Is it always necessary to perform an axillary lymph node dissection after neoadjuvant chemotherapy for breast cancer?

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ABSTRACT

INTRODUCTION Recent prospective studies support the feasibility of performing sentinel lymph node biopsy following neoadjuvant chemotherapy in initially fine-needle aspiration cytology or ultrasound-guided biopsy-proven node-positive breast cancer. The main aim is to identify preoperative features that help us predict a complete axillary response to neoadjuvant chemotherapy in these patients and thus select the candidates for sentinel lymph node biopsy post-neoadjuvant chemotherapy to avoid unnecessary axillary lymphadenectomy.

MATERIALS AND METHODS A retrospective observational study with a total of 150 patients, biopsy-proven node-positive breast cancer who underwent neoadjuvant chemotherapy followed by breast surgery and axillary lymphadenectomy were included and retrospectively analysed. A predictive model was generated by a multivariate logistic regression analysis for pathological complete response-dependent variable.

RESULTS The response of the primary lesion to neoadjuvant chemotherapy according to post-treatment magnetic resonance imaging, *Her2/neu* overexpression and a low estrogen receptor expression are associated with a higher rate of nodal pathologically complete response. The multivariate model generated a receiver operating characteristic curve with an area under the curve of 0.79 and a confidence interval of 0.72–0.87 at a 95% level of significance.

CONCLUSION This model could be a helpful tool for the surgeon to help in predicting which cases have a higher likelihood of achieving a pathologically complete response and therefore selecting those who may benefit from a post-neoadjuvant chemotherapy sentinel lymph node biopsy and avoid unnecessary axillary lymphadenectomy.

KEYWORDS

Neoadjuvant therapy – Axillary lymph node dissection – Lymph node metastases – Breast cancer

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Introduction

Surgical management of axillary lymph nodes in breast cancer has evolved over the past 20 years. Sentinel lymph node biopsy was first described in the early 1990s and has, since then, replaced routine axillary lymphadenectomy.¹ It provides accurate and comparable regional node stage information to guide tailored adjuvant treatment. The results obtained in the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-32,² the American College of Surgeons Oncology Group Z0011 trial³ and the

AMAROS trial,⁴ concluded that in some patients with a positive sentinel lymph node biopsy and a low axillary metastatic tumour burden (T1/2, involvement of up to three sentinel nodes and without extra-nodal extension), axillary lymphadenectomy can be omitted, with no difference in terms of disease-free and overall survival rates. However, these studies do not take into account patients requiring neoadjuvant chemotherapy, in which the diagnostic and therapeutic approach of the axillary lymph nodes remains controversial.

The best timing for sentinel lymph node biopsy in the neoadjuvant chemotherapy setting remains a question. When sentinel lymph nodes are biopsied before neoadjuvant chemotherapy, the knowledge of the initial nodal status can be used to establish a prognosis and to guide postoperative treatment decisions. However, when a biopsy is positive, it implies an axillary lymphadenectomy, even though there is a possibility that some patients could have achieved a pathologically complete response to neoadjuvant chemotherapy.^{5–7} When sentinel lymph node biopsy is performed after neoadjuvant chemotherapy and the result is negative, an unnecessary axillary lymphadenectomy can be avoided. However, the feasibility of performing a sentinel lymph node biopsy following neoadjuvant chemotherapy in patients initially presenting with biopsy-proven node-positive breast cancer is a subject of controversy, owing to concerns about a lower detection rate and higher false negative rate.^{5,8} Nevertheless, it has been suggested that response to neoadjuvant chemotherapy affects not only the breast tumour but also the axillary nodes. According to published studies, axillary complete response rate after neoadjuvant chemotherapy in node-positive breast cancer is estimated to be somewhere between 21% and 41%, depending on the tumour subtype.⁹

Given these concerns, the correct approach for patients with an axillary complete response after neoadjuvant chemotherapy is arguable. Axillary lymphadenectomy remains the standard approach for patients with biopsy-proven node-positive breast cancer, although it is not exempt from morbidity and its benefit when a good response to neoadjuvant chemotherapy has been achieved is unclear.

