Clinical versus histopathological staging of axillary lymph node, in breast cancer patients

Nashwan K. Mahjob[a], Faris H. Raoof[b]

From the [a] Department of Surgery, College of Medicine, University of Mosul, [b]Aljamhori Teaching Hospital, Mosul.
Correspondence: Nashwan K. Mahjob. Assistant Professor and Consultant Surgeon, Department of Surgery, College of Medicine, University of Mosul, Mosul, Iraq. Email: nashwanmahjob@yahoo.com.

ABSTRACT

Objective: To evaluate the validity of clinical examination of the axilla for detection or exclusion of presence of lymph nodes and performing clinical staging, in patients with breast carcinoma, in comparison with histopathological evaluation and staging

Patients and methods: A case series study included ninety patients with breast carcinoma, done at Aljamhori Teaching Hospital in Mosul, during the period from January 2010 to June 2011. The diagnosis of breast cancer was confirmed by FNA and or excisional biopsy. The size of the tumors was measured and (T) stage was performed. The clinical evaluation of the axilla included: the presence or absence of axillary lymph nodes, the size, number, level and fixation of lymph nodes were assessed when positive; the clinical (cN) staging was recorded. All the patients underwent modified radical mastectomy with axillary clearance. The breast and axillae specimens were subjected to histopathological evaluation which included: the presence or absence of axillary lymph nodes, the size, number, level and fixation of lymph nodes were assessed when positive, the histopathological (hN) staging was recorded, which is regarded as the gold standard. The state of axillary lymph node (N), the size of the tumor (T) in relation of clinical to histopathological stages were evaluated and compared by using validity indicators, which includes the sensitivity, specificity, positive and negative predictive values and accuracy. P value was estimated using 2-way Contingency Table Analysis, with 95% Conf. Interval.

Results: The study included 90 patients with breast carcinoma, the clinical evaluation revealed 20 patients (22%) with T1, 45 (50%) T2, 18 (20%) T3 and 7 (8%) T4. Sixty one (67.7%) patients had negative axillary lymph node (N0) on physical examination, those with positive lymph nodes were 19 (21%) patient with (N1), 7 (7.7%) patients with (N2) and 3 (3.3%) patients with (N3), while the histopathological evaluation showed that 35 (39%) patients had (N0), those with positive lymph nodes were 30 (33.3%) patient with (N1), 20 (22.2%) patients with (N2) and 5 (5.5%) patients with (N3). The sensitivity, specificity and accuracy of axillary lymph node examination were 40%, 70% and 57% respectively, the P value was 0.064.

Conclusion: Clinical staging of axillary lymph node is neither sensitive nor specific, with low accuracy rate and it shouldn't be relied on for final staging in patient with breast malignancy.

Keywords: Breast cancer, axillary lymph node, mastectomy.

دراسة مستوى الإصابة بين الفحص السريري والنسيجي للغدد اللمفية تحت الأبطية لمرضى سرطان الثدي

الخلاصة

الهدف: للتعرف على قابلية الفحص السريري للغدد اللمفاوية تحت الابطية في تشخيص إصابتها بورم سرطاني من الثدي بالمقارنة مع نتائج الفحص النسيجي عن طريق قياس مؤشرات الصلاحيةَ.

التصميم: دراسة سلسلة الحالات.

المشاركون: تسعون مريضة مصابة بسرطان الثدي.

زمان ومكان الدراسة: مستشفى الجمهوري التعليمي في الموصل من تاريخ كانون الثاني ٢٠١٠ لغاية حزيران ٢٠١١.

القياسات الإجرائية: تم تشخيص سرطان الثدي عن طريق الوخز بالإبرة او فحص الخزعة كاملة القطع. تم اختيار التداخل الجراحي من نوع الرفع الكامل للثدي مع تنظيف الإبط من قبل الجراح المسؤول عن علاج المريضة المعنية حيث ان هذا النوع من التداخل هو المتفق عليه من قبل كافة الجراحين العاملين في مستشفى الجمهوري التعليمي.

تم تسجيل نتائج الفحص السريري للعقدة السرطانية من حيث الحجم وكذلك الموقف السرطاني للغدد اللمفاوية تحت الابطية. تم تسجيل نتائج الفحص النسيجي للغدد اللمفاوية وموقفها السرطاني بالاعتماد على اللجنة الأمريكية المشتركة للسرطان وقد تم اعتماد الفحص النسيجي كمقياس ذهبي لغرض المقارنة باستخدام قياس مؤشرات الصلاحية والتي تضمنت قياس الحسّاسيةَ، الخصوصية ، القيمة التنبؤية الإيجابية والسلبية والدقة.

