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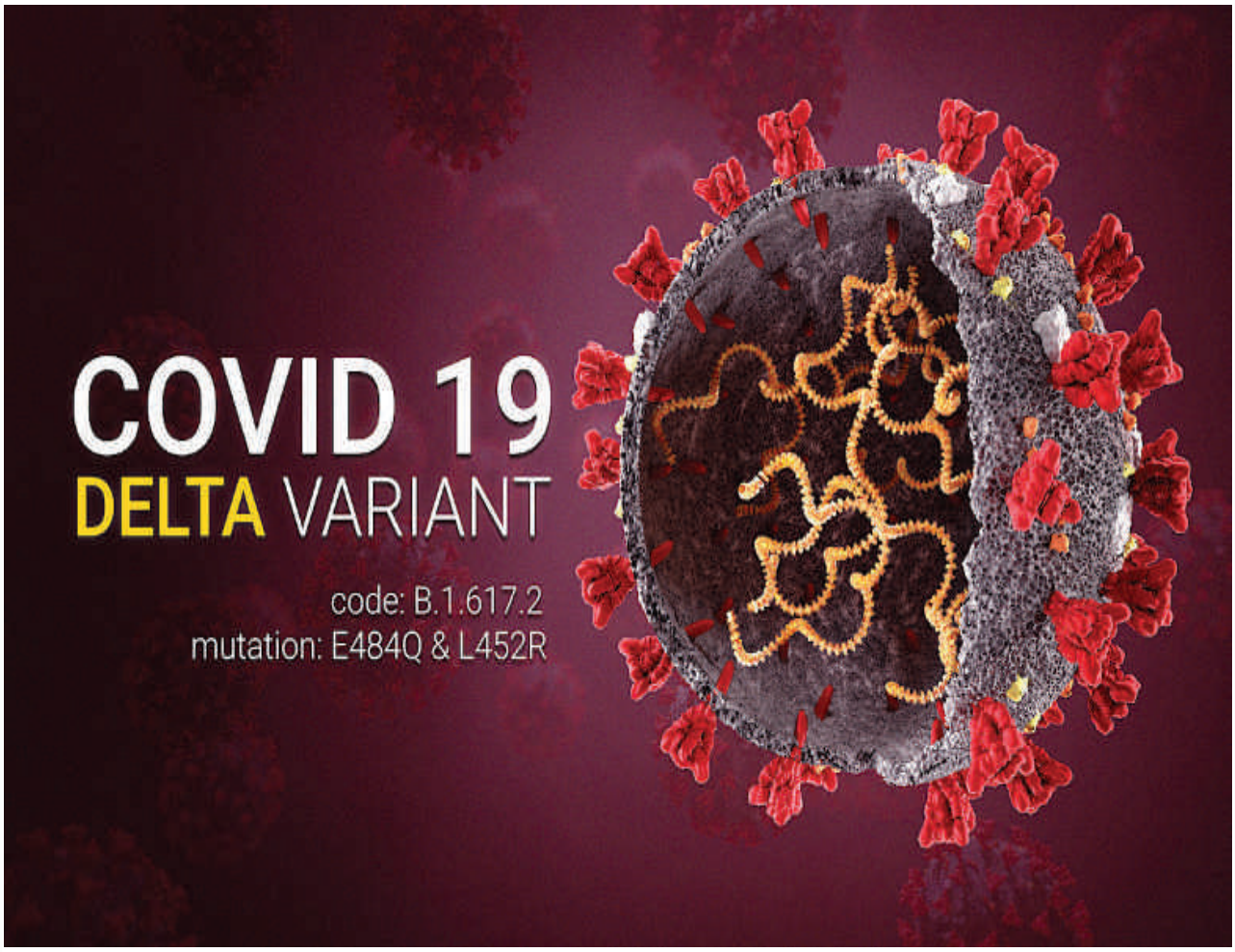

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Original Article

Evaluation Of Intraoperative Touch Imprint Cytology Of Axillary Sentinel Lymph Node Accuracy In Comparison To The Permanent Histology Diagnosis. A prospective study Of 25 Invasive Breast Cancers

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Abstract:

Background: Intraoperative evaluation of axillary sentinel lymph node (SLN) in patients with breast carcinoma reduces the need of re–operations for axillary lymph node dissection. Various methods such as touch imprint cytology (TIC) and frozen section histology (FS) have been used to determine the SLN status intra–operatively. The sensitivity of intraoperative TIC examination on SLN is not consistent and varies in different studies. The aim of this study was to determine the specificity and sensitivity of TIC, and itsfeasibility in clinical use.

