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# Predicting Axillary Nodal Positivity in 2282 Patients with Breast Carcinoma

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**Abstract. Axillary lymph node status continues to be the single most important prognostic variable for breast cancer survival despite significant progress in the molecular and genetic characterization of breast malignancies. All patients with invasive breast cancer who underwent axillary lymph node dissection as part of their treatment were evaluated by 11 clinical and pathologic factors, including the primary lesion's T category (TNM staging system), whether the lesion was clinically palpable, the presence of lymphatic or vascular invasion, nuclear grade, estrogen and progesterone receptors, S-phase, age, *HER2/neu* overexpression, histology (infiltrating lobular or ductal), and ploidy. A total of 2282 axillary dissections were performed: 391 in patients with ductal carcinoma in situ (DCIS) [3 of which (0.8%) contained metastases] and 1891 in patients with invasive breast cancer [680 of which (36%) contained metastases]. Multivariate analysis of patients with invasive cancer identified four factors as independent predictors of axillary lymph node metastases: lymph/vascular invasion, tumor size, nuclear grade, tumor palpability. Among a group of 189 patients with nonpalpable, non-high-grade invasive lesions 15 mm or smaller without lymph/vascular invasion, only 6 (3%) had metastases to lymph nodes. If any three of the favorable factors were present, lymph node positivity was 6% or less. Clinical and pathologic feature of the primary lesions can be used to estimate the risk of axillary lymph node metastases. Such risk assessment can be used for the treatment decision-making process.**

Despite a variety of new tumor markers, axillary lymph node status continues to be the single most important prognostic variable for breast cancer survival [1–3]. If axillary lymph node status could be accurately predicted prior to axillary dissection, selected patients with an acceptably low probability of axillary metastases might avoid axillary dissection and its associated morbidity.

The probability of axillary metastases increases with increasing tumor size [4, 5]; and within a given T category the probability of nodal positivity may range widely. An 11 mm T1c lesion is less likely to reveal axillary involvement than a 20 mm T1c lesion.

The T category of the TNM staging system divides primary tumors into a number of subgroups, most of which (T1mic through T3) are based on the greatest dimension of the invasive component of the primary lesion [6]. At the extremes, size is not considered. Tis is used for all noninvasive breast carcinomas, regardless of size; the subdivisions of T4 describe locally advanced breast cancer, again, regardless of size.

The T category was totally appropriate when the TNM system was first instituted because most breast cancers presented as palpable, visibly obvious masses and were therefore, easily measured by the pathologist. With the development and utilization of high quality mammography and ultrasonography, approximately 25% to 40% of all newly diagnosed breast cancer cases from centers utilizing these techniques are nonpalpable at diagnosis [7–9].

Nonpalpable lesions present a problem with measurement. After wire-directed excision of the nonpalpable lesion by the surgeon, specimen radiography by the radiologist, and margin marking and gross dissection by the pathologist, many clinically nonpalpable lesions remain pathologically nonpalpable and nonvisualizable, making measurement of the greatest dimension extremely difficult. Despite the difficulty, most pathologists are able to measure most nonpalpable tumors in at least one dimension from the microscopic slide. This dimension is recorded in the pathology report and is used within the TNM staging system as the T category.

Because many nonpalpable lesions are not visible even after gross dissection, their measurement is likely to be less accurate. Nonpalpable lesions lack the bulk that would make them palpable, so the number of tumor cells they contain may be less than that in a palpable tumor of equivalent diameter. Thus there may be significant volume differences between equally sized palpable and nonpalpable lesions.

The purpose of this study was to estimate the likelihood of axillary lymph node involvement based on a variety of clinical and pathologic factors and to analyze lesions by T category and method of diagnosis (nonpalpable mammographically detected versus clinically detected by palpation) to determine if there were differences in nodal positivity, survival, and other prognostic factors using this stratification. With improved accuracy in the preoperative prediction of axillary status, modification of both surgical and chemotherapeutic treatment strategies will optimize patient care.

