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Charles Coutant, Roman Rouzier, Eric Fondrinier, Frédéric Marchal, François Guillemin, et al.. Validation of the Tenon breast cancer score for predicting non-sentinel lymph node status in breast cancer patients with sentinel lymph node metastasis: a prospective multicenter study. *Breast Cancer Research and Treatment*, 2008, 113 (3), pp.537-543. 10.1007/s10549-008-9967-7 . hal-00478326

HAL Id: hal-00478326

<https://hal.science/hal-00478326>

Submitted on 30 Apr 2010

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Validation of the Tenon breast cancer score for predicting non-sentinel lymph node status in breast cancer patients with sentinel lymph node metastasis: a prospective multicenter study

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Received: 2 January 2008 / Accepted: 4 March 2008 / Published online: 14 March 2008
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Abstract *Background* Axillary lymph node dissection (ALND) is the standard treatment for patients with sentinel node (SN) metastasis, but most of these patients have negative non-sentinel nodes (non-SN). We have developed a scoring system (the Tenon score) to help identify a subgroup of patients who have a low risk of having non-SN metastases and who may thus forgo ALND. Here we validated the Tenon score in an independent cohort of SN-positive patients. *Patients and methods* We tested the accuracy of the Tenon score for predicting non-SN status in a prospective multicenter study of 226 SN-positive breast cancer patients. We calculated the false-negative rate, sensitivity, specificity, and positive (PPV) and negative predictive values (NPV). Receiver operating characteristics (ROC) curves were constructed and the areas under the curve (AUC) were calculated as a measure of discriminatory capacity. *Results* At least one non-SN was positive in

63 patients (27.9%). One hundred and twenty (53.1%) of the 226 patients had a Tenon score of 3.5 or less. Among these 120 patients, five had at least one positive non-SN. With a score cut-off of 3.5, the negative predictive value was 95.8% and the false-negative rate was 4.2%. Overall, the Tenon score accurately predicted non-SN status, with an AUC of 0.82 (95% confidence interval, 0.77–0.88). *Conclusion* In this multicenter study of an independent patient population, the Tenon score was accurate and reproducible for predicting non-SN status in breast cancer patients. The simplicity and reliability of the variables on which the Tenon score is based may be an advantage over other scoring systems.

Keywords Breast cancer · Scoring system · Sentinel lymph node · Non-sentinel lymph node metastasis · Prediction

Introduction

Sentinel lymph node (SN) biopsy can accurately stage the axilla in early breast cancer, and is less aggressive than axillary lymph node dissection (ALND) [1–3]. It remains to be determined whether ALND is always required for women with SN positivity on final histology, because 40–70% of these patients have no metastatic non-sentinel nodes (non-SN) [4–10]. The likelihood of non-SN metastasis depends on several factors, such as histological primary tumor size, the size of SN metastasis, the number of positive SN, the ratio of positive SN to all removed SN, and the extracapsular extension status of the positive SN [5, 8–16]. However, none of these characteristics can alone identify a subset of patients in whom ALND is unnecessary. Several mathematical models, including the Tenon score, have been developed to predict non-SN status in

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breast cancer patients with SN metastasis [9, 11, 13, 14, 17]. However, before being used in routine practice, such scoring systems must be validated in an independent population.

Here we evaluated the Tenon score in an independent multicenter cohort of SN-positive breast-cancer patients.

Patients and methods

Data on 226 consecutive patients with invasive breast cancer measuring <20 mm based on clinical and radiological features, normal physical examination of the axilla, and at least one positive SN were prospectively recorded in a database from May 2003 to May 2007. The patients were operated on in four institutions (Paul Papin Cancer Center (Angers, France), Alexis Vautrin Cancer Center (Nancy, France), Tenon hospital (Paris, France), and Jean Verdier hospital (Bondy, France)). None had neoadjuvant treatment before SN biopsy or ALND. All the patients signed an informed consent form.

SN biopsy and histological analysis

SN biopsy was performed with radioisotope and/or blue dye injection, as previously described, in line with French recommendations [11]. ALND was performed during the same procedure when the SN was positive by imprint cytology (IC) or when the primary tumor measured more than 20 mm intraoperatively. A second operation was performed when either hematoxylin and eosin (H&E) staining or immunohistochemistry (IHC) revealed tumor cells in the SN post-operatively. Pathological SN examination included IC, routine H&E and/or multiple-level (serial sectioning) H&E, and IHC with an anti-cytokeratin antibody cocktail (Cytokeratin AE1-AE3, Dako Corporation, Glostrup, Denmark). Each half-SN was sliced at 3-mm intervals, and each 3-mm section was analysed at four additional levels of 150 μ m and four parallel sections; one was used for H&E staining, and H&E-negative sections were examined by IHC with an anti-cytokeratin antibody cocktail. Non-SN obtained during axillary dissection were sliced at 3-mm intervals and H&E staining was performed on one slide per block. The size of nodal metastases was estimated with an eyepiece micrometer. Micrometastases were defined as a single focus of metastatic disease per node, measuring no more than 2 mm. The presence of single non-cohesive tumor cells was also recorded. SN were recorded as positive when they contained macrometastases, micrometastases, or isolated tumor cells.