To date, no non-invasive technique has proven to be precise enough to predict a pathologically complete response in the axilla and thus avoid axillary lymphadenectomy.¹⁰ Sentinel lymph node biopsy could potentially be of high importance in the restaging of the axilla, as it has been proven in three recently published prospective studies.^{11–15} The sensitivity of the technique may be increased with better patient selection. Ideally, if a pathologically complete response to neoadjuvant chemotherapy could be predicted, based on preoperative available data, patients who might benefit from a post-neoadjuvant treatment sentinel lymph node biopsy could be identified and separated from those who would require an axillary lymphadenectomy.¹⁴

Our main goal is to establish clinical, radiological and pathological features to predict a complete axillary response to neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer and thus to select those patients who could benefit from post-neoadjuvant chemotherapy sentinel lymph node biopsy, to avoid unnecessary axillary lymphadenectomy.

Methods

Inclusion criteria

Patients diagnosed with breast cancer in whom neoadjuvant chemotherapy was advised between 2012 and 2015 in two university hospitals were included. Every included

patient had pathologically confirmed invasive breast cancer characterised by molecular taxonomy, biopsy-proven node-positive axilla at presentation, and absence of metastatic disease at diagnosis. Patients presenting disease progression during the neoadjuvant treatment were excluded. We also excluded patients found to be clinically node negative who underwent sentinel lymph node biopsy with a positive result before neoadjuvant chemotherapy, because it is important to differentiate between a complete pathological response in a biopsy-proven node-positive axilla (fine-needle aspiration cytology or ultrasound-guided biopsy) and an occult axillary disease detected after sentinel lymph node biopsy.

Data were collected from each patient's medical record. Variables included age at diagnosis, family history of cancer, hormonal status and tumour characteristics, such as size, histological grade, pathological subtype and immunohistochemical markers (estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 [Her2], Ki67). Magnetic resonance imaging (MRI) performed before and after neoadjuvant chemotherapy, specific chemotherapy regimens (chemotherapeutic agents, administration of anti-Her2 therapy), surgical approach for primary lesion and pathological evaluation of the breast tumour and axillary nodes.

Diagnostic tests

All patients included in this study underwent a physical examination and imaging of the breast and axilla, including mammography, ultrasonography and MRI. MRI was performed prior to neoadjuvant chemotherapy and after completing the treatment, to assess the radiological response of the breast tumour and axillary nodes. When the axillary nodes appeared clinically and/or radiologically suspicious, an ultrasound-guided biopsy was performed to confirm malignancy.

Surgical technique

Surgical treatment was based on standard institutional guidelines. Either a mastectomy or a breast conserving technique was performed for the primary tumour, depending on the patient's characteristics, and a first and second level axillary lymphadenectomy was performed every time, regardless of clinical and/or radiological response of both the breast tumour and axillary nodes to neoadjuvant chemotherapy.

Pathological evaluation

Pathological evaluation following ultrasound-guided biopsy was performed for the diagnosis of the primary tumour, including immunohistochemistry and fluorescence in situ hybridisation for Her2 when HercepTest™ was equivocal. Data obtained included tumour subtype, quantitative measures of estrogen receptor and progesterone receptor expression, Her2 status and proliferation marker Ki67. The nodes retrieved from axillary lymphadenectomy were stained by haematoxylin eosin. Sentinel nodes with macrometastasis (greater than 2 mm) were considered positive. Pathological response to neoadjuvant chemotherapy was

evaluated separately in the breast tumour and in the axillary nodes according to the Miller and Payne classification. Final pathological response in the axilla was defined as complete when there was no evidence of residual malignancy and as pathological non-response where evidence existed.