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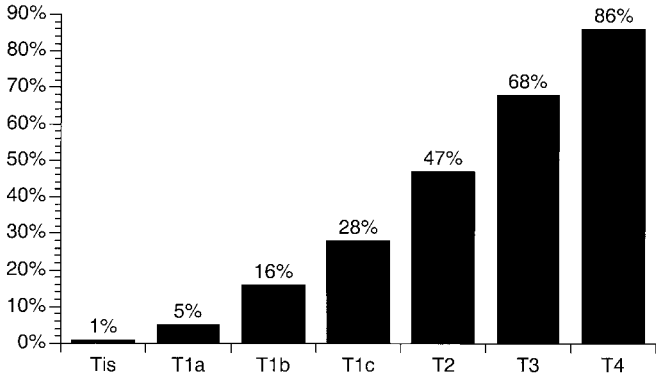


**Fig. 1.** Axillary node positivity by T category. There is a significant difference between each progressively larger T category (all $p$ values $\leq$ 0.005).

**Table 1.** T category predicts nodal positivity.

| T category | Positive dissections/patients (no.) | $p$ |
|---|---|---|
| Tis | 3/391 (0.8%) | 0.005 |
| T1a | 5/110 (5%) | 0.002 |
| T1b | 47/291 (16%) | 0.0001 |
| T1c | 195/689 (28%) | <0.00001 |
| T2 | 276/585 (47%) | <0.00001 |
| T3 | 106/157 (68%) | 0.006 |
| T4 | 51/59 (86%) | |
| Total | 683/2282 (30%) | |

## Methods

All patients with both invasive and noninvasive [ductal carcinoma in situ (DCIS)] breast cancer treated at The Breast Center, Van Nuys, California from 1979 through June 1998 who underwent axillary lymph node dissection as part of their treatment are included [10–12].

A lesion was recorded as palpable if it could be felt by a least one preoperative examiner prior to radiographic identification; it was scored as nonpalpable if it was discovered by mammography and the physical examination was recorded as negative. Palpable lesions were measured by the pathologist, in at least one dimension and generally in two or three. Tumor size was recorded to the nearest millimeter. The largest dimension of the invasive component was used to determine the T category for all invasive lesions except T4.

If a clinically nonpalpable lesion could be visualized or felt by the pathologist after excision, it was measured grossly to the nearest millimeter. The fact that it was visualizable or palpable did not change its preoperative clinically nonpalpable status.

If a nonpalpable lesion was neither palpable nor visualizable by the pathologist, size was determined using a combination of microscopic measurement and three-dimensional reconstruction. Nonpalpable lesions were serially sectioned at 2- to 3-mm intervals. The maximum dimension of a nonpalpable tumor was determine by direct measurement from the microscopic slides and by determining the number of serial sections in which the tumor appeared. Frozen sections were not done on clinically nonpalpable lesions [13, 14].

Tumors were categorized by T category using the TNM system of the American Joint Committee on Cancer [6]: Tis, any ductal carcinoma in situ, regardless of size; T1mic, 1 mm or less; T1a, 1.1 to 5.0 mm; T1b, 5.1 to 10.0 mm; T1c, 10.1 to 20.0 mm; T2, 20.1 to 50.0 mm; T3, 50.1 mm or more; T4, chest wall or skin fixation, skin edema or ulceration, inflammatory carcinoma. In this series there were few T1mic lesions ($n = 7$). Consequently, these lesions were grouped with the T1a lesions, as they would have been prior to introduction of the T1mic category.

Interrelations between clinical and pathologic characteristics and T categories were determined by contingency table analysis or the $t$-test. Life tables were computed using the Kaplan-Meier method [15]; comparisons of the groups were made with the log-rank test [16]. All variables found to be significant on univariate analysis were included in the multiple regression analysis with backward elimination.

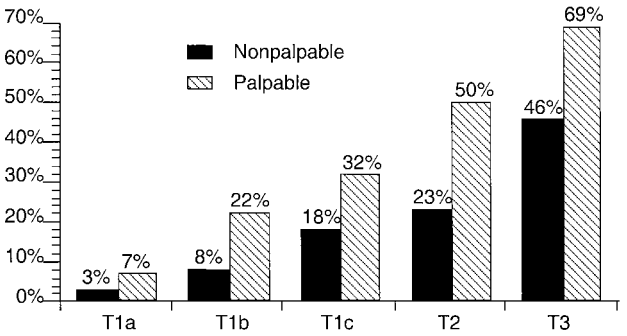


**Fig. 2.** Axillary node positivity by T category and palpability. The differences in nodal positivity between palpable and nonpalpable T1b through T2 lesions are significant (all $p$ values $\leq$ 0.003). The difference between T3 lesions is not significant because there are too few nonpalpable T3 lesions.