Tenon score

The Tenon axilla scoring system (range 0–7) was developed to predict non-SN metastasis in patients with positive SN biopsy [11]. The score is based on three variables,

namely (1) the number of positive SN divided by the total number of SN removed; (2) the presence or absence of macrometastasis in the SN; and (3) histological primary tumor size. A ratio of positive SN to all removed SN of 1 scores two points, a ratio 0.5–1 one point, and a ratio below 0.5 and zero points. SN macrometastasis scores two points, and its absence scores zero. Tumor size scores zero when ≤ 10 mm; 1.5 points when between 11 and 20 mm; and three points when >20 mm.

In multivariate analysis of the training set, women with a score of 3.5 (the median) or less had a 97.3% chance of having no positive non-SN (odds ratio, 42.75; 95% confidence interval, 20.5–90.0).

Validation of the Tenon score

The data collected for each patient in the validation set included age, histological primary tumor size (in millimeters), tumor type (ductal, lobular, other), nuclear grade, lymphovascular space involvement (LVSI; one or more tumor cells in a lymphatic or vascular structure), estrogen/progesterone receptor status (negative if <10% of cells stained positive), HER-2/neu status, the SN method (IC, routine H&E, serial H&E, IHC), the total number of SN removed, the numbers of positive and negative SN, the ratio of positive SN to all removed SN, and extracapsular extension.

For each potential Tenon score cutoff we calculated the number of false-negative cases, false-negative rate, sensitivity, specificity, and positive (PPV) and negative predictive values (NPV).

Receiver operating characteristics (ROC) curves were constructed with the method of Hanley and McNeil, and the area under the curve (AUC) and its 95% confidence intervals were calculated [18]. ROC curves show the relation between the sensitivity and false-positive rate (1-specificity) of a given test across all possible threshold values that define the positivity of a disease or condition. The AUC is a summary measure of the ROC that reflects the inherent capacity of a test to discriminate a diseased from a nondiseased subject across all possible levels of positivity. AUC values of 0.7–0.8 represent reasonable discrimination, and values exceeding 0.8 represent good discrimination.

Data were analysed with StatView[®] version 5.0 (SAS Institute Inc, Cary, North Carolina, USA) and the R package[®] with the Design, Hmisc and Verification libraries (<http://lib.stat.cmu.edu/R/CRAN/>).

Results

Patients and primary tumors (Table 1)

Two hundred and twenty-six patients with SN metastasis were enrolled in this multicenter study. Their mean age

Table 1 Patients and tumors characteristics in the 226 cases of breast cancer with at least one positive SN

Characteristics	Number of patients N = 226
Mean age, years (range)	56.8 (32–87)
Postmenopausal	144 (63.7%)
Mean invasive tumor size, mm (range)	16.1 (0.9–60)
Tumor size at final histology, mm	
≤10	45 (19.9%)
11–20	150 (66.4%)
21–30	24 (10.6%)
31–50	5 (2.2%)
>50	2 (0.9%)
Palpable mass	166 (73.5%)
Breast surgery	
Lumpectomy	218 (96.4%)
Mastectomy	8 (3.6%)
Histology	
Invasive ductal carcinoma	197 (87.2%)
Invasive lobular carcinoma	20 (8.8%)
Other	9 (4%)
Tumor grade	
Well differentiated (grade 1)	55 (24.3%)
Moderately differentiated (grade 2)	107 (47.4%)
Poorly differentiated (grade 3)	64 (28.3%)
Lymphovascular space involvement	
Absent	137 (60.6%)
Present	89 (39.4%)
Estrogen/Progesterone receptor status	
Positive	214 (94.7%)
Negative	12 (5.3%)
Her-2/neu status	
Negative	135/156 (86.5%)
Positive	21/156 (13.5%)
Not determined	70

was 57 years (range, 32–87 years) and 70% of the patients were over 50. The mean histological primary tumor size was 16.1 mm (range, 0.9–60 mm). The main histological subtype was invasive ductal carcinoma (87.2%), and 47.4% of tumors were nuclear grade 2.

