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## Review

# The sentinel lymph node of breast cancer and the radiation oncologist

## *L'oncologue radiothérapeute face au ganglion sentinelle*

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### ABSTRACT

If the indications of sentinel lymph node biopsy and axillary lymph node dissection have been the subject of many trials, the indications of radiotherapy, in the absence of axillary lymph node dissection are a matter of debate. We reviewed the available literature on this topic and tried to draw some practical applications. In case of negative result of a sentinel lymph node biopsy, patients could be viewed as having pN0 disease and indications of adjuvant radiotherapy based on this paradigm. However, when the result of a sentinel lymph node biopsy was positive and no axillary lymph node dissection performed, indications of adjuvant radiotherapy are not so clear. For example, micrometastases could indicate a nodal irradiation as in the AMAROS trial, or not as in the IBCSG trial. Indications of postmastectomy radiotherapy are also not clearly defined in this setting. In the end, a clinical proposal was designed, emphasizing the unanswered questions.

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### R É S U M É

Si les indications de la réalisation de la technique du ganglion sentinelle ont été bien étudiées, les indications de la radiothérapie en l'absence de curage ganglionnaire restent discutées. Nous avons effectué une revue de la littérature sur le sujet et essayé d'en tirer des conclusions pour la pratique clinique. En cas de ganglion sentinelle négatif, la maladie peut être considérée pN0 et les indications de la radiothérapie basée sur cette constatation. Mais, par exemple, en cas de micrométastases dans le ganglion sentinelle sans curage ganglionnaire complémentaire, l'irradiation axillaire sus claviculaire peut-être proposée (selon les données de l'essai AMAROS) ou pas (selon les données de l'essai de l'*International Breast Cancer Study Group* [IBCSG]). De même, les indications de la radiothérapie après mastectomie ne sont pas claires en l'absence de curage ganglionnaire. En conclusion, nous proposons un arbre décisionnel clinique en fonction des différentes situations.

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## 1. Introduction

Indications of nodal irradiation were usually based on lymph nodes status, defined by axillary lymph node dissection. Moreover, after mastectomy, the indication of chest wall irradiation is also

based mainly on the results of axillary lymph node dissection and could take into account the number of positive nodes.

However, indications of axillary lymph node dissection are decreasing and many patients have now only a sentinel lymph node biopsy, even in case of positive sentinel lymph node. This de-escalation of surgery spares the patient from complications associated with axillary lymph node dissection: pain, paraesthesia, and lymphedema. Some discussion could occur, in case of positive sentinel lymph node and no axillary lymph node dissection, about the usefulness of chest wall and/or lymph nodes irradiation. Positive sentinel lymph node includes isolated tumour cells (pN0(i+):

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deposits less than 0.2 mm), micrometastases (pN1mi: 0.2–2 mm) and macrometastases (pN1: > 2 mm).

This aim of this article is, after a literature review, to propose a practical management after positive sentinel lymph node without axillary lymph node dissection for the radiation oncologist.

## 2. Why axillary dissection is no more useful in case of positive sentinel lymph node?

The clinical value of sentinel lymph node biopsy has been validated in numerous randomized studies, including patients with an early clinically node negative breast cancer. Completion of axillary lymph node dissection is unnecessary in case of a negative sentinel lymph node biopsy, without any difference in terms of regional control or disease-free and overall survivals [1,2].

More recently, the interest of axillary lymph node dissection was challenged even in case of positive sentinel lymph node. Four randomized trials have evaluated the benefit of axillary lymph node dissection in this setting.

The ACOSOG Z0011 (Alliance) trial randomized, in case of clinically negative node and positive sentinel lymph nodes, axillary lymph node dissection vs. no dissection [3]. Patients ( $n=891$ ) with one or two positive sentinel lymph nodes and micro- or macrometastases could be included but they had to have less than three positive sentinel lymph nodes and no extracapsular extension. The main end-point was overall survival. All patients had to have a breast conservative procedure and adjuvant irradiation. There was no difference in overall survival, locoregional relapse free survival or disease-free survival.

The IBCSG 23-01 trial compared again axillary lymph node dissection vs. no dissection, but only in case of micrometastases, with disease-free survival as the main end-point [4]. Among 931 patients included, 9% had a mastectomy without irradiation. No difference in overall or disease-free survival was observed but a higher rate of lymphedema was observed in case of axillary lymph node dissection.