Statistical analysis

The descriptive study of qualitative variables was carried out through distribution of absolute and relative frequencies. The quantitative variables were summarised with the mean and the standard deviation (SD) or with the median and the interquartile range, depending on their distribution in each case. Two groups were established depending on the pathological response (pathologically complete response and non-response) and were compared by a univariate and multivariate study with the clinical and pathological variables. Univariate analysis was done to determine factors associated with pathologically complete response. Contingency tables were considered for qualitative variables and their analysis was performed using the chi-square statistic. For quantitative variables, the U Mann-Whitney test was used. The significant ($P < 0.1$) or clinically relevant factors were then included in the multivariate analysis.

A predictive model was generated by a multivariate logistic regression analysis for the dependent variable pathologically complete response. The capacity of the predictive model to differentiate between patients with a pathologically complete response or non-response was tested using a receiver operating characteristic (ROC) analysis.

Statistical tests were two-sided and a P value 0.05 was considered statistically significant. The confidence intervals (CI) were reported at a 95% level of significance. All the analyses were performed using SAS software version 9.3. The hospital ethical committee approved the study.

Results

A total of 150 patients with diagnosis of non-metastatic breast cancer who underwent neoadjuvant chemotherapy followed by breast surgery and axillary lymphadenectomy were included in the study. All patients presented with a biopsy-proven node-positive breast cancer (radiologically guided biopsy). Mean age at diagnosis was 51 years (SD 10, 7, range 28–84 years). All the patients in the study had received a taxane-based chemotherapy and Her2-positive patients were also treated with trastuzumab. The distribution of the main clinical and pathological characteristics can be seen in Table 1.

Incidence of pathological complete response in the breast and axillary nodes

Clinical evaluation of the neoadjuvant chemotherapy response was determined by physical examination and MRI. Some 74% of the patients presented a complete or a major partial response in the breast. A clinical and radiological nodal response was registered in most cases (91%).

The axillary pathologically complete response rate was 40% and the pathologically complete response rate for the primary tumour was 32%. A total of 27% of patients achieved a pathologically complete response both in the axillary nodes and breast tumour, while 5% had a pathologically complete response in the breast but not in the axilla and two patients achieved a pathologically complete response in the axillary nodes but not in the breast.

The relationship between the breast and axillary responses to neoadjuvant chemotherapy according to the MRI and the final pathological analysis of the primary tumour, based on the Miller and Payne classification and the pathologic node response, are shown in Table 2.

Comparison of the subgroups with and without pathologically complete response

Univariate analysis showed a direct association between Ki67 proliferation index and nodal response. Average Ki67 index in patients having a pathologically complete response was 47% compared with 34% in pathological non-response ($P < 0.01$). Hormone receptor percentage was inversely related to the axillary response: mean estrogen receptor and progesterone receptor expression was 32.4% and 11.4%, respectively, in cases with a pathologically complete response and 65% and 35%, respectively, in those with pathological non-response ($P < 0.001$). More than 50% of the patients with Her2-positive tumours (57%) and triple negative (55%) presented with a pathologically complete response, while luminal A and B (Her2-) pathologically complete response rates were lower than 20% ($P < 0.001$).

Radiological response of the breast evaluated by a post-neoadjuvant chemotherapy MRI was significantly associated with a node response. According to our results, patients with a complete response in the breast achieved a pathologically complete response in the axilla in 59.7 % of cases, while, 75.9 % of patients without complete response in the post-neoadjuvant chemotherapy MRI had residual nodal disease ($P < 0.001$).

Pathological response in the breast was significantly associated with a node response, when the response in the primary tumour was greater than or equal to a grade 4 in the Miller and Payne classification, a 72% of pathologically complete response in the axilla was found ($P < 0.001$).

These factors were then analysed through an adjusted multivariable regression to identify predictors for pathological node response. Pathological response of the primary tumour was excluded as it is obtained post-surgically. Three predictive variables were identified in our study: breast response to neoadjuvant chemotherapy according to post-treatment MRI, *Her2/neu* overexpression and the estrogen receptor expression. The multivariate model generates a ROC curve with an area under the curve of 0.79 (95% CI 0.72–0.87; Table 3 and Fig 1).

