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## REVIEW

# The role of preoperative axillary lymph node fine needle aspiration in locoregional staging of breast cancer

Rôle de la cytoponction ganglionnaire dans la stadification locorégionale des cancers mammaires

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## KEYWORDS

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**Summary** Preoperative ultrasound-guided fine needle aspiration cytology (UG-FNAC) of axillary lymph nodes in breast cancer emerged after the onset of the surgical sentinel node (SN) procedure. Today it is established as one of the preoperative routine procedures in patients with a cytological or histological confirmation or strong suspicion of breast carcinoma, the interest being that a positive UG-FNAC allows to avoid SLN biopsy or two-stage surgical procedure. Our article reviews the recent data in the literature regarding the diagnostic accuracy of lymph node FNAC in breast cancer staging, and presents the experience of the Breast Diagnostic Centre of Oslo University Hospital Ullevaal, Norway, in this context. Nowadays, UG-FNAC is indicated whenever the breast radiologist finds a suspicious or otherwise abnormal axillary lymph node, regardless of the size of the primary tumour. UG-FNAC is a cost effective and safe method. A diagnosis of metastatic malignancy has a very high accuracy and false-positives are virtually non-existent. False-negatives do occur, especially in lymph nodes with partial involvement as micrometastases and isolated tumor cells (ITC), and recent recommendations advocate that in these particular situations the axillary dissection is not necessary.

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## MOTS CLÉS

Cytoponction lymphoganglionnaire ;  
 Cancer mammaire ;  
 Stadification

**Résumé** La cytoponction échoguidée (CEPG) préchirurgicale des ganglions axillaires en cas de cancer mammaire a pris de l'ampleur après le développement de la technique du ganglion sentinelle (GS). La CEPG est aujourd'hui pratiquée en routine chez les patients présentant un carcinome mammaire confirmé cytologiquement et/ou histologiquement ou en cours de diagnostic, permettant d'éviter en cas de positivité la technique du GS ou une intervention

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chirurgicale en deux temps. Notre article résume les données récentes de la littérature concernant la précision diagnostique de la cytoponction ganglionnaire dans la stadification du cancer mammaire et présente l'expérience du Centre de diagnostic mammaire de l'Institution Oslo University Hospital Ullevaal, Norvège, dans ce contexte. Actuellement, la CPEG est indiquée pour tous les ganglions axillaires suspects ou échographiquement anormaux, indépendamment de la taille de la tumeur mammaire primitive. La CPEG est une méthode diagnostique précise et peu coûteuse. Le diagnostic des métastases ganglionnaires par cette méthode est très fiable et les faux-positifs sont quasi inexistantes. Des cas de faux-négatifs sont observés, surtout en cas de métastases de petite taille (micrométastases et cellules tumorales isolées) pour lesquelles des recommandations récentes indiquent que le curage axillaire n'est pas nécessaire.

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## Introduction/Background

The locoregional lymph node involvement is a key element in the staging of patients with invasive breast cancer, representing a major prognostic factor and contributing to an optimal therapeutic management [1].

For newly diagnosed breast carcinoma which are targeted initially by surgical treatment (small tumors), the complete axillary lymph node dissection (ALND) was the standard method in the evaluation of lymph node status and was widely employed for many years. This procedure was associated with significant morbidity (lymphedema, lymphorrhea, shoulder-arm morbidity, chronic pain, dysaesthesia). The concept of progressive lymph node involvement has enabled the development of the sentinel lymph node (SLN) biopsy, the first relay in the locoregional lymph node spread of the disease. In patients with low risk of lymph node metastasis, lymphadenectomy is currently substituted by SLN biopsy as the primary axillary procedure. The decision of limiting the axillary lymph node dissection to this less invasive procedure is based on the clinical and radiological examination of the axillae. In the absence of suspicious axillary lymph nodes (cN0), SLN biopsy may be performed for tumors less than 30 mm. If the sentinel node is negative, the risk of invasion of the remaining axillary lymph nodes is low and the surgical procedure is limited to this scope. Demonstration of isolated tumor cells (ITC) does not warrant axillary dissection. In some countries, that is the case for micrometastases (< 2 mm) also [2].

