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Non-histopathological Parameters Associated with Upgrade of Breast Tumours Yielding a Core Biopsy report of Histological Grade 2 Ductal no Special Type to Grade 3 on Excision

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Abstract

Purpose: The aim of the study was to identify clinical, radiological and immuno-histochemical factors that may help predict upgrade of invasive ductal cancers of no special type (IDC-NST) with a core biopsy grade of 2 to grade 3 on final histology.

Methods: A prospectively maintained database of ultrasound visible solid masses was used to identify lesions yielding a core biopsy result of IDC-NST grade 2 who underwent immediate surgery yielding a grade 2 or grade 3 tumour. Associations were sought between the source of patient (screening/symptomatic), core biopsy receptor status and imaging findings and the grade of the excision specimen tumour. Statistical analysis, which included the chi-squared test, ROC curves and Cox regression analysis, was used to compare upgrade vs no upgrade for each factor.

Results: 463 IDC-NST breast cancers of core biopsy grade 2 gave 344 grade 2 and 119 grade 3 tumours at excision. Factors significantly associated with upgrade were large ultrasound (US) size, hyperechogenicity, stiffness at shearwave elastography (SWE), calcification on mammography and oestrogen receptor (ER) and progesterone receptor (PR) negativity. Patient source, Human epidermal growth factor receptor 2 (HER-2) status, ultrasound (US) distal effect and mammographic spiculation were not significantly associated with chance of upgrade. On multivariate analysis, only US size maintained statistical significance.

Conclusion: Oncologists and surgeons should be aware that lesions with a core biopsy diagnosis of grade 2 IDC-NST measuring over 15mm on US have a 37% chance of being grade 3 on excision and this should be considered when deciding pre-operative management.

Introduction

The use of Neoadjuvant chemotherapy (NACT) is becoming increasingly common in the clinical management of breast cancer {ADDIN CSL_CITATION { "citationID" : "a2ht547ougg", "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/j.clon.2017.06.003", "ISSN" : "0936-6555", "abstract" : "Neoadjuvant treatment offers a number of benefits for patients with early breast cancer, and is an important option for consideration by multidisciplinary teams. Despite literature showing its efficacy, the use of neoadjuvant therapy varies widely. Here we discuss the clinical evidence supporting the use of neoadjuvant therapy in early stage breast cancer, including patient selection, monitoring response, surgery and radiotherapy considerations, with the aim of assisting multidisciplinary teams to determine patient suitability for neoadjuvant treatment.", "author" : [{ "dropping-particle" : "", "family" : "Cain", "given" : "H.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Macpherson", "given" : "I. R.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Beresford", "given" : "M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Pinder", "given" : "S. E.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Pong", "given" : "J.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }, { "dropping-particle" : "", "family" : "Dixon", "given" : "J. M.", "non-dropping-particle" : "", "parse-names" : false, "suffix" : "" }], "container-title" : "Clinical Oncology", "id" : "ITEM-1", "issue" : "10", "issued" : { "date-parts" : [["2017", "10"]] }, "page" : "642-652", "title" : "Neoadjuvant Therapy in Early Breast Cancer: Treatment Considerations and Common Debates in Practice", "type" : "article-journal", "volume" : "29" }, "uri" : ["http://zotero.org/users/local/N5k1xoZW/items/KEIR2A9L"], "uris" : ["http://zotero.org/users/local/N5k1xoZW/items/KEIR2A9L", "http://www.mendeley.com/documents/?uuid=4bfae2e9-a996-4910-9a59-c24367fd5900"] }], "mendeley" : { "formattedCitation" : "(1)", "plainTextFormattedCitation" : "(1)" }, "properties" : { "formattedCitation" : "(1)", "plainCitation" : "(1)" }, "schema" : "https://github.com/citation-style-language/schema/raw/master/csl-citation.json" }}. The benefits of NACT include down-staging the breast and axillary disease to allow less surgery as well as converting inoperable disease to operable (2). It is, however, important to clarify whether the patient requires chemotherapy before administration of NACT. This decision usually takes place in a multi-disciplinary team meeting. The initial diagnosis and decision for NACT is based on the breast and axillary core needle biopsy results as well as the clinical and imaging features of the tumour. An important factor in this decision is the grade of the tumour as high grade tumours are known to have a poorer prognosis but are more chemo-sensitive in comparison with lower grade tumours {ADDIN CSL_CITATION { "citationID" : "a1m71h77ono", "citationItems" : [{ "id" : "ITEM-1", "itemData" : { "DOI" : "10.1016/S0140-6736(13)62422-8", "ISSN" : "0140-6736", "abstract" : "Summary\nPathological complete response has been proposed as a surrogate endpoint for prediction of long-term clinical benefit, such as disease-free survival, event-free survival (EFS), and overall survival (OS). We had four key objectives: to establish the association between pathological complete response and EFS and OS, to establish the definition of pathological complete response that correlates best with long-term outcome, to identify the breast cancer subtypes in which pathological complete response is best correlated with long-term outcome, and to assess whether an increase in frequency of pathological complete response between treatment groups predicts

