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REVIEW

The Nottingham Prognostic Index for Invasive Carcinoma of the Breast

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Abstract A useful prognostic factor in breast cancer has key roles, including identification of a group of patients whose prognosis is so good they do not require further treatment, such as adjuvant systemic therapy, after local surgery, and secondly a group with a poor prognosis for whom additional treatment would be appropriate. To be of clinical use, prognostic factors must show a wide separation in the outcome of the groups identified and select adequate numbers in each group. No single prognostic factor in invasive carcinoma of the breast satisfies all these criteria. However, the Nottingham prognostic index (NPI), which combines nodal status, tumour size and histological grade, does satisfy these criteria. The NPI has been validated by further studies in Nottingham and by studies in several other countries. Predictive factors, such as oestrogen receptor and HER-2 status, predict whether a tumour is likely to respond to a treatment, and are complimentary to prognostic factors. The NPI can be used in combination with predictive factors to select patients for systemic adjuvant treatments. There is the potential to improve the NPI by inclusion of other factors, such as vascular invasion, but any such alterations would require further validation.

Keywords Carcinoma of breast · Histological grade · Prognosis · Nottingham prognostic index

Abbreviation
NPI Nottingham Prognostic Index

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Prognostic factors in invasive carcinoma of the breast have been studied for a long time, but have only recently become of routine clinical utility after the development of increasing numbers of therapeutic options producing a need for tools to stratify patients for selection for further treatment, for example systemic adjuvant therapy. A useful prognostic factor will identify a group of patients whose prognosis is so good that adjuvant therapy after local surgery would not be cost beneficial and a second group with a poor prognosis for which adjuvant treatment would be warranted [1]. To be of clinical use, prognostic factors must show a wide separation in the outcome of the groups identified and select adequate numbers in each group [2]. No single prognostic factor satisfies all these criteria. Predictive factors, which predict whether a tumour is likely to respond to a treatment, are complimentary to prognostic factors and are used to select the most appropriate additional therapy for a patient when required. The classical example is oestrogen receptor status, which predicts response to endocrine treatment such as tamoxifen.

The Nottingham Prognostic Index (NPI) combines three prognostic factors: nodal status, tumour size and histological grade. The NPI is not applied to patients with distant metastases; such patients will usually die from their disease and an alternative metastatic index can be used to guide treatment in this group.

Nodal status has traditionally been regarded as the most powerful prognostic factor in breast cancer. The greater the number of nodes involved, the worse the prognosis [3, 4]. For the NPI, three categories, comparable to the UICC categories, are used. Stage 1 includes patients with no nodal involvement. Stage 2 means involvement of either up to 3 low axillary nodes or of the internal mammary node (assessed in medially located tumours). Stage 3 means involvement of four or more low axillary nodes and/or the

apical axillary node or of both low axillary and internal mammary nodes. There has been recent interest in occult metastases detected with immunohistochemistry or polymerase chain reaction, but not seen on conventional haematoxylin and eosin sections. Although such small metastases are associated with a worse prognosis in some studies, they do not appear to add prognostic information to histological grade, tumour size and vascular invasion, which all have strong evidence as prognostic factors in node-negative patients [5]. We regard nodes with tumour deposits up to 0.2 mm (isolated tumour cells) as node-negative, and tumour deposits of 0.2 mm and above as metastases, consistent with the TNM guidelines [6].

Tumour size is based on measurement of the invasive component in histological sections. Increasing tumour size is associated with a worsening prognosis [4]. This is a time dependant factor—tumour size increases with time.

The third factor is the internationally accepted Nottingham modification of the Scarff–Bloom–Richardson method of assessing histological grade [7]. A score combining assessment of three features is used: the degree of tubule formation, nuclear pleomorphism and mitotic count. Histological grade requires well fixed tissue for accurate assessment. We receive surgical resections for cancer straight from the operating theatre and immediately incise the tumour to ensure good fixation. Histological grade is a measure of the biological aggressiveness of the tumour and usually does not change with time.

Each of these prognostic factors contribute important but qualitatively different information. Alone, no single prognostic factor satisfies all the desirable criteria mentioned in the opening paragraph. However in combination these factors become more potent by contributing both biological and time dependent prognostic information. The NPI was derived from an initial prospective study. The Nottingham Tenovus Primary Breast Cancer Study was set up in 1973 to investigate prognostic factors. Patients less than 71 years with primary operable breast cancer (clinically less than 5 cm) were included. The initial analysis was based on 9 factors studied in 387 patients [8]. Three factors, found to be independently associated with survival on multivariate analysis, were combined to give the NPI.

$$\text{Nottingham Prognostic Index} = \text{Lymph node stage}(1-3) + \text{Histological grade}(1-3) + \text{Tumour size(cm)} \times 0.2$$

The NPI has been validated by further studies in Nottingham and by studies from several other countries [9–11]. The latest study from Nottingham looked at two groups of patients from the 1980s when no adjuvant systemic treatment was given and from the 1990s after the start of mammographic screening and when adjuvant systemic treatment was given to selected patients, and there was more attention to surgical margins. Patients from both eras could be stratified using the NPI into six groups with good numbers in each group and very divergent outcome (see Table 1).

The NPI is an excellent tool for stratifying the prognosis of patients. The benefits of adjuvant systemic treatments, such as chemotherapy, are proportional to the risk of death from breast cancer. In combination with predictive factors (oestrogen receptor and HER-2 status), menopausal status and patient wishes, the NPI is useful for giving advice about the choice of adjuvant systemic treatments. For example, patients with a node-negative tumour less than 10 mm or with an NPI less than three have survival comparable to age matched controls. In Nottingham, such patients are usually not offered adjuvant systemic treatments as there is negligible, if any, potential benefit.

The NPI can also be used for counselling. For example, a woman who wants to have children can be told the risks associated with her tumour.

Other pathological factors can be useful for other clinical decisions. For example, the distance of tumour to the margin, presence of vascular invasion and patient age are used to decide if the margins are adequate after breast conserving surgery. Tumour grade, nodal status, vascular invasion and patient age are used to select patients for radiotherapy boost to the tumour bed after breast conserving surgery.

Table 1 The prognostic value of the NPI in two eras [ref 12]

Group	NPI	1980–1986		1990–1999	
		Proportion of patients (%)	10 year survival (%)	Proportion of patients (%)	10 year survival (%)
Excellent	2.02–2.4	12	88	15	96
Good	2.41–3.4	19	72	21	93
Moderate 1	3.41–4.4	29	61	28	81
Moderate 2	4.41–5.4	24	42	22	74
Poor	5.41–6.4	11	15	10	55
Very poor	6.41–6.8	5	12	4	38

The NPI includes only three factors and there is the potential to improve it. Microarray analysis has been used to generate gene profiles associated with prognosis [13]. Gene microarrays have also generated a new classification of breast carcinomas, which highlight the importance of hormone receptors, HER-2 and basal cytokeratins. This classification can be replicated using protein expression [14]. A recent analysis suggested that the NPI can be improved a little by the inclusion of other factors including vascular invasion, basal phenotype and HER-2 status [15]. Another factor worthy of study is histological types associated with a good prognosis (mucinous, tubular and cribriform). Of these factors, the one with the most evidence to support its inclusion is vascular invasion in patients with node-negative disease [16, 17]. One of the great advantages of the NPI is its simplicity and modification is likely to make it more complicated. Any revision of the NPI will need to be validated in the same way as the original NPI.

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