

Axilla management in sentinel node positive breast cancer patients at Mater Dei Hospital – An audit and literature review

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BACKGROUND

Surgical axillary clearance and axillary radiation therapy (ART) provide comparable loco-regional control and survival in patients with sentinel node positive breast cancer. Specifically, ART is associated with less post-therapeutic complications, such as lymphoedema. Our objective is to review the current axillary management for patients with positive SLN breast cancer, within our local hospital, and assess whether this therapeutic protocol complies to the international criteria as highlighted in 10-year follow-up of the large European Organisation for Research and Treatment of Cancer (AMAROS) trial. Ascertaining a safe and minimally invasive oncological therapeutic strategy, without compromising its efficacy, may improve long term morbidity in patients with breast cancer.

METHODS

A retrospective and quantitative analysis of 329 patients with breast cancer who underwent an axillary SLN procedure at Mater Dei Hospital (MDH) between January 2019 and 2020 was performed. The inclusion criteria were patient demographics, pre-/post-operative staging, tumour size, and treatment given. Data was analysed and compared to International randomised trials. The San Matteo Criteria based on the AMAROS trial, were reviewed, and used as a standard and compared to local practice.

RESULTS

329 patients were analysed, of which 284 patients fulfilled the inclusion criteria. 70 patients had a positive SLN with 74% having one SLN positive, of which 40% underwent ALND, 6% had ART, 2% refused ART and 52% received no treatment. 26% had 2 positive SLNs of which 44% underwent ALND, none received ART and 56% received no treatment in those with two positive SLN. Patients with more than 2 positive SLNs were excluded.

CONCLUSION

We have determined that ALND is the accepted management for breast cancer patients with positive SLN in MDH. ART should be considered as a

more favourable treatment option in patients with positive SLN being treated as it provides comparable results with significantly lower morbidity than ALND.

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INTRODUCTION

Breast cancer is a leading oncological diagnosis in women worldwide. Despite the incidence for breast cancer before the age of 50 in Western countries being 35%, and 5% occurring at a younger age,³⁰ the overall morbidity and mortality has decreased over the years due to the advent of breast cancer screening programmes, and the introduction of effective management protocols.

The diagnostic work-up of breast cancer involves a 'Triple Assessment' including a physical examination of the breast and locoregional lymph nodes (axilla, supraclavicular fossa), imaging (mammography, ultrasound, Magnetic Resonance Imaging), and pathological assessment of breast tissue or lymph nodes (core needle biopsy, Fine Needle Aspiration).

Following histological analysis of breast tissue, and lymph nodes respectively, staging of the tumour follows the 'tumour-node-metastases' (TNM) classification.

In the management of early breast cancer nodal status is the single most important prognostic factor. Nodal status is important because it serves as a marker of tumour metastatic potential, which translates to survival advantages of up to 40% at five years. Other factors such as grade, size of the tumour and hormonal receptor status (ER, PR, HER2), are of secondary importance as they are both less concerning in the absence of nodal involvement.^{6,25}

Studies have shown that accurate staging of the axilla and assessment of lymph node status is an essential component of breast cancer management.^{7,13} The TNM staging classifies the extent of metastasis in lymph nodes as follows: isolated tumour cells (<0.2mm), micro-metastases (tumour deposits 0.2-2mm), or macro-metastases (tumour deposits >2mm). Involvement of the

axillary nodes has an adverse effect on prognosis of breast cancer with a ten-year survival reduced from 75% to 25%.² In fact, level three lymph node involvement carries the worst prognosis.²⁴ Historically, management of the axilla ranged from limited level 1 axillary node excision through to full level three axillary nodal clearances.