Methods: A prospective study was conducted on 24 female and 1 male patients with histologically proven breast carcinoma and an at most clinical stage of cT2N0, between March 2017 and 2020. Axillary lymph nodes were not detected/palpable on physical examination. The patient underwent breast–conserving surgery i.e. quadrantectomy with sentinel lymph node biopsy. The intact lymph nodes were sent to histopathology laboratory for intraoperative TIC. The nodes were bisected, touch smears made and stained using the H&E and May–Grunwald–Giemsa methods. The remaining tissue was processed in formalin fixed paraffin–embedded blocks and the slides were stained with H&E.

Results: In the three– year period (2017–2020), sentinel lymph node intraoperative touch imprint cytology was performed on 25 patients' lymph nodes with primary breast cancer and clinically negative axillary lymph nodes in Muscat Private Hospital, Muscat, Oman. The average age of the patients was 54.69 year. SLN–TIC revealed 88.9% sensitivity, 93.75% specificity, 11.1% false negative rate and 6.25% false positivewith an overall accuracy 92%.

Conclusion: Touch imprint cytology has high sensitivity and specificity with an accepted accuracy. Intraoperative TIC is practical, time–efficient, and cost–effective procedure requiring minimal tissue preparation for SLN evaluation especially in clinical practice where FS is unavailable. Intraoperative touch imprint cytology can detect macrometastasis and micrometastasis to a lesser extent.

Key words: breast carcinoma, sentinel node biopsy, intraoperative diagnosis, touch imprint cytology, micrometastasis

Introduction:

Breast cancer is the most common malignancy and the second cause of death in women. The strongest predictors of long–term prognosis in primary breast cancer is the regional lymph node status [1]. In the past two decades, sentinel lymph node (SLN) biopsy has shown superior results to axillary dissection alone as the standard of care for staging in early, clinically node–negative breast cancer [2]. Intraoperative evaluation of the SLN status is desirable because patients with positive result can undergo a completion lymph–node dissection (CLND) in the same sitting, reducing the need for subsequent/second operation. While axillary lymph node dissection carries

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potential complication, a negative SLN status would not need any further surgery [4]. Diverse methods have been used to determine SLN status intra–operatively, e.g. frozen section histology (FS) [5], touch imprint cytology (TIC) , immunohistochemistry [5] and infrared spectroscopy . TIC is considered as tissue conserving method with reduced cost in comparison to FS with comparable accuracy [6]

The aim of this study is to evaluate the accuracy and feasibility of TIC in diagnosing metastatic tumorin breast cancer patients undergoing SLNB.

Materials and Methods:

This was a prospective study conducted from March 2017 to March 2020 in Muscat Private Hospital, Muscat, Oman. During this period, twenty–five breast–cancer cases underwent breast–conservative surgery i.e. quadrantectomy or mastectomy with sentinel lymph node biopsy and intraoperative touch imprint cytology.

Patient Inclusion criteria: Patients with breast cancer who were clinically and radiologically proven to be node negative and staged clinically as not more than T2 lesion.

Surgically: Peri–lesional injection of isosulfan blue was used intraoperatively to provide visual identification of the SLN. The dye was injected 15 minutes prior to the surgery in the peri–areolar region. The SLN was then harvested and sent fresh to pathology for intraoperative and permanent section evaluation. Breast–conservative surgery was performed on all cases; however, complete ALND was proceeded to only if the SLN–TIC was positive.

Pathologically: Each SLN was received fresh; patient name and hospital number were confirmed. The SLN was then bisected along the long axis aiming to obtain complete cross sections from the maximum diameter, preferably including the hilum and marginal sinus. For each half of the lymph node, a pair ofimprints was made by gently touching and scratching the cut surface on to a glass slide. All four slides were immediately fixed in 95% ethanol for 3 minutes followed by Hematoxylin and Eosin (H&E) staining. In addition, a fifth slide was air–dried and stained with May–Grunwald–Giemsa. A board– certified pathologist rendered a microscopic interpretation of the imprint slides. An intraoperative pathological diagnosis of either positive or negative for malignancy was made within 20–30 minutes and conveyed to the surgeon over the phone. The SLN was then fixed in 10% formalin, processed and finally embedded in paraffin in two cassettes. Three step sections at 50–micrometer were cut from each of the block, stained with H&E and examined result in six H&E levels to be examined.

Statistics: The results of TIC were compared with those of the formalin fixed paraffin–embedded tissue and the final pathology report was classified as true positive (TP), true negative (TN), false negative (FN) or false positive (FP), both on a patient and node basis. True–positive cases were those that were found to contain carcinoma both on TIC and subsequently on the paraffin processed tissue both the TIC and paraffin are stained with H&E stain. The formulae used to calculate statistical parameters were: Sensitivity = TP/(TP + FN); specificity = TN/(TN+ FP); overall accuracy = (TP + TN)/(TP + FP + TN+ FN); negative predictive value (NPV) = TN/(TN+ FN) and positive predictive value (PPV) = TP/(TP +FP)

Ethics: This study was approved by the Ethical Committee of Muscat Private Hospital. There was no conflict of interest.

