Diagnostic strategy for the assessment of axillary lymph node status in breast cancer

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Abstract
The nodal status in breast cancer is a major prognostic factor in terms of survival. It also plays a role in the therapeutic decision-making process. Therefore, the evaluation of lymph node involvement in breast cancer is imperative in establishing a personalized treatment scheme. The sentinel lymph node procedure has proved successful for small breast tumors (T1–T2), limiting axillary lymphadenectomy and its side effects without changing overall survival. Even so, a substantial number of women must undergo axillary lymphadenectomy during a second surgery when the analysis of the sentinel node discloses major nodal involvement. Imaging can improve patient selection, especially those who appear eligible for immediate axillary lymphadenectomy. Ultrasound is able to depict morphological abnormalities in the lymph nodes such as cortical thickening, peripheral vascularization, hilar infiltration and loss of the kidney-shaped appearance of a normal node. When ultrasound is negative, the risk of massive nodal involvement is limited, thus allowing the oncologist to take an approach with the sentinel lymph node procedure. Magnetic resonance imaging (MRI) can also be useful in detecting pathological lymph nodes, particularly with diffusion-weighted MRI sequence.

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Lymph node status reflects the interaction between, the aggressiveness of the tumor that tends to grow and metastasize and, on the other hand, the host’s resistance in its effort to contain the cancer. Lymph node involvement is the main prognostic factor — independently of other factors such as size — for predicting overall survival and progression-free survival. At 5 years, for all types of cancer, survival rates are greater than 82% for patients with negative nodes. This decreases to 73% when 1–3 lymph nodes are affected, 46% if 4–12 nodes are concerned and drops to 28% if more than 13 lymph nodes are invaded [1].

Nodal status also influences the therapeutic indications. Neoadjuvant chemotherapy is indicated in the event of type N2 axillary invasion, for example (Tables 1 and 2). The absence of clinical nodal involvement allows to consider opting for the sentinel lymph node procedure and thereby avoiding unnecessary surgical dissection. Tumor involvement of an axillary node is an indication for adjuvant chemotherapy and supraclavicular radiation therapy.

### Table 1 TNM Classification: pathological criteria.

<table>
<thead>
<tr>
<th>Regional lymph nodes pN</th>
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<tr>
<td>Nx</td>
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<tr>
<td>N0</td>
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<tr>
<td>N0 (i)</td>
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<td>N1</td>
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### Table 2 TNM classification: clinical and radiological criteria.

<table>
<thead>
<tr>
<th>Stade</th>
<th>Berg’s level</th>
<th>Stade</th>
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<tbody>
<tr>
<td>N1</td>
<td>I and II ipsilateral LOOSE</td>
<td>II</td>
</tr>
<tr>
<td>N2</td>
<td>I and II ipsilateral FIXED</td>
<td>IIIA</td>
</tr>
<tr>
<td>N3</td>
<td>Isolated internal mammary chain</td>
<td>LOOSE</td>
</tr>
<tr>
<td>N3c</td>
<td>Associated internal mammary I or II</td>
<td>LOOSE</td>
</tr>
<tr>
<td>N3b</td>
<td>Supraclavicular</td>
<td>LOOSE</td>
</tr>
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</table>

Axillary lymphadenectomy is the most reliable technique for assessing nodal involvement. However, it is limited by side effects following removal, such as lymphedema (2–18%), pain (16–56%), limitation of shoulder movement (4–45%) and weakness of the arm (19–35%). Axillary lymph node dissection appears to be less effective for women with
cancers < 20 mm (T1), for which a lesion is found in less than 15 to 20% of cases.

To reduce the side effects of axillary dissection, the sentinel lymph node procedure, which consists of collecting and analyzing the breast first axillary nodal relay, has been developed. If the sentinel lymph node is negative for tumor, the patient should not have axillary lymphadenectomy. For conservative treatment, when less than two positive sentinel nodes are present, thorough axillary dissection is not required. However, when a sentinel node is positive in a patient who underwent a mastectomy, axillary dissection is necessary. The sentinel lymph node procedure can be considered for patients for whom mastectomy is indicated (multi-focal cancer, ductal carcinoma in situ), and in the event of a previous history of breast or axillary surgery, both before and after neoadjuvant chemotherapy. However, the sentinel lymph node procedure is contraindicated for locally advanced tumors (T3 and T4), inflammatory cancers, DCIS if conservative treatment is being considered, and in the event of pregnancy.