In case of macrometastatic SLN (> 2 mm), a complete axillary lymphadenectomy is needed. Despite the evolution of this surgical procedure in the locoregional staging of breast cancer, SLN biopsy remains invasive and has disadvantages [3] such as exposure to ionizing radiation, high costs in terms of time, hospitalization and medical staff. Moreover, in a number of cases (less than 5% for experienced teams) it does not lead to the detection of SLN.

In this context, an accurate preoperative diagnostic test for lymph node metastasis would be helpful for both the patient and the surgeon, thus avoiding SLN biopsy or two-stage surgical procedure. For newly diagnosed breast cancer requiring neoadjuvant chemotherapy (large tumors), such an assessment would allow for staging of the disease before treatment, as well as for evaluating the therapy response at lymph node level.

## Preoperative assessment of axillary lymph node status

Physical examination, the oldest method of investigation of axillary lymph nodes, has limited reliability. According to

different series, the sensitivity varies widely, between 30 and 76% [4–8]. The specificity of the examination remains low, despite some features as predictors of metastasis (firm, rounded, fixed node), since palpation cannot differentiate reliably reactive lymph nodes from metastatic ones.

Imaging may improve detection of regional lymph nodes metastasis, but still remains unsatisfactory [9–12]. The high-resolution ultrasound is currently the most used technique for axillary exploration: it is non-invasive, economically convenient and is practical for performing fine needle biopsies. The diagnostic accuracy of axillary lymph node metastasis by ultrasound is currently equivalent to the one characterizing other imaging modalities [11–14]. Since the development of SLN biopsy, ultrasound characterization of axillary lymph nodes has improved and more specific criteria have been demonstrated. The most widely accepted ultrasonographic findings suspicious of metastasis are cortical thickening, loss of fatty hilum, irregular shape, intensely hypoechoic cortex and peripheral hypervascularization [15–19]. A cortical thickness superior to 2.5 mm was found predictive for metastasis by Cho et al. [19]. No standardization of criteria exists in the different studies. There is a variability of the criteria used and thus the results are very heterogeneous. The sensitivity of the ultrasound examination depends on the histopathologic subtype of the breast carcinoma. Lobular carcinomas usually have a higher false-negative rate compared to ductal carcinomas [20,21].

Needle biopsy (fine needle aspiration cytology or core needle biopsy) of the axillary nodes improves the diagnostic accuracy of lymph node metastasis. The majority of studies report specificity close to 100% [22,23]. Preoperative confirmation of axillary lymph node metastasis in breast cancer by fine needle biopsy therefore represents a contraindication for SLN biopsy [24].

Ultrasound-guided fine needle aspiration cytology (UG-FNAC) is more frequently employed than core biopsy. Nevertheless, both modalities show comparable diagnostic accuracy [25,26]. UG-FNAC is minimally invasive, well tolerated by patients, quick and inexpensive, and diagnosis is immediate [25]. However, the use of this technique may be limited by the lack of specialized personnel.

Fine needle aspiration cytology (FNAC) is known as an operator-dependent modality, the number of non-significant samples depending on the experience of the operator and on the cytological preparation technique. FNAC is usually performed by the radiologist under ultrasound guidance, and by the pathologist/surgeon under physical guidance (palpation). Following biopsy (with or without aspiration) performed using 22–25 gauge needles and 10 or 20 ml syringes, direct smears are made. The stains most widely employed are May-Grünwald-Giemsa or Diff-Quick for air-dried slides and Papanicolaou for alcohol fixed smears. The

rapid on-site evaluation (ROSE) of the specimen allows the operator to perform additional passes if the specimen is paucicellular, and thus to limit the non-significant samples [22,27,28]. Schiettecatte et al. [29] have reported excellent results by performing liquid-based cytology using the Surepath® (Becton Dickinson) technique, assisted by immunocytochemical study. In order to increase the sensitivity of the technique, Kim et al. suggest assessing the tumor marker concentration in the lavage fluid of FNAC [30].