improved EFS and OS. We searched PubMed, Embase, and Medline for clinical trials of neoadjuvant treatment of breast cancer. To be eligible, studies had to meet three inclusion criteria: include at least 200 patients with primary breast cancer treated with preoperative chemotherapy followed by surgery; have available data for pathological complete response, EFS, and OS; and have a median follow-up of at least 3 years. We compared the three most commonly used definitions of pathological complete response¹⁴ ypT0 ypN0, ypT0/is ypN0, and ypT0/is¹⁴ for their association with EFS and OS in a responder analysis. We assessed the association between pathological complete response and EFS and OS in various subgroups. Finally, we did a trial-level analysis to assess whether pathological complete response could be used as a surrogate endpoint for EFS or OS. We obtained data from 12 identified international trials and 11²⁰⁰⁸⁹⁵⁵ patients were included in our responder analysis. Eradication of tumour from both breast and lymph nodes (ypT0 ypN0 or ypT0/is ypN0) was better associated with improved EFS (ypT0 ypN0: hazard ratio [HR] 0^{00b744}, 95% CI 0^{00b739}²⁰¹³⁰0^{00b751}; ypT0/is ypN0: 0^{00b748}, 0^{00b743}²⁰¹³⁰0^{00b754}) and OS (0^{00b736}, 0^{00b730}²⁰¹³⁰0^{00b744}; 0^{00b736}, 0^{00b731}²⁰¹³⁰0^{00b742}) than was tumour eradication from the breast alone (ypT0/is; EFS: HR 0^{00b760}, 95% CI 0^{00b755}²⁰¹³⁰0^{00b766}; OS 0^{00b751}, 0^{00b745}²⁰¹³⁰0^{00b758}). We used the ypT0/is ypN0 definition for all subsequent analyses. The association between pathological complete response and long-term outcomes was strongest in patients with triple-negative breast cancer (EFS: HR 0^{00b724}, 95% CI 0^{00b718}²⁰¹³⁰0^{00b733}; OS: 0^{00b716}, 0^{00b711}²⁰¹³⁰0^{00b725}) and in those with HER2-positive, hormone-receptor-negative tumours who received trastuzumab (EFS: 0^{00b715}, 0^{00b709}²⁰¹³⁰0^{00b727}; OS: 0^{00b708}, 0^{00b703}, 0^{00b722}). In the trial-level analysis, we recorded little association between increases in frequency of patho²⁰²⁶, "author": [{ "dropping-particle": "", "family": "Untch", "given": "Michael", "non-dropping-particle": "", "parse-names": false, "suffix": "" }, { "dropping-particle": "", "family": "Mehta", "given": "Keyur", "non-dropping-particle": "", "parse-names": false, "suffix": "" }, { "dropping-particle": "", "family": "Costantino", "given": "Joseph P", "non-dropping-particle": "", "parse-names": false, "suffix": "" }, { "dropping-particle": "", "family": "Wolmark", "given": "Norman", "non-dropping-particle": "", "parse-names": false, "suffix": "" }, { "dropping-particle": "", "family": "Bonnetoi", "given": "Herv^{00e9}", "non-dropping-particle": "", "parse-names": false, "suffix": "" }, { "dropping-particle": "", "family": "Cameron", "given": "David", "non-dropping-particle": "", "parse-names": false, "suffix": "" }, { "dropping-particle": "", "family": "Gianni", "given": "Luca", "non-dropping-particle": "", "parse-names": false, "suffix": "" }, { "dropping-particle": "", "family": "Valagussa", "given": "Pinuccia", "non-dropping-particle": "", "parse-names": false, "suffix": "" }, { "dropping-particle": "", "family": "Swain", "given": "Sandra M", "non-dropping-particle": "", "parse-names": false, "suffix": "" }, { "dropping-particle": "", "family": "Prowell", "given": "Tatiana", "non-dropping-particle": "", "parse-names": false, "suffix": "" }, { "dropping-particle": "", "family": "Loibl", "given": "Sibylle", "non-dropping-particle": "", "parse-names": false, "suffix": "" }, { "dropping-particle": "", "family": "Wickerham", "given": "D Lawrence", "non-dropping-particle": "", "parse-names": false, "suffix": "" }, { "dropping-particle": "", "family": "Bogaerts", "given": "Jan", "non-dropping-particle": "", "parse-names": false, "suffix": "" }, { "dropping-particle": "", "family": "Baselga", "given": "Jose", "non-dropping-particle": "", "parse-names": false, "suffix": "" }, { "dropping-particle": "", "family": "Perou", "given": "Charles", "non-dropping-particle": "", "parse-names": false, "suffix": "" }, { "dropping-particle": "", "family": "Blumenthal", "given": "Gideon", "non-dropping-particle": "", "parse-

