**Name of Journal: *World Journal of Clinical Oncology***

**ESPS Manuscript NO: 20744**

**Manuscript Type: Minireviews**

**Locoregional treatment of early breast cancer with isolated tumor cells or micrometastases on sentinel lymph node biopsy**

Tallet A *et al.* Breast cancer treatment/lymph node micrometastases

**Agnès Tallet, Eric Lambaudie, Monique Cohen, Mathieu Minsat, Marie Bannier, Michel Resbeut, Gilles Houvenaeghel**

**Agnès Tallet, Mathieu Minsat, Michel Resbeut,** Departement of Radiotherapy, Institut Paoli Calmettes and CRCM, 13009 Marseille, France

**Eric Lambaudie, Monique Cohen, Marie Bannier, Gilles Houvenaeghel,** Departement of Surgery, Institut Paoli Calmettes and CRCM, 13009 Marseille, France

**Eric Lambaudie, Gilles Houvenaeghel,** Aix Marseille Université, Jardin du Pharo, 13284 Marseille, France

**Author contributions:** Tallet A, Lambaudie E and Houvenaeghel G performed the majority of the writing and prepared tables; others have contributed to the writing of manuscript.

**Conflict-of-interest** **statement:** There is no conflict of interest associated with any of senior author, coauthors, contributed their efforts in this manuscript.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to: Houvenaeghel Gilles, MD,** Departement of Surgery, Institut Paoli Calmettes and CRCM, 232 Bd de Sainte Marguerite, 13009 Marseille, France. houvenaeghelg@ipc.unicancer.fr

**Telephone:** +33-04-91223532

**Fax:** +33-04-91223613

**Received:** June 19, 2015

**Peer-review started:** June 27, 2015

**First decision:** July 31, 2015

**Revised:** February 25, 2016

**Accepted:** March 9, 2016

**Article in press:**

**Published online:**

**Abstract**

The advent of sentinel lymph-node technique has led to a shift in lymph-node staging, due to the emergence of new entities namely micrometastases (pN1mi) and isolated tumor cells [pN0(i+)]. The prognostic significance of this low positivity in axillary lymph nodes is currently debated, as is, therefore its management. This article provides updates evidence-based medicine data to take into account for treatment decision-making in this setting, discussing the locoregional treatment in pN0(i+) and pN1mi patients (completion axillary dissection, axillary irradiation with or without regional nodes irradiation, or observation), according to systemic treatment, with the goal to help physicians in their daily practice.

**Keys words**: Breast cancer; Micrometastases; Isolated tumor cells; Axillary lymph node dissection; Radiotherapy

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Sentinel lymph-node biopsy has led to a shift in lymph-node staging, due to the emergence of new entities namely micro-metastases and isolated tumor cells. The prognostic significance of this low positivity in axillary lymph nodes is currently debated, as is, therefore its management. This review provides updates evidence-based medicine data to take into account for treatment decision-making in this setting, discussing several loco-regional therapeutic strategies based on recent clinical trials results, particularly completion axillary dissection, axillary irradiation, regional nodes irradiation, with according to systemic treatment, with the goal to help physicians in daily practice.

Tallet A, Lambaudie E, Cohen M, Minsat M, Bannier M, Resbeut M, Houvenaeghel G. Locoregional treatment of early breast cancer with isolated tumor cells or micrometastases on sentinel lymph node biopsy. *World J Clin Oncol* 2016; In press

**INTRODUCTION**

Although adjuvant systemic treatments are mainly based upon biological tumor features, lymph-nodes status remains an important prognostic factor that influences the adjuvant treatment decision[1]. The sentinel lymph-node (SLN) technique in breast cancer (BC) (surgical technique as well as bio-pathological analyses) has altered the lymph-node status assessment, with the emergence of new entities formerly ignored such as isolated tumor cells (ITCs) [pN0(i+), metastasis size 0.2 mm or less] or micrometastases (MMs) (pN1mi, metastasis size above 0.2 mm up to 2 mm), that have been introduced in the sixth TNM classification[2]. In the latest case (MMs), two subpopulations with different prognosis have been described according to the detection mode (hematoxylin-eosin staining and/or immunohistochemistry on fine serial slices)[3,4].

The aim of this article is to determine what is the current evidence for the locoregional treatment of early BC patients, with limited axillary lymph-node metastases [pN0(i+) and pN1mi], discovered on SLN biopsy (SLNB).

**LYMPH-NODES MMS FREQUENCY**

In patients with small tumors suitable for a SLNB procedure, approximately one third present with a lymph node involvement[5-7], and 25% to 46% of positive SLNs are MMs[5,8,9] (Table 1); in other words, MMs are present in 10% to 15% of SLNB[5,10]. Noteworthy, this rate is closely dependent of the technique used for biopathological analyses, and discrimination between ITCs and MMs is fluctuant, even with trained pathologists[5,7,11-14] (Table 2).

**RATE OF NON-SENTINEL LYMPH-NODES INVOLVED IN AXILLARY LYMPH-NODE DISSECTION SUBSEQUENT TO POSITIVE SLN**

The rate of non-sentinel lymph-nodes (NSLN)involved is grossly from 40% to 50%: About 50% if positive SLN are macrometastases, 16% if positive SLN are MMs and 11% if ITCs were found in SLN[15-24] (Table 3). Once again, this rate depends on the method of detection of SLN involvement[15,18], the higher is the SLN metastasis size, higher is the rate of NSLN involvement. Some studies have reported that the risk of 3 or more positive NSLNs in patients with microscopically positive SLN, ranged from 1.5% to 5%. In the study reported by van Rijk *et al*[7], 5.6% patients (6/106) had 3 or more positive NSLNs. Rivers *et al*[25] reported the risk of 4 or more positive NSLNs at less than 1.5% in the group of patients with MMs in the SLN. In the study from Houvenaeghel *et al*[15], the risk of 3 or more positive NSLNs was 2.1% (15/700 patients), and the risk of 4 or more positive NSLNs was 1.4% (10/700 patients). Katz *et al*[26] reported a 3.4% risk (3/87 patients) of 4 or more positive NSLNs. In the IBCSG 23-01 trial[23], among 447 patients having had a complementary axillary lymph node dissection (cALND), 59 (13%) harbored at least one positive NSLN among whom one fourth had 2 or more positive NSLN.

The rate of NSLN involvement is also correlated with the tumor characteristics[18]. This has led some authors to seek for prognostic factors for NSLN involvement and predictive models guiding the axillary treatment decision.

**PREDICTIVE MODELS OF POSITIVE NSLN RISK**

Several predictive models of the risk of NSLN involvement have been developed in order to determine a low-risk group of patients (at low risk of harboring positive-NSLN, less than 10%)[16,17,22], and conversely a high-risk group of patients (at high risk of harboring positive-NSLN, more than 30%)[20,21]. Few of them were focused on patients with ITCs or MMs in the SLNs[16,17,20-22,27]. The risk of positive-NSLNs in patients with MMs or ITCs in the SLN is higher than that of patients with negative SLN (whose risk ranges from 7% to 8% related to the false negative rate), and lower than that of patients with macrometastases in the SLNs (whose risk ranges from 30% to 50%). Many clinical parameters were reported as risk factors of positive NSLNs, including size of the primary tumor, presence of lymphovascular invasion, the molecular subtype, the SLN metastasis detection mode or size of the SLN metastasis, tumor histologic type, number of positive SLNs or proportion of positive SLNs, and multicentric tumors (Table 4).