## Results

A total of 2282 patients were evaluable. As the T category increased, nodal positivity increased (Fig. 1). With each increase in T category, there was a statistically significant increase in the probability of nodal involvement (all $p$ values $< 0.01$) (Table 1).

Figure 2 divides T categories, T1a through T3, into palpable versus nonpalpable lesions. Table 2 shows the number of patients making up each of these subgroups and includes Tis and T4 patients as well. For T1b, T1c, and T2 lesions, the difference in nodal positivity is statistically different for palpable versus nonpalpable lesions.

Nodal positivity was higher for some smaller palpable lesions when compared with one T category with larger nonpalpable lesions (e.g., T1b palpable versus T1c nonpalpable or T1c palpable versus T2 nonpalpable), but none of the differences were statistically significant.

Table 3 compares the average maximum diameter for palpable and nonpalpable lesions by T categories T1a through T2. For all T categories, the average palpable lesion is slightly larger than the

**Table 2.** Nodal positivity by T category: nonpalpable versus palpable lesions.

| T category | Nonpalpable (no. positive/total) | Palpable (no. positive/total) | *p* |
|---|---|---|---|
| Tis | 2/301 (0.7%) | 1/90 (1.1%) | 0.67 |
| T1a | 2/65 (3%) | 3/45 (7%) | 0.37 |
| T1b | 10/125 (8%) | 37/166 (22%) | 0.001 |
| T1c | 24/148 (18%) | 171/541 (32%) | 0.0002 |
| T2 | 14/60 (23%) | 262/525 (50%) | 0.0001 |
| T3 | 5/11 (46%) | 101/146 (69%) | 0.1 |
| T4 | None | 51/59 (86%) | — |
| Total | 57/710 (8%) | 626/1572 (40%) | < 0.00001 |

**Table 3.** Average tumor size of T1a–T2 tumors.

| | | Size (mm) | | |
|---|---|---|---|---|
| T category | Total patients | Nonpalpable | Palpable | *p* |
| T1a | 110 | 3.2 | 3.4 | 0.55 |
| T1b | 291 | 8.3 | 9.1 | < 0.00001 |
| T1c | 689 | 14.4 | 16.1 | < 0.00001 |
| T2 | 585 | 27.7 | 31.2 | 0.0008 |

**Table 4.** Laboratory and pathologic findings 1891 patients (invasive cancers only).

| Parameter | Nonpalpable | Palpable | *p* |
|---|---|---|---|
| No. of patients | 409 | 1482 | |
| Positive axillary nodes | 55 (13%) | 625 (42%) | < 0.0001 |
| ER-positive | 205/260 (79%) | 759/1083 (70%) | 0.005 |
| PR-positive | 175/259 (68%) | 636/1068 (60%) | 0.02 |
| Lymph/vasculator invasion | 46/379 (12%) | 373/1356 (28%) | < 0.0001 |
| High nuclear grade (nuclear grade 3) | 106/282 (38%) | 547/1388 (39%) | 0.57 |

ER: estrogen receptor; PR: progesterone receptor.

**Table 5.** Eight-year breast cancer-specific survival nonpalpable versus palpable lesions: 1891 patients with invasive breast cancer.

| Category | Nonpalpable (%) ($n$ = 409) | Palpable (%) ($n$ = 1482) | *p* |
|---|---|---|---|
| Node-negative | 94 | 88 | 0.006 |
| Node-positive | 72 | 65 | 0.28 |
| All patients | 91 | 79 | < 0.0001 |

average nonpalpable lesion. The differences are significant for T1b through T2.

Table 4 shows a variety of laboratory and pathologic parameters for all patients with invasive breast cancer ($n$ = 1891), stratifying them by palpability (409 nonpalpable lesions versus 1482 with palpable lesions). Nonpalpable lesions are clearly more favorable. They were statistically more likely to be node-negative and estrogen receptor (ER)- and progesterone receptor (PR)-positive. Nonpalpable lesions were less likely to have lymphatic tumor emboli or vascular invasion. There was no difference in the nuclear grade based on palpability.

