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IS THERE A SAFE TUMOR SIZE FOR IDENTIFICATION OF BREAST CARCINOMA WITHOUT AXILLARY NODE METASTASIS?

Há um tamanho seguro para a identificação do carcinoma mamário sem metástase linfonodal?

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ABSTRACT

Objective: To evaluate the rate of absence of axillary pathological involvement in patients with clinically negative axilla, submitted to axillary lymphadenectomy (AL). **Method:** Retrospective longitudinal study, which clinically evaluated patients without axillary metastasis (cN0), who underwent oncologic treatment from 1998 to 2001. Patients were selected at clinical stage I to III. The axillary pathological impairment ratio was correlated with tumor size and clinical stage T and TNM. We also evaluated the locoregional and axillary (local) recurrences. **Results:** 519 clinically cN0 patients were selected. All were submitted to AL, with a mean of 18 lymph nodes dissected and 3.2 compromised. The axillary metastatic rate was 47.2%. Tumor size and clinical stage were associated with the presence of axillary lymph node metastasis (p<0.001). The axillary involvement was of 78.6% for tumors between 6.1 to 8 cm, and of 100% for tumors larger than 8.1 cm. Forty patients were T4-TNM, where the impairment rate was 57.5%. The specific survival at 120 months was 71.1%, with locoregional recurrence rate of 6.9% (n=36) and local rate of 0.4% (n=2). **Conclusion:** In patients submitted to axillary lymphadenectomy, the axillary recurrence was extremely low. There are patients with tumors greater than 5 cm, smaller than 8 cm, and selected T4-TNM without metastasis in axilla. Further studies are necessary to evaluate sentinel lymph node dissection in this selected group, but it is unacceptable for tumors larger than 8.1 cm.

KEYWORDS: breast neoplasms; sentinel lymph node biopsy; lymph node excision; recurrence; neoplasm recurrence, local.

RESUMO

Objetivo: Avaliar a taxa de ausência de comprometimento anatomopatológico axilar em pacientes com axila clinicamente negativa, submetidas à linfadenectomia axilar (LA). **Método:** Estudo retrospectivo longitudinal que avaliou pacientes clinicamente com ausência de metástase axilar (N0), submetidas a tratamento oncológico no período de 1998 a 2001. Selecionaram-se pacientes no estádio clínico de I a III. Avaliou-se a relação entre a taxa de comprometimento anatomopatológico axilar, o tamanho do tumor e o estádio clínico T e TNM. Avaliou-se também o risco de recidiva locorregional (RLR) e de recidiva local axilar (RLA). **Resultados:** 519 pacientes clinicamente N0 foram selecionadas. Todas foram submetidas à LA, com o número médio de 18 linfonodos dissecados e 3,2 comprometidos. A taxa de doença metastática axilar foi de 47,2%. O tamanho do tumor e o estádio clínico estiveram associados à presença de metástase linfonodal axilar (p<0.001). Tumores de 6,1 a 8 cm apresentaram 78,6% de comprometimento, e em tumores maiores que 8,1 cm essa taxa foi de 100%. Quarenta pacientes eram T4-TNM, nos quais a taxa de comprometimento foi de 57,5%. A sobrevida específica aos 120 meses foi de 71,1%, a taxa de RLR foi de 6,9% (n=36) e a RLA de 0,4% (n=2). **Conclusão:** Em pacientes submetidas à linfadenectomia axilar, a taxa de recorrência axilar foi extremamente baixa. Há pacientes com tumores maiores que 5 cm e menores que 8 cm, T4-TNM, em que a axila se mostrou sem doença metastática axilar. Fazem-se necessários mais estudos prospectivos para avaliar a dissecção do linfonodo sentinela em casos selecionados de tumores T3 e T4 clínico, sendo a dissecção inaceitável para tumores com tamanho superior a 8,1 cm.

PALAVRAS-CHAVE: neoplasia da mama; biópsia de linfonodo sentinela; excisão de linfonodo; recidiva; recidiva local de neoplasia.

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INTRODUCTION

Breast cancer is the most prevalent neoplasm in females and is a serious public health problem worldwide, as approximately 1.38 million new cases are diagnosed per year. Moreover, breast cancer has an increasing mortality rate, of which 60% occur in developing countries[1].