In recent years, many studies have been aimed at assessing the impact of UG-FNAC of axillary lymph nodes in the surgical treatment of breast cancer. The meta-analysis published in 2011 by Houssami et al. [31] including 31 studies, 2874 fine needle aspirations (UG-FNAC and core biopsy) and more than 6000 patients evaluated the accuracy and usefulness of this examination in the locoregional staging of breast cancer. Among these studies, 24 of them had used the UG-FNAC exclusively, two used either UG-FNAC or core biopsy, and the rest relied exclusively on core biopsy. The meta-analysis did not highlight any statistically significant difference between the diagnostic accuracies of these two types of sampling, stressing, however, that the vast majority of studies concerned UG-FNAC. With an overall sensitivity and specificity of respectively 79.6% and 98.3%, the positive predictive value was 97.1%. The sensitivity was higher for UG-FNAC on suspicious lymph nodes as opposed to radiologically visible nodes. Some authors have reported the usefulness of UG-FNAC for ultrasound non-suspicious lymph nodes [32,33]. This may be explained by discrete changes in the node morphology harboring small size metastasis and a liberal indication for doing UG-FNAC. In the aforementioned meta-analysis, the median proportion of patients triaged directly to a complete ALND was 19.8%, or 17.7% if restricted to the series of clinically negative patients. Some authors [33,34] highlighted a strong positive correlation between the sensitivity of UG-FNAC, the tumor size (20 mm or more) and the tumor grade, the largest lymph node metastasis arising in the series of patients with larger tumors. In the study by Park et al. [22], the negative predictive value of UG-FNAC was better for non-palpable versus palpable breast tumors. Houssami et al. did not find any statistically significant difference between metastases from ductal versus lobular carcinoma. Despite the methodological heterogeneity, all studies showed that a certain number of patients could avoid the SLN biopsy.

The FNAC (of palpable nodes) under clinical guidance has been less frequently reported. Recent studies have shown a sensitivity of 67.4% and 86%, respectively [27,35]. The median size of the breast tumor was 1.3 cm versus 2 cm, respectively. Since the risk of lymph node involvement is proportional to the tumor size, the best sensitivity obtained by Marti et al. may be related to tumor size. Both teams have a specificity of 100% and no false positive. The cases of false negatives, as for UG-FNAC, were sampling errors: in the case of partial metastasis, the fine needle aspiration may indeed sample a non-invaded region of the respective lymph node. Thus, the rate of false negatives may be more important in metastases, typically less than 0.5 mm [36]. In the study by Swinson et al., for the lymph nodes which were classified as positive following histological analysis, no micrometastasis had been previously diagnosed by preoperative UG-FNAC [37]. Using multivariate analysis, Marti et al. [27] found that an abnormal/pathological ultrasonographic finding and the final number of metastatic axillary nodes were positive predictive factors of metastatic disease.

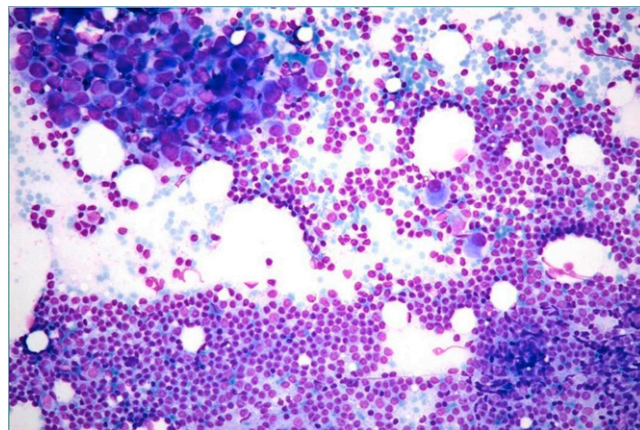
Preoperative diagnosis of axillary metastasis using UG-FNAC is cost effective. Genta et al. estimated a cost reduction of 8%, mainly due to a 12% decrease in the number of interventions for sentinel lymph node, but also in the number of ALND for palpable false positives lymph nodes [38]. By avoiding SLN biopsy, Lee et al. estimated a therapeutic cost reduction of more than \$4000 per patient [28].

## Our experience

Preoperative UG-FNAC of suspicious axillary lymph nodes emerged after the onset of the surgical SN procedure. Today it is established as one of the preoperative routine procedures in patients with a cytological or histological confirmation or strong suspicion of breast carcinoma. The close proximity to larger vessels in the axillae, often make FNAC the method of choice instead of core needle biopsy.