Results:

In a three–year period (2017–2020), SLN biopsy was performed on 24 female and 1 male patients withbreast cancer. The average age (32–74) is 54.69 years. Left side breast was more common than the right,14 and 11 cases respectively. Invasive ductal carcinoma (NST) reported in 16/22, invasive tubular carcinoma 2/22, invasive lobular carcinoma 1/22, mixed invasive ductal and lobular 1/22, solid papillary carcinoma 1/22 and sarcoma 1/22. Tumor grade I; 4/22, grade II; 13/22, and grade III; 5/22. Four cases have followed up after primary quadrantectomy because of positive margins or required second surgery for SLN biopsy (Table 1) (Figure 1).

Positive intraoperative touch imprint diagnosis was reported in 9/25 sentinel lymph nodes. One of the nine was identified to be reactive with no malignancy on permanent section diagnosis, false positive, whereas the others were all concordant with the histological diagnosis (Figure2). In addition, two case of positive SLN–TIC was reported as suspicious for micrometastasis, which was confirmed with SLN histology (pN1mi Micrometastasis; approximately 200 cells, larger than 0.2 mm, but none

Clinical information			
Age	**Age group (years)**	**No**	**%**
Average age= 54.69 year	31–40	3	12.0
	41–50	13	52.0
	51–60	6	24.0
	61–70	2	8.0
	71–80	1	4.0
Breast side			
	Right	11	44.0
	Left	14	56.0
	Total	25	100

Pathological findings			
Type of specimen		No	%
Total No. of cases are 25	SLN biopsy	3	12.0
	Quadrantectomy + SLN biopsy	20	80.0
	Mastectomy + SLN biopsy	2	8.0
Histological types			
Quadrantectomy and mastectomy specimens: (=22)	Invasive ductal carcinoma (IDC)	16	72.72
	Invasive lobular carcinoma (ILC)	1	4.54
	Mixed IDC and ILC	1	4.54
	Invasive tubular carcinoma (ITC)	2	9.09
	Solid papillary carcinoma (SPC)	1	4.54
	Sarcoma	1	4.54
Tumor grade			
Quadrantectomy and mastectomy specimens: (=22)	Grade 1	4	18.18
	Grade 2	13	59.09
	Grade 3	5	22.72
Angiolymphatic invasion			
Quadrantectomy and mastectomy specimens: (=22)	Present	11	50.0
	Absent	11	50.0
Tumor size			
Quadrantectomy and mastectomy specimens: (=22)	T1 (>2 cm)	6	27.27
	T2 (2–5 cm)	16	72.72
Lymph node status			
Sentinel lymph node specimen + Quadrantectomy and mastectomy specimens: (=25)	N0	16	64.0
	snN1mic	3	12.0
	N1	4	16.0
	N2	1	4.0
	N3	1	4.0
Tumor stage			
Quadrantectomy and mastectomy specimens: (=22)	pTis	1	4.54
	IA	5	22.72
	IIA	8	36.36
	IIB	6	27.27
	IIIA	1	4.54
	IIIC	1	4.54

Table 1: Patient and tumor characteristics.

larger than 2.0 mm) [7,8]. The negative SLN–TIC result were reported in 16/25 cases, one of which was found to show micrometastatic deposits on afferent blood vessels of the lymph node, false negative, whereas the remaining were corresponding with histological finding (Table 2) (figure 3).

Three of cases of quadrantectomy cases had received neoadjuvant chemotherapy. Two of these were of low grade (IA), while the third case was of higher grade (IIA) with prominent chemotherapy related cellular changes. However, all cases showed negative ITC and reactive SLN (Figure 3).

