

# Axillary management still needed for patients with sentinel node micrometastases

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**Abstract:** More attention has been paid to the axillary management over the past 50 years, and clinical practice has been changed as results of the random controlled trials. The American College of Surgeons Oncology Group Z0011 and International Breast Cancer Study Group (IBCSG) 23-01 trials provided high-level evidence to support the omission of axillary lymph nodes dissection (ALND) in sentinel lymph node (SLN)-positive patients receiving breast-conserving surgery (BCS) and adjuvant systemic treatment. In patients treated with BCS, whole breast irradiation (WBI) with tangential fields could lead to substantial axillary irradiation and control the residual tumor burden in axilla, whereas (intraoperative) partial breast irradiation has no therapeutic effect on these residual axillary metastases. In the observation group of the IBCSG 23-01 trial, 425 patients received BCS and 80 (18.8%) of them just underwent intra-operative radiotherapy. While the 10-year axillary recurrence rate was acceptable low (1.7%, 8/467) in the no ALND group, it was 4.5% (6/134) in patients without axillary management, which was significantly higher than that of 0.6% (2/333) in patients with axillary management ( $P=0.0024$ ). Should we accept an axillary recurrence rate as high as 4.5% in patients with only SLNs micrometastases? What is the best way to control the residual tumor burden in the axilla and decrease the recurrence rate if there is no ALND? The evidence showed that both WBI after BCS (Z0011, AATRM [Agència d'Avaluació de Tecnologia i Recerca Mèdiques]) and axillary regional nodal irradiation after mastectomy/BCS OTOASOR (Optimal Treatment Of the Axilla - Surgery Or Radiotherapy), AMAROS (After Mapping of the Axilla: Radiotherapy Or Surgery) could control the regional residual tumor burden when the SLN is positive and an ALND is omitted. In the modern era, systemic therapy could further decrease the risk of local/regional recurrences. After the subanalysis of the POSNOC (POSitive Sentinel NOde: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy), SERC (Sentinelle Envahiet Randomisation du Curage), and Dutch BOOG (BORstkanker Onderzoek Groep) trials, a prediction model might be established to identify those patients who could benefit from no axillary management as a guide to clinical practice. At present, axillary management should still be required for patients with SLN micrometastases.

**Keywords:** breast cancer, sentinel lymph node biopsy, micrometastasis, axillary treatment

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The 10-year results of American College of Surgeons Oncology Group Z0011 trial showed that cT1-2N0 breast cancer with one to two positive sentinel lymph nodes (SLNs) undergoing breast-conserving surgery (BCS) and whole breast irradiation (WBI) could omit axillary lymph nodes dissection (ALND), which provided evidence to change the clinical practice.<sup>1</sup> In the post-Z0011 era, Galimberti et al presented the 10-year outcomes of the International Breast Cancer Study Group (IBCSG) 23-01 trial, which provided additional evidence to support ALND omission in patients with one

or more micrometastatic ( $\leq 2$  mm) SLNs, tumor size  $\leq 5$  cm, and receiving BCS and adjuvant systemic therapy.<sup>2</sup> These two clinical trials provided high-level evidence to support changes of National Comprehensive Cancer Network Guidelines since 2017<sup>3</sup> and resulted in the “standard of care” practice in the surgical management of the axillary lymph nodes by breast surgeon.<sup>4</sup> An important difference in the study design and conclusion between Z0011 and IBCSG 23-01 trials is the application of radiotherapy, in which Z0011 required that WBI should be followed by BCS but IBCSG 23-01 did not. WBI has an important effect on the axillary control in patients with positive SLNs who underwent BCS without ALND.

Although 27.3% of patients had metastatic non-SLNs in the Z0011 trial, which means a similar percentage of patients had metastatic nodes that were not surgically excised in the SNL biopsy (SLNB) alone group, the port design of WBI with tangential fields could led to substantial axillary irradiation and control the residual tumor burden in axilla.<sup>1</sup> The radiation field of Z0011 trial showed that some patients received high tangential irradiation fields, which means more prescribed dose delivered to lymph nodes (Table 1).<sup>5,6</sup> However, (intraoperative) partial breast irradiation alone used in 27% of patients in the IBCSG 23-01 trial could not have made any therapeutic effect on the residual axillary metastases.<sup>7</sup> In the observation group (ie, those with ALND omission) of IBCSG 23-01, 425 patients received BCS in which 80 (18.8%) just underwent intraoperative radiotherapy (ie, single-dose intraoperative radiotherapy with electrons in breast).<sup>2</sup> After a 10-year follow-up, 5 of these 80 patients (6.3%) with intraoperative partial breast irradiation alone had an ipsilateral axillary recurrence,<sup>2,7</sup> which is totally different from that of the Z0011 trial, which had only five (0.9%) axillary relapse in the SLNB + WBI group with 10-year follow-up. In the group of ALND omission, there were 12 cases without radiotherapy in patients with BCS, 42 cases without ALND in patients with mastectomy, but 333 cases receiving axillary treatment (WBI). The total axillary recurrence rate was 1.7% (8/467), which is still acceptable low, but the axillary recurrence rate was 4.5% (6/134) in patients without axillary management, which was significantly higher than that of 0.6% (2/333) in patients with axillary management