For a long time, axillary lymphadenectomy (AL) was the standard treatment for breast cancer, since 97% of the drainage is axillary[2]. The NSABP-04 clinical trial demonstrated that the conventional AL alone did not provide a survival benefit[3]. Many patients without axillary metastasis were subjected to AL, which led to the sentinel lymph node concept[4]. Sentinel lymph node biopsy (SLNB) can accurately predict axillary status[5,6]. The NSABP B-32 trial showed a false-negative rate of up to 9.8% for sentinel lymph nodes, and even with a high false-negative rate, axillary recurrence after metastasis-negative SLNB was of only 0.25% after an average follow-up period of 21 months[7].

Thus, over time, SLNB was considered the best breast cancer axillary management in patients with clinically N0 axillary nodes, and was initially proposed for tumors smaller than 3 cm and later for tumors up to 5 cm (T2-TNM), although studies of tumors that ranged from 3.1 to 5.0 cm were limited. The American Cancer Society considers SLNB acceptable for T1 and T2 tumors[8,9]. Estimates of SLNB accuracy based on tumor size suggest that, for primary lesions greater than 3.0 cm, this value reaches 96%. However, according to the literature, several isolated studies on the use of SLNB for T3 and T4 tumors without the use of neoadjuvant chemotherapy (NAC) have been reported[9-13].

Similarly, the N0 axillary node concept also became controversial since the performance of an ultrasound examination allowed questioning the clinical event, and it was observed that the ultrasound indicated disease in the axillary nodes of many clinically N0 patients who are often subjected to biopsy with positive results[14]. This finding has been reinforced by the diagnostic evaluation method (fine needle puncture or core biopsy)[15]. In fact, there is no defined cut-off point for morphological change or cortical lymph node thickening, and many patients who undergo puncture or core biopsy will not demonstrate axillary involvement[15,16].

Many initial contraindications to SLNB have become debatable and relative over the years[17]. Recently, this type of axillary surgical management has been increasingly associated with NAC. Many patients with locally advanced tumors are candidates for NAC, but a portion of them are clinically N0 prior to chemotherapy or become negative after NAC[18]. SLNB after NAC is feasible, but it is associated with a reasonably high rate of false-negative results, especially when three lymph nodes are resected. No study with a long follow-up period that has demonstrated the safety of this procedure with respect to local axillary recurrence has been published. Many patients who are diagnosed as N0 prior to NAC could be candidates for SLNB, and based on a good response to NAC, they would not be candidates for SLNB or AL after it. Those patients would avoid the confounding effects generated by their responses to NAC, which determine a tumor sub-stage; this in turn may lead to unnecessary AL[4,19].

Breast cancer is the most prevalent neoplasm in women, and thus, even if a procedure is performed in a select group of patients, the number of procedures will be high. The larger the tumor is, the greater the probability of regional lymph node involvement[13], but studies on the applicability of SLNB to T3 or T4 tumors are limited. In turn, studies that have evaluated the rate of metastatic disease in patients with clinically N0 axillary nodes in T3 or T4 tumors are also limited in number, and little information is available on the rate of axillary recurrence under these specific conditions. This justifies the need for additional studies on this subject, especially since in the pre-SLNB era, such patients were systematically subjected to AL. Axillary evaluation and treatment play a therapeutic role, but these processes are increasingly seen as part of clinical staging and not as treatments. This leads to increased questioning about the need for AL, and therefore justifies the present study.

MATERIALS AND METHODS

This retrospective, longitudinal study was based on a historical series of all clinical stage I to III patients with no clinical axillary lymph node disease (N0) who were treated at the Barretos Cancer Hospital (Hospital de Câncer de Barretos — HCB) from 1998 to 2001 and who were subjected to AL. This study was approved by the HCB's Research Ethics Committee under number 495/2011.

Out of 1,493 patients, those with a previous cancer diagnosis and those who received prior treatment were excluded. From the remaining 956 patients, those with clinical stage 0 and IV were excluded, like those patients whose tumor histologies were not classifiable by the TNM system. Next, from the 728 remaining patients, those who did not undergo AL and those with fewer than five lymph nodes dissected were excluded. Patients with occult primary tumors were excluded from the 670 patients who remained, which resulted in 652 patients. Out of these, 108 with clinical N0 disease who underwent NAC and 25 patients for whom information on tumor size was lacking were excluded, which resulted in the 519 cases composing the sample of the present study.

The rate of axillary lymph node involvement as a function of tumor size and T-TNM stage was evaluated (Table 1). The 7th edition of the TNM staging system was used.