النتائج: أثبتت الدراسة إن الموقف السرطاني عن طريق الفحص السريري ذو حسّاسية تصل إلى ٤٠%، خصوصية ٧٠%، قيمة تنبؤية إيجابية ٧٥%، قيمة تنبؤية سلبية ٤٥%، ودقة ٥٧%.

الاستنتاج: إن التقييم السريري للعقد اللمفاوية تحت الابطية لا يعطي مصداقية عالية لغرض تقييم الانتشار السرطاني لسرطان الثدي ولا يمكن الاعتماد عليه.

التوصيات: يوصي الباحثان بإتباع طرق أكثر تقصّياً لغرض الوصول الى نتائج أفضل.

الكلمات الدليلية: سرطان الثدي، الغدد اللمفية تحت الابطية، قطع الثدي.

The assessment of lymph nodes in the axilla is crucial to staging and prognostic correlate of disease free and overall survival in patients with operable breast cancer[1]. A growing awareness that systemic disease is already present in patients with involved axillary nodes, led to increase the awareness about designing more accurate methods to diagnose the axillary state. On the other hand, an accurate knowledge of axillary lymph node involvement is essential when planning treatment of apparently operable breast cancer, irrespective of what form of primary surgical treatment is undertaken[2].

It is estimated that about one third of patients with a clinically negative axilla have nodal metastases after histopathological examination of the axillary lymph node dissection specimen, and further one third of patients with clinically positive axilla have no nodal metastases after histopathological examination [3-5].

Methods of assessment of the axillary nodal status include physical examination, imaging techniques, including ultrasonography and MRI, but none has equaled the "gold standard" of histology of lymph nodes recovered from axillary dissection specimens [6]. The criticism of physical exam is that even if the lymph nodes are enlarged, it does not always indicates involvement by malignancy, at the same time, non-palpable lymph node does not guarantee noninvolvement and the only way to determine if they truly contain cancer or not is to examine a sample of the tissue under the microscope[7].

Unfortunately, most of our patients were diagnosed when the tumor exceeds 2cm, there is no adequate screening program adopted in Mosul city till now [8], as well as, sentinel lymph node biopsy is not practiced in our hospital to date, so, the only certain way of assessing axillary node status accurately is by total axillary clearance.

In this study the investigators aimed to evaluate the validity of clinical examination, in detecting and staging lymph node at axilla in proven breast cancer patients, in comparison with histopathological study and is clinical examination dependable or not in the assessment of axillary state.

PATIENTS AND METHODS
Official permission was obtained before the study performance. The study was conducted during the period from January 2010 to June 2011 at Aljamhori Teaching Hospital in Mosul. A case series study design was adopted. The study included (90) female patients, all were diagnosed to have breast cancer by FNA and or excisional biopsy, all were subjected to modified radical mastectomy with axillary clearance at Aljamhori Teaching Hospital. The physical examinations of the axillae were done by consultant surgeons who were responsible for the surgical management of particular patient. The histopathological evaluation was done by consultant histopathologists, both

surgeons and pathologist work under the authority of the ministry of health at Aljamhori Teaching Hospital in Mosul city. The data were collected retrospectively from the case sheet of the patients and from the laboratory center of the hospital with permission, these included: size of the tumor in centimeters, state of axillary lymph node on physical examination, regarding presence or absence of lymph nodes, number, size, consistency, shape, mobility, level and fixity evaluation in positive lymph node(s) cases. The clinical stage of the tumor size and lymph node state were recorded depending on American Joint Committee on Cancer (AJCC) criteria[9]. Histopathological evaluation included, state, number, size of lymph node involvement. The histopathological stage was recorded depending on American Joint Committee on Cancer (AJCC) criteria (listed below)[9]. American Joint Committee on Cancer (AJCC) criteria for primary tumor and regional lymph nodes in breast cancer.

Primary tumor (cT)
T1 Tumor 2 cm in greatest dimension.T2 Tumor >2 cm but not >5 cm in greatest dimension. T3 Tumor >5 cm in greatest dimension. T4 Tumor of any size with direct extension to (a) chest wall or (b) skin, edema (including peau d'orange), or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast.