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Multiple studies have shown that the upgrade rate of all grades 1 and 2 IDC-NST breast cancers on final histology, from core to excision biopsy, is between 13-25% (4-9). These patients may be denied NACT based on their estimated core needle biopsy grade when in fact they may have benefited from such therapy. There have been attempts to reduce the upgrade rate by modifying the grade definitions at core biopsy, however these modifications are yet to gain widespread acceptance (10,11). Upgrades are more common in ductal cancers than

lobular cancers because the proportion of lobular cancers which are grade 3 is lesser than ductal cancers.

A number of previous studies have shown correlations between imaging features and histological grade, in particular, mammographic calcification has been shown to be a high-grade feature (12), whereas spiculation is more common in low grade lesions (13). At ultrasound (US), a well-circumscribed margin and distal bright up (acoustic enhancement) are common features of high grade (13), especially triple negative tumours (14-16). Shearwave elastography (SWE) is an ultrasound technique gaining widespread acceptance and stiffness at SWE has been shown to be associated with high histological grade (17). High grade cancers are known to be more common in symptomatic cancers compared to screen detected cancers (18). The aim of the study was to identify clinical, radiological and immunohistochemical factors that may help predict upgrade of IDC-NST tumours with a core biopsy grade of 2 to grade 3 on final histology of the excision specimen.

Methods

A prospectively maintained database of ultrasound visible solid masses has been kept since January 2010. The requirement for patient consent was waived by the local ethics committee. Parameters such as US size, stiffness at SWE, the source of the patient (screening/symptomatic), core biopsy grade, receptor status and final histopathological features were also collected prospectively. The assessment of hormone receptor status (ER, PR, HER2) were carried out as described (19). HER2 testing was in line with UK guidelines (20). CNB was performed using a 14 gauge needle under US control with two passes through the region of interest. Lesions yielding a core biopsy result of IDC-NST grade 2 who underwent immediate surgery yielding a grade 2 or grade 3 tumour were the study group.

An experienced breast radiologist, who was blinded to the histopathological outcome, conducted a retrospective analysis of greyscale US and mammographic features. Particularly, attention was given to features previously shown to be associated with histological grade. US features collected included echogenicity (hypoechoic, isoechoic, hyperechoic and heterogenous), distal effect (shadowing, none, enhancement) lesion orientation and whether the lesion was circumscribed. Mammographic features documented were the presence or absence of spiculation and calcification.

Associations between individual parameters and upgrade from grade 2 to grade 3 were performed using the chi-squared test and chi-squared test for trend. For continuous variables, ROC curves were generated and the area under the curve (AOC) measured. Multivariate analysis using Cox regression analysis was performed including those factors shown to be statistically significant at univariate analysis. Medcalc software (version) was used for statistical analysis.

Results

A total of 490 invasive IDC-NST breast tumours of core biopsy grade 2, treated by immediate excision were identified. The age range was 23-91 with a mean age of 62 years. The number of breast tumours that remained grade 2, were upgraded to grade 3 or downgraded to grade 1 on excision from core biopsy grade 2 were 344 (70.1%), 119 (24.2%) and 27 (5.5%) respectively. Breast lesions that were downgraded were excluded from the study, as they did not meet inclusion criteria. This left a study group of 463 lesions. Table 1 summarises results from of clinic factors, mammographic and ultrasound features.

