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Sentinel lymph node biopsy following neoadjuvant chemotherapy for breast cancer patients with axillary node metastasis: A cross-sectional survey

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ABSTRACT

Background: A survey of breast surgeons in Saudi Arabia was conducted to evaluate changes in clinical practice regarding sentinel node biopsy (SNB) among clinically node-negative patients after neoadjuvant chemotherapy for breast cancer with axillary node metastasis. *Methods and Materials*: The study was conducted in a tertiary university hospital in Riyadh between August and October 2020 and utilized a 22-question, online survey to examine various factors leading to the omission of axillary lymph node dissection (ALND) among KSA breast surgeons. The questions pertained to basic demographics and the participant's cited influencing factors. Cross-tabulation and the chi-square square test were used to analysis subgroups, and binary logistics regression was used to assess doctor-related factors contributing to a decision to omit ALND after NAC. *Results:* A total of 24 participants completed the survey. The proportion of surgeons preferring SLNB adjunctively or replaced by axillary radiotherapy in patients with clinically positive axilla and receiving NAC was 70.8%. *Conclusion*: The implementation of SLNB post-neoadjuvant chemotherapy has led to a wide variation in clinical practice. Further prospective randomized clinical trials should be conducted in order to evaluate the clinical outcomes of SNB versus more conventional therapies.

Keywords: Breast, cancer, surgery, sentinel lymph node biopsy, neoadjuvant chemotherapy

1. INTRODUCTION

Axillary lymph node (ALN) status is a significant prognostic factor for breast cancer. Axillary lymph node dissection (ALND) may provide precise lymph node staging (Han et al., 2013; Hashem & Farahat, 2020), but often leads to morbidities including lymphedema, nerve injury, pain, shoulder stiffness and weakness (Kim et al., 2006). As an alternative approach, sentinel lymph node

biopsy (SLNB), which is associated with fewer complications, has now become a standard procedure in clinical node-negative primary breast cancer diagnostics (Vugts et al., 2016). Pathological complete response (pCR) of the axillary lymph node after neoadjuvant chemotherapy (NAC) can be observed in 20-42% of clinically node-positive patients, (Byun et al., 2019) therefore, it seems pragmatic to presume that in patients with an axillary pCR, aggressive surgical treatment of the axilla with an ALND may be omitted, thereby reducing the risk of related morbidities (Alvarado et al., 2012).

The efficacy of SLNB after NAC has been discussed in three recent prospective trials; ACOSOG, Z1071 and SENTINA (Lee et al., 2019). These studies report lower detection and higher false negative rates, therefore the efficacy of this process remains unclear. However, several meta-analyses have shown a reasonable comparable result for patients with breast cancer who have undergone up-front breast surgery (Straver et al., 2009). Regardless, despite the available data, breast surgeons still tend to perform additional ALND in the absence of ALN metastasis, ascertained by SLNB following NAC.

A survey of breast and oncology surgeons in Saudi Arabia was conducted to evaluate changes in clinical practice regarding sentinel lymph node biopsies among clinically node-negative patients presenting with axillary node metastasis after receiving neoadjuvant chemotherapy for breast cancer.

2. METHOD AND MATERIALS

Our work has been reported in line with the STROCSS criteria (Agha et al., 2017). Data was collected from surgeons specializing in breast and oncology surgery. The study was conducted in a tertiary university hospital in Riyadh between August and October 2020. The study comprised an online 22 question, quantitative and observational cross-sectional approach directed at breast and oncology staff working in Saudi Arabia. The questionnaire was structured and self-administered, consisting of basic demographic information including gender, age, practice specialty and professional experience years (Table 1).

The study was approved by the King Saud University, College of Medicine Institutional Review Board: Project No. E-20-4722. Consent was obtained, and we ensured participant confidentiality by not requesting names or other forms of identification. Statistical analysis was performed using the chi-square and Fisher's exact tests. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics, version 21.0 (SPSS Inc., Chicago, USA).