Attempts to minimise the morbidity of axillary node clearance led to targeted operations including axillary nodal sampling and sentinel lymph node biopsy (SLNB). The sentinel lymph node (SLN) is the most likely lymph node to harbour metastasis from the breast tumour. It is identified, biopsied and surgically removed by using tracers that mimic the route of cancer cells from the tumour site through the lymphatic vessels towards the nodes. To assess the pathological status of the axillary lymph nodes (ALNs), in patients with clinical stage I/II breast cancer and without cytohistological evidence of metastatic axillary metastases, SLN mapping and concomitant resection during surgery is highly recommended for diagnosis.^{5,22} SLNB is an accurate way of determining further adjuvant treatment and prognosis.⁸

Our current practice of identifying the SLN during breast cancer surgery involves an injection of methylene blue dye around the tumour directed towards the axilla and pre-operative radiological-assisted administration of radioactive labelled technetium-99m colloid around the area of the tumour. The latter is a gamma-emitting colloid commonly used in the scintillation scanning of the reticulo-endothelial system. This will be confirmed clinically during surgery using a gamma probe which detects technetium-99m decay. The SLN will be the first to take up both methylene blue and technetium-99m colloid, and hence have a higher uptake.^{14,15}

Treatment options for breast cancer include local and systemic treatment. Local treatment involves surgery (to the breast and to the axilla) and radiotherapy. Randomised clinical trials have shown that survival rates were similar for women treated by mastectomy or breast conservation surgery (BCS).^{3,11} Currently, 60-80% of newly diagnosed breast cancers in Western Europe are amenable to BCS (wide local excision and radiation therapy).

Adjuvant systemic treatment involves endocrine therapy in all patients with detectable ER expression i.e., pre-menopausal are treated with nonsteroidal anti-oestrogen such as tamoxifen, and post-menopausal with aromatase inhibitors.

In contrast, chemotherapy is recommended in most patients with triple negative hormone receptors, HER2-positive breast cancers and in high-risk HER2-negative tumours. The benefit from chemotherapy is more pronounced in ER-negative tumours.

Management of Axillary Metastasis: ALND vs ART vs no treatment

The optimal management of micro-metastatic spread and isolated tumour cells is the subject of ongoing research. Based on the results of the IBCSG 23-01 trial, further axillary treatment does not seem to be required when a sentinel node has micro-metastasis.^{15,16} The presence of macro-metastatic spread in the sentinel node traditionally mandated conventional axillary lymph node clearance. Thus, patients with isolated tumour cells (ITC) (<0.2 mm) in the sentinel node and patients with limited involvement of the sentinel lymph node undergoing tangential breast irradiation may not need to have any further axillary procedure.¹²

Aim

This audit will review the clinical practice of axillary management of breast cancer patients in Malta, following identification of positive SLN. The data retrieved through MDH databases will be compared to international criteria. We will assess whether the possibility of de-escalating therapy might improve the morbidity of our patients without compromising their outcomes.

MATERIALS AND METHOD

Audit Design

Data protection approval was obtained from the Data Protection Office at Mater Dei Hospital (MDH). Permission to access patient data from the MDH database was obtained via written consent form from the three breast cancer consultant surgeons operating at our local government hospital. Furthermore, access to the histology reports of such patients was retrieved from histopathologists and their databases. A list of breast cancer patients who underwent an axillary sentinel lymph node procedure at the Agatha Breast Unit at Mater Dei Hospital, during the period of January 2019 to January 2020 was obtained from the Clinical Performance Unit at MDH with the approval of the consultants. Data was collected in a retrospective manner.

Every patient was assigned an individual numerical code and was included in a data sheet shared among the researchers and assistants. This data was stored for two months. Patient demographic data and information relating to preoperative imaging and histology, size, grading, lymph node involvement of the breast malignancy was gathered and further substantiated through online software systems including iSoft Clinical Manager® and Electronic Case Summary®. No Health Ethics Committee

Approval was required for this initiative as this was a retrospective study with no patient contact.

Inclusion and Exclusion criteria

A sample of 284 patients were included in this audit who appropriately fit the inclusion criteria. This cohort consisted of patients with a tumor size of pT1 and T2, had a Wide Local Excision (WLE) or Mastectomy, had a SLNB performed, and/or had no neoadjuvant chemotherapy.