**PROGNOSTIC IMPACT OF MMS**

The clinical significance and the therapeutic implication of this weak positivity in the axillary lymph nodes remain controversial, although, there is growing evidence to suggest that micrometastatic disease in the SLN is associated with worse outcomes (Table 5). It seems that the metastatic tumor burden in axillary lymph nodes acts as a continuous variable, prognostic of locoregional recurrence (LRR) and of survival[4,28-33].

In the study from Weaver *et al*[4], investigating the prognostic impact of occult metastases in the SLNs, in patients included in the NSABP-B32 trial[6] (for whom no treatment has been planned for this minimal nodal involvement since physicians were not aware of it at the time of the treatment decision), a significant difference was found in the 5-year overall survival (OS) (absolute value: 1.2%) and in the 5-year recurrence-free survival (RFS) (absolute value: 2.8%), between pN0 patients and patients with occult metastases in the SLN, as detected by additional tissue section levels and the use of Immunohistochemistry. This difference was all the greater than the size of the lymph node metastasis increased. The occult metastases incidence was correlated to other prognostic factors (age and tumor size). In a Surveillance, Epidemiology and End Results (SEER) population-based analysis including 209720 patients treated between 1992 and 2003, a micrometastatic node has been shown to carry a prognosis intermediate to pN0 [hazard ratio (HR): 1.35] and pN1 disease (HR: 0.82)[28]. In a systematic review assessing the outcomes of patients with minimal nodal positivity compared to those without disease in the axillary lymph nodes, categorized by pathologic assessment of the excised lymph nodes (SLNB or ALND), de Boer *et al*[29] found that micrometastatic disease in the lymph nodes, as detected by staining with hematoxylin-eosin in one section of each axillary lymph node, was associated with decreased DFS and OS (HR: 1.44, 95%CI: 1.29-1.62). Nonetheless, when considering studies in which axillary lymph nodes were obtained by SLNB, definite conclusions could not be drawn due to poor sample sizes and short follow-up. Lupe *et al*[30] have focused on long-term LRR outcomes in 9616 patients, according to their nodal status (pN0:7977, pN1mi:490, pN1:1149). This study was carried out in a population of patients treated before the era of SLNB. Women with pN1mi disease were found to be at greater risk of LRR than those with pN0 disease (HR, 1.6; *P* = 0.002). In the study from Andersson *et al*[31], the presence of a MM in the axillary lymph nodes was also associated with a worse outcome, since both the 5-year specific survival and the 5-year RFS were significantly lower in pN1mi disease than in pN0 disease (94.1% *vs* 96.9% and 79.6% *vs* 87.1%, respectively), but without significant difference in OS. The prognosis of patients with pN0- and pN0(i+)-disease was similar. On the other hand, a dutch study (MIRROR study: Micrometastases and ITC: Relevant and Robust or Rubbish?), on 856 patients with small tumor sizes, found statistically significant differences in 5-year RFS between pN0(i+) and pN0 as well as between pN1mi and pN0, without significant difference between pN1mi and pN0(i+)[32]. Moreover, systemic treatment (hormonal therapy and/or chemotherapy) was able to improve RFS both in pN0(i+)- and pN1mi-disease. In the same way, several retrospective studies comparing survival outcomes of patients with pN0-, pN0(i+)-, pN1mi -and pN1-disease have found a similar prognosis of pN0-, pN0(i+-) and pN1mi-patients, emphasizing that the patients with nodal involvement had much higher frequently received adjuvant treatments such as systemic treatments and radiotherapy[5,34]. In the study from Cox *et al*[33], including 2381 patients having had a SLNB, with 2108 pN0(i-), 151 pN0(i+), and 122 pN1mi patients, and a median follow-up of 1.5 to 2 years, OS and RFS were significantly worse in pN1mi patients than in pN0(i-) patients (*P <* 0.001 and *<* 0.006, respectively), whereas they were similar between patients pN0(i+) or pN0(i-). In a cohort study of 18370 patients, [16011 pN0, 703 pN0(i+), and 1656 pN1mi], with a median follow-up of 5 years, after adjusting for prognostic factors, patients with ITCs in the SLN had a LRR risk and a metastatic recurrence risk similar to those without disease in the SLN (pN0) (HR: 1.2), whereas patients with a micrometastatic SLN had a 38%-50% higher risk (HR = 1.50: *P* = 0.001). Similar results were obtained in a subgroup analysis of patients without any adjuvant treatment[35].

In the same time, several studies didn’t find any significant difference in outcomes between patients with minimal axillary nodal involvement and patients without axillary nodal disease[3,36-38]. The ACOSOG Z10 trial did not find any impact on survival of occult axillary metastases as detected by IHC exclusively[3]. In this study, physicians were not aware of IHC results at the time of treatment decision, but patients with occult axillary metastases received systemic treatment significantly more often due to the correlation between occult axillary metastases and other unfavorable prognostic factors (such as age and tumor size). Imoto *et al*[38] also found that ITCs in SLNs detected by immunohistochemical staining had no impact on RFS. In the dutch study from Maaskant-Braat *et al*[36], with a median follow-up of 50 mo, no significant difference of survival was found between patients with a MM (*n* = 128) or with ITCs (*n* = 53) in the SLN and patients without disease in the SLN (*n* = 3285), even after adjusting for tumor- and patient-related factors (age, grade, tumor size, systemic treatment or not). A lack of significant difference in OS or RFS has also been reported in other series[37].

To summarize, ITCs as well as MMs in the SLNs have been correlated with an increased recurrence risk, and were inconstantly related to a poorer survival. The prognostic significance of minimal nodal involvement could be different according to the molecular subtype.

Finally, the presence of a minimal nodal involvement after a SLNB procedure raises two questions: Is a complementary axillary treatment mandatory? And, is this minimal nodal involvement prognostic enough to prompt an adjuvant systemic treatment?

**IS A CALND MANDATORY?**

This question could be otherwise formulated: what is the risk to leave disease in the NSLNs? Is the axillary recurrence (AR) risk increased? Is there an increased risk of under-treatment (particularly for adjuvant chemotherapy and regional radiotherapy)?

***AR***

The AR rates observed in patients with involved SLNs spared of cALND, are extremely low (0% to 2%), and widely lesser than the rates of positive NSLNs observed in cALND performed for positive SLNs. This fact could be due to the contribution of tangential fields of breast external beam radiation therapy, and also due to the efficacy of adjuvant systemic treatments such as hormonal therapy, chemotherapy and targeted therapies.

In the above-mentioned MIRROR trial, the 5-year rate of AR in patients with pN1mi-disease without cALND was 5%[32]. In the ACOSOG Z0011 trial randomizing patients with positive SLNs to either cALND or observation, half of the population had a minimal SLN involvement [pN0(i+) or pN1mi]; no significant difference in AR rates was observed between treatment groups (0.9% and 0.5% in the SLND alone group and in the ALND group, respectively, at 6.3 years of follow-up); all patients enrolled in this trial underwent a breast-conserving therapy with adjuvant whole breast irradiation; most of them (> 96%) received an adjuvant systemic treatment[39]. The IBCSG trial was designed to determine whether no axillary dissection was non-inferior to axillary dissection in patients with one or more micrometastatic (≤ 2 mm) sentinel nodes[23]. In this trial, patients have had either a conservative surgery or a mastectomy, and no significant difference in AR rate was observed between the 2 groups of patients (with cALND: 1AR/465 patients, without cALND: 4AR/464 patients). In the Spanish randomized trial, which assessed cALND versus clinical follow-up, in patients with SLN MM, 233 patients have been analysed (112 in the cALND group, 121 in the observation group), only one AR has been reported in the “observation” group[40].

