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## **Factors predicting the sentinel node metastases in T1 breast cancer tumor: An analysis of 1416 cases**

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# Accepted Manuscript

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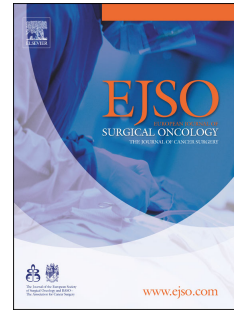
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**Abstract*****Factors predicting the sentinel node metastases in T1 breast cancer tumor:  
An analysis of 1416 cases*****Aim**

To determine the factors associated with the metastatic involvement of sentinel lymph node (SLN) biopsy in patients with early breast cancer.

**Study design**

This was a retrospective study of patients with T1 invasive breast cancer who underwent SLN biopsy at Claudius Regaud Institute between January 2001 and September 2008.

**Results**

1416 patients were recruited into this study. SLN metastases were detected in 368 patients (26 %). Younger age, tumor size and location, histological type, nuclear grade, and lymphovascular invasion appear to be significant risk factors of SNL involvement. In multivariate analysis, tumor size, tumor location, histological type and lymphovascular invasion are significant factors. When the tumor size is >20mm, the OR is 6.6 compared to a T1a tumor (3.145- 14.175,  $p < 0.001$ , confidence interval 95%). When the tumor is found in the inner quadrant, the risk of SLN involvement is reduced compared to external locations with an OR of 0.53 (0.409- 0.709,  $p < 0.001$ , confidence interval 95%). Non ductal/lobular compared to infiltrative ductal cancer have a lower risk of SLN involvement with an OR of 0.423 (0.193- 0.927,  $p < 0.03$ , confidence interval 95%). Lymphovascular invasion increase the risk of positive SLN with an OR of 2.8 (1.9-4.1,  $p < 0.001$ , confidence interval 95%).

**Conclusion**

It appears reasonable to avoid axillary lymph node dissection in older patients with T1a tumors of good histopathological type and in the absence of lymphovascular invasion.

**Keywords**

Sentinel node, early breast cancer, T1 tumor, axillary lymphadenectomy

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**Introduction**

Lymph node status seems to be one of the most important prognosis factor in breast cancer .<sup>1</sup> Several years ago, the only way to evaluate the lymph node metastases was to perform complete axillary lymphadenectomy but at the expense of several functional consequences such as lymphoedema ,shoulder restriction , numbness , weakness and pain syndrome. <sup>2,3,4</sup> Sentinel lymph node (SLN) biopsy has evolved as a technique for staging accurately the axilla with less morbidity than lymph node dissection. <sup>2,3,4</sup> However, morbidity of such a technique exists. <sup>2,3,4,7</sup> Technical failure occurs in about 2 to 6 percent <sup>5,6</sup> of cases necessitating a complete axillary lymphadenectomy. Sentinel lymph node is positive for metastases in about 25% of cases.<sup>6,8</sup>

On the other hand, it means that 75 % of sentinel lymph node (SLN) biopsy is performed without need for any adjuvant treatment. Moreover, there is a general agreement that removal of negative lymph nodes does not provide any significant survival benefit <sup>9</sup>

The aim of this study is to determine the factors associated with the metastatic involvement of SLN in patients with early breast cancer.

## Study design

All patients with clinical T1 invasive breast cancer (size < 2 cm) who underwent sentinel lymph node biopsy at Claudis Regaud Institute in Toulouse, France were recruited into the study between January 2001 and September 2008. The study was approved by the ethics committee, and all participating patients gave informed consent.

The patient clinical records were retrospectively reviewed to collect the necessary clinicopathologic data such as age, primary tumor size, type of breast cancer surgery (lumpectomy or mastectomy), histologic type, nuclear grade, estrogen and progesterone status, HER 2 status. All patients had a biopsy proven invasive cancer.

Patients with obvious clinical lymph node metastases or had neoadjuvant chemotherapy were excluded from this study.

### *Operative procedures and lymphatic mapping :*

Lymphatic mapping was performed using technetium Tc 99m sulfur colloid, which was injected into the peri-areolar area around the tumor one day before surgery in the department of nuclear medicine. On the day of surgery, 2 ml of blue dye is injected in the peri-areolar area 5 minutes before incision. During surgery, the SLN is identified by a hand held gamma probe and/or blue dye.

### *Pathologic examination of lymph node:*

At least seven sections were obtained from each block of sentinel node at 200  $\mu$ m intervals and stained with hematoxylin and eosin (H&E) for blocks 1, 2, 5 and 7. Nodes with negative H&E staining were further evaluated by the immunohistochemical (for seven blocks) staining with antibody. Anti-Epithelial (AE1 and AE3) staining was considered positive when a cluster of positively stained tumor cells are detected.

### *Statistical analysis:*

Statistical analysis was performed using STATVIEW software.