3. RESULTS

Characteristics of surgeon participants

A total of 24 participants completed the survey. Fifteen (62.5%) were male and 37.5% were female. The majority (62.5%) conformed to the 36-40 year-old age group, with 25% above 40 years, and 12.5% between 30–35 years old. Ten (41.7%) participants were located in the Central region; eight (33.3%) in the Western region; four (16.7%) were located in the South, and two (8.3%) were from the Eastern region. Ten (41.7%) participants cite more than five years of experience; seven (29.2%) between 5-10 years, four (16.7%) had 10–15 years of experience, and three (12.5%) reported more than fifteen years of experience. All participants were consultants, with 22 (91.7%) specializing in breast surgery, and two (8.3%) specialize in surgical oncology (Table 1).

Table 1 Characteristics of participating surgeons (n = 24)

Variables		Frequency	Percentage
Gender			
	Female	9	37.5
	Male	15	62.5
Age			
	30 – 35	3	12.5
	36 – 40	15	62.5
	>40	6	25
Region			
	Central	10	41.7
	Southern	4	16.7
	Western	8	33.3
	Eastern	2	8.3
Years of experience			

	0 – 5	10	41.7
	5 – 10	7	29.2
	10 -15	4	16.7
	>15	3	12.5
Level of expertise			
	Consultant	24	100
Specialty			
	Breast Endocrine	22	91.7
	Surgical Oncologist	2	8.3

Hospital characteristics

Seventeen (70.8%) of the participants are practicing in tertiary hospitals, while seven (29.2%) practice in secondary hospitals. Thirteen (54.2%) of the hospitals; offer an on-site radiotherapy facility, while 11 (45.8%) surgeons are practicing in hospitals without. Twenty-one (87.5%) were employed in hospitals with a nuclear medicine facility, with 3 (12.5%) practicing in facilities without. Regarding the treatment of breast cancer patients, eight physicians (33.3%) reported treating approximately 50-100 annually, three (12.5%) treat between 100–50 patients; two (8.3%) treat 150–200; one treats 200–250; three (12.5%) treat 250–300 patients annually, and seven (29.2%) treat more than 300 breast cancer patients per year (Table 2).

Table 2 Hospital characteristics

Variables	Frequency	Percentage
Hospital		
Secondary	7	29.2
Tertiary	17	70.8
Do you have a radiotherapy facility present at your hospital?		
No	11	45.8
Yes	13	54.2
Do you have a nuclear medicine facility in your hospital?		
No	3	12.5
Yes	21	87.5
How many breast cancer patients are treated in your hospital annually?		
50 - 100	8	33.3
100 - 150	3	12.5
150 - 200	2	8.3
200 - 250	1	4.2
250 - 300	3	12.5
>300	7	29.2
Total	24	100

Axillary mapping after neoadjuvant chemotherapy

Fourteen (58.3%) surgeons documented that pathological confirmation via fine needle aspiration (FNA) or core needle biopsy is performed if an axillary ultrasound identifies lymph nodes with radiologically suspicious features, while ten (41.7%) stated they do not utilize any additional testing. On the other hand, 15 (62.5%) surgeons perform additional axillary imaging using CT, four (16.7%) use MRI and five (20.8%) surgeons use PET-CT. There was no consensus among the group regarding localizing clinically tumour positive lymph nodes prior to NAC. The majority (29.1%) of the surgeons use clip markers, 25% use ultrasound markers, and 4.2% report the use of alternate markers.

The practice of neoadjuvant chemotherapy (NAC) was surveyed among the surgeons. In cases of clinically node positive, physically-fit breast cancer patients <70 years; nine (37.5%) surgeons report always administering NAC, while four (16.7) surgeons

state they omit this in the presence of invasive lobular carcinoma (ILC). In addition, two (8.3%) surgeons administer NAC only if clinically N2 disease is present, while the remaining nine (37.5%) base their therapy decisions on aggressive tumour biology (grade III, HER2þ, >2 cm tumour diameter). To evaluate the axillary response to NAC, fifteen surgeons opt for sentinel node biopsies after using NAC. Six surgeons report using imaging modalities and two incorporate other methods, while one surgeon excises lymph nodes that are localised prior to NAC ('MARI-procedure,' targeted axillary dissection) to evaluate axillary response.