Clinical factors

Lesions presenting through screening had an upgrade rate of 21.7% (48/221) compared to symptomatic lesions where the upgrade rate was found to be 29.3 % (71/242). These differences were of borderline significance ($p=0.06$).

Lesions in patients > 50 years old had an upgrade rate 26.3%(105/400) of compared to 22.2% (14/63) for those \leq 50 years old. This difference was not statistically significant.

Mammographic features

Spiculated lesions had an upgrade rate of 23.6% (55/233) compared to non spiculated lesions which had an upgrade rate of 27.8% (64/230). This difference was not statistically significant ($p=0.30$).

Lesions which were calcific on mammography had an upgrade rate of 35.2% (upgrade 37, no upgrade 68) compared to 22.9% for non-calcific lesions (82/358). This difference was statistically significant ($p=0.011$)

Ultrasound and Shearwave Elastography features

The relationship between US size and upgrade is demonstrated in an ROC curve (figure 1) for which a ROC curve was generated (Graph 1). The area under curve was 0.65 and ($p = <0.0001$) was statistically significant. The upgrade rate by US size group is shown in Table 2.

US lesions that were circumscribed had an upgrade rate of 27.2% (22/81) compared with an upgrade rate of 25.4% for lesions that did not exhibit this feature ($p=0.74$)

Lesions on US scan which were parallel had an upgrade rate of 27% (87/322) compared to 22.7% for lesions that were non-parallel ($p=0.33$).

Breast lesions that displayed a hyper-echoic element on US had an upgrade rate of 37.2% (29/78) compared to 23.4% (90/384) for those that did not exhibit this feature. The difference between these two groups was found to be statistically significant ($p=0.01$)

Breast lesions that displayed enhancement for posterior effect had an upgrade rate of 34.9% (15/43) compared to 24.8% (104/419) for those that did not exhibit this feature ($P=0.15$).

A ROC curve was generated for stiffness on SWE and upgrade. This showed an AUC of 0.56 and the result was found to be statistically significant ($p=0.037$) with stiff lesions more likely to be upgraded.

Receptor Status

An upgrade rate of 40% (14/35) was found in lesions that were HER2+ve compared to 25.4% (106/418) for HER2-ve lesions. This difference was of borderline significance ($p=0.059$). A ROC curve was generated for ER receptor status which showed an AUC of 0.55 and a statistical significant result ($p=0.034$) associating ER negativity and upgrade. For PR receptor status, an ROC curve was also generated which showed an AOC of 0.55 and a statistical significant result (0.034) associating PR negativity and upgrade.

Multivariate analysis

On multivariate analysis of parameters significant at univariate analysis using Cox regression analysis only US size maintained statistical significance.

Discussion

A number of clinical, radiological and immunohistochemical factors were analysed to study their value in predicting upgrade from a CNB estimate of IDC-NST grade 2 carcinoma to grade 3 on excision. Although a number of factors had weak but significant associations with upgrade, the only factor with independent prediction of upgrade was found to be lesion size on US. The addition of other factors did not significantly improve upgrade prediction.

Prognostic factors, such as receptor status, are known to correlate well between CNB and excision specimen (21, 22). On the other hand, grading on CNB is known to be less accurate with a concordance of 71.1% between core grade and excision grade on a recent meta-analysis by Knuttel et al (23). Furthermore, this meta-analysis found there to be an issue of both over and underestimation of grade between CNB and excision in 9.3% (7.7-11.4%) and 19.1% (17.1-21.3%) respectively. These findings are comparable to our study where we found over and underestimation in 5.5% and 24.2% respectively. Nonetheless, CNB grade estimation is useful in clinical practice and is used widely to guide pre-operative therapy.

A number of studies have shown that a peak agreement for diagnosis of malignancy on CNB is achieved after 4-5 core biopsies are taken (24-27). Histological grade, which is usually assessed using the Nottingham Scoring system, looks at tubular formation, nuclear pleomorphism and mitotic count has been widely accepted as an independent and significant prognostic factor in breast cancer (28). A major factor causing underestimation of histological grade at CNB is the mitotic count which may be underestimated due to the small sample size (29). Previous attempts at reducing the rate of upgrade have focused on histological factors such as mitotic count as concordance for mitotic count between core and excision specimen may be as low as 62.4% (23), however suggested alterations to grading practice for core biopsies to improve concordance are yet to gain wide-spread acceptance (10, 30). The heterogeneous nature of large breast tumours may also be a factor in producing an unrepresentative CNB samples (31).