All patients underwent adjuvant treatment (Table 2). Since this was a historical series, standard chemotherapy was used at that time (only 10.4% of the patients did not undergo chemotherapy), and most of the patients received an adjuvant regimen based on CMF (69.5%) or FAC (9.2%). At the time of the study, adjuvant tamoxifen was used for two years, but trastuzumab was not used. The indications for radiotherapy remained unchanged.

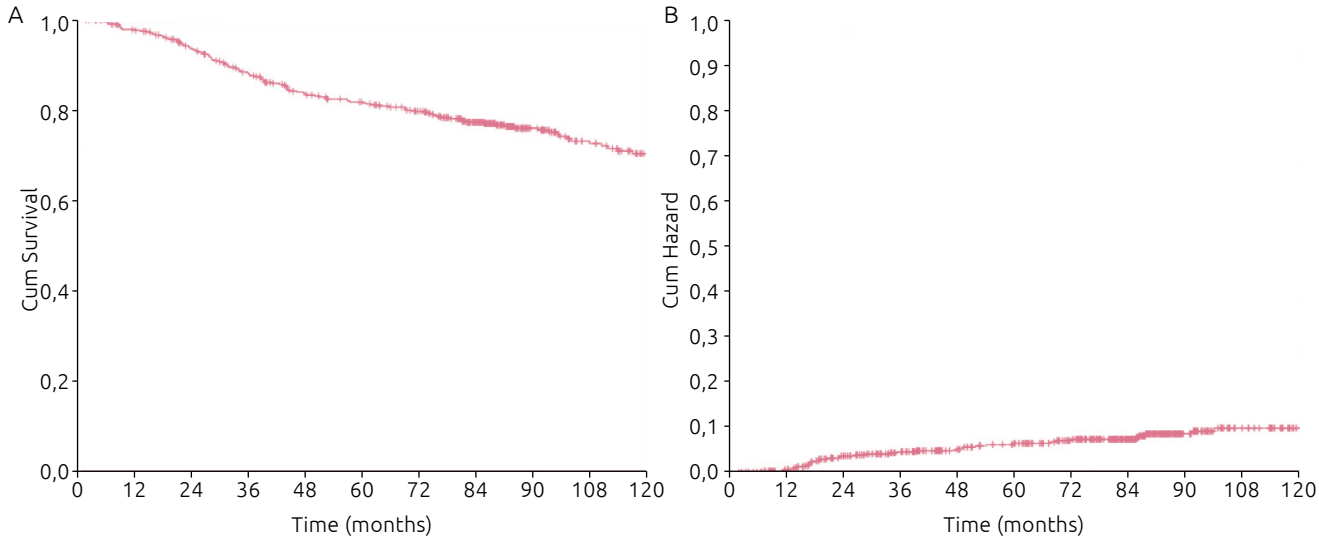

Figure 1. Results regarding follow-up time. (A) Cancer-specific survival; (B) hazard ratio for locoregional recurrence.

Table 1. Distribution of lymph node involvement according to tumor size and clinical stage.

	Category	Negative	Positive	Total	P
		n (%)	n (%)		
Size	0.1–1	23 (76.7)	7 (23.3)	30	<0.001
Segmental	1.1–2	74 (64.3)	41 (35.7)	115	
	2.2–3	90 (52.3)	82 (47.7)	172	
	3.1–4	51 (46.4)	59 (53.6)	110	
	4.1–5	21 (41.2)	30 (58.8)	51	
	5.1–6	12 (52.2)	11 (47.8)	23	
	6.1–7	2 (20.0)	8 (80.0)	10	
	7.1–8	1 (25.0)	3 (75.0)	4	
	8.1–9	0	2 (100)	2	
	9.1–10	0	2 (100)	2	
Size	0.1–3	187 (59.0)	130 (41.0)	317	<0.001
Grouped	3.1–5	72 (44.7)	89 (55.3)	161	
	5.1–6	12 (52.2)	11 (47.8)	23	
	6.1–8	3 (21.4)	11 (78.6)	14	
	8.1–10	0	4 (100)	4	
T-TNM Clinical	T1	92 (67.2)	45 (32.8)	137	<0.001
Staging	T2	153 (49.5)	156 (50.5)	309	
	T3	12 (36.4)	21 (63.6)	33	
	T4	17 (42.5)	23 (57.5)	40	
Subgroup	0.1–3	9 (69.2)	4 (30.8)	13	0.156
T4-TNM	3.1–5	5 (26.3)	14 (73.7)	19	
	5.1–6	1 (50.0)	1 (50.0)	2	
	6.1–8	2 (40.0)	3 (60.3)	5	
	8.1–10	0	1 (100)	1	

TNM: TNM 7th edition; T: tumor TMN.