In the Netherlands Cancer Registry study, Pepels *et al*[41] have found a higher 5-year regional recurrence rate in patients with MMs in the SLN who were not submitted to cALND, compared to those in whom cALND was performed (5.6% *vs* 2.3%, with an adjusted HR of 4.39, 95%CI: 1.46-13.24). The authors also showed that the omission of adjuvant systemic treatment and of breast irradiation was significantly associated with a higher AR rate and that these adjuvant treatments significantly lowered the risk.

In the meta-analysis from Francissen *et al*[42], AR rates ranged from 0% to 0.9% in patients with SLN MMs, and from 0.2% to 1.2% in patients with SLN macrometastses. These rates compare favorably with those (0.2% to 1%) of patients with positive SLNs who have had a cALND[39], and those (0% to 1.4%) of patients with negative SLN without cALND[43,44].

Actually, minimal nodal involvement seems to confer a worse outcome if ignored, reversed by the adjuvant treatments, and ARs are not of concern, likely due to the efficacy of adjuvant treatments. Therefore ARs are probably not an adapted end-point to judge the importance of axillary treatment.

***Breast external beam radiotherapy by tangential fields and its impact on axillary nodes control***

The role of external beam radiotherapy in the axillary area control, in patients with positive SLN without cALND has been widely commented in literature[45]. In the ACOZOG Z0011 trial, despite 27% of positive NSLNs, only 1% of AR rate has been observed in the SLN alone group[46]. The authors explained this unexpected low rate of AR, by the use of adjuvant systemic treatments combined with the use of external beam radiation therapy through tangential fields encompassing the vast majority of axillary levels I and II, although exact radiotherapy data were known in only one third of cases[47]. Therefore, the authors suggest limiting the ALND omission in patients meeting strictly the inclusion criteria of the ACOSOG Z0011 trial and suggest a radiotherapy scheme adapted to several tumor characteristics such as histologic type, the tumor grade, hormonal status, LVI presence, the size of node metastasis and number of positive nodes. Nonetheless, it has been recently reported that standard tangential fields used for breast irradiation do not allow optimal coverage and dose distribution in axillary levels I-II and sentinel node area[48,49].

On the other hand, when adapted tangential fields targeting axillary area, are used, it has also been shown in the AMAROS randomized trial, that, in the T1-2 BC patients with positive SLNs, axillary surgery or radiotherapy provide excellent and comparable axillary control[50]. However, AR rate was far less common than what was hypothesized, making the trial’s primary test underpowered. With this reserve in mind, axillary radiotherapy would seem equivalent to cALND in positive SLNs, but with less 5-years lymphedema rate, without any difference in quality of life[50].

***Systemic chemotherapy and its impact on axillary nodes control***

The positive impact of systemic treatments on locoregional control has been already documented. In the early 1990s, the NSABP B13 trial, which randomized node-negative, estrogen receptor-negative women, to chemotherapy or no-treatment control group, reported an 8-year LRR of 2.6% and 13.4% in the chemotherapy group and in the no-treatment control group, respectively[51]. More recently, a chemo-induced downstaging was observed in the SENTINA trial: Among 474 patients with a documented axillary lymph node involvement, 248 patients (52.3%) were free of disease after neoadjuvant chemotherapy[52]. Among the 1023 evaluable patients from NSABP B-14, the 10-year Kaplan-Meier estimate of the proportion of patients with LRR was 14.9% (95%CI: 10.7% to 19.1%) for patients treated with placebo and 7.7% (95%CI: 5.7% to 10.2%) for those treated with tamoxifen[53]. The addition of trastuzumab to chemotherapy also has resulted in a reduction in LRR (4% *vs* 6%, with and without trastuzumab)[54].

***Impact of omission of cALND on OS and RFS in patients with micrometastatic lymph node involvement***

Three phase III, randomized controlled trials addressed the question of the impact on survival of completion ALND (cALND) in patients with minimal SLN involvement[23,40,46]; all of them were in favor of cALND omission, but all of them with limitations and shortcomings precluding any definitive conclusion.

Criticisms and shortcomings of these trials related to statistical methods as well as lack of radiation data. Relative to the statistical methods, all of the 3 trials have been criticized due to: (1) a lack of accrual (70% of the planned sample size has been enrolled in the spanish trial, less than half of the required sample size to verify the non-inferiority hypothesis has been enrolled both in the IBCSG 23-01 and the ACOSOG Z0011 trials); (2) the expected number of events was always superior to the number observed (5 times superior both in the IBCSG 23-01 and the ACOSOG Z0011 trials); and (3) a 5-years OS or a 5-years RFS (used for the sample size calculation) underestimated in all the trials (IBCSG 23-01: expected RFS: 70%, observed RFS: > 87%; ACOSOG Z0011: expected OS: 80%, observed OS: > 91%; spanish trial: expected RFS: 48%, observed RFS: > 97%). Relative to the radiation data, no information was provided in the IBCSG 23-01 trial as well as in the ACOSOG Z0011 trial, and it has been suggested, particularly in the IBCSG 23-01 trial, that radiation beams have been modified in patients without cALND in this non-blinded study. This is all the more important that some authors explained the difference between the positive-NSLN rate after cALND (13%) and the low AR rate in the ”observation” arm (< 1%) through the efficacy of systemic treatments and breast irradiation and its axillary contribution[23]. Furthermore, surgery performed in all these 3 randomized trials was mainly conservative (mastectomy rate 0%, 9%, and 7.7% in the ACOSOG Z0011, IBCSG 23-01, and Spanish trial, respectively[23,40,46]), therefore precluding recommendation of cALND omission in patients with MM in the SLN treated by mastectomy (without adjuvant irradiation). A recent meta-analysis, including the above-mentioned randomized trials found no difference in RFS according to the performance of cALND or not, with a HR of 0.94 (95%CI: 0.79-1.13), however emphazising on important shortcomings in these trials[55]. A French randomized trial (SERC trial, Clinicaltrials.gov NCT01717131) assessing the impact of cALND in patients with positive (MM or macrometastases) SLNs, is ongoing[56]. This trial was designed to determine the tangential field contribution to the radiation of each levels of the axilla.

Completion ALND omission has never been assessed in a phase III trial in patients without adjuvant treatments. This issue has already been discussed in the subsection “Prognostic impact of MMs”.

**IS CALND A COMPONENT OF ADJUVANT TREATMENT DECISION-MAKING?**

Since tumor biological criteria (tumor size, grade, LVI, hormonal receptors status, HER2 status) are commonly used for adjuvant treatment decision-making, NSLN status is nowadays of lesser importance in this regard. The majority of studies that have reported the rate of patients receiving adjuvant systemic treatment according to axillary staging (cALND or SLNB alone), concluded that the absence of knowledge regarding the extent of nodal involvement seemed to have no major impact on the administration of adjuvant systemic treatments[23,40,57-61] (Table 6). The proportion of additional patients being considered for adjuvant chemotherapy upon cALND information ranges from 2% to 10% (median 4%). Only 2 authors out of 6 concluded that this difference was relevant[58,61]. Aigner *et al*[58] have also found a 4.6% increase in adjuvant chemotherapy administration taking into account cALND information, but also studied the type of chemotherapy related to the number positive nodes. Twelve percent of patients would be offered a more aggressive chemotherapy regimen upon the knowledge of more than 3 positive axillary nodes. This was the reason why the authors concluded to the relevance of cALND information. In the study from Montemurro *et al*[61], 16% more patients would have receive an adjuvant chemotherapy based on cALND information. Nonetheless, this study raised some criticisms[62]. The main concern was related to the study design. The authors have selected from their institutional database, patients meeting the ACOSOG Z0011 criteria (having had a cALND), and their breast team have blindly reviewed these cases in two rounds, and the total number of positive lymph nodes was disclosed only in the second. At each round was discussed the recommendation of chemotherapy (mandatory, discussed, or not required). The “chemotherapy discussed” group brings somewhat confusional because chemotherapy would have probably been considered in these patients. Indeed, if the 2 groups “chemotherapy mandatory” and “chemotherapy discussed” had been combined, then the absolute difference of chemotherapy administration between the 2 rounds would have been 3%.