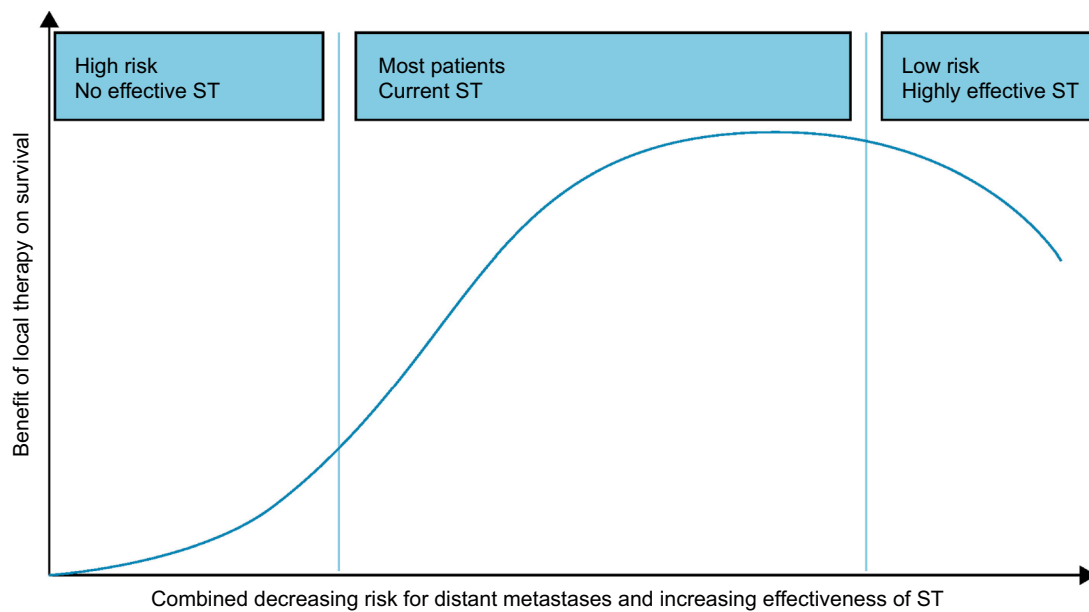
( $P=0.0024$ ). Should we accept an axillary recurrence rate as high as 4.5% in patients with only SLNs micrometastases?

The residual tumor burden in the axilla is a serious risk factor to lead axillary failure, and more attention should be paid. Patients with SLN micrometastases might have a low axillary disease burden, but it does not mean there is no additional axillary node involvement. In Z0011 trial, 10% of patients with SLN micrometastases were found to have macrometastases in the non-SLNs after ALND.<sup>1</sup> In the AATRM (Agència d’Avaluació de Tecnologia i Recerca Mèdiques) 048/13/2000 trial, 13% (15/112) of patients with SLN micrometastases identified additional positive node after ALND.<sup>8</sup> Also, 13% of patients identified additional involved axillary lymph nodes after ALND in this IBCSG 23-01 study.<sup>2</sup> What is the best way to control the residual tumor burden in the axilla if there is no ALND? The evidence from clinical trials showed that both WBI after BCS (Z0011<sup>1</sup>, AATRM<sup>8</sup>) and axillary regional nodal irradiation (RNI) after mastectomy/BCS OTOASOR (Optimal Treatment Of the Axilla - Surgery Or Radiotherapy),<sup>9</sup> AMAROS (After Mapping of the Axilla: Radiotherapy Or Surgery)<sup>10</sup> could control the regional residual tumor burden when the SLN is positive and an ALND is omitted.

Systemic therapy will decrease the risk of local/regional recurrences and distant metastasis in the era of molecular subtype-guided adjuvant system therapy (Figure 1).<sup>11</sup> However, with optimized systemic therapy guided by molecular subtypes, all patients with SLN micrometastases may not need ALND or axilla RNI. Currently, there are three ongoing clinical trials aiming to evaluate whether axilla management could be omitted in patients receiving modern-era therapy. The POSNOC (POSitive Sentinel NODE: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy) trial (NCT 02401685) will assess whether systemic therapy alone is noninferiority to systemic therapy plus axillary treatment (dissection or irradiation) to control the residual tumor burden in early stage breast cancer with one or two SLN macrometastases.<sup>12</sup> The SERC (Sentinelle Envahiet Randomisation du Curage) trial will randomly assign to observation only or ALND with positive SLN and demonstrate the noninferiority of ALND omission

**Table 1** Comparison of the average dose delivered to levels I–III in the standard and the high tangential irradiation fields

Axillary nodes	Prescribed dose		95% Prescribed dose	
	Standard tangents	High tangents	Standard tangents	High tangents
Level I	66%	86%	51%	79%
Level II	44%	71%	26%	51%
Level III	31%	73%	15%	49%



**Figure 1** Combined hypothetical benefit of local tumor control on survival with increasing effectiveness of systemic therapy (ST) and decreasing risk of distant metastases of the primary tumor.

**Notes:** Patients in the left part of the slope have high-risk disease without effective systemic therapy and are not expected to benefit from improving locoregional treatments. For patients in the right part of the slope, treatment deintensification (surgery, radiation, or systemic therapy) might be appropriate. The middle group will represent most past and current patients with breast cancer, for whom an optimum multidisciplinary approach results in the greatest benefit.

vs ALND.<sup>13</sup> The Dutch BOOG (BORstkanker Onderzoek Groep) 2013-07 trial (NCT 02112682) will investigate whether completion axillary treatment can be safely omitted in SLN-positive breast cancer patients treated with mastectomy.<sup>14</sup> After the subanalysis of these trials, a prediction model might be established to identify the patients who can benefit from no axilla management as a guide to clinical practice. In our opinion, axillary management should still be required at the present time for patients with SLN micrometastases, ie, either WBI after BCS and axillary RNI or surgical dissection after mastectomy.

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## Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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