Follow-up was assessed from the first until the last visit, and patients were considered to be lost of follow up if they did not return to the clinic at least two times, with the schedule time during 120 months. Cancer-specific survival and locoregional recurrence were also evaluated. Locoregional recurrence indicates recurrence in the chest wall, contralateral breast, supraclavicular fossa, or the ipsilateral or contralateral axilla. Axillary recurrence refers to the presence of axillary, retropectoral or axillary cavity disease, near the entrance of the subclavian artery.

Descriptive statistics were used to evaluate the results. Values with loss of information below 1% were reported and were excluded from the analysis. To evaluate the variables related to tumor size and lymph node positivity, the chi-square test was used. Survival was analyzed using Kaplan's and Meier's method, and the risk of recurrence was evaluated using hazard ratios; the log-rank method was used in both situations. Differences in which $p<0.05$ were considered significant. IBM SPSS for MAC version 20 was used for all statistical analyses.

Table 2. Characteristics of the treatment population.

Variable	Category	n	%
Pretreatment and staging			
Age	Up to 40	72	13.9
	40–69	367	70.7
	>70 years	80	15.4
TNM Clinical	I	88	17.1
Staging	II	320	62.0
	III	12	20.9
N-TNM Clinical	N0	274	52.8
Staging	N1	131	25.2
	N2	52	10.0
	N3	62	11.9
Treatment			
Surgery	Mastectomy	364	70.1
	Quadrantectomy	155	29.9
Chemotherapy*	Not performed	56	10.8
	Adjuvant	393	75.9
	Palliative	28	5.4
	Adjuvant and palliative	41	8.0
Hormone therapy*	Not performed	258	49.9
	Adjuvant	233	45.1
	Adjuvant and palliative	26	5.0
Radiotherapy	Not performed	30	5.8
	Adjuvant breast / axilla	329	63.4
	Adjuvant breast and fossa	170	32.8
	Recurrence	6	1.2
Follow-up			
Recurrence	Absent	480	93.0
Locoregional*	Present	36	6.9
Metastasis	Absent	383	73.8
	Present	136	26.2
Final status	DC	124	23.9
	DAS	31	6.0
	DWOO	10	1.9
	AWD	311	59.9
	AWOD	43	8.3

TNM: TNM 7th edition; N-TNM: TNM lymph node evaluation; *missing <1%; DC: death due to cancer; DAS: death due to associated disease; DWOO: death without observation; AWD: alive with disease; AWOD: alive without disease.

RESULTS

In all, 519 patients were evaluated. All patients underwent axillary lymphadenectomy; the mean number of dissected lymph nodes was 18 (range 7–49), and the mean number of lymph nodes involved was 3.2 (range 0–40). Overall, 47.2% of the patients were diagnosed with metastatic axillary disease. Table 1 shows the relationship between tumor size, T-TNM clinical stage and the presence of axillary metastatic disease. It was observed that the larger the tumor size, the higher the axillary metastatic disease rate. However, for tumors between 6.1 and 8.0 cm, this rate was 78.6%, while for tumors larger than 8.1 cm, this rate was 100% (Table 1).

Most of the patients were older than 40 years (86.1%) and had stage II or III disease (82.9%), but 52.8% of the patients had pathological N0 disease. Regarding the treatment performed, most patients underwent mastectomy (70.1%), while chemotherapy (75.9%), hormone therapy (50.1%), and radiotherapy (93.0%) were used as adjuvant therapies (Table 2).

The follow-up time spanned from January 1998 to October 2010, with a mean follow-up of 78.6 months (range 0.6–142 months). The percentage of patients considered to be lost of follow up was 5.4% (n=28); they had a median follow-up time of 37.7 months and data on locoregional recurrence of these patients were unavailable for only three patients. The cancer-specific survival was 81.4% at 60 months and was 71.1% at 120 months (Figure 1A).