Associations between involvement of SLN and clinicopathologic factors such as age, clinical aspect of the tumor, location, multifocality, tumor size, histological and nuclear grade, oestrogen, progesterone and Her2/neu receptor status, lymphovascular invasion and lymph node metastases were studied. A two tailed, Fisher exact test was used for hypothesis testing, at 0.05 significance level. Factors that were found to be statistically significant in univariate

analysis were further evaluated by multivariate logistic regression for model building to identify the independent factors associated with presence of SLN metastases.

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## Results

A total of 1416 patients were recruited into this study and 1623 sentinel node procedures were performed with a rate of SLN detection of 97.2% for the combined blue dye and radioisotope technique. The mean number of sentinel nodes biopsied per patient was 1.8 (1-8). The median age was 59 years (range 17-92) and the mean size of tumor was 12.9 mm (0.5 -80 mm). SLN metastases were detected in 368 patients. All clinico pathological characteristics are described in tables 1 and 2.

Age appears to be a risk factor as patients with SLN metastases appear to be younger than patients without SLN metastases (55 vs 60 years) and older women above 70 years have a lower rate of SLN metastases. 28% of women below 50 years have SLN metastases compared to 20.3% above 50 years (see table 2).

Tumor size and location, histological type, nuclear grade, and lymphovascular invasion appear to be significant risk factors as well in univariate analysis.

Linked to tumor size, a palpable tumor is often associated with lymph node metastases. This fact was correlated with histological tumor size: more than 50% of tumors without lymph node involvement were T1a or T1b vs 23% when the sentinel node was positive.

The tumor seems to have a more aggressive characteristic (higher nuclear grade and positive lymphovascular invasion) when the SLN is positive. Non ductal/lobular types (other) such as apocrine, tubulous and mucinous tumors are more frequently associated with negative SLN.

In multivariate analysis, tumor size, tumor location, histological type and lymphovascular invasion are significant. (see table 3)

Compared with a T1a tumor, a T1c tumor has an odds ratio (OR) of 3.69 of SLN metastases. When the tumor size is >20mm (T2 tumor) the OR is 6.94 compared to a T1a tumor.

When the tumor is found in the inner quadrant, the risk of SLN involvement is reduced compared to external locations with an OR of 0.53

Non ductal/lobular tumor type such as tubulous mucinous or apocrine tumors compared to infiltrative ductal cancer have a lower risk of SLN involvement with an OR of 0.41. Lymphovascular invasion increases the risk of positive SLN with an OR of 2.9.

## Discussion



Sentinel lymph node biopsy has been shown to be a good procedure to evaluate the axillary lymph node status<sup>13,14</sup>. In our study, 75.4 % of patients did not have any metastases in their sentinel lymph node hence in these cases, SLN biopsy did not give any complementary information for the need of adjuvant treatment and it can produce some morbidity without any benefit.<sup>4,5,7</sup> There was a technical failure rate of 2.5%, which necessitated a complete axillary lymphadenectomy in this group of patients.

Based on this information, we wanted to define any factors/criteria that can lead to an avoidance of lymph node dissection ( axillary lymphadenectomy or SLN biopsy).

#### *Predictives factors of lymph node involvement*

In our study we found that women >50 years old appear to have a lower risk of SLN involvement and this fact has been confirmed in some studies for patients with lymph node dissection<sup>15,16,17</sup> Noh<sup>15</sup> et al found that the risk of lymph node invasion increased by three when they compared women under 40 years old vs women above 60 years old .

We also found that tumor size is a significant factor influencing the lymph node involvement. There is a 4mm difference between a tumor with lymph node metastases and a tumor without such an involvement. Moreover, we showed that T1a tumor has a low risk of lymph node metastases (<10%); this information correlates with other bibliographic<sup>16 17</sup> data which confirm that nodal involvement is linked with an increase in tumor size . Cutuli<sup>16</sup> et al also showed that the rate of lymph node metastases increased from 11% to 36% when the tumor size increases from 10mm to 25mm.

Lymphovascular invasion is also defined as a risk factor in our study and the risk of lymph node metastases is increased by 3 times. This is also shown in the literature to predict lymph node involvement<sup>11,12 ,18,19</sup>. Ozmen et al<sup>11</sup> also found that patients with lymphovascular invasion had an increased risk of SLN nodal metastases

Non ductal histological type is also associated with a lower risk of SLN metastases. Tumor type of tubulous, mucinous or apocrine origin compared to infiltrative ductal cancer is associated with a lower risk of lymph node involvement. Barkley et al<sup>10</sup> showed in a retrospective study that mucinous tumors are associated with a lower risk of lymph node metastases and there were no metastases for patients with small tumors <1cm.

Inner quadrant tumors appear to have lower risk of lymph node metastases) and this may be linked with the drainage of inner quadrant tumors, more frequently into the internal mammary

area. Our data concurs with Bevilacqua et al <sup>20</sup> who showed that the frequency of axillary lymph node metastases in upper-inner-quadrant (UIQ) tumours was 20.6%, compared with 33.2% for all other quadrants.