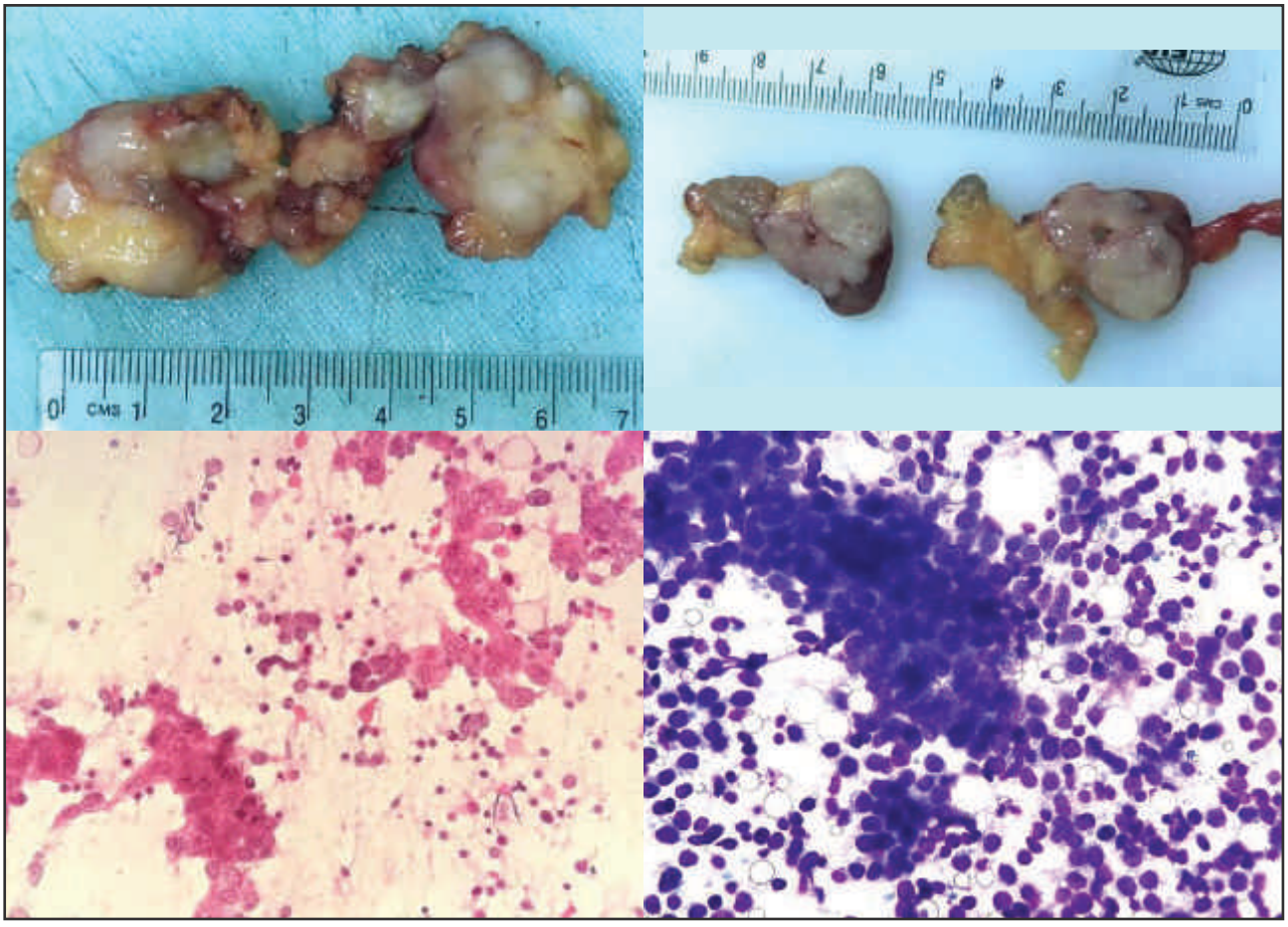

Figure 1: A and B Metastases in SLNs, C Clusters of metastatic carcinoma (H&E, X200), D Cluster of metastatic Carcinoma (MMG, X400)