At the end of the evaluation, 23.9% had died due to disease progression, 8.3% experienced recurrence after treatment, and 7.9% had died by another cause. During this period, 26.2% developed distant metastasis and 6.9% (36) developed locoregional recurrence (LRR). In the three patients who died, it was not possible to evaluate data regarding LRR. The mean time to LRR was 39.1 months (range 6.9–101.3 months). Figure 1B shows the hazard ratio for the LRR. The LRR (n=36) was evident in 66.7% (n=24) of the cases, and the main site of recurrence was chest wall (47.2%, n=17). The next most frequent was recurrence after quadrantectomy and in contralateral axilla (22.2%; n=8 each), contralateral breast, and ipsilateral and contralateral supraclavicular fossa

(11.1%, n=4 each). Ipsilateral axillary recurrence was observed in only 0.4% of all patients (5.6% of all local recurrences).

Of the two patients with local recurrence, both had triple-negative invasive ductal carcinoma and underwent mastectomy with AL; they also received 5,040 cGy radiotherapy and chemotherapy (12 CMF) and were followed-up. The first patient was primarily T2N0MO, had a tumor 3.5 cm in diameter and experienced recurrence in the chest wall, subclavian region and pectoral muscle at 17 months. The second patient was diagnosed as T3N1M0, had a tumor with 6.0 cm in diameter, and experienced retropectoral recurrence at 26 months.

DISCUSSION

In the past several years, the concept of clinically N0 (cN0) axillary nodes has been subjected to a greater debate since. SLNB for cN0 was first associated with AL for tumors lower than 3 cm and it was later extended for tumors under 5 cm. Now, SLNB is considered safety of tumors lower than 5cm; we also evaluated AL for T3 and T4 tumors, where we observed a considerable number of patients without axillary metastasis. This study gives bases for evaluating SLNB for T3 and T4 tumors, and probably, in the presence of pathological negative SLNB, AL can be avoided. Imaging exams can help our evaluation. Likewise, with the addition of imaging exams, especially axillary ultrasound, new parameters were added due to the improved characterization of lymph node shape, cortical thickening, and internal halo loss. These conditions often lead to the performance of axillary puncture or biopsy, which is associated with positive or false-negative findings[15,16]. When axillary puncture of biopsy is performed, some studies evaluate patients clinically, while others only consider the N0 axillary nodes after exclusion by ultrasound and axillary puncture. Axillary evaluation has only been important in the post-SLNB era. Few studies have exclusively evaluated axillary positivity in N0 axillary nodes since all patients were systematically subjected to AL, which justifies the present study since it is based on a historical series from the pre-SLNB era.

The present study has some limitations that must be considered. One of the major ones may actually be its merit, since this study is based on a historical series from the period before SLNB was performed, when patients underwent lymphadenectomy I-III regardless of their axillary condition. During the same period, neoadjuvant chemotherapy was beginning to be used at a greater frequency, and we attempted to exclude such patients from the sample to exclusively evaluate the axillary status in clinically N0 patients. Based on the results presented, negative axillary nodes in tumors up to 8 cm were observed in patients subjected to AL, but this finding has already been reported in tumors up to 10 cm[20]. However, the present study is grouped with a similar study[20] (Figure 2), for tumors 7.1 to 8 cm and 7.1 to 10 cm in size, 12 and 23 patients were evaluated, respectively, and a pathological negativity rate of 25 and 11.7% was observed, respectively. The limit that should be considered acceptable for SLNB for tumors larger than 5 cm is still under debate.

Other study limitation was to not present all prognostic variable related to breast cancer, as histologic grade and the main molecular characteristics. The treatment data (Table 2) was presented to show the conditions related to low axillary recurrence in patients submitted to AL. In 2001, the molecular classification was not instituted, and some of the treatment drugs used today were quite different, a fact the reinforces the low axillary recurrence.

Since this study is based on a retrospective series, the reasons associated with the primary treatment of T4-TNM tumors are unknown, thus there may have been a selection bias. Until the publication of the 7th edition of the TNM classification system, T4-TNM tumors were considered to be associated with the presence of skin invasion, skin edema, or "peau-d'orange" appearance. In this group of patients, 32/40 presented tumors smaller than 5 cm, which indicates the presence of edema or localized infiltration as a possible criterion that can be used in these patients. The assessment of SLNB in T4 tumors is limited, and generally those studies contained a small number of patients[21-24], which prompts us to reflect on which patients would be the best candidates for SLNB.