Histological findings on SN and non-SN (Table 2)

Five hundred and fifty-five SN were removed. The mean number of SN per patient was 2.45 (range, 1–9). One hundred and twenty-four patients (54.9%) had at least one macrometastatic SN. Micrometastasis was detected with H&E in 63 patients (27.9%) and micrometastasis was detected by IHC in 22 patients (9.7%). In 17 patients (7.5%), the SN contained only isolated tumor cells.

Table 2 Histology of sentinel and non-sentinel nodes recovered from 226 patients with breast cancer and at least one positive SN

Characteristics	Number of patients
Sentinel lymph nodes (SN)	
Number of SN removed	555
Mean number of SN per patient (range)	2.45 (1–9)
Number of positive SN	288
Number of patients with	
Macrometastases	124 (54.9%)
Micrometastases on H&E	63 (27.9%)
Micrometastases on IHC	22 (9.7%)
Isolated tumors cells	17 (7.5%)
Histological detection of SN metastasis	
Routine H&E	53 (23.4%)
Serial H&E	136 (60.2%)
IHC only	37 (16.4%)
Ratio of metastatic SN to total SN	
Mean ratio (range)	0.62 (0.11–1)
1	78 (34.5%)
0.5–1	91 (40.3%)
<0.5	57 (25.2%)
Extracapsular extension	
Present	46 (20.4%)
Absent	180 (79.6%)
Non sentinel lymph nodes (non-SN)	
Number of non-SN removed	2857
Mean number of non-SN per patient (range)	12.63 (2–37)
Number of patients with positive non-SN	63 (27.9%)

SN = Sentinel lymph node, Non-SN = Non sentinel lymph node
H&E = Hematoxylin and eosin, IHC = immunohistochemistry

Extracapsular extension was present in at least one SN in 20.4% of patients. Seventy-eight patients (34.5%) had a positive to total SN ratio of 1, while 91 patients (40.3%) had a ratio between 0.5 and 1, and 57 patients (25.2%) had a ratio below 0.5. Two thousand eight hundred and fifty-seven non-SN were removed. The mean number of non-SN per patient was 12.6 (range, 2–37). Sixty-three (27.9%) of the 226 patients had at least one positive non-SN.

Performance of the Tenon score (Table 3, Figure 1 and Appendix 1)

One hundred and twenty (53.1%) of the 226 patients had a score of 3.5 or less. Among these 120 patients, five had at least one positive non-SN. With a score cutoff of 3.5, the NPV was 95.8% and the false-negative rate was 4.2%.

For each potential score cutoff, the specificity, sensitivity, NPV, PPV, number of false-negatives and the false-negative rate are shown in Appendix 1.

Table 3 Prospective validation of the Tenon score

	Number of patients with negative non-SN	Number of patients with positive non-SN
ALND unnecessary score ≤ 3.5	115/120	5/120
ALND recommended score > 3.5	48/106	58/106
Sensitivity = 92.1%		
Specificity = 70.1%		
Negative predictive value = 95.8%		
Positive predictive value = 54.7%		

ALND = axillary lymph node dissection, non-SN = non-sentinel lymph node

The Tenon score accurately predicted non-SN status in the 226 patients, with an AUC of 0.82 (95% confidence interval, 0.77–0.88) (Fig. 1).

Discussion

This study validates the use of the Tenon score to predict non-SN status in breast cancer patients with SN metastasis.

Other scoring systems and nomograms proposed to predict non-SN status including the Memorial Sloan-Kettering Cancer Center nomogram (MSKCC nomogram) [13], the M. D. Anderson Cancer Center score (MDA score) [9], the score developed by Saidi et al. [17], and the nomogram developed by Degnim et al. [14]. Each model performed reasonably well in the training set of patients

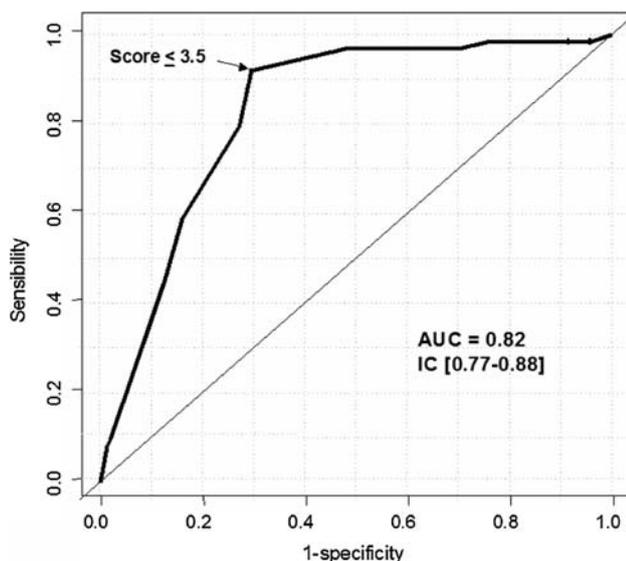


Fig. 1 A receiver operating characteristics (ROC) curve assessing the discriminatory capacity in the Tenon score

with breast cancer and SN metastasis, with areas under the ROC curve of about 0.7 [9, 13, 14, 17]. However, the results of external validation by other teams were less relevant.