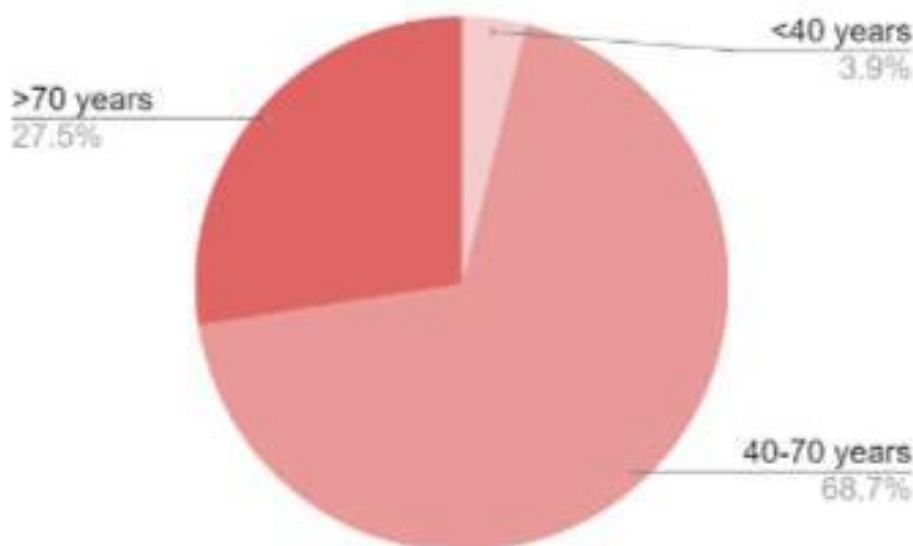
A sample of 48 patients were excluded. The following exclusion criteria were applied based largely on the San Matteo Criteria 2019: patients who had large tumors (pT3 and over), patients who had >2 positive SLN, patients who had complete primary axillary clearance, patients who received neoadjuvant treatment, and patients whose

histological result was not invasive ductal or lobular carcinoma. The latter criterion included patients diagnosed with ductal carcinoma in-situ (DCIS), papillary carcinoma and phyllodes tumours.

Data Analysis

The 284 eligible breast cancer patients who met our inclusion criteria were divided into two categories as follows: patients with a positive SLN ($n=70$) and patients with a negative SLN ($n=214$). The patients with a positive SLN were further subdivided into two categories: patients with one positive SLN ($n=52$), and patients with two positive SLN ($n=18$). In addition, these latter groups were analysed based on the presence of micro- vs macro-metastases. A flow diagram outlines the structure of the study (Reference of the flow chart i.e. Figure 1)

Figure 1: Demographic Data



RESULTS

329 patients were included in this audit. Out of these, 45 patients (13.68%) were excluded since they did not meet the inclusion criteria. These patients were as follows:

- 8 patients (2.43%) had more than two positive SLN.
- 10 patients (3.04%) had a pT3 primary lesion.
- 17 patients (5.17%) had a postoperative histology report showing DCIS.
- 5 patients (1.52%) had a postoperative histology report showing Papillary Carcinoma.
- 1 patient (0.30%) had a postoperative histology report showing Phyllodes Tumor.
- 7 patients (2.13%) received neoadjuvant chemotherapy.

Demographics

The overall mean age of subjects was 61 years. Breast cancer patients were categorised according to the age as follows (shown in Figure 1):

- Less than 40 years of age, of which there were 11 patients (3.87%).
- Between 40-69 years of age, of which there were 195 patients (68.66%).
- More than or equal to 70 years of age, of which there were 78 patients (27.46%).

Procedure

Out of 284 patients, 264 patients (92.96%) underwent a Wide Local Excision (WLE) and 20 patients (7.04%) underwent a mastectomy. Patients who underwent a mastectomy have a lower representation rate and do not represent a large tumor size.

Post-operative histological grade and type

Out of 284 patients, 223 patients (78.52%) had an invasive ductal carcinoma (IDC), 44 patients (15.49%) had an invasive lobular carcinoma (ILD), one patient (0.35%) had tubular carcinoma, four patients (1.41%) had a mucinous tumour, two patients (0.70%) had a micropapillary cancer and one patient (0.35%) with an apocrine carcinoma. Nine patients (3.17%) had a mixed histology result.