In the ALMANAC study, 1031 patients with predominantly small breast cancers (T1 < 2 cm) were randomized into two arms, one with an immediate axillary lymphadenectomy, the other beginning with the sentinel lymph node procedure with a second surgery in the event of a positive sentinel node. The results showed that the rate of patients undergoing complementary axillary dissection was 17% [2]. This rate is estimated to be between 24 and 48% in other studies [3]. To avoid a second surgery, some teams offer an extracapsular analysis in the operating room (OR). However, this procedure immobilizes a pathologist, the surgical team and the OR for nearly an hour. These data show the limits of clinical analysis to assess the indications for the sentinel lymph node procedure.

The American Society of Clinical Oncology (ASCO) recommendations regarding the sentinel lymph node procedure indicate that the rate of identification of pathological lymph nodes is greater than 90% and the false-negative rate is less than 5% [4]. An analysis of the literature shows that the false-negative rate seems higher than expected, estimated at between 5.2% and 13.6% [3]. These rates could be improved by better selection of the patients who require an axillary lymphadenectomy and those who could benefit from the sentinel lymph node procedure.

Neoadjuvant chemotherapy induces rearrangements in nodal structure that may decrease the identification rate and therefore increase the rate of false-negatives for sentinel nodes at an estimated 11.5% [5]. Some teams even perform sentinel node identification before neoadjuvant chemotherapy to reduce the risk of losing information on the initial nodal status [6].

In all these situations, imaging can play a key role in assessing nodal status and can provide improved guidance for sentinel node indications.

**Axillary anatomical landmarks**

The sentinel node is usually located at the lower part of the axilla (i.e. Berg level 1) [7]. Three anatomical levels delimited by the pectoralis minor muscle are individualized (Figs. 1 and 2). Level I is located outside the pectoralis minor muscle. Level II nodes are located behind the pectoralis minor muscle. Level III nodes are found in the inner part of the pectoralis minor muscle. The tumor invasion pattern is sequential, starting with the level I lymph nodes and then level II lymph nodes are invaded. Finally, the tumor reaches the level III nodes (Figs. 3 and 4). Clinical and

![Figure 1](image1.png)

**Figure 1.** Location of the left pectoralis minor muscle on PET-CT in the sagittal (A) and transverse plane (B). The pectoralis minor (blue) is located posterior to the pectoralis major muscle (green). Level I of Berg is located external to the pectoralis minor muscle. It may be located posterior to or external to the pectoralis major muscle.
Evaluation of axillary lymph nodes with imaging

Pathological lymph nodes can be found on mammograms, ultrasound and magnetic resonance imaging (MRI), which are the best techniques for the assessment of lymph node status.

Ultrasound

Ultrasound is the first line examination. Ultrasound should be performed using a 7.5 MHz or more frequency probe. Pathological nodes are generally located in the lower part of the axilla and external or posterior to the lateral edge of the pectoralis major muscle. The analysis of the node should be focused not only on its size but also on other morphological criteria such as general shape, the aspect of the cortex, the hilum and vascularization. Reported diagnostic performances vary among studies. Regarding the size, the estimated sensitivities vary between 49 and 94%, the specificities between 53 and 97%, with positive predictive values (PPV) of 69% and negative predictive values (NPV) of 72% [8–10]. When morphological criteria are used, the sensitivity of ultrasound in terms of the detection of lymph node involvement varies between 26 and 80% and its specificity ranges from 88 to 98% [8]. In a study involving 577 patients, Schipper et al. showed that, for the detection of N0 patients, the NPV was 98%. However, ultrasound did not seem to be effective in distinguishing between pN1 and pN2–pN3 [11]. In their studies of over 500 patients, Abe et al. observed that ultrasound was useful in detecting massive nodal infiltration (pN2 and pN3) with a PPV of 82% [9].