The main benefits of SLNB include a better pathological evaluation of axillary involvement and a significant decrease in morbidity compared with AL[25-27], which justifies studies that aim at expanding SLNB indications. In recent years, the condition of clinically N0 axillary nodes has been further discussed due to the reported observer-dependent variation and to the general sensitivity of the physical examination ranges from 32 to 68% for the determination of axillary involvement[28,29]. Ultrasound has been added to the preoperative evaluation, but the result is influenced by biopsy indication criteria, and initially negative results may be modified by small unobserved tumor foci[15,30-32]

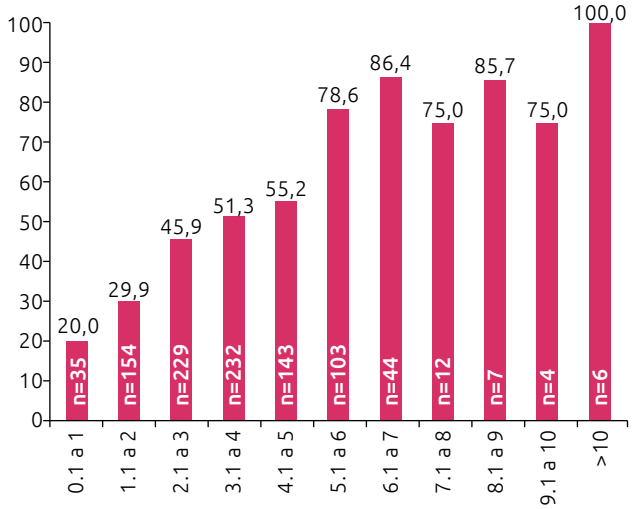

Figure 2. Percentage of metastatic disease using the current study and Corros et al. study[20].

NAC has been widely used as a way to reduce breast tumor size and to reduce axillary condition[18], but limited studies have evaluated SLNB in T3 or T4 tumors prior to NAC, and those that have been published generally involved a limited number of patients[19,23,33]. The potential advantage of SLNB before NAC is related to a higher sensitivity and a decrease in false-negative rates[19]. The identification of the axillary status prior to NAC allows more reliable clinical staging and, in the selected cases, allows for the primary surgical treatment of the breast and axillary nodes. The identification of the axillary status also makes a non-posterior axillary approach feasible[22] and safe in patients who are responsive to NAC.

Relative to the previously used treatment, breast cancer treatment has changed considerably, as taxanes have been added to anthracyclines, trastuzumab is used and hormone therapy is used for 5 or 10 years. These treatments may have a positive influence as they aim to reduce recurrence and increase survival in this group of patients. Even in these conditions, we attempted to evaluate locoregional recurrence and observed that the rate was low (8.1%) considering the tumors' size and the long follow-up time. The axillary recurrence rate was extremely low (0.4%), which is consistent with what have been reported in the literature. Veronesi et al., in a retrospective analysis of 3,548 patients with negative sentinel lymph nodes who were not subjected to AL, demonstrated that only 0.9% of the patients presented axillary recurrence and that the overall 5-year survival for the entire series was 98% after an average follow-up of 48 months[34]. In 2010, this same author reported a series of only two cases of axillary recurrence after SLNB, and those patients had a breast cancer event-free survival of approximately 89% after 10 years of follow-up[35]. These data are in agreement with the results of the NSABP B-32 trial, which presented a regional recurrence rate of 0.4% in the AL arm and 0.7% in the SLNB arm, with a false-negative rate in the AL arm of 9.8%. Even so, the disease-free survival was indistinguishable between the two groups and was approximately 82% after eight years[3].

The current consensus allows SLNB to be performed for tumors up to 5 cm, but the acceptable limit remains open. A prospective controlled study in which SLNB in one arm is compared with AL in another does not seem acceptable for us today, considering the availability of neoadjuvant and adjuvant treatment. In this sense, the present study allows us to observe that, in the presence of clinically negative axillary tumors up to 8 cm, regardless of whether the tumor is classified as T3 or T4, we can discuss the possibility of SLNB. This is because in up to 25% of these patients, AL is unnecessary and may result in negative effects in the patients.

CONCLUSION

When patients with clinically negative axillary nodes and tumors larger than 5 cm (T3-TNM), and T4-TNM were evaluated, 36.4% and 42.5%, respectively, did not present metastatic disease after AL.