Discussion

The widespread use of neoadjuvant chemotherapy in operable breast cancer has changed the perspective in surgical

Table 1 Clinical and pathological characteristics.

Characteristic	Patients		Nodal pathologically complete response		Nodal pathological non-response		P-value
	(n)	(%)	(n)	(%)	(n)	(%)	
Menopausal status:							ns
Premenopausal	71	47.3	27	38	44	62	
Postmenopausal	79	52.7	33	41.8	46	58.2	
First-degree family history:							ns
No	121	80.7	48	39.7	73	60.3	
Yes	29	19.3	12	41.4	17	58.6	
Histology:							ns
Ductal	141	94	58	41.1	83	58.9	
Non-ductal	9	6	2	22.2	7	77.8	
Grade:							ns
1	5	3.6	2	40	3	60	
2	64	46	21	32.8	43	67.2	
3	70	50.4	33	47.1	37	52.9	
Size:							ns
T1	10	6.7	4	40	6	60	
T2	81	54	40	49.4	41	50.6	
T3	48	32	11	22.9	37	77.1	
T4	11	7.3	5	45.5	6	54.5	
Tumour subtype:							P < 0.001
Luminal A	11	7.3	4	40	6	60	
Luminal B (Her2-)	55	36.7	40	49.4	41	50.6	
Her2	56	36.7	11	22.9	37	77.1	
Triple negative	29	19.3	5	45.5	6	54.5	
Her2/neu:							P < 0.001
Positive	56	36.7	32	56.4	24	43.6	
Negative	94	36.7	28	30	66	70	
	(Mean)	(SD)	(Mean)	(SD)	(Mean)	(SD)	
Estrogen receptors	51.97	44	32.43	43.4	65	39.5	P < 0.001
Progesterone receptors	25.33	36	11.43	27.4	34.6	38.4	P < 0.001
Ki67	39	24.8	46.77	25.5	33.8	23.18	P < 0.001

ns, not significant; SD, standard deviation from the mean.

decision making, especially in cases where a complete clinical response is achieved. Currently, there is a debate on how to avoid extensive breast surgery and what is the most appropriate management of the axilla in patients treated with neoadjuvant chemotherapy presenting a major response.

In the management of the axilla, the real dilemma is posed not by patients with negative axilla prior to the neoadjuvant chemotherapy but by those with a biopsy-proven node-positive axilla, since we do not really know what

their axillary response will be after receiving initial systemic treatment.^{6,9} Being able to predict both pathologically complete response and non-response after neoadjuvant chemotherapy in patients with breast cancer and positive nodes is important not only to determine the prognosis of the disease, but also to identify those patients who would benefit from an axillary lymphadenectomy and those in whom it could be avoided.^{6,9,15}

The aim of our study was to develop a predictive model based on clinicopathological and radiological

Table 2 Response to neoadjuvant chemotherapy according to magnetic resonance imaging and the final pathological analysis of the primary tumour.

Response	Patients		Nodal pathologi- cally complete response		Nodal pathological non-response		P-value
	(n)	(%)	(n)	(%)	(n)	(%)	
Tumour (MRI):							$P < 0.001$
Complete	67	44.6	40	59.7	27	40.3	
Not complete	83	55.3	20	24.1	63	75.9	
Axillary response (MRI):							$P < 0.001$
Yes	137	91.3	59	43.1	78	56.7	
No	13	8.7	1	7.7	12	92.3	
Pathological breast response:							$P < 0.001$
Grade 4/5	75	50	54	72	21	28	
Grade 1–3	75	50	6	8	69	92	

Table 3 Adjusted multivariate binary logistic regression predicting nodal pathologically complete response.

Variable	B	P-value ^a	OR	95% Confidence interval (OR)
Estrogen receptor (%)	−0.016	< 0.001	0.984	0.976–0.993
Her2(+)	1.028	< 0.01	2.796	1.267–6.701
Post-neoadjuvant chemotherapy MRI (complete)	1.591	< 0.001	4.99	2.255–10.668
Intercept	−0.784	< 0.05	0.457	

^a Based on 1000 bootstrap samples.