Moreover, in the multivariate analysis from AMAROS trial, the patient age, tumor grade, size of SLN metastasis (ITCs, HR: 1.9; MMS, HR: 4.1; macrometastases, HR: 10.8), and multifocality were all significantly associated to chemotherapy administration, whereas number of positive nodes were not[60]. Mazouni *et al*[57] also showed the low impact of NSLN status in adjuvant treatment decision-making. Indeed, tumor grade was the major factor considered for adjuvant systemic treatment, followed by HER2 status, and then NSLNs positivity for low grade, HER2-negative tumors.

To summarize, the need for further axillary treatment (cALND or axillary radiation) in pN0(i+)- and pN1mi-positive SLN remains uncertain. It seems that usual adjuvant treatment, combining systemic treatment and classic radiation therapy (usual tangential fields) leads to a comparable survival to completion axillary treatment, without that we could assign this equivalence to either of the adjuvant treatments (radiation therapy, systemic therapy or both)[45].

The risk of positive NSLNs in pN0(i+) SLNs is quite similar to those of pN0 (5% and 4% respectively), the prognostic impact of ITCs seems negligible in the above-mentioned studies, all which lead to consider pN0(i+) as pN0. Lastly, the risk of positive NSLNs is also correlated to other patient- and tumor-related prognostic factors[3,4], that can be taken into account in the decision for further axillary treatment, particularly for patients treated with mastectomy without adjuvant irradiation, and for adjuvant systemic therapy consideration.

**REGIONAL NODE IRRADIATION (RNI) IN PN1MI SLNS PATIENTS**

The objective of RNI is to eradicate micrometastatic disease, which could lead to LRR and also, and above all, to distant recurrence, if we trust the Halsted’s theory (secondary diffusion hypothesis)[63], which do not preclude the systemic theory from Fisher (hematogenous diffusion)[64], both phenomenons probably coexisting, the preponderance of one or the other being related to tumoral characteristics, particularly molecular subtype. The present subject is not to discuss these two hypotheses, but just to remember that recent studies support the Halsted’s hypothesis (sanctuary role of lymph nodes areas), justifying RNI. The NCIC CTG MA20 randomized trial have compared, in patients with “high risk of LRR” BC, after systemic treatment, breast and RNI to breast irradiation only[65]. RNI was associated with a significantly improved LRR-free survival, but also, and above all, an improved distant DFS. There was a trend to better OS (*P* = 0.07), and survival curves diverging after 5 years (“carry-over effect”), it could result in a larger difference with time and a significant impact on survival. The assessment of the risk of positive regional nodes has mainly been studied for internal mammary chain, in relation to tumor characteristics. As expected the first risk factor for accessory nodal involvement is the macroscopic axillary nodal involvement[66-69]. These studies have not assessed the impact of ITCs or micrometastatic disease in the axillary lymph nodes, because they were conducted long before the advent of SLNB.

With the lack of focused studies, and in sofar as pN0(i+) patients are assumed to have a comparable prognosis to pN0 patients, it seems reasonable not to consider RNI only on the basis of ITCs in the SLN. In patients with micrometastatic disease in the SLN (pN1mi), no recommendation can be drawn, since several studies have shown its unfavorable impact. It seems reasonable to consider that if tumor characteristics ask for adjuvant chemotherapy (due to the risk of systemic diffusion), these same characteristics must be considered for a RNI, regional nodes that have no reason to be spared of metastatic diffusion even if mechanisms could be different.

The putative positive impact on survival of RNI in this setting must be weighted against the risk of adverse events. It has, for example, been suggested that RNI increased the dose delivered to the lung, resulting in a significant increase in lung cancer incidence[70].

**CONCLUSION**

The AR rate has been proved to be very low (< 2%), even without cALND, despite a NSLN-positivity proved to range from 10% to 18%, likely in relation to adjuvant treatments such as chemotherapy, hormonal therapy and radiotherapy. In the setting of BCS and MMs in the SLN, the literature data favor the omission of cALND but with a low level of evidence, precluding any definitive conclusion. Axillary irradiation in positive-SLN patients is an alternative to cALND. In pN1mi patients, treated with mastectomy without adjuvant radiotherapy, current data are insufficient to support the omission of cALND.

**REFERENCES**

1 **Goldhirsch A**, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol* 2011; **22**: 1736-1747 [PMID: 21709140 DOI: 10.1093/annonc/mdr304]

2 **Singletary SE**, Greene FL. Revision of breast cancer staging: the 6th edition of the TNM Classification. *Semin Surg Oncol* 2003; **21**: 53-59 [PMID: 12923916]

3 **Giuliano AE**, Hawes D, Ballman KV, Whitworth PW, Blumencranz PW, Reintgen DS, Morrow M, Leitch AM, Hunt KK, McCall LM, Abati A, Cote R. Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. *JAMA* 2011; **306**: 385-393 [PMID: 21791687 DOI: 10.1001/jama.2011.1034]

4 **Weaver DL**, Ashikaga T, Krag DN, Skelly JM, Anderson SJ, Harlow SP, Julian TB, Mamounas EP, Wolmark N. Effect of occult metastases on survival in node-negative breast cancer. *N Engl J Med* 2011; **364**: 412-421 [PMID: 21247310]

5 **Houvenaeghel G**, Classe JM, Garbay JR, Giard S, Cohen M, Faure C, Hélène C, Belichard C, Uzan S, Hudry D, Azuar P, Villet R, Penault Llorca F, Tunon de Lara C, Goncalves A, Esterni B. Prognostic value of isolated tumor cells and micrometastases of lymph nodes in early-stage breast cancer: a French sentinel node multicenter cohort study. *Breast* 2014; **23**: 561-566 [PMID: 24874284 DOI: 10.1016/j.breast.2014.04.004]

6 **Krag DN**, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, Ashikaga T, Weaver DL, Mamounas EP, Jalovec LM, Frazier TG, Noyes RD, Robidoux A, Scarth HM, Wolmark N. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol* 2010; **11**: 927-933 [PMID: 20863759 DOI: 10.1016/S1470-2045(10)70207-2]

7 **van Rijk MC**, Peterse JL, Nieweg OE, Oldenburg HS, Rutgers EJ, Kroon BB. Additional axillary metastases and stage migration in breast cancer patients with micrometastases or submicrometastases in sentinel lymph nodes. *Cancer* 2006; **107**: 467-471 [PMID: 16804924]

8 **Yi M**, Giordano SH, Meric-Bernstam F, Mittendorf EA, Kuerer HM, Hwang RF, Bedrosian I, Rourke L, Hunt KK. Trends in and outcomes from sentinel lymph node biopsy (SLNB) alone vs. SLNB with axillary lymph node dissection for node-positive breast cancer patients: experience from the SEER database. *Ann Surg Oncol* 2010; **17** Suppl 3: 343-351 [PMID: 20853057 DOI: 10.1245/s10434-010-1253-3]

