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Adjuvant nodal radiotherapy in the era of sentinel node biopsy staging of breast cancer: A review of published guidelines and prospective trials and their implications on clinical practice

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1. Introduction

Metastasis to the axillary lymph nodes (ALN) is a major prognostic factor in early-stage breast cancer (BC) (De Boer et al., 2010). Traditionally, nodal involvement, along with other clinicopathologic factors, have been used to guide decisions for adjuvant locoregional therapy including radiotherapy (RT). Over the past decade, the management of the axilla has shifted from axillary lymph node dissection (ALND) to sentinel lymph node biopsy (SLNB) as the standard of care for the majority of patients with clinically node-negative (cN0), early-stage disease. Data from randomized trials have cohesively provided strong evidence that ALND can be omitted when the SLNB is negative, or involvement is limited to 1 or 2 metastases, given the low risk of axillary relapse (Giuliano et al., 2010; Krag et al., 2010; Galimberti et al., 2013). For more extensive axillary disease involvement detected by SLN biopsy, ALND remains standard of care in the majority of patients. More recent data suggest that ALND may be omitted in selected patients without detrimental effect on regional control or survival (Wazir et al., 2014). The evolution from ALND to SLNB has raised new questions, especially among radiation oncologists, with regards to regional nodal irradiation (RNI) indications in cases of SLN-positive disease when ALND has not been performed. Furthermore, recent data from randomized trials report improvements in distant metastasis-free survival after RNI, with the aim of "stopping metastases at their source", (Hellman, 1997) namely in the nodes, which have added to the complexity of regional nodal management and selection criteria for RNI use and volume definition (Whelan et al., 2015; Poortmans et al., 2015; Budach et al., 2013; Jagsi et al., 2014). In this review, we will discuss the potential impact of recently published data and updated clinical practice guidelines.

2. Methods

To conduct this review, a literature search was performed using MEDLINE database from 2000 to 2015. The aim was to select prospective randomized studies, meta-analyses, systematic reviews on RNI and published guidelines for clinical practice in terms of indications for adjuvant RNI and nodal RT volume definition after SLNB and/or ALND. The search was performed, initially by using the terms "regional nodal irradiation" and "breast cancer". Subheadings were searched with "supraclavicular", "internal mammary chain", "internal mammary nodes", "axilla", "breast radiotherapy" or "breast guidelines" as major terms. Then, "nodal radiotherapy" was searched in combination with "sentinel lymph node biopsy" or "axillary lymph node dissection". Full text articles were retrieved and reviewed for the selected titles and abstracts with particular attention to contemporary randomized trials and recent international/national guidelines.

3. Results

3.1. Prospective surgical trials

3.1.1. Sentinel lymph node biopsy versus axillary lymph node dissection trials

The *National Surgical Adjuvant Breast and Bowel* Project (NSABP) B 32 trial (n = 3986) was one of the randomized trials which established that ALND was not required for cN0 patients with a negative SLNB. This trial demonstrated that the outcome of SLNB-staged pN0 patients (n = 2011) was equivalent to those undergoing full ALND (n = 1975) after mainly breast conserving therapy (n = 3490) (Krag et al., 2010). At 8 years of follow-up, differences in overall survival (OS), disease free survival (DFS), and loco-regional relapse were not signficant in patients with pN0 disease irrespective of whether ALND was performed or not. The presence of micrometastasis (in 793 and 829 of SLNB and ALND staged patients, respectively) was demonstrated to adversely impact outcomes. Two additional trials, (Giuliano et al., 2010; Galimberti et al., 2013) have similarly assessed SLNB vs ALND in $pN0_{(sn)}$ patients, and also support the omission of ALND when SLNB is negative.

The design of surgical trials for axillary management has progressed to compare the outcomes of patients with metastases in SLN with or without ALND and determine whether ALND may be omitted in patients with SLN positive disease. The American College of Surgeons Oncology Group (ACOSOG)Z0011 trial (Giuliano et al., 2010) included patients with cN0, stage T1-T2, with 1 or 2 positive SLN, randomized to ALND (n = 420) versus no ALND (n = 436). All subjects received whole breast irradiation (WBI) using tangential fields (TgF) after breast conserving surgery (BCS). After 6.3 years of follow-up, no statistically significant differences were observed in OS or progression free survival (PFS) between the two groups. The authors concluded that ALND may not be needed in patients with T1-2 stage tumors and 1 or 2 positive SLN, treated with adjuvant breast irradiation and systemic therapy.