Currently, most centres will only perform two US guided core biopsies passes of an US visible mass routinely and only take more samples if the needle has missed the lesion on previous passes. It is likely that histological upgrade would be less frequent if more tissue was taken. This could either be achieved more passes using a 14 gauge CNB or using a vacuum assisted biopsy (VAB) device to increase the size of each core. The use of VAB has previously been shown to significantly reduce the upgrade rate from DCIS at biopsy to invasion at excision (32, 33). However, we are not aware of any studies using VAB to achieve greater concordance between percutaneous biopsy and excision grade for invasive cancers. It is debatable whether the additional morbidity and cost is outweighed by the gain in grade consistency. However, a large American study has shown that VAB is more cost-effective than CNB, specifically tethered and large gauge VAB instruments, in the context of mean cost per diagnosis of malignancy (34). However, such cost effective scenarios are likely to be very different in a European setting.

Nonetheless, the importance of histological grade in estimating the need for, and sensitivity to NACT as well as the increased use of NACT means the balance between morbidity and cost compared with the benefits of accuracy of pre-operative grading needs revisiting. A number

of publications have emphasized the relationship between histological grade and chemosensitivity (35, 36). Recent studies have focused on expression of cytokeratins (CK) which are intermediate filament proteins found in the cytoskeleton that suggest the epithelial cell type, tissue growth and differentiation of breast tumours. A large study has shown that expression of basal phenotype (CK 5/6, CK14) and ER –ve receptor status was significantly associated with histological grade 3 (37). Another study found that about 20% of ductal NST grade 3 expressed CK14 (38). Currently, these markers are not used in routine practice but future research focusing on role of basal markers in predicting upgrade may be useful.

Calcification at mammography is known to be associated with high grade invasive cancer, especially HER-2 positive disease (39). The association we found between upgrade and mammographic calcification was therefore not surprising. However hyperechogenicity of tumours on US is not known to be associated with high histological grade. Our finding of an association between high upgrade rate in hyperechogenic tumours was therefore unexpected and is difficult to explain. Stiffness at SWE is known to be associated with high histological grade and large tumour size (17). The weak correlation between high stiffness and high upgrade rate is therefore to be expected.

The limitations of this work include being a single centre study where grading has been performed by four expert pathologists. However, the size of the study is large with over 100 events (upgrades from grade 2 to grade 3). Therefore, the borderline nature of some of the associations found reflect a true weakness of associations rather than a consequence of small sample size. A small percentage of invasive cancers not apparent on US were not included in the data as the data source was a US database.

In conclusion, our study has shown that the most significant factor associated with upgrade from grade 2 IDC NST at core biopsy to grade 3 on excision was US size. Other weaker associations of upgrade such as micro-calcification on mammography, hyperechogenicity on US, ER negativity, PR negativity and stiffness at SWE did not maintain significance at multivariate analysis. We therefore suggest clinicians need to be aware that lesions over 15mm in US size which have a core grade of 2 have a 37% chance of being grade 3 on excision and this should be considered when deciding pre-operative management.

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Table 2:

US size	Grade 2 at excision	Grade 3 at excision
<10mm	112	14(11%)
10-15mm	123	42(25%)
16-20mm	54	29(35%)
21-30mm	39	23(37%)
>30mm	16	11(41%)

Table 1

	Factor	Number of patients upgraded/total	Upgrade rate (%)	P-value
Clinical factors	>=55 years old	105/400	26.3	0.497
	< 55 years old	14/63	22.2	
	Screening	48/221	21.7	0.060
	Symptomatic	71/242	29.3	
Mammography	Spiculation	55/233	23.6	0.300
	No spiculation	64/230	27.8	
	Calcification	37/105	35.2	0.011
	No calcification	82/358	22.9	
Ultrasound	Circumscribed	22/81	27.2	0.740
	Non-circumscribed	97/382	25.4	
	Parallel	87/322	27	0.330
	Non-parallel	32/141	22.7	
	Hyperechoic feature	29/78	37.2	0.010
	No hyperechoic feature	90/385	23.4	
	Posterior effect	15/43	34.9	0.150
	No posterior effect	104/420	24.8	
Receptor Status	HER2 positive	14/35	40	0.059
	HER 2 negative	106/419	25.4	

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