9 **Madsen EV**, Elias SG, van Dalen T, van Oort PM, van Gorp J, Gobardhan PD, Bongers V. Predictive factors of isolated tumor cells and micrometastases in axillary lymph nodes in breast cancer. *Breast* 2013; **22**: 748-752 [PMID: 23313060 DOI: 10.1016/j.breast.2012.12.013]

10 **Cserni G**, Bianchi S, Vezzosi V, van Diest P, van Deurzen C, Sejben I, Regitnig P, Asslaber M, Foschini MP, Sapino A, Castellano I, Callagy G, Arkoumani E, Kulka J, Wells CA. Variations in sentinel node isolated tumour cells/micrometastasis and non-sentinel node involvement rates according to different interpretations of the TNM definitions. *Eur J Cancer* 2008; **44**: 2185-2191 [PMID: 18691877 DOI: 10.1016/j.ejca.2008.06.033]

11 **Cserni G**. Metastases in axillary sentinel lymph nodes in breast cancer as detected by intensive histopathological work up. *J Clin Pathol* 1999; **52**: 922-924 [PMID: 10711258]

12 **Weaver DL**, Le UP, Dupuis SL, Weaver KA, Harlow SP, Ashikaga T, Krag DN. Metastasis detection in sentinel lymph nodes: comparison of a limited widely spaced (NSABP protocol B-32) and a comprehensive narrowly spaced paraffin block sectioning strategy. *Am J Surg Pathol* 2009; **33**: 1583-1589 [PMID: 19730364 DOI: 10.1097/PAS.0b013e3181b274e7]

13 **Meretoja TJ**, Strien L, Heikkilä PS, Leidenius MH. A simple nomogram to evaluate the risk of nonsentinel node metastases in breast cancer patients with minimal sentinel node involvement. *Ann Surg Oncol* 2012; **19**: 567-576 [PMID: 21792511 DOI: 10.1245/s10434-011-1882-1]

14 **Tvedskov TF**, Meretoja TJ, Jensen MB, Leidenius M, Kroman N. Cross-validation of three predictive tools for non-sentinel node metastases in breast cancer patients with micrometastases or isolated tumor cells in the sentinel node. *Eur J Surg Oncol* 2014; **40**: 435-441 [PMID: 24534362 DOI: 10.1016/j.ejso.2014.01.014]

15 **Houvenaeghel G**, Nos C, Mignotte H, Classe JM, Giard S, Rouanet P, Lorca FP, Jacquemier J, Bardou VJ. Micrometastases in sentinel lymph node in a multicentric study: predictive factors of nonsentinel lymph node involvement--Groupe des Chirurgiens de la Federation des Centres de Lutte Contre le Cancer. *J Clin Oncol* 2006; **24**: 1814-1822 [PMID: 16567771]

16 **Meretoja TJ**, Leidenius MH, Heikkilä PS, Boross G, Sejben I, Regitnig P, Luschin-Ebengreuth G, Žgajnar J, Perhavec A, Gazic B, Lázár G, Takács T, Vörös A, Saidan ZA, Nadeem RM, Castellano I, Sapino A, Bianchi S, Vezzosi V, Barranger E, Lousquy R, Arisio R, Foschini MP, Imoto S, Kamma H, Tvedskov TF, Kroman N, Jensen MB, Audisio RA, Cserni G. International multicenter tool to predict the risk of nonsentinel node metastases in breast cancer. *J Natl Cancer Inst* 2012; **104**: 1888-1896 [PMID: 23117131 DOI: 10.1093/jnci/djs455]

17 **Houvenaeghel G**, Nos C, Giard S, Mignotte H, Esterni B, Jacquemier J, Buttarelli M, Classe JM, Cohen M, Rouanet P, Penault Llorca F, Bonnier P, Marchal F, Garbay JR, Fraisse J, Martel P, Fondrinier E, Tunon de Lara C, Rodier JF. A nomogram predictive of non-sentinel lymph node involvement in breast cancer patients with a sentinel lymph node micrometastasis. *Eur J Surg Oncol* 2009; **35**: 690-695 [PMID: 19046847 DOI: 10.1016/j.ejso.2008.10.003]

18 **Cserni G**, Gregori D, Merletti F, Sapino A, Mano MP, Ponti A, Sandrucci S, Baltás B, Bussolati G. Meta-analysis of non-sentinel node metastases associated with micrometastatic sentinel nodes in breast cancer. *Br J Surg* 2004; **91**: 1245-1252 [PMID: 15376203]

19 **Viale G**, Maiorano E, Pruneri G, Mastropasqua MG, Valentini S, Galimberti V, Zurrida S, Maisonneuve P, Paganelli G, Mazzarol G. Predicting the risk for additional axillary metastases in patients with breast carcinoma and positive sentinel lymph node biopsy. *Ann Surg* 2005; **241**: 319-325 [PMID: 15650643]

20 **Tvedskov TF**, Jensen MB, Lisse IM, Ejlertsen B, Balslev E, Kroman N. High risk of non-sentinel node metastases in a group of breast cancer patients with micrometastases in the sentinel node. *Int J Cancer* 2012; **131**: 2367-2375 [PMID: 22344558 DOI: 10.1002/ijc.27499]

21 **Tvedskov TF**, Jensen MB, Balslev E, Kroman N. Robust and validated models to predict high risk of non-sentinel node metastases in breast cancer patients with micrometastases or isolated tumor cells in the sentinel node. *Acta Oncol* 2014; **53**: 209-215 [PMID: 23772767 DOI: 10.3109/0284186X.2013.806993]

22 **Houvenaeghel G**, Bannier M, Nos C, Giard S, Mignotte H, Jacquemier J, Martino M, Esterni B, Belichard C, Classe JM, Tunon de Lara C, Cohen M, Payan R, Blanchot J, Rouanet P, Penault-Llorca F, Bonnier P, Fournet S, Agostini A, Marchal F, Garbay JR. Non sentinel node involvement prediction for sentinel node micrometastases in breast cancer: nomogram validation and comparison with other models. *Breast* 2012; **21**: 204-209 [PMID: 22014859 DOI: 10.1016/j.breast.2011.09.013]

23 **Galimberti V**, Cole BF, Zurrida S, Viale G, Luini A, Veronesi P, Baratella P, Chifu C, Sargenti M, Intra M, Gentilini O, Mastropasqua MG, Mazzarol G, Massarut S, Garbay JR, Zgajnar J, Galatius H, Recalcati A, Littlejohn D, Bamert M, Colleoni M, Price KN, Regan MM, Goldhirsch A, Coates AS, Gelber RD, Veronesi U. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol* 2013; **14**: 297-305 [PMID: 23491275 DOI: 10.1016/S1470-2045(13)70035-4]

24 **Calhoun KE**, Hansen NM, Turner RR, Giuliano AE. Nonsentinel node metastases in breast cancer patients with isolated tumor cells in the sentinel node: implications for completion axillary node dissection. *Am J Surg* 2005; **190**: 588-591 [PMID: 16164927]

25 **Rivers AK**, Griffith KA, Hunt KK, Degnim AC, Sabel MS, Diehl KM, Cimmino VM, Chang AE, Lucas PC, Newman LA. Clinicopathologic features associated with having four or more metastatic axillary nodes in breast cancer patients with a positive sentinel lymph node. *Ann Surg Oncol* 2006; **13**: 36-44 [PMID: 16378156]