The histological grade of these carcinomas was as follows (shown in Figure 2):

- 87 specimens were Grade 1 (30.63%)
- 132 specimens were Grade 2 (46.48%)
- 62 specimens were Grade 3 (21.83%)
- 2 specimens were Grade 1/2 (0.70%)
- 1 specimen was Grade 2/3 (0.35%)

Post-operative Tumor Size (pT)

Out of 284 patients, 197 patients (69.37%) had a tumor size of ≤ 2 cm i.e., T1. 87 patients (30.63%) had a tumor size of > 2 cm but ≤ 5 cm i.e., T2 as per TNM staging classification (shown in Figure 3). Most of the subjects had small to medium sized tumors. The cut-off size in this research was 5cm.

Lymph node involvement: Amount and presence of micro- or macro-metastasis

Out of 284 patients, 214 patients (75.35%) had no lymph nodes involvement, and 70 patients (24.65%) had a positive SLN as shown in Figure 4.

52 patients (74.29%) out of the 70 breast cancer patients had one positive SLN, of whom 17 patients (32.69%) had micro-metastasis and 35 patients (67.3%) had macro-metastasis. From the 17 patients who had micro-metastasis in one positive SLN, 16 (94.12%) received no treatment to the axilla, while 1 patient (5.88%) had axillary clearance and none of the patients received radiotherapy as seen in Table 1

Figure 2: Post-operative Histological Grade data

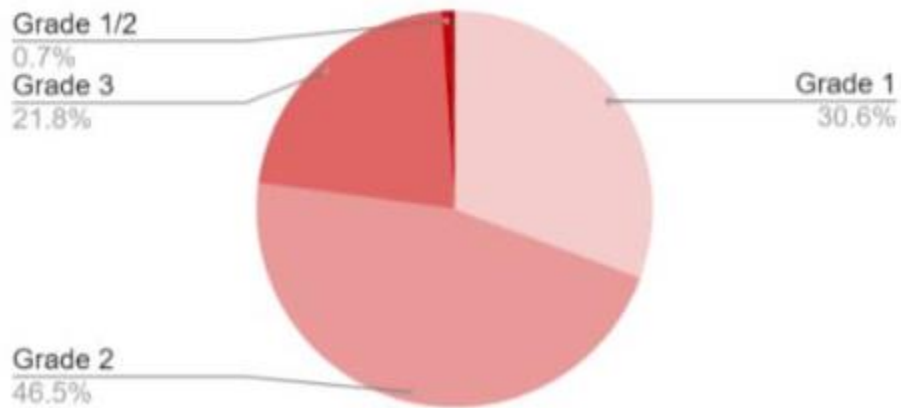


Figure 3: Post-operative Tumor Size (pT)

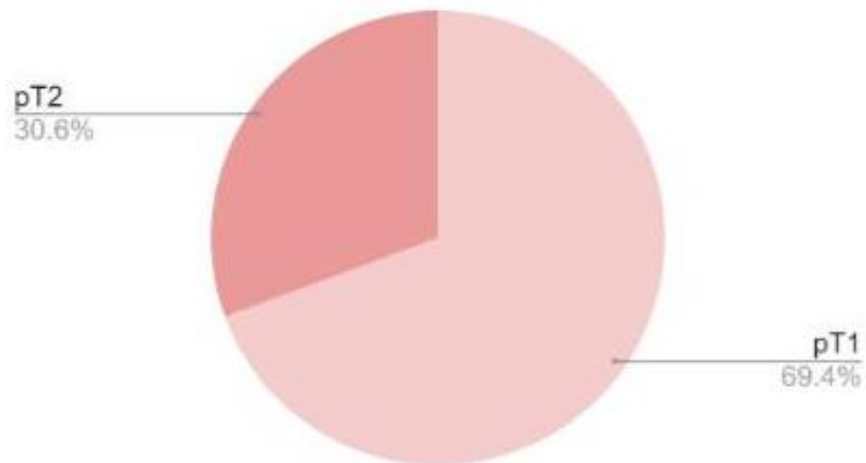


Figure 4: Number of eligible patients with positive and negative SLNB.