The 8-year breast cancer-specific survival for nonpalpable versus palpable invasive lesions without regard to T category is shown in Table 5. For node-negative patients palpability was a poor prognostic finding, and these patients had a lower survival rate than patients with nonpalpable lesions ($p$ = 0.006). For node-positive patients, palpability did not statistically affect survival.

**Table 6.** Association between incidence of axillary lymph node metastases and 11 clinicopathologic factors by univariate and multivariate analysis.

| Variable | No. | % Node positive | Univariate *p* | Multivariate *p* |
|---|---|---|---|---|
| Palpable | | | | |
| Yes | 1482 | 42 | < 0.0001 | < 0.0001 |
| No | 409 | 13 | | |
| Nuclear grade | | | | |
| 1 | 206 | 12 | < 0.0001 | < 0.0001 |
| 2 | 917 | 32 | | |
| 3 | 653 | 49 | | |
| LVI | | | | |
| Present | 419 | 68 | < 0.0001 | < 0.0004 |
| Absent | 1316 | 25 | | |
| Size | | | | |
| Continuous Variable | 1891 | | < 0.0001 | < 0.0001 |
| ER | | | | |
| Positive | 964 | 40 | 0.3 | |
| Negative | 379 | 43 | | |
| PR | | | | |
| Positive | 811 | 38 | 0.03 | |
| Negative | 516 | 44 | | |
| S phase | | | | |
| High ≥ 6.0 | 296 | 41 | 0.41 | |
| Low < 6.0 | 329 | 38 | | |
| Age (years) | | | | |
| < 50 | 854 | 40 | 0.25 | |
| ≥ 50 | 1030 | 37 | | |
| *HER2* | | | | |
| Positive | 124 | 35 | 0.91 | |
| Negative | 278 | 35 | | |
| Histology | | | | |
| Ductal | 1638 | 37 | 0.09 | |
| Lobular | 237 | 31 | | |
| Ploidy | | | | |
| Diploid | 315 | 37 | 0.25 | |
| Aneuploid | 397 | 41 | | |

LVI: lymphovascular invasion; S phase: percent of cells in the S growth phase; *HER2*: *HER-2/neu*.

Table 6 analyzes 11 variables among the 1891 patients with invasive breast cancer. On univariate analysis the palpability, nuclear grade, lymph/vascular invasion, size (as a continuous variable), and PR status were significant predictors of lymph node positivity. A multivariate analysis with backward elimination yielded four variables that were independent predictors of lymph node involvement: palpability, nuclear grade, lymph/vascular invasion, and size. There were 189 patients in whom all of these factors were favorable (for this analysis, size < 15 mm was considered favorable). In this subgroup, only 3% of patients (6/189) had lymph node metastases. If any three of these independent predictors were favorable, lymph node positivity was 6% or less.

## Discussion

Are patients with clinically palpable tumors, compared with patients with clinically nonpalpable tumors within the same T category, at greater risk of nodal metastases? These data suggest that the answer is yes, but the TNM staging system does not single out

palpability as a prognostic or coding factor. In the TNM system the T category for all lesions, other than in situ (Tis) or locally advanced (T4) lesions, is generated by the maximum dimension of the invasive component of the lesion [6]. Therefore a 15 mm invasive tumor is a T1c lesion, regardless of whether it is palpable. If the outcomes for palpable and nonpalpable tumors of the same diameter are different, the current criteria used to assign a tumor to a specific T category, without regard to palpability, may benefit from modification.

Rosen and associates [3, 17–20], in a series of articles, described a large group of patients with T1 and T2 lesions followed a median of 18 to 20 years. They showed that tumor size, the number of axillary lymph node metastases, lymphatic tumor emboli, tumor histology and differentiation, blood vessel invasion, and lymphoplasmocytic reaction around the primary tumor were important predictors of survival. They also showed that as tumors increased in size the probability of nodal positivity increased. Because these patients were accrued from 1964 to 1970, few had nonpalpable lesions discovered mammographically, and palpability could not be evaluated as a separate prognostic feature.

The series presented here differs, in that patients were accrued during an era of modern mammography. Among our patients with invasive cancer, 409 (22%) had nonpalpable, mammographically detected lesions. This allowed evaluation of many of the prognostic factors that Rosen et al. [3, 17–20] showed to be important, comparing the factors for various T categories stratified by palpability.