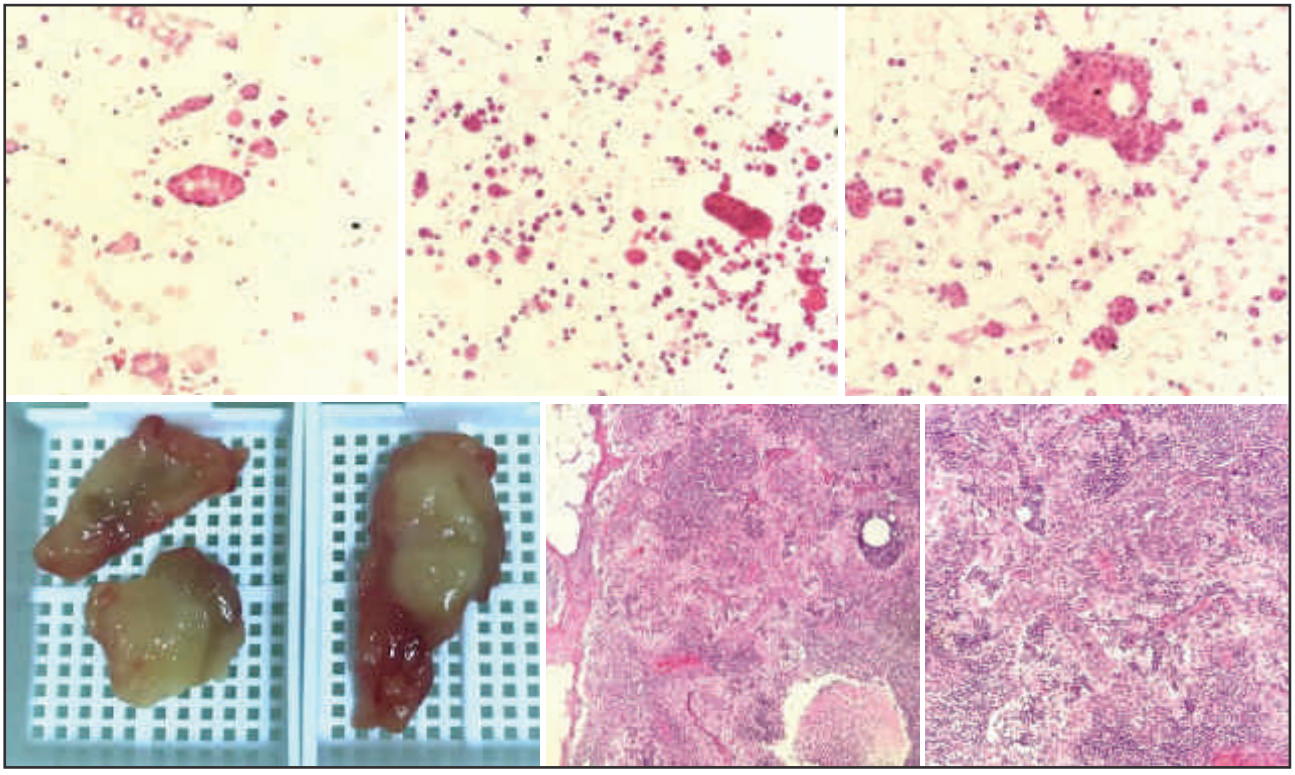

Figure 2: False negative case; A&B Vascular endothelial cells in clusters (H&E, X100), C follicular center cells (H&E, X200), D gross appearance of SLN, E Histology of the SLN (H&E, X100), F Histology show prominent post– capillary venules and sinus histiocytosis (H&E, X200).

No	SLN–TIC	SLN–histology	No of SLNB	ALND perf	Additional information
1	Positive	Metastatic	1	Nil	
2	Positive	Reactive	1	Yes / Reactive	Post neoadjuvant chemotherapy
3	Positive	Metastatic	2/5	Yes / Metastatic N1	
4	Negative	Reactive	1	Nil	Previous quadrantectomy
5	Negative	Reactive	2	Nil	Post neoadjuvant chemotherapy
6	Negative	Reactive	2	Nil	
7	Negative	Reactive	1	Yes / Reactive	
8	Negative	Reactive	2	Nil	
9	Negative	Reactive	1	Nil	
10	Negative	Reactive	1	Nil	
11	Negative	Reactive	1	Nil	
12	Negative	Reactive	1	Nil	
13	Negative	Reactive	1	Nil	
14	Positive	Metastatic	2/2	Yes / MetastaticN1a	
15	Negative	Negative	3	Nil	
16	Negative	Negative	1	Nil	
17	Positive	Metastatic	1	Yes / MetastaticpN3a	
18	Negative	Negative	1	Nil	Previous quadrantectomy with DCIS involved margin
19	Positive	Metastatic	1/2	Yes / MetastaticpN1a	Previous quadrantectomy with DCIS involved margin
20	Negative	Reactive	2	Nil	
21	Suspicious of micrometastasis	Micrometastasis snpN1mic	2/2	Nil	
22	Negative	Reactive	1	Nil	Post neoadjuvant chemotherapy
23	Positive	Positive	1	Yes / MetastaticN2a	
24	Negative	Micrometastasis	1	Nil	Male breast ca
25	Positive	Micrometastasis	1	Nil	

Table 2: Comparison of the SLN–TIC and the SLN–histological diagnosis

Axillary lymph node dissections were performed in 5 out of 7 SLN–TIC positive cases. One of which revealed to be reactive on histology. This was the only false positive case. The cases with ITC suspicious for micrometastasis did not undergo axillary lymph node dissection.

The current study of the SLN–TIC revealed 88.9% sensitivity, 93.75% specificity, 11.1% false negative rate and 6.25% false positive rate with overall accuracy is 92% (Table 3).

Discussion:

Touch imprint cytology is a simple, time–efficient and a cost–effective technique for intraoperative axillary lymph node assessment. It also spares the SLN for further histological examination and ancillarytests.