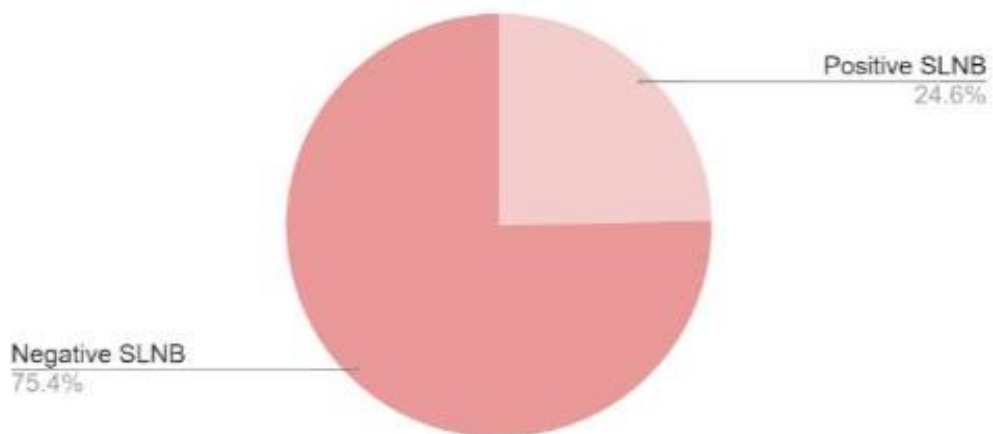


Table 1: Result table of patients with one positive SLN.

1 Sentinel lymph node positive: 52 patients (74.29%)	
Micro-metastasis: 17 (32.69%)	Macro-metastasis: 35 (67.3%)
Axillary clearance: 1 (5.88%)	Axillary clearance: 20 (57.14%)
Radiotherapy: 0 (0%)	Radiotherapy: 3 (8.57%) Radiotherapy refused: 1 (2.86%)
No treatment: 16 (94.12%)	No treatment: 11 (31.43%)

Out of 35 patients who had macro-metastasis in one positive SLN, 11 patients (31.43%) received no treatment to axilla (2 of which had distant metastasis), 3 patients (8.57%) received radiotherapy to the axilla, 1 (2.86%) refused radiotherapy to axilla and 20 patients (57.14%) had axillary clearance (1 of whom had distant metastasis) as seen in Table 2.

Out of the 70 patients with positive SLN, 18 (25.71%) had two positive SLNs; of whom three patients

(16.67%) had micro-metastasis and 15 patients (18.33%) had macro-metastasis. Out of the 3 patients with micro-metastases; one patient (33.33%) (pT2) received no treatment, none received radiotherapy and two (66.67%) (pT1) had axillary clearance. Out of the 15 patients with macro-metastasis, six (40%) had axillary clearance, nine (60%) received no treatment. From the nine who received no treatment, two (22.22%) were diagnosed with distant metastasis and another two patients (22.22%) were above the age of 70.

Table 2: Result table of patients with two positive SLN.

2 Sentinel lymph nodes positive: 18 patients (25.71%)	
Micro-metastasis: 3 (16.67%)	Macro-metastasis: 15 (18.33%)
Axillary clearance: 2 (66.67%)	Axillary clearance: 6 (40%)
Radiotherapy: 0 (0%)	Radiotherapy: 0 (0%)
No treatment: 1 (33.33%)	No treatment: 9 (60%)

DISCUSSION

The focus on SLNB has led to more detailed pathological evaluation of excised lymph nodes e.g., the use of immunohistochemistry, allowing for more detailed analysis of axillary nodal micro-metastases. Tumor nodal burden is a continuous variable. The size of LN metastasis i.e., whether it is ITC (<0.2mm), micro-metastasis (0.2-2mm) or macro-metastasis (>2mm) has a proportional effect on the survival outcome in early breast cancers. Therefore, the smaller the metastasis the less effect on the patient's outcome, which in turn means that further axillary management will not be beneficial.²³

Clinically apparent axillary disease is treated as for advanced breast cancer. On the other hand, breast cancer patients with negative clinical examination undergo SLNB. Patients with clinically node negative but positive SLNB, have historically been managed with ALND following the rationale that this has a better prognostic outcome. However, this surgery has side effects as mentioned above without improving survival.¹⁶⁻²²