Beginning with T1b lesions, there was a clear and statistically significant difference in nodal positivity, with palpable lesions showing more frequent nodal involvement (Table 2). Nodal positivity is the single most important predictor of outcome for patients with breast cancer; and over time the higher rate of nodal positivity seen in patients with palpable lesions will likely translate into a decrease in survival for patients with T1b lesions and larger.

The survival differences in favor of nonpalpable lesions in each subgroup are not statistically significant in this series (data not shown). Subgroup analysis by T category and palpability produced too many small subgroups with insufficient statistical power [21]. When all T categories are grouped together, patients with nonpalpable invasive lesions have a 12% survival advantage at 8 years ($p < 0.0001$) (Table 5). In all likelihood, patients with nonpalpable lesions stratified by T category will have a higher survival when compared with patients with palpable lesions if they are followed for a sufficiently long period of time.

Patients with nonpalpable lesions had a number of prognostic factors in their favor (Table 4). They were more likely to be ER- and PR-positive ($p \leq 0.02$). Nonpalpable tumors were less likely to demonstrate lymphatic tumor emboli or vascular invasion microscopically ($p \leq 0.0001$). These favorable factors exhibited by nonpalpable tumors may account for their lower rate of lymph node positivity.

Patients who undergo routine screening mammography are more likely to have their tumors diagnosed as nonpalpable lesions. These nonpalpable tumors are more likely to be smaller and their nodal positivity lower. Despite the 3- to 4-year lead-time bias introduced by mammographic screening [22], these favorable prognostic features should translate into a superior long-term survival advantage for patients with nonpalpable lesions.

In view of this survival advantage, consideration could be given to amending the T category of the TNM staging system to reflect this difference. Perhaps a small "n" for nonpalpable and a small "p" for palpable inserted before the T category would suffice (e.g., nT1b to indicate a nonpalpable lesion 5.1 to 10.0 mm in maximum diameter). This distinction, which was inconsequential prior to the era of screening mammography, may now be much more important because as many as 25% of all new breast cancers diagnosed are nonpalpable.

Long-term studies of breast cancers detected by mammography reveal that these cancers are different from palpable breast lesions. Nonpalpable cancers have a low overall nodal positivity rate of approximately 12% to 15% [7, 8, 23–26] and far superior survivals when compared with patients who present with palpable breast cancer [27]. The difference between palpable and nonpalpable breast cancers is highlighted by this series. Patients with nonpalpable invasive breast carcinomas had a 13% chance of nodal positivity and an 8-year breast cancer-specific survival of 91% compared with a 42% chance of nodal positivity ($p < 0.0001$) and 79% 8-year breast cancer-specific survival for patients with palpable breast cancer ($p < 0.0001$).

Although the surgical approach to the breast in patients with breast cancer has become less aggressive over recent years, routine axillary lymph node dissection continues to be performed for most patients. This has occurred because lymph node status continues to be the single most important prognostic factor in patients with breast cancer. Furthermore, axillary dissection lowers the risk of axillary recurrence; and, in general, most medical oncologists require axillary nodal status before determining the exact nature of the chemotherapy prescribed.

There are, however, subgroups of patients who can be identified in whom the risk of axillary positivity is low, in particular patients with T1a lesions, those with t1b nonpalpable lesions, or those with any three of the four favorable factors detailed in the multivariate analysis, above. The relative low risk of axillary metastases in these patients must be weighed against the known potential morbidity (e.g., arm edema, nerve paresthesias and damage, prolonged seroma, infection, pain, and decreased arm mobility) [28, 29]. A reasonable intermediate position may be the use of sentinel node biopsy in patients with extremely low risks of positive axillary nodes. For illustration, based on the data herein, a patient with a nonpalpable T1b lesion has a predicted nodal positivity of 8%. If it is assumed that the sentinel node technique has an accuracy of approximately 90% [30], patients with nonpalpable T1b lesions undergoing sentinel node biopsy would incur a less than 1% chance of having a false-negative sentinel node.