The International Breast Cancer Study Group (IBCSG) trial 23-01 evaluated ALND in patients with micrometastases in SLN. This 2-arm study (ALND, n = 465 vs no ALND, n = 469) (Galimberti et al., 2013), consistently demonstrated no difference in outcomes when ALND was omitted for patients with pN_{mic} disease. To provide an overview of the patients evaluated in the trials that evaluate axillary surgical management in the SLNB era, Table 1 summarizes the characteristics and differences between the IBCSG 23-01 and ACOSOG Z0011 trials. Nodal burden was lower in the IBCSG 23-01 study than ACOSOG Z0011. The IBCSG 23-01 study limited enrollment to patients with micrometastases or isolated tumoral cells while ACOSOG Z0011 allowed micro or macrometastatic disease. Additionally, in the IBCSG study, 95% of patients had only one positive SLN whereas in the SLN group of the ACOSOG Z0011 trial, a single positive node was detected in 68% of the patients. One important difference between these two studies was that IBCSG 23-01 study allowed enrollment of patients undergoing mastectomy (9%) or partial breast irradiation (PBI) (19%). Finally, while the IBCSG 23-01 trial supports omission of ALND for the selected group of patients with small, estrogen receptors (ER) positive tumors undergoing BCS with planned WBI, it suggests that the effect of omitting ALND in SLN positive patients undergoing total mastectomy or PBI warrants further investigation. In the lasts, no data are available in the literature.

With respect to the radiotherapy (RT) volumes used in the ACOSOG Z0011 trial, subsequent analyses of radiation fields delivered suggest that a substantial proportion of patients received RT that either encompassed the low axilla in the TgF or received directed nodal RT. However, without RT quality assurance for this study, the ability to draw conclusions about which nodal regions require RT when axillary dissection is omitted remains unclear.

3.1.2. The use of radiotherapy as an alternative to axillary lymph node dissection

The Phase III AMAROS (***A**fter **M**apping of the **A**xilla: **R**adiotherapy **O**r **S**urgery?*) trial (Donker et al., 2014) compared the efficacy of axillary lymph node (including the supra-clavicular (SC) fossa) RT (ALN/SC-RT) versus ALND. In this trial, 1425 patients with clinical T1-2N0 breast cancer with 1–2 positive SLN (including 40% with micro-metastases or isolated tumor cells) were randomized to either ALND or comprehensive ALN/SC-RT. At 5 years, no differences were observed in loco-regional recurrence or OS. However, the lymphedema rate was twice as frequent in the ALND arm versus the ALN/SC-RT arm at 5 years (23% vs 11%, $p < 0.0001$). Of note, among patients who underwent ALND, 67% had no additional

Table 1
Comparisons of Characteristics of the ACOSOG Z0011 and IBCSG 23-01 Trials.

Trial	ACOSOG Z0011 (Giuliano et al., 2010)	IBCSG 23-01 (Galimberti et al., 2013)
Number of patients randomized	891 (target = 1900)	934 (target = 1960)
Number of patients enrolled	856	931
Number of institutions	115	27
Eligibility criteria	Micro and macrometastases	Only micrometastases
SLN involvement	Patients with matted nodes, gross extranodal and ≥3 SLNs should be excluded	
Primary outcome	Overall survival	Disease-free survival
Median follow-up (years)	6.3	5
Micrometastasis in both SLN and ALND	41% (301/731)	98% (909/930)
Single positive SLN*	68% (295/436)	96% (450/467)
Solitary positive LN#	65% (494/758)	88% (819/931)
Breast conserving surgery followed by partial breast radiation	0	19% (159/823)
Total mastectomy	0	9% (86/931)
Chemotherapy	58%	30% (285/931)
Endocrine therapy	46%	88% (817/931)

Abbreviations: SLN: sentinel lymph node.
*information limited to SLN only arm.
#information includes both arms.