#### *Role of axillary lymph node dissection*

Axillary lymph node dissection is supposed to provide local control, accurate staging and prognostic information in patient with breast cancer. Many authors refer to a meta analysis <sup>21</sup> that demonstrated an overall survival benefit of 5.4% after axillary lymph node dissection. However, this meta-analysis predated the use of routine mammographic screening and other modern imaging modalities which have led to detection of earlier stages of breast cancer which have lower risks of lymph node involvement. Moreover, adjuvant treatment such as chemotherapy or hormonal therapy <sup>22</sup> are widely used nowadays, even if there was no lymph node involvement.

A recent meta-analysis <sup>23</sup> also concluded that axillary node dissection does not confer a survival benefit in the setting of early stage clinically lymph node negative breast cancer.

There were 2 studies that tried to compare axillary node dissection, versus observation for patient older than 60 years old. Martelli and al <sup>24</sup> showed that only two patients (1.8 %) developed an axillary disease after 5 years of follow-up. There was no difference in breast cancer specific mortality (4% in each arm), rate of distant metastases (5.5 vs 5.3%) and overall survival (87% vs 92%). The international Breast Cancer Study Group (IBCSG)<sup>25</sup> trial showed that 3% of patient in the non axillary dissection arm and 1% in the dissection arm had an axillary evolution after primary treatment during the 6.6 years of follow up. There was no difference seen in the overall survival (75 vs 73%), nor in the disease free survival (67 vs 66%).

**Conclusion**

Based on our findings, it appears reasonable to avoid axillary lymph node dissection in older patients (more than 70 years ) with T1a tumors of good histopathological type and in the absence of lymphovascular invasion and if the tumor is located in the inner quadrant. In this group of patients the indication for even sentinel node biopsy as a minimally invasive procedure should be individualized and discussed with the patient.

**Conflict of interest**

The authors state that they have no conflict of interest.

**Tables**

Table 1: Univariate analysis between clinical characteristics and SLN status

	positive SLN	negative SLN	total	p value
<b>Age (years)</b>	55	60,6	59	<0.05
<b>Size (mm)</b>	15,7	11,9	12,9	<0.05
<b>clinical</b>				
palpable	262	440	702	
non palpable	105	606	711	
paget	1	2	3	<0.0001
<b>location</b>				
outer and lower	37	114	151	
inner and lower	44	167	211	
inner and upper	65	287	352	
outer and upper	190	429	619	
central	32	51	83	<0.0001
<b>age distribution</b>				
under 30 years	1	3	4	
between 30 and 50 years	104	216	320	
between 50 and 70years	212	590	802	
70 years and more	51	239	290	0.005

Table 2: Univariate analysis between clinicopathological characteristics and SLN status

	positive SLN	negative SLN	total	p value
<b>tumor size</b>				
T1a	11	105	116	
T1b	75	421	496	
T1c	216	448	664	
T2	61	71	132	
T3	5	3	8	<0.0001
<b>HISTOLOGY</b>				
DUCTAL	314	874	1189	
LOBULAR	46	117	163	
OTHER	8	57	64	0.03
<b>nuclear grade</b>				
grade 1	83	352	435	
grade 2	202	478	680	
grade 3	82	217	300	
unknown		1	1	0.003
<b>oestrogen receptor</b>				
positive	309	861	1170	
negative	59	186	245	
unkwown		1	1	0.45
<b>progesterone receptor</b>				
positive	248	645	893	
negative	120	402	522	0.12
unkwown	0	1	1	
<b>her2/neu status</b>				
positive	328	775	73	
negative	22	51	1103	0.94
unkwown	18	222	240	
<b>hormonal status</b>				
RH -	40	153	194	
RH+(RE and /or RP positive)	328	893	1221	
unkwown		1	1	0.16
<b>lymphovascular invasion</b>				
yes	78	69	147	
no	290	979	1269	<0.0001
<b>focality</b>				
unifocal	336	974	1310	
multifocal	32	74	106	0.3

Table 3: Multivariate analysis

	OR	95 % confidene intervalle	p
<b>clinique</b>			
palpable vs non palpable	0,862	0.648-1.114	0.3
<b>location</b>			
inner vs outer	0,53	0.407-0.708	<0.001
central vs outer	0,63	0.742-1.227	0.42
<b>Tumor size</b>			
T1b vs T1a	1,4	0.765-2.971	0.23
T1c vs T1 a	3,698	1.898-7.2	<0.001
T2 vs T1a	6,94	3.2-14.7	<0.001
T3 vs T1 a	10	1.915-54.615	0.065
<b>Histology</b>			
LOBULAR vs DUCTAL	1,113	0.75-16.38	0.58
non LOBULAR non DUCTAL vs DUCTAL	0,41	0.188-0.894	0.025
<b>Nulcear grade</b>			
Grade 2 vs grade 1	1,2	0.93-1.747	0.11
Grade 3 vs grade 1	0,85	0.554-1.2	0.299
<b>Lymphovascular invasion</b>			
LVI vs none	2,9	2-4.234	<0.001
<b>Age(years)</b>			
between 30 and 50 vs under 30	1,78	0.163-19.3	0.63
50-70 vs under 30	1,56	0.145-16.9	0.71
More than 70 vs under 30	0,9	0.079-9.5	0.9
under 70 vs 70 years and more	1,867	1.325-2.63	0.004

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