## Conclusions

Nodal positivity is significantly higher for palpable invasive breast cancer than for nonpalpable invasive breast cancer with T1b lesions and larger. Palpability is a poor prognostic sign. Palpable and nonpalpable lesions should not be grouped together by T category for the purposes of predicting outcome and selecting therapy. The possibility of amending the T category of the TNM staging system to reflect palpability should be considered.

Multivariate analysis identified four factors as independent predictors of axillary lymph node metastases: lymph/vascular invasion, tumor size, nuclear grade, tumor palpability. Among a group of 189 patients with nonpalpable, non-high-grade invasive lesions 15 mm or smaller and without lymph/vascular invasion, only 6

(3%) had metastases to lymph nodes. If any three of the favorable factors were present, lymph node positivity was only 6% or less.

Clinical and pathologic feature of the primary lesion can be used to estimate the risk of axillary lymph node metastases. Such risk assessment can be used during the treatment decision-making process.


## Résumé

L'état des ganglions de l'aisselle est le facteur pronostic parmi les plus importants dans l'évaluation de la survie du cancer du sein, en dépit des progrès en biologie moléculaire et génétique. Toutes les patientes ayant eu un cancer invasif du sein avec curage axillaire ont été évaluées par 11 facteurs cliniques et anatomopathologiques, y compris le stade «T» (système TNM) de la lésion, que la lésion soit palpable cliniquement ou pas, qu'il y avait une invasion lymphatique/vasculaire ou pas, l'indexe nucléaire, la présence ou pas de récepteurs d'œstrogène et de progestérone, la phase-S, l'âge, la surexpression HER2/neu, l'histologie (infiltration lobulaire ou intracanulaire) et la ploïdie. On a réalisé 2282 curages axillaires chez 391 patientes ayant un carcinome intracanalaire in situ (3 [0.8%] seulement avec métastases) et chez 1891 patientes ayant un cancer invasif (680 [36%] avec des métastases). Par analyse multifactorielle, on a identifié chez les patientes ayant un cancer invasif, quatre facteurs indépendants, prédicteurs de métastases axillaires: invasion lymphatique/vasculaire, taille de la tumeur, indexe nucléaire et détection de la tumeur par la palpation. Parmi un groupe de 189 patientes sans tumeur palpable, invasive mais de bas grade, 15 mm ou moins sans invasion lymphatique/vasculaire, seulement 6 (3%) avaient des métastases lymphatiques. Si un des trois facteurs favorables était présent, l'envahissement lymphatique n'était retrouvé que dans 6% des cas ou moins. Les caractéristiques cliniques et anatomopathologiques des lésions primitives pourraient être utilisées pour évaluer le risque de métastases ganglionnaires axillaires, pour intervenir ensuite dans la décision thérapeutique.

## Resumen

A pesar del significativo progreso en la caracterización molecular y genética de los tumores mamarios malignos, el estado de los ganglios axilares sigue siendo el factor de pronóstico más importante en cuanto a supervivencia. En el presente estudio se informa la evaluación de todas las pacientes con cáncer mamario invasor sometidas a disección axilar como parte del tratamiento, considerando 11 factores clínicos y patológicos: categoría T de la lesión primaria (sistema TNM de estadificación), si la lesión era o no clínicamente palpable, presencia de invasión linfática o vascular, grado nuclear, receptores de estrógeno y progesterona, fase-S, edad, sobreexpresión de HER2/neu, histología (lobular o ductal infiltrante) y ploidia. Se realizaron 2282 disecciones axilares en 391 pacientes con carcinoma ductal in situ (3 de ellas [0.8%] mostraron metástasis), y en 189 con cáncer mamario invasor (680 de ellas [36%] mostraron metástasis). El análisis multivariable de las pacientes con cáncer invasor identificó cuatro factores independientes de predicción de metástasis axilares: invasión linfática/vascular, tamaño del tumor, grado nuclear y tumor clínicamente palpable. En un grupo de 189 pacientes con lesiones no palpables, de bajo grado, de 15 mm o menos y sin invasión linfática/vascular, sólo 6 (3%) presentaron metástasis ganglionares. Entre los pacientes con tres de estos factores favorables sólo 6 presentaron ganglios positivos. Las características clínicas y patológicas de las lesiones primarias pueden ser utilizadas para estimar el riesgo de metástasis ganglionares axilares; tal estimación de riesgo es útil en el proceso de toma de decisiones terapéuticas.


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