessment of *cerbB2* (Her2/neu) on NCBs might be useful to identify those patients with tumours suitable for inclusion in therapeutic trials. This may be performed by the determination of the oncoprotein by immunohistochemistry or the identification of gene amplification by fluorescent *in situ* hybridisation.

Conclusion

The evaluation of pathological prognostic factors in preoperative breast samples is a worthwhile activity, providing useful information on the presence of invasion (NCB) and tumour grade (NCB and FNAC). It occasionally provides information on vascular channel invasion (NCB) and also some clues as to tumour type (NCB and FNAC). More usefully, hormone receptors may be evaluated. However, as in any other field in histopathology, the evaluation of all of these features requires regular practice and audit of the techniques and methodologies used, with respect to sampling (smear, cytospin, or cytoblock preparation), staining, and pathological interpretation. The use of some of these techniques allows the identification of patients who might benefit from particular treatment modalities and may provide useful information regarding individual patient prognosis.

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