The advantage of ALND is that it optimizes regional control, provides additional prognostic information, and potentially improves overall survival (OS). However, some patients do not need ALND because of a low risk of residual disease or recurrence.¹⁶⁻¹⁷

If the sentinel node is negative, then patients do not need to proceed with ALND. This recommendation is supported by results of multiple randomized clinical trials which show that in 15–20% of cases, an ALND leads to persistent and troublesome complications such as impairment of shoulder function, shoulder pain, paresthesia over the inner aspect of upper arm and axilla due to intercostobrachial nerve injury or lymphoedema.^{11,29} Additionally, studies have shown that there is no difference between SLNB or Level I

and II dissection in determining the metastatic status of axillary nodes if an experienced team performs such a procedure.¹⁰

The presence of micro-metastasis and its impact on survival is debated. In some studies, it seems to confer an increased risk of locoregional recurrence⁴ and a reduction of disease-free survival¹⁹, whilst in others it shows no overall impact.⁶ It is important to distinguish between micro-metastasis and isolated tumour cells, as the latter do not have an adverse impact on prognosis.²⁵

The need for definitive treatment of the axilla in breast cancer patients with positive sentinel nodes was addressed by the ASCOG Z0011 trial. In this trial, women were randomised to undergo axillary lymph node clearance or to observation without surgery. Groups were further adjusted for other prognostic factors and treatments. The investigators found no survival benefit in routinely undertaking axillary node clearance, where axillary nodal disease was limited in its extent. Regardless of the options in women with a low-risk axilla, those individuals who have overt evidence of axillary nodal involvement either through positive SLNB or preoperative ultrasound and fine needle aspiration, should still receive complete axillary treatment be it clearance or radiotherapy.¹⁶⁻¹⁷

75.35% of the patients who satisfied the inclusion criteria had a negative SLNB. These patients did not need any further axillary treatment as the recurrence risk is very low. In contrast, 24.65% of the patients in our study had a positive SLN, which were further categorized as highlighted in the 'Results' section. In this category of breast cancer patients, a cut-off of two positive SLN was used as per recommendations listed in the '*San Matteo Criteria*'.

Recent clinical trials also suggest that ALND may be omitted safely in selected patients who are clinically

node negative, with metastatic carcinoma limited to one or two SLNs.²³ SLNB is equivalent to ALND for staging of the axilla in patients with clinically node-negative (cN0) disease as proven in many studies. This also offers the advantage of significantly less morbidity, most notably lymphoedema and shoulder pain.²³

Our audit showed that 94.12% of breast cancer patients with one positive SLN with micro-metastasis had no further treatment to axilla and only 5.88% underwent axillary clearance. On the other hand, 66.67% of patients who had two positive SLNs with micro-metastasis, an axillary clearance was performed, while 33.33% had no treatment. No radiotherapy to the axilla was performed in both these groups. The St. Gallen Consensus Panel (2009) did not recommend ALND to three distinct groups of breast cancer patients as follows: those with SLN detected micro-metastasis, patients with isolated tumour cells, and other with well-differentiated and small tumours. It was agreed that axillary radiotherapy would be a better alternative to ALND, as it had the same outcome with less morbidity.³⁰ More than half of the patients (57%) with one positive SLN with macro-metastasis underwent ALND, 8.6% received axillary RT while 31% received no treatment to the axilla. In contrast, 60% of patients who had two positive SLN with macro-metastasis, received no treatment to the axilla. Reasons for this included the presence of distant metastasis, underlying multiple comorbidities and age above 70 years. 40% of patients who had two positive SLN with macro-metastasis received ALND and none received ART. This shows that various factors may affect the decision to treat the axilla and which modality of treatment is chosen. Studies have shown that not performing a SLNB in patients with cN0 and aged 70 years or older may

reduce morbidity associated with such a procedure due to similar outcomes and better quality of life. The reasoning behind this is that treatment recommendations were unlikely to be altered based on the SLN status. Elderly patients were more susceptible to dying of alternative causes other than breast cancer, thus SLNB did not affect their survival. In fact, the NCCN guidelines suggest that in the lack of data showing superior survival, SLNB for axillary staging may be optional in patients with serious comorbidities and the elderly.²³