Normal aspect on ultrasound

A normal sized lymph node is less than 10 mm with a thin cortex of less than 3 mm. A normal node has an oval shape. Its cortex is thin and of uniform thickness. The cortex is hypoechoic. The contours are well delineated. The hilum,
Figure 4. Examples of right axillary and internal thoracic nodal involvement by ultrasound. A. Invasion of I (external, arrowheads) and III (internal, arrowheads) Berg levels, of the pectoralis minor (asterisk) corresponding to a TNM stage N3. B. Involvement of level II, posterior location (arrowhead) and III, internal location, (arrow) of the pectoralis minor (asterisk) corresponding to a TNM stage N3. C. Right supraclavicular nodal invasion (arrow) corresponding to a TNM stage N3. D. Right internal thoracic involvement outside the sternum (ST) in contact with the internal thoracic vessels (red and blue color Doppler) corresponding to a TNM stage N2 if isolated or N3 if associated with axillary involvement.

Figure 5. Lymph node with normal appearance on ultrasound. The shape is oval. The cortex is thin and of uniform thickness. The cortex is hypoechoic. The contours are delineated. The hilum is mostly fat and wide. Doppler analysis shows only hilar vascularization.

consisting mostly of fat, is wide (Fig. 5). The hilar fat is usually hyperechoic but can also take on a non-suspicious hypoechoic aspect (Fig. 6). Doppler analysis shows vascularization in the hilum exclusively [12].

Pathological aspect on ultrasound

Tumoral infiltration starts at the periphery of the lymph node. Metastases arrive by afferent lymphatic ducts in the
subcapsular sinus. After a phase of growth in the subcapsular sinus, a peripheral neoangiogenesis begins. Then the tumoral infiltration progresses to the medullary sinus and the perinodal fat (Fig. 7). This results in morphological changes of the cortex, the hilum and the shape of the lymph node.

Cortical abnormalities include a focal or diffuse thickening of >3 mm, the presence of focal bulges and a peripheral vascularization with the color Doppler (Fig. 8). Isolated changes in the cortex have a low positive predictive value. It is therefore best to validate the presence of several associated anomalies before asserting a suspicious appearance. The invasion of the hilum is a specific sign but occurs later, as do the round shape and the very hypoechoic aspect of the node (Fig. 9) [13]. The last step consists of the tumoral infiltration of perinodal fat [12,14–16].

Figure 6. Lymph node with normal appearance on ultrasound with an oval shape, a fine and regular cortex. The hilum is composed of fat with a hypoechoic central area corresponding to a benign fatty infiltration not to be confused with tumoral infiltration, which is always associated with cortical involvement.

Figure 7. Illustration of the steps of the metastatic lymph node infiltration. Lymph node tumoral infiltration begins at the periphery of the node. Metastases are brought into the subcapsular sinus (light green) by afferent lymphatic ducts. After growing in the subcapsular sinus, peripheral neoangiogenesis occurs. Then the tumor progresses to the medullary sinus (brown).

Figure 8. Early morphological abnormalities due to metastatic lymph node infiltration. Tumoral infiltration of the cortex is initially responsible for focal thickening (A, B) and infiltration progresses throughout the cortex (C). Finally, cortical neoangiogenesis is visible on color Doppler (D).
Ultrasound-guided fine-needle aspiration (FNA) and microbiopsies

FNA biopsy and lymph node interventional procedures are simple, fast and efficient with a very limited risk of complications (<0.1%). The combination of ultrasound and biopsy in the event of a suspicious lymph node improves sensitivity (88% vs. 61%), specificity (100% versus 85%), PPV (91% versus 73%) and NPV (100% versus 77%) compared to ultrasound alone (Table 3) [8,13,14]. Rautiainen et al. also showed that histological samples can reduce the number of sentinel nodes that require a second dissection by 20 to 25%, thereby enabling patients to avoid having two surgical interventions [17].

Biopsy is slightly more effective than lymph node FNA [17]. FNA requires an experienced cytologist. The comparison between the performance of FNA and biopsy shows fewer insufficient samples with the microbiopsy (1% vs. 10%, respectively), fewer false-negative finding with biopsy, and similar risks for both techniques. Nevertheless, the PPV of ultrasound with puncture (cytology or histology) must be optimized in order to properly select patients requiring immediate axillary lymphadenectomy without reducing the number of correct indications for sentinel nodes. In this context, it appears that the characteristics of the primary tumor are important. Thus, ultrasound + puncture PPV would be 56% for small tumors (T1 < 2 cm) and 100% for locally advanced tumors, extended to the skin or chest wall for which the risk of metastases is much higher (Fig. 10) [18]. Similarly, the characteristics of the node would affect the PPV for ultrasound + cytopathology (Fig. 11). The PPV is 11% for normal ganglion, 44% for indeterminate aspect nodes and 93% in the event of a suspicious lymph node [10,19,20].