The aim this study was to evaluate the accuracy of TIC, its clinical value, and feasibility, to avoid axillary clearance in node negative cases since axillary clearance

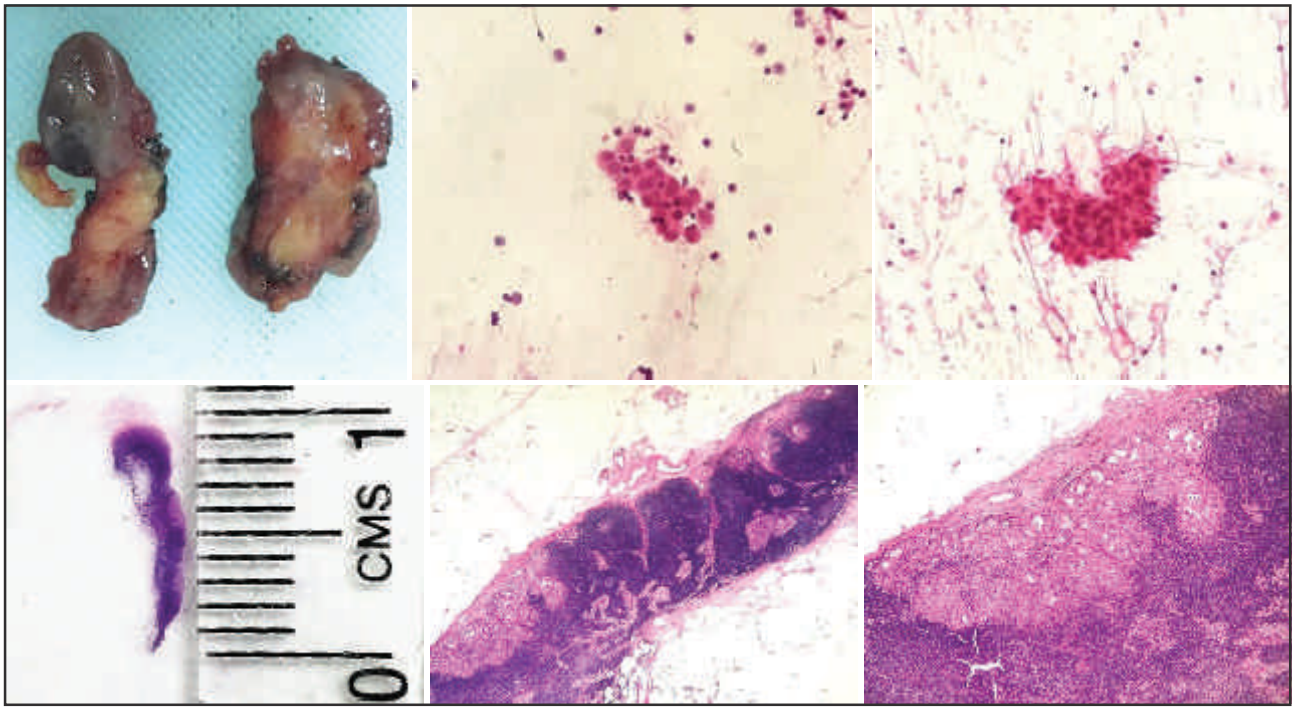

Figure 3: Micrometastasis: A gross SLN, A&B 2 clusters only, suggestive of micrometastasis, C Micrometastasis 1.8mm deposit size, D Micrometastasis (H&E, X40), E Micrometastasis (H&E, X100).