The EORTC AMAROS trial compared directly, in case of positive sentinel lymph nodes, axillary lymph node dissection vs. postoperative nodal irradiation in patients with cT1-T2, N0 disease [5]. A supraclavicular field was systematically added to the axillary irradiation. Patients were randomized before surgery: it was necessary to screen 4806 patients to include 1425 patients. The main hypothesis was to obtain less than 4% axillary recurrence rate in the postoperative nodal irradiation arm. Indeed, the axillary recurrence rates were 0.43% after axillary lymph node dissection and 1.19% after radiotherapy, without any differences in disease-free survival or overall survival. The risk of arm lymphedema was

significantly higher in the axillary lymph node dissection arm (23 vs. 11% at 5 years).

The OTOASOR trial had the same design as AMAROS trial and included 474 patients [6]. The rate of axillary recurrences was identical in both arm (axillary lymph node dissection: 2%; radiotherapy: 1.9%) as disease-free survival and overall survival.

These trials are summarized in Table 1, emphasizing the radiation treatment characteristics. In view of these trials, axillary lymph node dissection is not required if there was less than three positive sentinel lymph nodes and no extracapsular extension [7]. These trials have included a small number of patients with isolated tumour cells; but for this group, the risk of residual disease and axillary recurrence is very low [8] and it could be assimilated to a pN0. At this moment, trials are now looking at the omission of sentinel lymph node biopsy during breast-conserving surgery, in case of cN0 after a negative axillary ultrasound.

## 3. What was the role of radiotherapy in these three trials?

In the ACOSOG trial, around 89% of the patients received a post-operative radiotherapy; high-tangents (cranial border no larger than 2 cm of humeral head) were used in 50% of the patients [9]. Moreover, 15 to 18.9% received also a supraclavicular irradiation, which was not allowed in the protocol. There was no difference in terms of locoregional control according to the type of radiotherapy.

In the IBCSG trial [4], 91% of the patients had a lumpectomy and 89% received adjuvant radiotherapy. However, this radiotherapy was delivered as an intraoperative procedure with electron beam in 19% of the patients, with, so, no axillary irradiation. At the end, only 71% of the patients received a post-operative standard irradiation.

In the AMAROS and OTOASOR trials, all patients were irradiated on axillary and infra/supraclavicular lymph nodes. A quality assurance of radiotherapy with an initial dummy run was performed in the EORTC study [10].

So, most of the patients received a postoperative radiotherapy, which could have explained in part the good results observed in these trials. In the MIRROR analysis, a large cohort study, the rate of axillary recurrence without axillary treatment (surgery or radiotherapy) was 2 and 5.6% for isolated tumour cells and micrometastases, respectively, compared to 0.9 and 1% after axillary lymph node dissection or radiotherapy, the difference was highly significant for pN0mi (hazard ratio: 4.39) [11]. However, in the IBCSG trial, 29% of the patients had no postoperative radiotherapy without any difference in locoregional control. The usefulness of postoperative radiotherapy in case of micrometastases could be discussed.

**Table 1**  
Randomized trials comparing axillary dissection vs no axillary dissection in patients with breast cancer [3–6,9].

	ACOSOG ( $n=891$ )	IBCSG ( $n=931$ )	AMAROS ( $n=1425$ )	OTOASOR ( $n=474$ )
Type of sentinel lymph nodes (%)				
Isolated tumour cells			11	6.1
Micrometastases (0.2–2 mm)	33	100	29	33.5
Macrometastases (> 2 mm)	67		60	60.4
Breast-conserving surgery (%)	100	91	82	83
Nodal recurrence (%)				
Axillary lymph node dissection	0.5	0.002	0.43	2
No axillary lymph node dissection	1	0.1	1.19	1.9
Adjuvant radiotherapy in the no axillary lymph node dissection arm	89.6	91	100	100
Type of radiotherapy (%)				
Standard tangential fields	≈50	71	100	100
High tangential fields	≈50			
Supraclavicular	17–20		100	100
Lymphoedema (%)				
Axillary lymph node dissection	–	13	23	15.3
Sentinel lymph node ± radiotherapy	–	3	11	4.7

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