Clinical (cN)
N0 No regional lymph node metastasis. N1 Metastasis to movable ipsilateral axillary lymph node(s). N2 Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis. N3 Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without

axillary or internal mammary lymph node involvement.

Pathologic (pN)
pN0 No regional lymph node metastasis histologically. pN1 Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph nodes dissection, not clinically apparent. pN2 Metastasis in 4 to 9 axillary lymph nodes, or in clinically apparent internal mammary lymph.

pN3 Metastasis in 10 axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in >3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes.

The statistical analysis done by using 2-way Contingency Table Analysis, with 95% Conf. Interval.

RESULTS
The study included 90 patients with breast carcinoma, their age ranged from 28 to 72 years, there were 42 tumors in left side, and 38 one in right side, all of them underwent modified radical mastectomy with complete axillary clearance. The breast specimens including the axillary content were subjected to histopathological examination. The number of patients in relation to the size of the tumor is shown in **Table 1**. The state and stage of axillary lymph node at physical examination and histopathology reports are shown in **Table 2**.

The T stage in relation to clinical and histopathological stages is shown in **Tables 3 & 4**. The validity test of the clinical evaluation using the histopathology as a standard regarding the stages of lymph node is shown in **Table 5**.

Table 1. The percentage distribution of patients in relation to the size of the tumor.

Size of the tumor	T1	T2	T3	T4
Number of patients	20 (22%)	45 (50%)	18 (20%)	7 (8%)

Table 2. Stage of lymph node at physical examination and histopathology report.

Type of evaluation of axillary lymph node state	State of lymph node				
	Negative (NO)	positive	N1	N2	N3
Clinical examination	61 (67.7%)	29 (32.3%)	19 (21%)	7 (7.7%)	3 (3.3%)
Histopathological examination	35 (39%)	55 (61%)	30 (33.3%)	20 (22.2%)	5 (5.5%)

Table 3. Size of tumor according to the N stage clinical evaluation.

Size of tumor	T stage in relation to clinical and histopathological N stages. State of lymph node on physical examination				
	N0	N1	N2	N3	Total
T1	16 (80%)	3 (15%)	1 (5%)	0 (0%)	20
T2	28 (62%)	13 (30%)	2 (4.5%)	2 (4.5%)	45
T3	14 (78%)	2 (11%)	2 (11%)	0 (0%)	18
T4	3 (43%)	1 (14.25%)	2 (28.5%)	1 (14.25%)	7
Total	61	19	7	3	90

Table 4. Size of tumor according to the N stage in histopathological evaluation.

Size of tumor	State of lymph node on histopathological examination				
	N0	N1	N2	N3	Total
T1	15 (75%)	1 (5%)	2 (10%)	2 (10%)	20
T2	10 (22%)	21 (47%)	13 (29%)	1 (2%)	45
T3	8 (44%)	6 (33%)	3 (17%)	1 (6%)	18
T4	2 (28.5%)	2 (28.5%)	2 (28.5%)	1 (14.5%)	7
Total	35	30	20	5	90

Table 5. Validity indicators of clinical examination in the detection of stages of axillary lymph node.

Validity Indicator	Lymph node state on Clinical examination			
	N0	N1	N2	N3
Sensitivity (%)	40%	41%	42%	66%
Specificity (%)	70%	64%	60%	72%
Positive predictive value (%)	75%	60%	63%	74%
Negative predictive value (%)	45%	55%	56%	60%
P value	0.064	0.07	0.08	0.05
Accuracy	57%	61%	59%	70%

DISCUSSION

Malignant breast disease is considered to be the commonest malignancy that affects female worldwide, having an incidence of 19 to 24% and mortality of about 20% of cancer death in women [10,11]. In Iraq, breast was the most common site of cancer in females, accounting for 18% of all cases of malignant conditions [12]. Axillary lymph node involvement is the most significant and durable prognostic factor for women with breast cancer[1,13]. Small cancers without nodal involvement have an extremely favorable prognosis. Metastasis to a single axillary node more than doubles the risk of distant disease[14]. Consequently, nodal involvement in T1 cancers often determines whether a patient is treated with adjuvant chemotherapy or not[14]. The physical examination of axillary lymph node is influenced by many factors including, experience of examiner, presence of deferent types of tissue at the axilla, associated bacterial infection and the extent of metastasis within the lymph node. McNair TJ and Dudly H [15] cast a debate about the validity of axillary lymph node examination. They asked 5 senior surgeons to examine the axillae of 10 ladies whose breast were covered, 3 of them with normal breast and with no reason expecting the axillary lymph node to be enlarged, 3 patients had breast cancer and 4 patients with breast abscess. There was astonishing lack of agreement between the examiners regarding the finding, which indicates that staging by clinical examination for axillary lymph node is both valueless and misleading. In Davies G et al study [16], they assessed clinically 149 patients with breast cancer, positive nodes were not detected in 31 (45%) of 69 patients with pathologic Stage II [16], other study showed that clinical examination of axilla has a broad range of