26 **Zhou W**, He Z, Xue J, Wang M, Zha X, Ling L, Chen L, Wang S, Liu X. Molecular subtype classification is a determinant of non-sentinel lymph node metastasis in breast cancer patients with positive sentinel lymph nodes. *PLoS One* 2012; **7**: e35881 [PMID: 22563412 DOI: 10.1371/journal.pone.0035881]

27 **Katz A**, Smith BL, Golshan M, Niemierko A, Kobayashi W, Raad RA, Kelada A, Rizk L, Wong JS, Bellon JR, Gadd M, Specht M, Taghian AG. Nomogram for the prediction of having four or more involved nodes for sentinel lymph node-positive breast cancer. *J Clin Oncol* 2008; **26**: 2093-2098 [PMID: 18445838 DOI: 10.1200/JCO.2007.11.9479]

28 **Chen SL**, Hoehne FM, Giuliano AE. The prognostic significance of micrometastases in breast cancer: a SEER population-based analysis. *Ann Surg Oncol* 2007; **14**: 3378-3384 [PMID: 17899293]

29 **de Boer M**, van Dijck JA, Bult P, Borm GF, Tjan-Heijnen VC. Breast cancer prognosis and occult lymph node metastases, isolated tumor cells, and micrometastases. *J Natl Cancer Inst* 2010; **102**: 410-425 [PMID: 20190185 DOI: 10.1093/jnci/djq008]

30 **Lupe K**, Truong PT, Alexander C, Speers C, Tyldesley S. Ten-year locoregional recurrence risks in women with nodal micrometastatic breast cancer staged with axillary dissection. *Int J Radiat Oncol Biol Phys* 2011; **81**: e681-e688 [PMID: 21300456 DOI: 10.1016/j.ijrobp.2010.12.020]

31 **Andersson Y**, Frisell J, Sylvan M, de Boniface J, Bergkvist L. Breast cancer survival in relation to the metastatic tumor burden in axillary lymph nodes. *J Clin Oncol* 2010; **28**: 2868-2873 [PMID: 20458033 DOI: 10.1200/JCO.2009.24.5001]

32 **de Boer M**, van Deurzen CH, van Dijck JA, Borm GF, van Diest PJ, Adang EM, Nortier JW, Rutgers EJ, Seynaeve C, Menke-Pluymers MB, Bult P, Tjan-Heijnen VC. Micrometastases or isolated tumor cells and the outcome of breast cancer. *N Engl J Med* 2009; **361**: 653-663 [PMID: 19675329 DOI: 10.1056/NEJMoa0904832]

33 **Cox CE**, Kiluk JV, Riker AI, Cox JM, Allred N, Ramos DC, Dupont EL, Vrcel V, Diaz N, Boulware D. Significance of sentinel lymph node micrometastases in human breast cancer. *J Am Coll Surg* 2008; **206**: 261-268 [PMID: 18222378 DOI: 10.1016/j.jamcollsurg.2007.08.024]

34 **Gobardhan PD**, Elias SG, Madsen EV, van Wely B, van den Wildenberg F, Theunissen EB, Ernst MF, Kokke MC, van der Pol C, Borel Rinkes IH, Wijsman JH, Bongers V, van Gorp J, van Dalen T. Prognostic value of lymph node micrometastases in breast cancer: a multicenter cohort study. *Ann Surg Oncol* 2011; **18**: 1657-1664 [PMID: 21153885 DOI: 10.1245/s10434-010-1451-z]

35 **van der Heiden-van der Loo M**, Schaapveld M, Ho VK, Siesling S, Rutgers EJ, Peeters PH. Outcomes of a population-based series of early breast cancer patients with micrometastases and isolated tumour cells in axillary lymph nodes. *Ann Oncol* 2013; **24**: 2794-2801 [PMID: 23864096 DOI: 10.1093/annonc/mdt243]

36 **Maaskant-Braat AJ**, van de Poll-Franse LV, Voogd AC, Coebergh JW, Roumen RM, Nolthenius-Puylaert MC, Nieuwenhuijzen GA. Sentinel node micrometastases in breast cancer do not affect prognosis: a population-based study. *Breast Cancer Res Treat* 2011; **127**: 195-203 [PMID: 20680679 DOI: 10.1007/s10549-010-1086-6]

37 **Hansen NM**, Grube B, Ye X, Turner RR, Brenner RJ, Sim MS, Giuliano AE. Impact of micrometastases in the sentinel node of patients with invasive breast cancer. *J Clin Oncol* 2009; **27**: 4679-4684 [PMID: 19720928 DOI: 10.1200/JCO.2008.19.0686]

38 **Imoto S**, Ochiai A, Okumura C, Wada N, Hasebe T. Impact of isolated tumor cells in sentinel lymph nodes detected by immunohistochemical staining. *Eur J Surg Oncol* 2006; **32**: 1175-1179 [PMID: 16979316]

39 **Giuliano AE**, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, Saha S, Hunt KK, Morrow M, Ballman K. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg* 2010; **252**: 426-432; discussion 432-433 [PMID: 20739842 DOI: 10.1097/SLA.0b013e3181f08f32]

40 **Solá M**, Alberro JA, Fraile M, Santesteban P, Ramos M, Fabregas R, Moral A, Ballester B, Vidal S. Complete axillary lymph node dissection versus clinical follow-up in breast cancer patients with sentinel node micrometastasis: final results from the multicenter clinical trial AATRM 048/13/2000. *Ann Surg Oncol* 2013; **20**: 120-127 [PMID: 22956062 DOI: 10.1245/s10434-012-2569-y]

41 **Pepels MJ**, de Boer M, Bult P, van Dijck JA, van Deurzen CH, Menke-Pluymers MB, van Diest PJ, Borm GF, Tjan-Heijnen VC. Regional recurrence in breast cancer patients with sentinel node micrometastases and isolated tumor cells. *Ann Surg* 2012; **255**: 116-121 [PMID: 22183034 DOI: 10.1097/SLA.0b013e31823dc616]

42 **Francissen CM**, Dings PJ, van Dalen T, Strobbe LJ, van Laarhoven HW, de Wilt JH. Axillary recurrence after a tumor-positive sentinel lymph node biopsy without axillary treatment: a review of the literature. *Ann Surg Oncol* 2012; **19**: 4140-4149 [PMID: 22890590 DOI: 10.1245/s10434-012-2490-4]

43 **Naik AM**, Fey J, Gemignani M, Heerdt A, Montgomery L, Petrek J, Port E, Sacchini V, Sclafani L, VanZee K, Wagman R, Borgen PI, Cody HS. The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection: a follow-up study of 4008 procedures. *Ann Surg* 2004; **240**: 462-468; discussion 462-468 [PMID: 15319717]

44 **Rutgers EJ**. Sentinel node biopsy: interpretation and management of patients with immunohistochemistry-positive sentinel nodes and those with micrometastases. *J Clin Oncol* 2008; **26**: 698-702 [PMID: 18258976 DOI: 10.1200/JCO.2007.14.4667]

45 **Haffty BG**, Hunt KK, Harris JR, Buchholz TA. Positive sentinel nodes without axillary dissection: implications for the radiation oncologist. *J Clin Oncol* 2011; **29**: 4479-4481 [PMID: 22042942 DOI: 10.1200/JCO.2011.36.1667]

46 **Giuliano AE**, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall LM, Morrow M. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* 2011; **305**: 569-575 [PMID: 21304082 DOI: 10.1001/jama.2011.90]