Table 2
Description and results of axillary volume irradiation in ACOSOG Z0011 and AMAROS trials.

Criteria	ACOSOG Z0011 (Giuliano et al., 2010)	AMAROS trial (Donker et al., 2014)
N	891	1425
Randomization	SLNB only vs SLNB + ALND	ALND vs ALN-RT
Type of surgery	BCS (100%)	BCS (89%) and TM (11%)
pN status	SLNB only SLNB + ALND (n = 436) (n = 420)	ALND arm ALN-RT arm (n = 744) (n = 681)
Isolated tumor cells	–	87 (12%) 67 (10%)
Micrometastases	164 (44.8%) 137 (37.5%)	215 (29%) 195 (29%)
Macrometastatses	202 (55.2%) 228 (62.5%)	442 (59%) 419 (61%)
Unknown	55 70	–
Radiotherapy	WBI using TgF partially covering axillary nodes	ALN-RT covered all three levels of the axilla and the medial part of the supraclavicular fossa
Outcome endpoints		
DFS and OS	No difference	No difference
Lymphoedema	Not assessed	Increased in ALND arm (vs ALN-RT arm)
Implications for RT consideration in 1–2 positive SLN	ALND not needed in case of WBI with TgF and systemic therapy	ALN-RT is an option to ALND

Abbreviations: ALND: axillary lymph node dissection; SLNB: sentinel lymph node biopsy; BCS: breast conserving surgery; TM: total mastectomy; WBI: whole breast irradiation; TgF: tangential fields; ALN-RT: axillary lymph node radiotherapy; pN: pathologic nodal status; DFS: disease free survival; OS: overall survival.

positive nodes, 25% had 1–3 additional positive nodes and 8% had 4 additional positive nodes (Table 2).

3.2. Prospective regional nodal irradiation trials

3.2.1. Radiation to the internal mammary chain (IMC)

3.2.1.1. NCIC-CTG MA20 trial. In 2015, the National Cancer Institute of Canada Clinical Trial Group (NCIC-CTG) MA20 trial was published after a median follow-up time of 9.5 years (Whelan et al., 2015). In this multicentre trial, 1832 patients who underwent BCS and sytemic therapy were randomized to receive WBI alone (n = 916) versus WBI plus RNI (including IMC and SC/level III axilla in all patients and the entire axilla in selected patients; n = 916). Among patients randomized to RNI, the SC fossa and IMC in the first 3 intercostal spaces were encompassed in all subjects, while the extent of axillary coverage was determined according to the number of positive and dissected nodes. A small proportion of enrolled patients (10%) had high-risk node-negative (pN0) disease (defined as tumors > 2 cm with ≤ 10 nodes removed, plus at least one of the following features: grade III, lymphovascular invasion, ER negative). Among the patients, 85% had 1–3 positive nodes and 5% had ≥ 4 positive nodes. At 10 years, RNI was associated with improved loco-regional relapse-free survival (95.2% vs. 92.2%; p = 0.009), distant metastasis-free survival (DMFS) (86.3% vs. 82.4%; p = 0.03) and DFS (82.0% vs. 77.0%; p = 0.01). There was no significant difference in OS between the RNI and control groups (82.8% and 81.8%; p = 0.38) (Whelan et al., 2015). However, there was a significant difference in OS in a preplanned subset analysis among patients with ER-negative disease. While the MA20 data suggest a demonstrable benefit with RNI, it cannot differentiate which irradiated nodal basins have led to the improvement in DFS. Furthermore, the treatment effect was associated mainly with a reduction in the rate of regional recurrence. Among patients who experienced nodal relapse, the majority (63%) occurred in the axillary nodes and 27% occurred in the supraclavicular nodes (Whelan et al., 2015).

As the number of patients with node-negative was relatively small, the application of these results to patients with pN0, pN0i+, and pNmic disease remains unclear. Moreover, extrapolation of the MA20 trial data to patients who undergo SLNB alone must be done with caution: only 39% of patients on this trial initially underwent initial SLNB, and the protocol stipulated full ALND for those with SLN positive disease. The median number of lymph nodes removed in this study was 12 and two-thirds had > 10 nodes removed.