sensitivity and specificity; (33%–68% and 36%–73% respectively)[17]. Clinical determination of axillary lymph node metastases has an accuracy of only 33% in Singletary SE et al study [18].

In our evaluation, the sensitivity of clinical examination of axillary lymph node was 40% with specificity 70% and accuracy of 57%. This may be attributed to presence of many types of tissue at the axilla like fat, lymph nodes, accessory breast tissue, arteries, veins and nerves which are embedded in a dense connective tissue that may give a false impression for a mass. Axillary lymph node involvement is found in 21% to 42% of patients with T1 lesions, the incidence is increases in T2 and T3 [19]. Even with primary tumors ≤ 1 cm (clinically not detected) the chance of positive nodes is approximately 5% to 10%[20,21]. In this series, node positive was found in 4 in T1, 15 in T2, 6 in T3 and 4 in T4, but it was 5, 35, 10 and 5 in histopathological evaluation respectively. This variability in the incidence of nodal metastases may be related to the number of lymph nodes removed and the histopathological methods used to find metastases[19]. On the other hand, histopathology examination can detect micro metastases in a lymph node that is not large enough to be palpable clinically, this means that clinical stage may under stage patients, and leads to under treatment, resulting in an increased regional relapse rate and poorer survival [22].

In our study, there was a disagreement, regarding lymph node status between clinical negative as well as clinical positive nodes in comparison to histopathology; with a great discrepancy and mismatching figures when we compared the N stage in various T stages, as also proved in other studies[22,23]. It's assumed that histopathological evaluation is the gold standard for staging of axillary lymph nodes in breast malignancy[7], and we depended on it in this series, although its accuracy may be influenced by several factors. For example, it is dependent on the extent of surgery. Complete axillary dissection yields more nodes than level I and II or level I dissections alone. Axillary "four node" sampling selects nodes by location and consistency, and significantly reduces the number of nodes recovered [24-26]. In our study, all the patients underwent complete axillary dissection, and all the axillary lymph nodes were subjected to histopathological evaluation.

Anatomical factors may contribute to differences in the numbers of lymph nodes examined [27,28]. The main factor seems to be the ability of the pathologist to retrieve the nodes from the axillary fat[29]. Although this may increase the median number of recovered lymph nodes from 10 to 22, this did not influence the proportion of node positive cases[30]. Fat clearing techniques may increase lymph node yield further, but do not influence staging fundamentally,[30,31] and this is why these costly methods are not considered essential.

The histological assessment of axillary lymph nodes is probably most affected by the methods of microscopic investigation applied. Examining a single central cross-section was advised against as early as 1961[32], but is still routine in many laboratories. Multiple level sectioning and/or immunohistochemistry (IHC) may result in nodes previously regarded as negative being reclassified as positive in 10–30% of patients[33,34]. However, the biological relevance of these occult, previously undetected metastases is controversial; some studies have concluded that they represent no survival disadvantage[35].

The protocol of histopathology department at Aljamhori Teaching Hospital in which this study was done is to use multiple level sectioning and immunohistochemistry (IHC). Apostolikas N et al study[36] highlights the role of the individual pathologist as a factor influencing the histopathological evaluation of lymph nodes, they found that (3.8%) of 1203 axillae originally considered negative were found to be positive on a centralized review of the slides. Actually no such study available in our center.

In conclusion, clinical staging of axillary lymph node is neither sensitive nor specific, with low accuracy rate and it shouldn't be depended for final staging in patients with breast malignancy and shouldn't be depended on for planning the type of surgery, or further management.

RECOMMENDATION

We recommend using more investigative ways for better assessment of axillary lymph node like axillary ultrasound and MRI of the axilla.

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