Most (70.8%) of the surgeons agreed that ALND could be withheld or replaced by axillary radiotherapy in patients with a clinically positive axilla ultrasound (þ FNA/core needle biopsy proven) who are receiving NAC; while seven (29.2%) disagreed with this methodology (Table 3).

Table 3 Surgery-related characteristics

Variables	Frequency	Percentage
If an axillary ultrasound shows lymph nodes with a pathological aspect, either (FNA) or core needle biopsy is performed:		
No	10	41.7
Yes	14	58.3
(NAC) is administered in a clinically node positive, physically fit breast cancer patient <70 years:		
Always	9	37.5
Always unless their breast cancer is an invasive lobular carcinoma (ILC)	4	16.7
If clinically N2 disease is present	2	8.3
Based on aggressive tumour biology (grade III, HER2þ, >2 cm tumour diameter)	9	37.5
Further axillary imaging is performed using:		
CT	15	62.5
MRI	4	16.7
PET-1	5	20.8
Prior to NAC, do you localize clinically tumour positive lymph nodes?		
No	12	50
Yes	12	50
If Yes, which type of marker do you use?		
(Ultrasound) marker	6	25
Clip	7	29.2
Other (please specify)	1	4.2
In patients with a clinically positive axilla (proven with ultrasound þ FNA/core needle biopsy) receiving NAC; could ALND be reserved considering that the patient will receive axillary radiotherapy?		
No	7	29.2
Yes	17	70.8
Axillary response to NAC is assessed using:		
Excision of a lymph node that was localised prior to NAC ('MARI-procedure', targeted axillary dissection)	1	4.2
Imaging modalities	6	25
Other (please specify)	2	8.3
SLNB after NAC	15	62.5
Which type of imaging modality do you use?		
CT	1	4.2

MRI	2	8.3
PET-CT	3	12.5
Ultrasound	13	54.2

Factors influencing the choice to omit ANLD

Sixteen (66.7%) of the participants stated they would omit ANLD based on the degree of radiological response to NAC; 15 (62.5%) due to the age of patient, 11 (45.8%) due to presence of N2 disease prior to NAC, and ten (41.7%) stated they would omit ANLD due to a triple negative (ER, PR and HER2). Four (16.7%) would omit due to the presence of a HER2 positive tumor; five (20.8%) due to a grade III tumor, two (8.3%) due to invasive lobular histology, four (16.7%) would omit ANLD due to surgical treatment of the breast, and one participant reported omitting standard ANLD due to ER negative (Table 4 and figure 1).

Table 4 Factors influencing the choice to omit ANLD

Factors	Frequency	Percentage
Amount of radiological response to NAC	16	66.7
Age	15	62.5
Presence of N2 disease prior to NAC	11	45.8
Triple Negative (ER, PR, HER2)	10	41.7
HER2 positive tumour	4	16.7
Grade III tumour	5	20.8
Invasive lobular histology	2	8.3
Surgical treatment of the breast	4	16.7
ER negative	1	4.2