In Ullevaal Hospital in Oslo, Norway, there is a history of close cooperation between the breast radiologists and the cytopathologists in the department of pathology. A cytopathologist is present at the Breast Diagnostic Centre (BDC) 2½ days per week, performs the FNAC on palpable lesions, and assists directly in the sampling and preparation of material from ultrasound-guided aspirations of non-palpable lesions. This assures an optimal communication between radiologist and cytopathologist. In case of suboptimal or nondiagnostic aspirated material, the FNAC can be repeated at once and representative material can be secured. Discrepancies between radiological and cytological findings can be dealt with immediately. Both direct, air-dried smears (Fig. 1) and liquid-based preparations (PreservCyt®, Hologic) are well suited for diagnostics, the latter also for eventual investigations using ancillary methods, such as immunocytochemistry (Fig. 2) or fluorescent in situ hybridization.

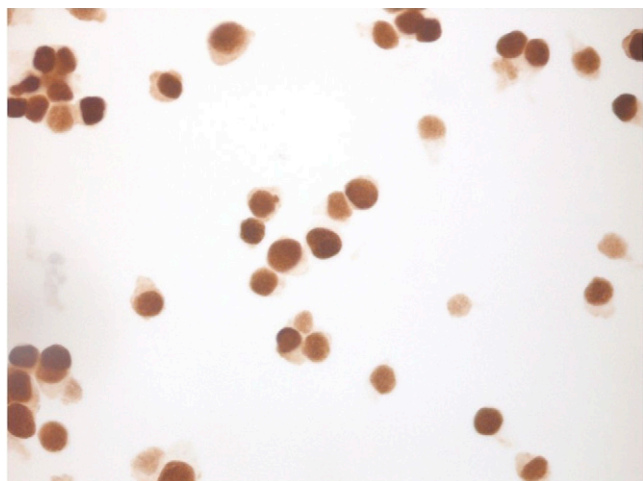
Ultrasound examination of both axillae is standard procedure when the breast radiologist finds a malignant or suspicious lesion in the breast. The ultrasound - guided aspiration of a suspicious axillary lymph node is done by the radiologist. The cytopathologist prepares the material, makes a rapid Diff-Quick stain (ROSE), gives a preliminary diagnosis to the radiologist and, if necessary, also to the clinician. If there is a metastasis on cytological examination,



**Figure 1.** A group of carcinoma cells and some isolated tumor cells in a lymphocytic background (MGG original magnification  $\times 200$ ).

*Un amas et quelques cellules carcinomateuses isolées sur un fond riche en lymphocytes (MGG  $\times 200$ ).*





**Figure 2.** Immunocytochemical staining for ER in carcinoma cells. Liquid-based preparation from PreservCyt® (Hologic) (original magnification  $\times 400$ ).

*Marquage immunocytochimique pour les récepteurs aux estrogènes: cytologie en milieu liquide  $\times 400$  (PreservCyt®, Hologic).*

an axillary dissection is done directly at surgery. If there is no metastasis on cytology, the patient will have the SN removed.

The majority of axillary lymph nodes aspirated as above, are metastatic (72, 5%) with no false positive cytological diagnoses. About 12% of cases diagnosed as benign had a positive SN, mostly as a micrometastasis or ITC. Insufficient material was obtained in one, 5% of cases (unpublished results, Oslo University Hospital Ullevål).

If the axillary lymph nodes are unremarkable on ultrasound examination, no FNAC is done, and the SN is removed and examined by frozen section during the primary surgery. SN positivity rate in our Institution is 24% [39]. Of these, 9% had a benign preoperative cytological diagnosis from FNAC of axillary lymph nodes. In the future, not all of these will have an axillary dissection. Recent recommendations advocate that it is not necessary to do so in micrometastases and ITC [2].

## Conclusions/Indication for FNAC in the locoregional staging of breast cancer

Ultrasound examination of axillary lymph nodes in patients with a confirmed or probable carcinoma of the breast is standard practice. UG-FNAC is indicated whenever the breast radiologist finds a suspicious or otherwise abnormal axillary lymph node, regardless of the size of the primary tumour. A cytopathologist, cytotechnologist or the equivalent should be present at the Breast Diagnostic Centre (BDC) to assist the breast radiologist and handle the aspirated material.

UG-FNAC is a cost effective and safe method. A diagnosis of metastatic malignancy has a very high accuracy and false positives are virtually non-existent. False negatives do occur, especially in lymph nodes with partial involvement as micrometastases and ITC.

## Disclosure of interest

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

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