Thus, SLNB can be considered in selected cases of tumors with N0 axillary nodes and in tumors larger than 5 cm and smaller than 8 cm and T4-TNM, whereas SLNB is unacceptable for tumors larger than 8.1cm. Further prospective studies are needed to evaluate the rate of axillary recurrence after SLNB since the rate is low in patients undergoing axillary lymphadenectomy.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90. https://doi.org/10.3322/caac.20107
2. Vieira RA, da Costa AM, de Souza JL, Coelho RR, de Oliveira CZ, Sarri AJ, et al. Risk Factors for Arm Lymphedema in a Cohort of Breast Cancer Patients Followed up for 10 Years. Breast Care. 2016;11(1):45-50. https://doi.org/10.1159/000442489
3. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347(16):1233-41. https://doi.org/10.1056/NEJMoa022152
4. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. Jama. 2013;310(14):1455-61. https://doi.org/10.1001/jama.2013.278932
5. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. Ann Surg. 1994;220(3):391-8; discussion 398-401.
6. Veronesi U, Paganelli G, Galimberti V, Viale G, Zurrida S, Bedoni M, et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. Lancet. 1997;349(9069):1864-7. https://doi.org/10.1016/S0140-6736(97)01004-0
7. Smidt ML, Janssen CM, Kuster DM, Bruggink ED, Strobbe LJ. Axillary recurrence after a negative sentinel node biopsy for breast cancer: incidence and clinical significance. Ann Surg Oncol. 2005;12(1):29-33. https://doi.org/10.1007/s10434-004-1166-0
8. Lyman GH, Giuliano AE, Somerfield MR, Benson AB 3rd, Bodurka DC, Burstein HJ, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol. 2005;23(30):7703-20. https://doi.org/10.1200/JCO.2005.08.001
9. Layeequr Rahman R, Crawford SL, Siwawa P. Management of axilla in breast cancer - The saga continues. Breast. 2015;24(4):343-53. https://doi.org/10.1016/j.breast.2015.03.010
10. Beumer JD, Gill G, Campbell I, Wetzig N, Ung O, Farshid G, et al. Sentinel node biopsy and large (>/=3 cm) breast cancer. ANZ J Surg. 2014;84(3):117-20. https://doi.org/10.1111/ans.12139