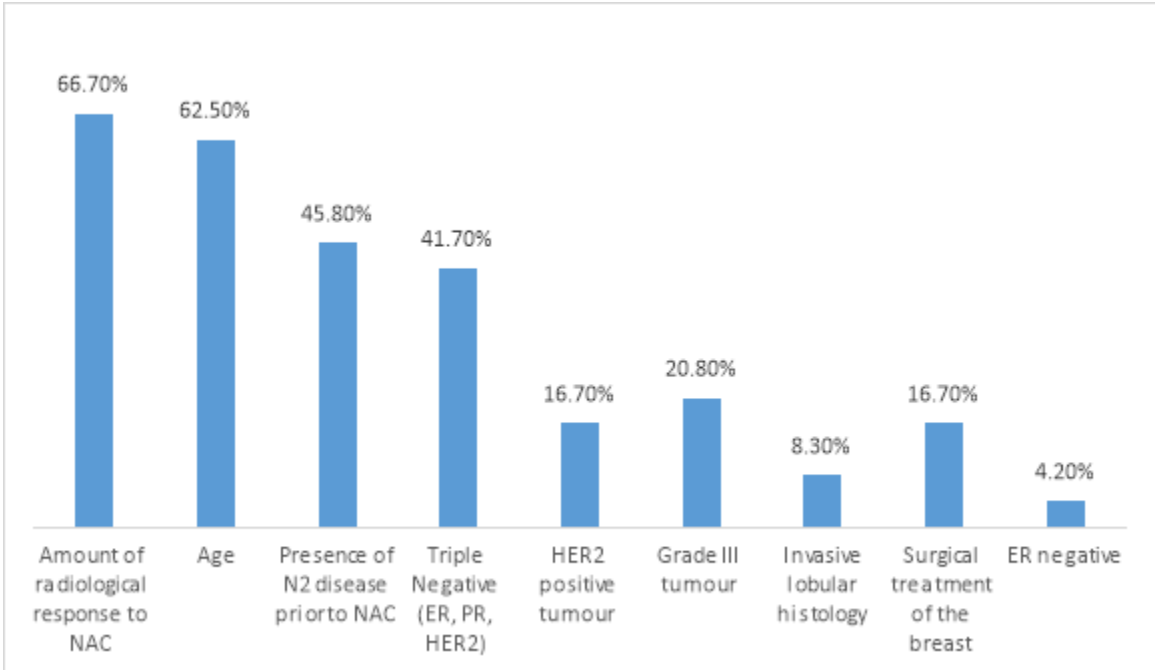

Figure 1 Factors influencing the choice to omit ANLD

Multivariate analysis

Multivariate analysis for physician-related factors influencing decisions to omit ANLD demonstrated that neither gender, age, years of experience, hospital nor number of patients treated annually was associated (Table 5).

Table 5 Multivariable analysis regarding surgeon-related factors associated with the omission of ALND after NAC; in patients with clinically node positive breast cancer

	OR	95% C. I		Sig.
		Lower	Upper	
Gender				
Female				
Male	0	0	.	0.997
Age				
30 - 35				1
36 - 40	3.71E+23	0	.	0.997
>40	0	0	.	0.998
Years of Experience				
0 - 5				1
5 - 10	6.59E+31	0	.	0.997
10 -15	72980106	0	.	0.998
>15	9.33E+15	0	.	0.999
Hospital				
Secondary				
Tertiary	1	0.02	50.397	1
Approximately, how many breast cancer patients are treated in your hospital on a yearly basis				
50 - 100				1
100 - 150	0	0	.	0.998
150 - 200	0	0	.	0.999
200 - 250	5.14E+41	0	.	0.998
250 - 300	7.42E+08	0	.	0.999
>300	8.59E+08	0	.	0.999

4. DISCUSSION

Axillary lymph node (ALN) status is an important prognostic factor in establishing accurate lymph node staging in breast cancer, and axillary lymph node dissection (ALND) is an excellent tool for determining lymph node involvement (Lee et al., 2019). However, ALND is often the precursor to significant morbidities, and the sentinel lymph node biopsy (SLNB) sequelae are less likely when compared to ALND (Fourme et al., 1974). Sentinel lymph node biopsies provide satisfactory staging information in early breast cancers patients (Lee et al., 2019) and therefore, have become the standard of care in a clinically and radiologically negative axilla (Haigh et al., 2000).

Neoadjuvant chemotherapy is often used to downgrade breast cancer prior to surgery (Kuwajerwala et al., 2013), as pathologic complete response (pCR) of the axillary lymph node after neo adjuvant chemotherapy (NAC) can be observed in 20-42% of clinically node-positive patients (Kuwajerwala et al., 2013). It is even more pronounced in HER2-positive disease, with an axillary (pCR) seen in up to 74% of patients (Dominici et al., 2010). In light of that finding, the use of SLNB in patients administered with NAC has the potential to decrease the need for axillary surgery (Gradishar et al., 2017).