The combination of ultrasound + biopsy would be useful in predicting lymph node involvement. In a study of over 500 patients followed for breast cancers with limited size (<5 cm, T1 and T2), Caudle et al. showed that when ultrasound associated with microbiopsy proved positive, it showed an advanced invasion with more positive nodes during the axillary dissection, larger metastases and more extranodal extensions. Conversely, in the event of negative ultrasound, patients could benefit from the sentinel lymph node procedure with an ultrasound NPV estimated at 96% to exclude significant nodal invasion, N2 and N3 [21].

Other imaging techniques

MRI

MRI allows the analysis of the axilla but morphological analysis is more limited than with ultrasound, because the
**Figure 10.** Left breast cancer measuring 7 cm along the long axis on ultrasound (A) and magnetic resonance imaging (B). The risk of nodal metastasis is significant in this patient. The positive predictive values of ultrasound coupled with sampling of the axillary lymph nodes that have a suspicious aspect [hilum loss (C) and peripheral vascularization (D)] is close to 100%.

**Figure 11.** Breast cancer measuring 40 mm on ultrasound (A). The isolated thickening of the cortex of the lymph node in B has an indeterminate aspect, the positive predictive values (PPV) of the association of ultrasound and tissue sample of this node is around 40%. The PPV of ultrasound coupled with a sample of node C, of much more suspicious appearance with its round shape without hilum is around 100%.
main criteria (intracortical nodule, round shape) are rather not specific [22]. However; loss of hilum, irregular edges, irregular cortical thickness and asymmetry in number or size of lymph nodes compared to the contralateral axilla are some useful MRI criteria that help detect nodal invasion: (Fig. 12). MRI is also effective in detecting perinodal edema, easily visible on T2-weighted sequences, and the more important invasions with a ring-like enhancement denoting central necrosis. MRI has a NPV of 94% when the absence of asymmetric nodes and a uniform thickness of the cortex are observed. Conversely, the presence of an asymmetry and jagged edges yield a PPV of 100% for MRI [23]. Similarly, diffusion-weighted MR sequence using high b values (750–1200 s/mm²) is useful in detecting metastatic lymph nodes, especially those in the limits of the field of view, which must be confirmed by analyzing whether or not they are pathological with the T1- and T2-weighted sequences. ADC measurement may also be useful in characterizing pathological nodes. An ADC value of less than 1.10^{-3} mm².s⁻¹ is considered pathological (Fig. 13) [24].

CT and PET-CT
CT can detect advanced nodal lesions. The main criteria are a major axis/minor axis ratio of < 2 and cortical abnormality (focal or irregular thickening). Similar to MRI, CT can detect signs of advanced nodal invasion such as perinodal extensions. However the loss of the hilum, diffuse cortical thickening and small axis measurement > 10 mm are not discriminating [25]. The sensitivity of PET-CT is 56%. PET-CT is especially useful for evaluating the general extension of breast cancer in particular forms (locally advanced tumors, inflammatory breast cancer) [26–28]. PET-CT enables the detection of supraclavicular, subclavicular and internal thoracic lymph nodes in patients followed for locally advanced cancer with II and III clinical stages in 15% of cases, which would otherwise be undetected in traditional radiological imaging because they are located outside of the field of view of MRI or the mammogram and are difficult to access by ultrasound [27].

Evaluation of the internal thoracic chain in imagery
Internal thoracic lymph node involvement has an important prognostic value. It classifies a patient at N2 if the involvement is isolated or at N3 if it is associated with axillary lymph node involvement. Predicting factors of internal thoracic extension include the size of the primary tumor, the inner/medial or deep location of the lesion and axillary lymph node status (Figs. 14 and 15). Isolated internal thoracic invasion is only found in 1–5% of cases. In the event of internal thoracic node involvement, a remote secondary location should be actively screened for, and radiation of the internal mammary chain should be considered (as coverage of the internal thoracic region is not systematic). Internal thoracic lymphadenectomy does not change survival rates.