Recent results of the AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery?) trial from the EORTC (European Organisation for Research and Treatment of Cancer) compared the locoregional control and survival of patients who had clinical T1–T2 cN0 invasive breast cancer and 1 to 2 sentinel lymph nodes containing metastases. This trial showed that there were no significant differences in 10-year (10y)-OS, 10y-axillary recurrence and 10y-DMFS (Distant metastasis-free survival) and between patients who underwent Breast Conserving Surgery (BCS) with surgical lymph node dissection and tangential adjuvant Whole Breast Radiotherapy (WBRT) or Mastectomy randomised to axillary radiotherapy (ART) against ALND.^{7,11}

CONCLUSION

We have determined that ALND is the preferred management option for breast cancer patients with positive SLN at MDH, even though the AMAROS trial has shown that ART is not inferior to ALND. The trial did not find any significant difference between ART and ALND in treating this category of breast cancer patients. However, such findings cannot be applied to all groups of patients, as in some groups (distant metastasis and elderly) no treatment was commoner.

Limitations

While performing data collection it was noted that there was missing information relating to the booking of the 'Radiotherapy Planning CT scan' on iSoft Clinical Manager®. Oncologists failed to specify the area of breast to be irradiated, and whether such radiotherapy was adjuvant treatment to the breast or ART. Furthermore, oncological follow up information on breast cancer patients is documented and stored separately in files at the Sir Anthony Mamo Oncology Centre. Therefore, crucial information such as management plans, could have been missed. Secondly, breast cancer patients in Malta are seen by different oncologists with their own preferred approaches to managing breast cancer, specifically axillary treatment which influences management of patients. Also, missing data relating to radiological or histological investigations performed at private institutions were not uploaded on the online software systems, which in turn resulted in untraceable data. Lastly, 284 breast cancer patients fulfilled the inclusion criteria for our study. Out of this cohort only 70 patients had positive SLN, which is not significant and not representative. A prime example is the demographic data. Like other international studies the younger cohort are under-represented, where only 3.87% were less than 40 years of age at the time of diagnosis. This was a result of the natural history of the disease and selection bias. Mastectomies were also underrepresented in this audit, with only 7.04% of eligible patients who underwent such a procedure.

Suggestions and Recommendations

Over the years, there have been international changes in practice guidelines which are shifting away from the management option of ALND. Several randomised controlled trials have shown that in terms of outcome both ART and ALND are

similar, however ALND carries a greater morbidity risk towards the patient. As we discussed earlier, the preferred management option at Mater Dei Hospital is ALND. We recommend that another study in the form of a questionnaire should be carried out amongst the Maltese breast cancer specialists (surgeons, oncologists, radiologists) to try to understand why the majority prefer ALND to ART.

We suggest that better documentation should be given priority, especially when it comes to writing the indication of ART, and the area of therapy through the online request forms and on the oncology notes. Documents from SAMOC should be made available and accessible to MDH staff through online software systems to allow better continuity of care within a multi-disciplinary team environment.

Although our audit included 284 breast cancer patients, only 70 patients had a positive SLN. Thus, we recommend that the data collected through this study is re-audited at a later stage and larger sample size should be considered.

Finally, ART should be considered as a more favourable treatment option in patients with positive SLN at MDH, as it provides comparable results with significantly lower morbidity than ALND, in terms of causing significantly less lymphoedema, shoulder pain and stiffness than the surgical management alternative.

SUMMARY

- The size of the LN metastasis has a proportional effect on survival outcome in early breast cancers.
- ALND is preferred management option for breast cancer patients with positive SLNB in MDH.

- Patients with positive SLNB managed with ALND have significant side effects.
- Various factors may affect the decision to treat the axilla and which modality of treatment is chosen.
- AMAROS trial has shown that ART is not inferior to ALND in breast cancer patients with positive SLNB.

- Findings cannot be applied to all groups of patients as in cases with distant metastases and elderly no treatment was commoner.

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