47 **Jagsi R**, Chadha M, Moni J, Ballman K, Laurie F, Buchholz TA, Giuliano A, Haffty BG. Radiation field design in the ACOSOG Z0011 (Alliance) Trial. *J Clin Oncol* 2014; **32**: 3600-3606 [PMID: 25135994 DOI: 10.1200/JCO.2014.56.5838]

48 **Belkacemi Y**, Allab-Pan Q, Bigorie V, Khodari W, Beaussart P, Totobenazara JL, Mège JP, Caillet P, Pigneur F, Dao TH, Salmon R, Calitchi E, Bosc R. The standard tangential fields used for breast irradiation do not allow optimal coverage and dose distribution in axillary levels I-II and the sentinel node area. *Ann Oncol* 2013; **24**: 2023-2028 [PMID: 23616280 DOI: 10.1093/annonc/mdt151]

49 **Belkacemi Y**, Bigorie V, Pan Q, Bouaita R, Pigneur F, Itti E, Badaoui H, Assaf E, Caillet P, Calitchi E, Bosc R. Breast radiotherapy (RT) using tangential fields (TgF): a prospective evaluation of the dose distribution in the sentinel lymph node (SLN) area as determined intraoperatively by clip placement. *Ann Surg Oncol* 2014; **21**: 3758-3765 [PMID: 25096388 DOI: 10.1245/s10434-014-3966-1]

50 **Donker M**, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJ, Mansel RE, Cataliotti L, Westenberg AH, Klinkenbijl JH, Orzalesi L, Bouma WH, van der Mijle HC, Nieuwenhuijzen GA, Veltkamp SC, Slaets L, Duez NJ, de Graaf PW, van Dalen T, Marinelli A, Rijna H, Snoj M, Bundred NJ, Merkus JW, Belkacemi Y, Petignat P, Schinagl DA, Coens C, Messina CG, Bogaerts J, Rutgers EJ. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014; **15**: 1303-1310 [PMID: 25439688 DOI: 10.1016/S1470-2045(14)70460-7]

51 **Fisher B**, Dignam J, Mamounas EP, Costantino JP, Wickerham DL, Redmond C, Wolmark N, Dimitrov NV, Bowman DM, Glass AG, Atkins JN, Abramson N, Sutherland CM, Aron BS, Margolese RG. Sequential methotrexate and fluorouracil for the treatment of node-negative breast cancer patients with estrogen receptor-negative tumors: eight-year results from National Surgical Adjuvant Breast and Bowel Project (NSABP) B-13 and first report of findings from NSABP B-19 comparing methotrexate and fluorouracil with conventional cyclophosphamide, methotrexate, and fluorouracil. *J Clin Oncol* 1996; **14**: 1982-1992 [PMID: 8683228]

52 **Kuehn T**, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, Lebeau A, Liedtke C, von Minckwitz G, Nekljudova V, Schmatloch S, Schrenk P, Staebler A, Untch M. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol* 2013; **14**: 609-618 [PMID: 23683750 DOI: 10.1016/S1470-2045(13)70166-9]

53 **Mamounas EP**, Tang G, Fisher B, Paik S, Shak S, Costantino JP, Watson D, Geyer CE, Wickerham DL, Wolmark N. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. *J Clin Oncol* 2010; **28**: 1677-1683 [PMID: 20065188 DOI: 10.1200/JCO.2009.23.7610]

54 **Perez EA**, Romond EH, Suman VJ, Jeong JH, Sledge G, Geyer CE, Martino S, Rastogi P, Gralow J, Swain SM, Winer EP, Colon-Otero G, Davidson NE, Mamounas E, Zujewski JA, Wolmark N. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol* 2014; **32**: 3744-3752 [PMID: 25332249 DOI: 10.1200/JCO.2014.55.5730]

55 **Ram R**, Singh J, McCaig E. Sentinel Node Biopsy Alone versus Completion Axillary Node Dissection in Node Positive Breast Cancer: Systematic Review and Meta-Analysis. *Int J Breast Cancer* 2014; **2014**: 513780 [PMID: 25383226 DOI: 10.1155/2014/513780]

56 **Houvenaeghel G**, Resbeut M, Boher JM. [Sentinel node invasion: is it necessary to perform axillary lymph node dissection? Randomized trial SERC]. *Bull Cancer* 2014; **101**: 358-363 [PMID: 24793627 DOI: 10.1684/bdc.2014.1916]

57 **Mazouni C**, Reitsamer R, Rimareix F, Stranzl H, Uzan C, Garbay JR, Delaloge S, Peintinger F. The positive non-sentinel status is not the main decisional factor for chemotherapy assignment in breast cancer with micrometastatic disease in the sentinel lymph node. *J Surg Oncol* 2012; **106**: 703-707 [PMID: 22674094 DOI: 10.1002/jso.23188]

58 **Aigner J**, Smetanay K, Hof H, Sinn HP, Sohn C, Schneeweiss A, Marmé F. Omission of axillary dissection according to ACOSOG Z0011: impact on adjuvant treatment recommendations. *Ann Surg Oncol* 2013; **20**: 1538-1544 [PMID: 23389469 DOI: 10.1245/s10434-012-2798-0]

59 **Sávolt A**, Polgár C, Musonda P, Mátrai Z, Rényi-Vámos F, Tóth L, Kásler M, Péley G. Does the result of completion axillary lymph node dissection influence the recommendation for adjuvant treatment in sentinel lymph node-positive patients? *Clin Breast Cancer* 2013; **13**: 364-370 [PMID: 23773380 DOI: 10.1016/j.clbc.2013.04.004]

60 **Straver ME**, Meijnen P, van Tienhoven G, van de Velde CJ, Mansel RE, Bogaerts J, Demonty G, Duez N, Cataliotti L, Klinkenbijl J, Westenberg HA, van der Mijle H, Hurkmans C, Rutgers EJ. Role of axillary clearance after a tumor-positive sentinel node in the administration of adjuvant therapy in early breast cancer. *J Clin Oncol* 2010; **28**: 731-737 [PMID: 20038733 DOI: 10.1200/JCO.2008.21.7554]

61 **Montemurro F**, Maggiorotto F, Valabrega G, Kubatzki F, Rossi V, Magistris A, Marocco F, Gatti M, Sarotto I, Aglietta M, Ponzone R. Omission of axillary dissection after a positive sentinel node dissection may influence adjuvant chemotherapy indications in operable breast cancer patients. *Ann Surg Oncol* 2012; **19**: 3755-3761 [PMID: 22805871 DOI: 10.1245/s10434-012-2505-1]

62 **Cody HS**. Does the rapid acceptance of ACOSOG Z0011 compromise selection of systemic therapy? *Ann Surg Oncol* 2012; **19**: 3643-3645 [PMID: 22847121 DOI: 10.1245/s10434-012-2508-y]

63 **Halsted WS**. I. The Results of Radical Operations for the Cure of Carcinoma of the Breast. *Ann Surg* 1907; **46**: 1-19 [PMID: 17861990]

64 **Fisher B**. Laboratory and clinical research in breast cancer--a personal adventure: the David A. Karnofsky memorial lecture. *Cancer Res* 1980; **40**: 3863-3874 [PMID: 7008932]

65 **Whelan TJ**, Olivotto I, Ackerman I, Chapman JW, Chua B, Nabid A. NCIC CTG MA.20: An intergroup trial of regional nodal irradiation in early breast cancer. *J Clin Oncol* 2011; ASCO meeting abstracts; **29**: LBA1003