With imaging, the analysis usually starts with the 2nd or 3rd intercostal space. The internal thoracic nodes are not normally visible. All nodes measuring over 5 mm are
Figure 13. Right breast cancer measuring 5 cm on magnetic resonance imaging. A. T1-weighted subtracted MR image after IV of gadolinium chelate. Analysis of the axilla shows a suspicious lymph node of 20 mm in size located posterior to the right pectoralis minor muscle (Berg level 1). This lesion is difficult to see (B, T2) but is rather evident on DWI sequence (b750 s.mm$^{-2}$) (C). The ADC value of that node is $0.922 \times 10^{-3}$ mm$^2$.s$^{-1}$ (D).

Figure 14. Locally advanced tumor, located in the deep third of the lower inner quadrant of the left breast; T2-weighted (A), T1-weighted (B), T1-weighted subtracted MR image after IV of gadolinium chelate (C) and diffusion-weighted MR sequence (D). The location of the primary breast tumor and its size make the presence of an internal thoracic lymphadenopathy likely.
Figure 15. Same patient as on Fig. 14. Screening left axillary involvement is difficult because this region is obscured by the pectoralis minor muscle on T2-weighted sequence (A) and T1-weighted (B) and by local fat after IV of gadolinium chelate (C). Diffusion-weighted MR sequence (b750 s.mm$^{-2}$) is better at detecting this lymphadenopathy (D). Axillary involvement is the third risk factor for internal thoracic invasion.

Figure 16. Diagnostic strategy for evaluating axillary lymph nodes in patients with breast cancer.
suspicious with in MRI a sensitivity measured at 93% and specificity at 89% [29].

**Diagnostic strategy**

The strategy (Fig. 16) is based on a PPV of 93% for ultrasound in cases of suspicious appearance of lymph nodes, [14] on the PPV of 100% of ultrasound when the size of the primary tumor is > 4 cm, [18] on the PPV of ultrasound to predict nodal and extranodal involvement in the event of ultrasound + positive micro biopsy, [21] and the NPV of close to 96% for ultrasound + micro biopsy to exclude N2-N3 advanced invasion [21].

Thus, when the clinical examination shows an extended lesion: T3–T4 (tumor > 5 cm, skin lesions and/or chest wall), sentinel lymph node biopsy is contraindicated and axillary lymphadenectomy shall be systematic. However, ultrasound is useful in performing biopsy of suspicious lymph nodes [30] before neoadjuvant chemotherapy (PPV close to 100%), before chemotherapy alters the histological pattern of the node, or to collect evidence of lymph node involvement (N > 4), which enables to discuss the possibility of radiation of the chest wall in the event of tumors > 5 cm after mastectomy. When the lesion is clinically limited (T1 or T2), the sentinel lymph node procedure is indicated but there is a significant risk that it will be followed by an axillary dissection during a second surgical phase. Ultrasound performed before the sentinel lymph node procedure can be useful to set down better indications and guidelines.

Thus, when the nodes have a suspicious appearance on ultrasound, ultrasound’s PPV is sufficient to propose a biopsy (93%). If it is negative, the high NPV of the combination ultrasound + micro biopsy to rule out massive nodal involvement (96%) enables us to prescribe an approach utilising the sentinel lymph node procedure, thus limiting the risk of secondary lymphadenectomy. If the biopsy is positive for cancer, then the risk of advanced invasion is significant and justifies the proposal of an immediate axillary lymphadenectomy. When lymph nodes have a normal appearance on ultrasound, the sentinel lymph node procedure can be proposed. If the latter is positive then the NPV of ultrasound reduces the risk of lymph node involvement and thus the risk of secondary lymphadenectomy. In most cases, nodal involvement will be limited (N1). If the sentinel node is negative, no axillary dissection is necessary.

**Take-home messages**

- Lymph node status is a major prognostic factor in breast cancer in terms of survival.
- Ultrasound is efficient in detecting massive nodal involvement.
- Any suspected nodal involvement on imaging must be proven by an ultrasound-guided biopsy.
- In the event of nodal involvement, which is proven on imaging + biopsy, the sentinel lymph node procedure should not be used and instead should be replaced by an axillary lymph node dissection.
- When no axillary lymphadenopathy is suspected on imaging, the sentinel lymph node procedure is recommended when indicated.
- Isolated internal thoracic nodal involvement is exceptional and must lead to screening being carried out for unnoticed axillary involvement.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

**References**