Several institutions have tested the MSKCC nomogram, with AUCs ranging from 0.63 to 0.82 [13, 14, 19–28] (Table 4). This nomogram has been validated twice, once in a prospective patient group from the same cancer center [25], and once in a regional teaching hospital in the Netherlands [24]. The latter study validated the nomogram's originally calculated predictive accuracy, but the authors of the former study did not recommend its use in routine practice. Alran et al. [27] tested the accuracy of the MSKCC nomogram in 588 patients, and found that it was reliable for patients with macrometastatic SN but not those with micrometastatic SN [27].

The MDA score has been evaluated by only two institutions, one of which considered it unreliable [20, 22] (Table 4).

Degnim et al. [14] proposed a model integrating metastasis size. However, to our knowledge, this nomogram has not been evaluated in an independent patient population.

Dauphine et al. [22] recently compared the performance of the Tenon score, the MSKCC nomogram [13] and the MDA score [9] in a population of 48 patients of whom only 39 had complementary axillary dissection. The areas under the ROC curves were respectively 0.68, 0.63 and 0.7.

Validation of scores and nomograms designed to predict non-SN status comes up against several obstacles. The first consists of differences in the tumor characteristics and study population between the training and validation sets. In the study by Dauphine et al. [22], histological primary tumor size was 25 mm on average (range, 1.7–40 mm), and more than 20 mm in 60% of patients. In the MSKCC and Tenon training sets, respectively 66.5% and 87.3% of patients had tumors smaller than 20 mm [11, 13]. SN micrometastases were under-represented in the study by Dauphine et al. [22] because 9 out of 14 patients with SN micrometastases did not undergo ALND, thus explaining the high proportion (59%) of patients with non-SN involvement compared to previous series. It is classically recommended that training and validation populations have similar characteristics [29]. Otherwise, it may unfairly decrease the accuracy of the scores that are tested.

A second pitfall consists of differences in the pathological assessment of SN. The authors of the MSKCC nomogram [13] found major differences in the accuracy of their score depending on the SN detection method. Soni et al. [21] found that non-SN involvement was two or three times more frequent with routine H&E rather than with serial section. Histopathological ultrastaging methods differ widely among institutions [11, 14, 20–25, 27]. This could explain why Alran et al. [27] found that the MSKCC

Table 4 Validation of other scores and nomograms in the literature

Study	Year	Single-center or multicenter study	Nb of patients with positive SN undergo ALND	Area under the ROC curve			
				MSKCC nomogram	MDA score	Degnim nomogram	Tenon score
Van Zee et al. [13]	2003	Mono	373	0.76			
Kocsis et al. [23]	2004	Mono	140	Not valid			
Soni et al. [21]	2005	Mono	149	0.75			
Degnim et al. [14]	2005	Multi	462	0.72		0.77	
Smidt et al. [24]	2005	Mono	222	0.71			
Specht et al. [28]	2005	Mono	33	0.72			
Lambert et al. [25]	2005	Mono	200	0.71			
Coutant [30]	2006	Mono	48				0.86
Cripe et al. [26]	2006	Mono	92	0.82			
Dauphine et al. [22]	2007	Mono	39	0.63	0.7		0.68
Alran et al. [27]	2007	Mono	588	0.72			
		Mono	213 ^a	Not valid (0.54)			
Ponzone et al. [20]	2007	Mono	186	0.71	Not valid		
Bevilacqua et al. [19]	2007	Mono	1545	0.75			
Present study		Multi	226				0.82

^a Subgroup of patients with only SN micrometastasis

Nb = number, SN = sentinel node, ALND = axillary lymph node dissection, ROC = receiver operating characteristics
MSKCC = Memorial Sloan-Kettering Cancer Center, MDA = M.D. Anderson Cancer Center

nomogram was reliable for patients with a macrometastatic SN but not for patients with a micrometastatic SN. Van Zee et al. [13] incorporated the method of SN metastasis detection, which is an indirect measure of size: the detection method correlates with the size of SN metastasis [21]. These latter authors found that frozen section and routine histopathology with H&E detected large metastases, while only IHC detected the smallest metastases. However, Kocsis et al. [23] found that the use of thinner sections and extensive sampling could increase the detectability of metastases using methods other than IHC, thus potentially affecting the accuracy of the MSKCC nomogram.