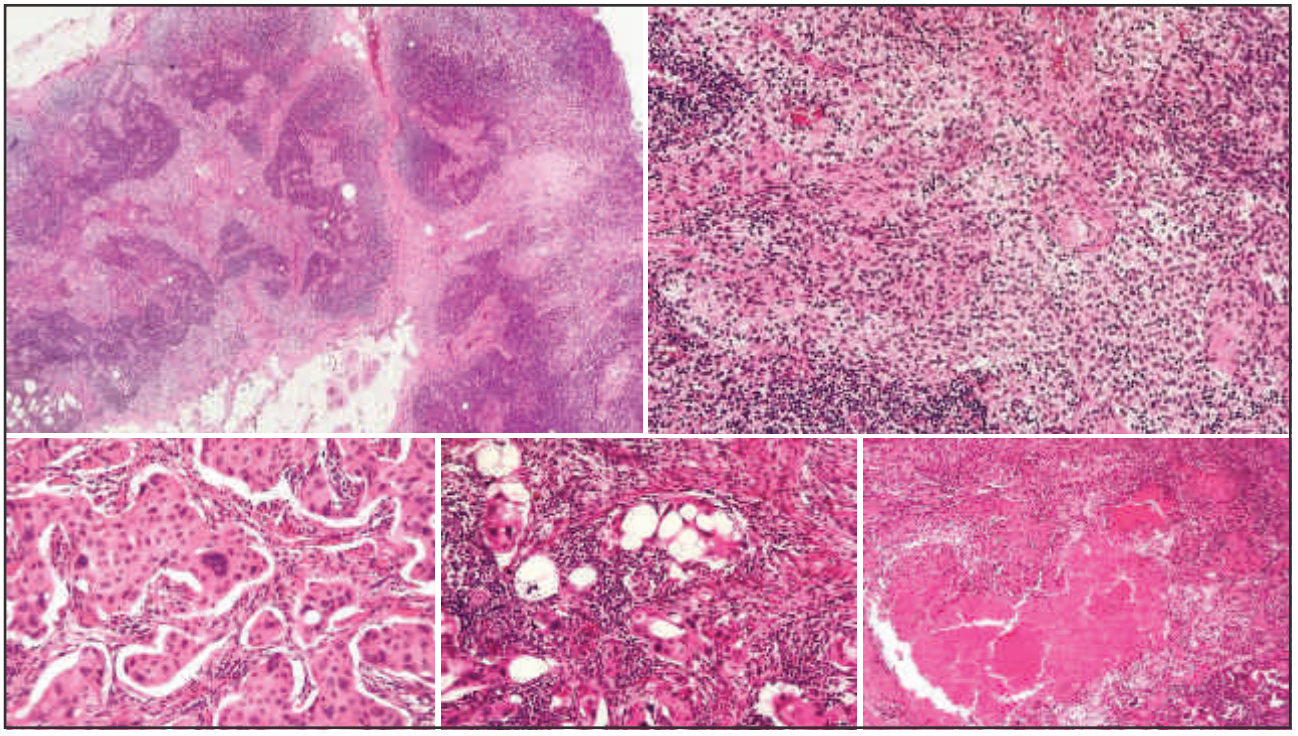

Figure 4: Post neoadjuvant chemotherapy. A SLN (H&E, X40), B SLN (H&E, X200), C&D chemotherapy–related changes (H&E, X200), E Necrosis (H&E, X 100)

Results	Positive TIC	Negative Histology	Total	Sensitivity	Specificity	False positive	False Negative	Overall accuracy
Positive	8	1	9	88.9%	93.75%	6.25%	11.1%	92%
Negative	1	15	16					
Total	9	16	25					

Table 3: The statistic result

is associated with a high rate of morbidity. TIC can be applied in setups where frozen section is unavailable.

There was one false positive TIC, diagnosed in a case with post–neoadjuvant chemotherapy. The main reason of this result was misinterpretation of prominent endothelial cells in TIC as malignant nests. The histology of this SNL showed very active lymphoid follicles, frequent immunoblasts and prominent epithelioid post–capillary venules. The patient underwent axillary lymph node dissection, which showed no evidence of metastasis. Other studies have also highlighted the difficulty of TIC interpretation in post–neoadjuvant chemotherapy cases with an overall low sensitivity [9].

Two of the cases were diagnosed as suspicious of micrometastasis. In one of which, there were two sentinel lymph nodes, which looked normal on gross examination, however on cytological examination, two suspicious clusters were identified in five touch imprint slides. The SLN histology in those cases showed micrometastasis in both cases (pN1mi; micro–metastasis; approximately 200 cells, larger than mm, but none larger than 2.0 mm). Studies showed patients with micro–metastasis have 85%–90% free non–sentinel axillary lymph nodes disease with low loco–regional failure rate [10]. Therefore, the role of ALND with its associated morbidity such as lymphedema, pain, shoulder dysfunction, and neuropathy in these patients remains controversial [11]. Accordingly, our patients did not undergo axillary lymph node dissection (ALND), but alternatively, they had chemotherapy for further treatment. On the one hand, some authors recommend ALND in all patients with micrometastases because of the likelihood of non–SLN metastasis and staging purposes [12]. Studies found that SLN micrometastases greatly affect clinical outcome, with a reduced 5–year rate of disease–free survival among women with favorable early–stage breast cancer [13]. Disease–free survival was improved in patients who received systemic adjuvant therapy [14]. However, other studies found IICN is less accurate in the detection of micrometastases, therefore, intraoperative immunohistochemical staining and step–sectioning of lymph applied to reduce the number of second procedures needed for patients with breast carcinoma [15]

Axillary lymph node metastasis after neoadjuvant chemotherapy (NAC) in breast cancer is considered to be a poor prognostic factor. Thus, the prediction of lymph node metastasis is important to estimate the prognosis of breast cancer patients after NAC [16]. Therefore, prediction of lymph node metastasis is important for prognosis and choosing an optimal therapeutic strategy for the treatment of breast cancer after NAC. There were 3 post neoadjuvant chemotherapy cases in the current study. Their SLN were negative for malignancy. However, they showed prominent lymphoid hyperplasia, active immunoblasts, prominent post–capillary venules and hemosiderin–laden macrophages. Delgado–Bocanegra et al reported high–rate false negatives post neo–adjuvant chemotherapy SLNB–ITC reaching to 17.6%. Nevertheless, he indicated the necessity of post neo–adjuvant chemotherapy intraoperative assessments of SLNs [17]. Chemotherapy may lead to fibrosis of the lymphatic duct of the sentinel lymph node and thus the blue dye or technetium molecule is directed to travel to other lymph nodes that are not the true sentinel nodes. In addition, the order of response of the nodes in the axilla is not known; the sentinel node may respond to treatment and become free of tumor. This is of particular concern in patients with clinically node–positive disease who undergo chemotherapy before surgery. Thus, the accuracy of SLNB has been questioned following neoadjuvant chemotherapy [18]. One of post NAC breast carcinoma show poor chemotherapy response with grade 2 Miller–Payne grade and Residual cancer Burden II. This tumor showed prominent chemotherapy–related changes in form of bizarre hyperchromatic nuclei, vacuolated cytoplasm, low mitosis, excessive elastosis and hyalinization with fibrinoid necrosis.

