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MINIREVIEWS

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

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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.

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

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.

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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 immuno-histochemistry 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). Zhou *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

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
Yi *et al*[8]	Positive SLNB	26986	-	25	-	75
Madsen *et al*[9]	cT1-2N0	517	10	24	34	66

SEER: Surveillance, epidemiology and end results; 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.

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 population-based analysis including 209720 patients treated between 1992 and 2003, a micrometastatic node has been shown to carry a prognosis intermediate to pN0 (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

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*[26]	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; ECE: Evaluable capsular effraction; NR: Not reported; NE: Non evaluable.

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]	[4,29,30,34]
pN0(i+)/pN1mi	=		[33]		
	>		[4]		[4]
pN1mi/pN1	=				
	>				[30]

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

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%-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 ($\leqslant$ 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 *vs*

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 loco-regional 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%-19.1%) for patients treated with placebo and 7.7% (95%CI: 5.7%-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 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 emphasizing 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

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	
Montemurro *et al*[61]	566 pN0(i+)	Systemic treatments[1]	cALND	58	78	-	-	-	No difference
	pN1mi		ART	61	76	-	-	-	
	pN1a		Absolute difference	3	2	-	-	-	
Galimberti *et al*[23]	931 pN0(i+)	Systemic therapy	cALND	9	63	23	95	-	No difference
	pN1mi		SLNB	7	67	22	97	-	
			Absolute difference	2	4	1	2	-	
Aigner *et al*[58]	132 pN0(i+)	Administration of CT and type of CT	cALND	72.7	-	-	-	-	Relevant difference (type of CT)
	pN1mi		SLNB	77.3	-	-	-	-	
	pN1a		Absolute difference	4.6	-	-	-	12.1	
Pepels *et al*[41]	233 pN1mi	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*[59]	474 pN0(i+)	Systemic therapy	cALND	78	87	65	-		No difference
	pN1mi		ART	69	89	58	-		
	pN1a		Absolute difference	9	2	7	-		
Montemurro *et al*[61]	321 pN0(i+)	Adjuvant chemotherapy	cALND	62	-	-	-	-	Relevant difference
	pN1mi		SLNB	52	-	-	-	-	
	pN1a		Absolute difference	10	-	-	-	-	

[1]Proportion 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; SLNB: Sentinel lymph node biopsy; ART: Axillary radiation therapy.

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.

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