11. Galimberti V, Manika A, Maisonneuve P, Corso G, Salazar Moltrasio L, Intra M, et al. Long-term follow-up of 5262 breast cancer patients with negative sentinel node and no axillary dissection confirms low rate of axillary disease. Eur J Surg Oncol. 2014;40(10):1203-8. https://doi.org/10.1016/j.ejso.2014.07.041
12. Wey PD, Neidich JA, Hoffman LA, LaTrenta GS. Midline defects of the orofaciodigital syndrome type VI (Varadi syndrome). Cleft Palate Craniofac J. 1994;31(5):397-400. https://doi.org/10.1597/1545-1569_1994_031_0397_mdotos_2.3.co_2
13. Trocha SD, Giuliano AE. Sentinel node in the era of neoadjuvant therapy and locally advanced breast cancer. Surg Oncol. 2003;12(4):271-6. https://doi.org/10.1016/j.suronc.2003.08.002
14. Bailey A, Layne G, Shahan C, Zhang J, Wen S, Radis S, et al. Comparison between Ultrasound and Pathologic Status of Axillary Lymph Nodes in Clinically Node-negative Breast Cancer Patients. Am Surg. 2015;81(9):865-9.
15. Gruber I, Hahn M, Fehm T, Hann von Weyhern C, Stäbler A, Winckelmann A, et al. Relevance and methods of interventional breast sonography in preoperative axillary lymph node staging. Ultraschall Med. 2012;33(4):337-43. http://dx.doi.org/10.1055/s-0031-1273317
16. Mainiero MB. Regional lymph node staging in breast cancer: the increasing role of imaging and ultrasound-guided axillary lymph node fine needle aspiration. Radiol Clin North Am. 2010;48(5):989-97. https://doi.org/10.1016/j.rcl.2010.06.010
17. Filippakis GM, Zografos G. Contraindications of sentinel lymph node biopsy: are there any really? World J Surg Oncol. 2007;5:10. https://doi.org/10.1186/1477-7819-5-10
18. Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol. 2013;14(7):609-18. https://doi.org/10.1016/S1470-2045(13)70166-9
19. Jones JL, Zabicki K, Christian RL, Gadd MA, Hughes KS, Lesnikoski BA, et al. A comparison of sentinel node biopsy before and after neoadjuvant chemotherapy: timing is important. Am J Surg. 2005;190(4):517-20. https://doi.org/10.1016/j.amjsurg.2005.06.004
20. Coros MF, Stolnicu S, Georgescu R, Rosca A, Sorlea S, Dobre A, et al. [Axillary lymph node metastases in breast cancer. Anatomo-clinical correlation and surgical approach]. Chirurgia (Bucur). 2009;104(5):557-64.
21. Cox CE, Cox JM, White LB, Stowell NG, Clark JD, Allred N, et al. Sentinel node biopsy before neoadjuvant chemotherapy for determining axillary status and treatment prognosis in locally advanced breast cancer. Ann Surg Oncol. 2006;13(4):483-90. https://doi.org/10.1245/ASO.2006.03.592
22. Schrenk P, Tausch C, Wölfl S, Bogner S, Fridrik M, Wayand W. Sentinel node mapping performed before preoperative chemotherapy may avoid axillary dissection in breast cancer patients with negative or micrometastatic sentinel nodes. Am J Surg. 2008;196(2):176-83. https://doi.org/10.1016/j.amjsurg.2007.08.068
23. Chung MH, Ye W, Giuliano AE. Role for sentinel lymph node dissection in the management of large (> or = 5 cm) invasive breast cancer. Ann Surg Oncol. 2001;8(9):688-92. https://doi.org/10.1007/s10434-001-0688-y
24. Moghimi M, Ghoddosi I, Rahimabadi AE, Sheikhvatan M. Accuracy of sentinel node biopsy in breast cancer patients with a high prevalence of axillary metastases. Scand J Surg. 2009;98(1):30-3. https://doi.org/10.1177/145749690909800106
25. Krag D, Weaver D, Ashikaga T, Moffat F, Klimberg VS, Shriver C, et al. The sentinel node in breast cancer--a multicenter validation study. N Engl J Med. 1998;339(14):941-6. https://doi.org/10.1056/NEJM199810013391401
26. Swenson KK, Nissen MJ, Ceronsky C, Swenson L, Lee MW, Tuttle TM. Comparison of side effects between sentinel lymph node and axillary lymph node dissection for breast cancer. Ann Surg Oncol. 2002;9(8):745-53.
27. Giuliano AE, Haigh PI, Brennan MB, Hansen NM, Kelley MC, Ye W, et al. Prospective observational study of sentinel lymphadenectomy without further axillary dissection in patients with sentinel node-negative breast cancer. J Clin Oncol. 2000;18(13):2553-9. https://doi.org/10.1200/JCO.2000.18.13.2553
28. Herrada J, Iyer RB, Atkinson EN, Sneige N, Buzdar AU, Hortobagyi GN. Relative value of physical examination, mammography, and breast sonography in evaluating the size of the primary tumor and regional lymph node metastases in women receiving neoadjuvant chemotherapy for locally advanced breast carcinoma. Clin Cancer Res. 1997;3(9):1565-9.
29. Pamilo M, Soiva M, Lavast EM. Real-time ultrasound, axillary mammography, and clinical examination in the detection of axillary lymph node metastases in breast cancer patients. J Ultrasound Med. 1989;8(3):115-20.
30. Bruneton JN, Caramella E, Héry M, Aubanel D, Manzino JJ, Picard JL. Axillary lymph node metastases in breast cancer: preoperative detection with US. Radiology. 1986;158(2):325-6. https://doi.org/10.1148/radiology.158.2.3510440
31. Fisher B, Wolmark N, Bauer M, Redmond C, Gebhardt M. The accuracy of clinical nodal staging and of limited axillary dissection as a determinant of histologic nodal status in carcinoma of the breast. Surg Gynecol Obstet. 1981;152(6):765-72.
32. Tate JJ, Lewis V, Archer T, Guyer PG, Royle GT, Taylor I. Ultrasound detection of axillary lymph node metastases in breast cancer. Eur J Surg Oncol. 1989;15(2):139-41.
33. Ollila DW, Neuman HB, Sartor C, Carey LA, Klauber-Demore N. Lymphatic mapping and sentinel lymphadenectomy prior to neoadjuvant chemotherapy in patients with large breast cancers. Am J Surg. 2005;190(3):371-5. https://doi.org/10.1016/j.amjsurg.2005.01.044
34. Veronesi U, Galimberti V, Paganelli G, Maisonneuve P, Viale G, Orecchia R, et al. Axillary metastases in breast cancer patients with negative sentinel nodes: a follow-up of 3548 cases. Eur J Cancer. 2009;45(8):1381-8. https://doi.org/10.1016/j.ejca.2008.11.041
35. Veronesi U, Viale G, Paganelli G, Zurrida S, Luini A, Galimberti V, et al. Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study. Ann Surg. 2010;251(4):595-600. https://doi.org/10.1097/SLA.0b013e3181c0e92a