This study shows a very low false positive rate (6.25%) which based on serial histological sections with hematoxylin and eosin staining. Although false positive was detected in one case only, we identified the most striking cytology which may mislead is the prominent post capillary venules which appear as clumps of large and epithelioid endothelial cells making the interpretation within a short time difficult. However, another larger study that focused false positive results explained other causes for the false TIC result include; First, micrometastatic foci may be overlooked by SS with H&E. Second, the TIC may have contained the only metastatic deposit in the part of the lymph node that was lost in the deeper sections of the lymph node and, consequently, was not detected in final histopathology. Finally, the clinical impression of the surgeon regarding the appearance of the nodes may mislead the pathologist [19].

In the current study there was one ITC case diagnosed falsely as negative, where it appeared in histology has a micrometastasis where the metastatic deposits present in the capsular afferent vessels of the lymph node. This made the false negative result reaching 11.1%. This may reflect the poor sensitivity of detecting in particularly of the micrometastatic disease, which make some suggest the use of intraoperative cytokeratin immunohistochemistry protocols to decrease the intraoperative false negative rate [20]. Delgado–Bocanegra reported similar rate in neoadjuvant chemotherapy cases with 17.6% false–negative rate in which most cases resulted from the presence of micrometastases. However, study stated the

rate decreased to 9.1% when more than two SLNs were sampled [21]. Other study has found the main reason for the false–negative results of the imprint cytology was poor quality of the imprint samples due to sampling error [22].

The sensitivity SLN–TIC is 89.9%. This indicates the usefulness of this rapid, easy and cost–effective method in the diagnosis of SLN metastasis and its influence on axillary lymph node dissection decision. However, the sensitivity for TIC has been reported elsewhere to vary widely from 34% to 96%, which make it difficult to compare data across much of the current literature, due to large differences in case types [34]. According to a study by Tew K, et al., intraoperative imprint cytology has a sensitivity of 63% with a false–negative rate of 37%, and the pooled sensitivity for macrometastases is higher (81%) than that for micrometastases (22%) [23]. Some studies have shown increase sensitivity of intraoperative cytology evaluation with an increase in the primary tumor size [24].

In the current study, the overall accuracy was 92%, which concluded the high feasibility of TIC in clinical use for detecting metastasis in the SLNs of early stage invasive breast cancer. This is in agreement with the previously published data that indicating TIC as an acceptable technique to detect macrometastasis to the sentinel node in particular and micrometastasis to a lesser extend [25–26]. Cutting the lymph node at 2–3mm interval exposes a larger surface area and therefore increases the sensitivity of TIC by detecting tiny metastatic deposits. Examination of at least four slides within acceptable time is an important factor to be considered to increase the chance of diagnosis, as was concluded in previous studies as well [25]. In addition, the gross appearance of the lymph node cut surface also given a clue towards macrometastasis. Therefore, ITC interpretation should be evaluated by an experienced pathologist. This fact is taken into consideration in other studies as well [14–25].

Touch imprint cytology appeared to be marginally more sensitive over frozen section in detecting SLN metastasis [27]. Almarzooq et al found in their study that the sensitivity of intraoperative SLN frozen section was 77.7% with accuracy of 93.2% and specificity of 98.7% [28]. Similarly, Wada et al found relatively high overall false–negative reaching to 16% particularly for T1b and T1c tumor, 33%, and 19% respectively. Furthermore, FS may fail to detect micro–metastases, especially in case of small tumors [29]. Wong et al identified higher false negative FS rates in post–neoadjuvant chemotherapy patients with Estrogen receptor–positive/HER2–negative status, and in sentinel lymph node with pN1mic and pN0i deposits. The sensitivity rate was 71.9%, which often was due to under–sampling at time of FS[30].

Conclusion:

In conclusion, TIC is considered to be an accurate, practical, time– efficient and cost–effective procedure with minimal tissue preparation for SLNs evaluation intra–operatively. It is also feasible for clinical use and detects macro–metastasis in SLNs intra–operatively with an acceptable accuracy in early stages breast cancer patients. It can save patients from axillary LN dissections complications, and can be afforded in almost all centers with basic cytological setup, offering patients best option of treatment.

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