The main aim of scores or nomograms is to identify the largest subgroup of patients with a low risk of non-SN involvement. Several authors consider that a risk of non-SN involvement <10% is an acceptable cutoff to select candidates who may avoid ALND [20, 24, 25]. This criteria identified 20% of such patients (40/200) in Lambert's series using the MSKCC nomogram and only 8% of patients in Degnim's series (37/462) and (40/200) in Lambert's serie [14, 25]. Hwang et al. [9] reported that none of their patients with a MDA score ≤ 0 had additional positive non-SN identified during ALND. However, these patients corresponded to 24% of their population. Similarly, Ponzone et al. noted that this sub-group of patients

corresponded to only 26% of all cases [9, 20]. These low proportions of patients in whom ALND could be dispensed with clearly undermine the value of such scores and nomograms in routine practice. In contrast, in our study, ALND could be dispensed in the 53% of patients with a score equal or <3.5.

One advantage of the Tenon score lies in the use of commonly recorded and reliable parameters such as tumor size, SN macrometastasis, and the positive to total SN ratio. It is therefore easy to use. However, while nomograms consider continuous variables, the Tenon score uses arbitrary cutoff values. This means, for example, that the difference between isolated tumor cells and micrometastases is not taken into account in the Tenon score.

In conclusion, this validation study shows that the Tenon score is accurate, reproducible and exportable. The simplicity and reliability of the common variables on which the Tenon score is based may be an advantage over other scoring systems and nomograms.

Further large multicenter studies are required to definitively validated the Tenon score especially in women with micrometastases or isolated tumour cells.

Acknowledgments We thank the Dr Martine ANTOINE, pathologist from the department of histology "Hôpital Tenon, Assistance Publique des Hôpitaux de Paris, Paris, France".

Appendix 1

Specificities, sensitivities, negative and positive predictive values, number of false-negatives and false-negative rates for each cutoff of the Tenon score

Score	Nb of patients	Nb of FN	FN rate (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
=0	8/226	0	0	100	4.9	28.9	100
≤1	15/226	0	0	100	9.2	29.9	100
≤1.5	41/226	1	2.4	98.4	24.5	33.5	97.6
≤2	51/226	2	3.9	96.8	30.1	34.9	96.1
≤2.5	74/226	2	2.7	96.8	44.2	40.1	97.3
≤3	87/226	2	2.3	96.8	52.2	43.9	97.7
≤3.5	120/226	5	4.2	92.1	70.1	54.7	95.8
≤4	132/226	13	9.8	79.4	73	53.2	90.2
≤4.5	163/226	26	16	58.7	84.1	58.7	84.1
≤5	178/226	35	19.7	44.4	87.7	58.3	90.3
≤5.5	208/226	52	25	17.5	95.7	61.1	75
≤6	217/226	57	26.3	9.5	98.2	66.7	73.7
≤6.5	219/226	58	26.5	7.9	98.8	71.4	73.5
≤7	226	63	27.9	0	100	*	72.1

Nb = number, FN = false negative

PPV = positive predictive value refers to the ability to predict additional positive non-SN

NPV = negative predictive value refers to the ability to predict negative non-SN

* = not calculable

Appendix 2

Frequency of macrometastases, micrometastases and isolated tumor cells in patients with negative and positive non-SN according to Tenon score

Tenon score	Nb of patients	Patients with negative non-SN				Patients with positive non-SN			
		Nb of patients	Macro	Micro	Isolated tumor cells	Nb of patients	Macro	Micro	Isolated tumor cells
0	8	7		5	2	1			1
1	7	7		5	2	0			
1.5	26	26		23	3	0			
2	10	9	3	6		1	1		
2.5	23	23		18	5	0			
3	13	13	5	8					
3.5	33	30	13	13	4	3	3		
Score ≤ 3.5	120	115	21	78	16	5	4	0	1
4	12	4	4			8	7	1	
4.5	31	17	15	2		14	14		
5	15	6	4	2		9	7	2	
5.5	30	13	13			17	17		
6	9	4	4			5	5		
6.5	2	1	1			1	1		
7	7	2	2			5	5		
Score > 3.5	106	47	43	4	0	59	56	3	0
TOTAL	226	162	64	82	16	64	60	3	1

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