66 **Handley R**. Natural history of breast cancer. In Harris J, Lippman ME, Morrow M, et al (eds): Diseases of the Breast. Philadelphia, PA, WB Saunders, 1996: 364

67 **Urban JA**. Is there a rationale for an extended radical procedure? *Int J Radiat Oncol Biol Phys* 1977; **2**: 985-988 [PMID: 591417]

68 **Lacour J**, Le M, Caceres E, Koszarowski T, Veronesi U, Hill C. Radical mastectomy versus radical mastectomy plus internal mammary dissection. Ten year results of an international cooperative trial in breast cancer. *Cancer* 1983; **51**: 1941-1943 [PMID: 6339026]

69 **Veronesi U**, Valagussa P. Inefficacy of internal mammary nodes dissection in breast cancer surgery. *Cancer* 1981; **47**: 170-175 [PMID: 7459805]

70 **Deutsch M**, Land SR, Begovic M, Wieand HS, Wolmark N, Fisher B. The incidence of lung carcinoma after surgery for breast carcinoma with and without postoperative radiotherapy. Results of National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials B-04 and B-06. *Cancer* 2003; **98**: 1362-1368 [PMID: 14508821]

**P-Reviewer:** Li LW, Surlin VM **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Table 1 Incidence of micrometastatic lymph-nodes among positive sentinel lymph nodes**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Ref. | Population | *n* | ITCs (%) | MMs (%) | ITCs + MMs | Macrometastases |
| Houvenaeghel *et al*[5] | cT0-2N0 | 2413 | 13 | 33 | 46 | 54 |
| SEER database[8] | Positive SLNB | 26986 | - | 25 | - | 75 |
| Madsen *et al*[9] | cT1-2N0 | 517 | 10 | 24 | 34 | 66 |

SLNB: Sentinel lymph node biopsy; ITC: Isolated tumor cells; MMs: Micrometastases.

**Table 2 Distribution between pN0(i+) and pN1mi**

|  |  |  |  |
| --- | --- | --- | --- |
| Ref. | *n* | ITCs (%) | MMs (%) |
| Houvenaeghel *et al*[5] | 1099 | 28 | 72 |
| van Rijk *et al*[7] | 253 | 42 | 58 |
| Meretoja *et al*[13] | 484 | 43 | 57 |
| Tvedskov *et al*[14] | 1881 | 16 | 84 |

ITC: Isolated tumor cells; MMs: Micrometastases.

**Table 3 Rate of non-sentinel lymph node involved**

|  |  |  |
| --- | --- | --- |
| Ref. | *n* | Rate of positive-NSLN  |
| IHC (%) | ITC (%) | pN1mi (%) | pN1a (%) |
| Houvenaeghel *et al*[15] | 700 | 10.8 | 12.6 | 12 | - |
| Meretoja *et al*[16] | 1000 | 13.9 | 5.8 | 12.2 | 42.6 |
| Viale *et al*[19] | 1228 | - | 14.6 | 21.3 | 50.2 |
| Tvedskov *et al*[20] | 1881 | - | 9 | 18 | - |
| Tvedskov *et al*[21] | 900 | - | 13 | 17 | - |
| Calhoun *et al*[24] | 61 | - | 4.9 | - | - |

NSLN: Non-sentinel lymph node; IHC: Immunohistochemistry; ITC: Isolated tumor cells.

**Table 4 Studies of Prognostic factors for positive-non-sentinel lymph nodes in patients with micrometastasis or isolated tumor cells in sentinel lymph nodes**

|  |  |  |
| --- | --- | --- |
| Ref. | *n* | Prognostic factors for positive NSLNs |
| Tumor grade | Size of positive SLN | Proportion of positive SLN | Molecular subtype | Tumor size | Age | Nb of SLN examined | Presence of LVI | Histologic type | Multicentric tumor | ECE | Tumor location |
| Zhou *et al*[27] | 130(pN1mi 25%) | + | + | + | + | + | - | - | NR | NE | NE | NE | NE |
| Meretoja*et al*[16] | 1000(pN1mi 28%) | - | + | + | + | + | NR | NR | + | - | + | + | NE |
| Houvenaeghel *et al*[17] | 909(pN1mi 100%) | - | + | NR | NR | + | NR | NR | + | + | NE | NE | NE |
| Tvedskov *et al*[20] | 1881(pN1mi 100%) | - | NR | + | + | + | - | - | + | - | - | - | + |

NSLN: Non-sentinel lymph node; SLN: Sentinel lymph node; LVI: Lymphovascular invasion; NR: Not reported.

**Table 5 Recurrence-free survival, disease-specific survival and overall survival according to the burden of axillary positivity**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| LN status | LRR | RFS | DSS | OS |
| pN0/pN0(i+) | = |  | [3,34,36,39] |  | [3,32,34,36,38]  |
| > |  | [4,33] |  | [4] |
| pN0/pN1mi | = |  | [38] |  | [32,37,38] |
| > | [30] | [4,29,32,33,34,36] | [32] | [4,30,29,34] |
| pN0(i+)/pN1mi | = |  | [33] |  |  |
| > |  | [4] |  | [4] |
| pN1mi/pN1 | = |  |  |  |  |
| > |  |  |  | [30] |

LRR: Locoregional recurrence; RFS: Recurrence-free survival; DSS: Disease-specific survival; OS: Overall survival.

**Table 6 Impact of completion axillary lymph node dissection on adjuvant therapy decision-making**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Ref. | *n* | Variable analysed | Results | Conclusion |
| Treatment arm | CT | HT | CT + HT | any | type |
| AMAROS[61] | 566 pN0(i+)pN1mipN1a | Systemic treatments1 | cALND | 58 | 78 | — | — | — | No difference |
| ART | 61 | 76 | — | — | — |
| Absolute difference | 3 | 2 | — | — | — |
| IBCSG 23-01[23] | 931pN0(i+)pN1mi | Systemic therapy | cALND | 9 | 63 | 23 | 95 | — | No difference |
| SLNB | 7 | 67 | 22 | 97 | — |
| Absolute difference | 2 | 4 | 1 | 2 | — |
| Aigner *et al*[59] | 132pN0(i+)pN1mipN1a | Administration of CT and type of CT | cALND | 72.7 | — | — | — | — | Relevant difference (type of CT) |
| SLNB | 77.3 | — | — | — | — |
| Absolute difference | 4.6 | — | — | — | 12.1 |
| AATRM[41] | 233pN1mi | Systemic therapy | cALND | 36.8 | 6.2 | 57 | — | — | No difference |
| SLNB | 40.2 | 9.8 | 51 | — | — |
| Absolute difference | 3.4 | 3.6 | 6 | — | — |
| Sávolt *et al*[60] | 474pN0(i+)pN1mipN1a | Systemic therapy | cALND | 78 | 87 | 65 | — |  | No difference |
| ART | 69 | 89 | 58 | — |  |
| Absolute difference | 9 | 2 | 7 | — |  |
| Montemurro *et al*[62] | 321pN0(i+)pN1mipN1a | Adjuvant chemotherapy | cALND | 62 | — | — | — | — | Relevant difference |
| SLNB | 52 | — | — | — | — |
| Absolute difference | 10 | — | — | — | — |

1Proportion of patients treated with adjuvant systemic therapy, based on Adjuvant!

Absolute differences in proportion of prescriptions appear in grey. cALND: Completion axillary lymph node dissection; CT: Chemotherapy; HT: Hormonal therapy; SLN: Sentinel lymph node; SLNB: Sentinel lymph node biopsy; ART: Axillary radiation therapy.