B, coefficients of regression model; Her2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; OR, odds ratio.

characteristics, to estimate the probability of achieving a complete axillary response after neoadjuvant chemotherapy in patients with node-positive breast cancer, in an attempt to avoid axillary lymphadenectomy in selected cases with a higher likelihood of achieving ypN0 status. For this purpose, we performed a retrospective review of the data in 150 patients with breast cancer and axillary involvement who received neoadjuvant chemotherapy. The results obtained align with what has been described by other authors.^{6,8,10}

In our study, pathologically complete response was achieved in 40% (60 of 150) of patients. Tumours with a lower hormone receptor expression, Her2 overexpression and higher Ki67 proliferation index presented a greater pathologically complete response rate.^{16,17} Regarding the tumour subtypes, our findings are consistent with what has been published in the literature: the Her2 positive and triple negative tumours showed a higher pathologically complete response rate compared with luminal subtypes, although no significant differences were found.^{5,9}

The association between tumour size at diagnosis and nodal outcome has been described by several authors. Mamtani *et al* observed a higher percentage of positive

axilla after neoadjuvant chemotherapy in elderly patients and larger tumours.⁵ In our study, we noticed that the patients who achieved a pathologically complete response had smaller tumours (73% T2 vs 27% T3), although a statistically significant association could not be established ($P > 0.05$). Interestingly, some other authors do not find any association and suggest a greater influence of the molecular factors over the clinicopathological features in terms of response to primary systemic treatment.¹⁴

There are several authors who describe the association between the nodal status and the response of the primary tumour to neoadjuvant treatment, considering that a major pathological response of the breast tumour is highly predictive of axillary pathologically complete response and related to a higher disease-free survival.^{18,19} Our results have similar findings; 72% of patients with a pathological response ($\geq$ grade 4 Miller and Payne) of the primary tumour reached pathologically complete response, while 92% of patients with partial or no pathological response (grade 1–3 of Miller and Payne) presented residual nodal disease ($P < 0.05$). Pathological response in the breast was not incorporated in the multivariate analysis, owing to the fact that this information is not available preoperatively;

this follows the methodology described in previous studies.^{10,14} However, unlike these studies, we included the response of the primary tumour on the MRI instead, and we observed that 66.6 % of the cases with pathologically complete response showed a complete response.

This model is based on the radiological response of the primary tumour assessed by post-neoadjuvant chemotherapy MRI, estrogen receptor expression and *Her2/neu* overexpression. Our findings are consistent with the previously published models. Schipper RJ *et al* correlates pathologically complete response with age at diagnosis, tumour size, tumour histology, hormone receptor expression, amplification of *Her2* and chemotherapy regimens,¹⁰ while Kantor *et al* correlates response with age at diagnosis, tumour subtype, tumour grade, tumour histology, clinical node stage at diagnosis and breast pathological response.¹⁴ However, our model incorporates only three variables and generates a ROC curve with an area under the curve of 0.79 (95% CI 0.72–0.87), comparable with those obtained by Schipper *et al* or Kantor *et al*.^{10,14}

Our study has several limitations. Data were collected retrospectively and the total number of patients was relatively small. Thus, a multicentre study with more patients would be needed for internal validation of our results.

Conclusions

Complete response in the post-treatment MRI, *HER2/neu* overexpression and a low expression of hormone receptors in the breast tumour are associated with a complete axillary pathological response after neoadjuvant chemotherapy

for patients with biopsy-proven positive nodes prior to treatment. This association could help the surgeon to predict which cases have a higher likelihood of achieving a pathologically complete response and avoiding an unnecessary axillary lymphadenectomy. The model could be helpful to select those patients who may benefit from a post-neoadjuvant chemotherapy sentinel lymph node biopsy and also those cases less likely to achieve a pathologically complete response.

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