The efficacy of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients identified as positive axillary lymph node prior to NAC has been questioned in two prospective trials: ACOSOG Z1071, and SENTINA; published in 2013 (Gradishar et al., 2017). However, this debate has been addressed in greater detail in the 2017 ASCO guidelines and 2015 ESMO guidelines; where for patients receiving NAC, the use of SLNB can be considered (Senkus et al., 2015). In addition, the AMORAS study of 2015 demonstrates that axillary lymph node dissection and axillary radiotherapy of a positive sentinel node provide comparable axillary control for patients with T1–2 primary breast cancer without palpable lymphadenopathy, however when applied in combination with radiotherapy results in significantly less morbidity (Donker et al., 2015). Unfortunately, it must be noted that the time between the publication of study results and subsequent implementation in clinic practice is often protracted.

In our study, the proportion of surgeons preferring SLNB adjunctively or replaced by axillary radiotherapy in patients with clinically positive axilla and receiving NAC was 70.8%. In contrast, a similar survey conducted by Byung Ho Son et al. among

Korean breast surgeons in 2017 revealed that only 52.6% of breast and oncology surgeons adopted this practice. Interestingly, our results were quite similar to a Dutch survey conducted by G. Vugts et al., where 70% of the participants agreed to SLNB post NAC. In the Dutch study, the decision to omit ALND appeared to be linked with clinicians who utilize NAC more often, along with their individual years of professional experience. This was not the case in our survey; however, these may simply be attributed to the sample size difference between the two studies, with 148 versus 24 participants, respectively.

Despite these recommendations, 29.2% of the surgeons in our study did not subscribe to the reliability and accuracy of SLNB after NAC. This may be due in part to the low number of patients treated with NAC annually, or the individual surgeon's level of experience. Interestingly, our multivariate analysis for physician-related factors failed to show that a relationship between gender, age, years of experience, type of hospital nor number of patients treated annually was in fact, associated with this decision. Major factors influencing the choice to omit ANLD were the degree of radiological response to NAC, and the age of patients, at 66.7 and 62.5%, respectively. This is a logical result, as the life expectancy in younger patients is greater and therefore typically commands the implementation of more aggressive treatment. In addition, it follows that a greater radiological response to NAC elicits a better response by the axillary lymph nodes as well. Unexpectedly, the tumor's hormonal characteristics did not appear to change the ALND-omitting decision although significantly, evidence proves that HER status is associated with an increased likelihood of pCR (Mougalian et al., 2016).

As anticipated, more than half of the participants (58.3%) state that when an ultrasound appears suspicious, they use additional pathological testing utilizing various different modalities such as FNA and core needle biopsies. This could be attributed to the availability of services within their hospitals. Additionally, although additional axillary imaging modalities such as CT, MRI and PET-CT are relatively common, the vast majority of participating clinicians in our survey state they use CT as their first choice for radiological axillary imaging. Conversely, the Dutch survey cited PET-CT as the modality of choice for 73% of the participating surgeons. PET-CT has a high accuracy rating in the prediction of axillary pCR when used before or after NAC, which may in part be due to its prevalence throughout healthcare organizations (Koolen et al., 2013).

Limitations

We note a potential limitation in our study. Given that the number of participating surgeons was relatively low at twenty-four, the use of such a small sample size to represent the entire field may affect the feasibility of the findings, and a larger sample size would be required to obtain more comprehensive data.

5. CONCLUSION

In conclusion, there is a wide variation in clinical practice throughout the Kingdom of Saudi Arabia related to the implementation of SLNB following neoadjuvant chemotherapy. Further prospective, randomized clinical trials are required to evaluate the clinical outcomes of SNB versus conventional ALND and ensure more consistent practice in this region.

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Author Contributions

Nuha, conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Amal, designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. Abdullah conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Conflict of Interest

The authors declare that there are no conflicts of interests.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical approval

The study was approved by the Medical Ethics Committee of King Saud University (ethical approval code: 984635909).

Data and materials availability

All data associated with this study are present in the paper.

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