3.2.1.2. EORTC 22922 trial. The *European Organisation for Research and Treatment of Cancer (EORTC 22922-10925)* trial evaluated elective RT to the IMC and medial SC fossa in conjunction with WBI after BCS or chest wall RT after mastectomy (Poortmans et al., 2015).

Table 3
Results of published trials evaluating nodal irradiation according to extent of axillary nodal involvement.

Criteria	Randomized trials of nodal irradiation			
Trials	MA20 trial (Whelan et al., 2015) BCS N = 1832	EORTC (Poortmans et al., 2015) BCS/TM * N = 4004	French trial TM (Hennequin et al., 2013) N = 1334	German Metaanalysis N = 7170 (Budach et al., 2013)
Inclusion criteria and radiation parameters in the trials				
RT volumes	WBI + IMC + SCN + ALN vs. WBI alone	WBI/CWI + IMC + SCN vs. WBI/CWI alone	All patients had CWI + SCN and randomized to IMC RT vs no IMC Rt	–
Dose to RNI	Breast and IMC: 50 Gy in 25 fr (80% of the dose to IMC) # SCN and ALN: 45 or 50 Gy in 25 fr	IMC and SCN: 50 Gy in 25 fr	Ô50 Gy in 25 fr to IMC	–
Benefit with RNI according to pN status				
Rate of pN0	10%	44%	25%	33%
Benefit in pN0	Unknown due to small sample	Benefit in Inner/central tumors	No Benefit	*Benefit: DFS, DMFS,OS*
Micrometastasis in SLN	ND	ND	ND	–
Macrometastasis in SLN	Unknown among pN1a (85%)	Unknown among pN1a (43%)	Unknown among pN1a (75%)	–
Rate of pN+	90%	56%	75%	67%
Impact of RNI on outcome	Benefit: - LRRFS - DFS, - DMFS - Trend for OS	Benefit: - DFS - DMFS - Trend for OS	No Benefit	Benefit: - DFS, - DMFS - OS

Abbreviations: *TM: total mastectomy;* WBI: whole breast irradiation; IMC: internal mammary chain; SCN: supraclavicular nodes; ALN: axillary lymph nodes; CWI: chest wall irradiation; RNI: regional nodal irradiation; RT: radiotherapy; fr: fractions; ND: not done; SLN: sentinel lymph node; pN: pathologic nodal status; DFS: disease free survival; OS: overall survival; DMFS: distant metastasis free survival; LRRFS: locoregional recurrence free survival.
*TM patients in the EORTC trial: *23.9% of the patients.*
RT to supraclavicular/axillary nodes in MA20 trial: The dose to the anterior supraclavicular and axillary field was 50 Gy in 25 fractions prescribed at a depth of 3 cm. For patients who were treated with anterior and posterior fields, a dose of 45 Gy in 25 fractions was prescribed at mid-separation at the center of the fields.
Ô The prescribed dose of irradiation to the target volumes was 50 Gy or equivalent. The first 5 intercostal spaces were included in the IM target volume, and two-thirds of the dose (31.5 Gy) was given using electrons.

Between 1996 and 2004, 4004 patients were enrolled with either node positive (55.6%) and/or inner/central tumors (44.4%) following BCS (76%) or total mastectomy (24%). Of note, the rate of pN0 in the EORTC trial was higher than in the MA20 trial (44% versus 10%). With total mastectomy, chest wall RT was delivered simultaneously with RNI in 76% of patients. A total of 7.4% of the patients in the control group and 8.3% of the patients in the RNI group underwent RT encompassing the level I–II axilla. The vast majority of patients (84.4%) received systemic chemotherapy (all N+ and two-third of N- patients). Like the MA.20, IMC-RT was directed to the first three intercostals; however for lower inner quadrant tumors the first five intercostals were included.

The rate of any first recurrence of BC at 10 years was 19.4% in the RNI group, as compared with 22.9% in the control group ($p = 0.02$). The 10-year DFS and DMFS were 72% and 78% in the RNI group versus 69% and 75% in the control group ($p = 0.04$ and $p = 0.02$, respectively). At 10 years, the rate of death from BC was 12.5% in the RNI patients and 14.4% in the control group ($p = 0.02$). The 10-year OS rates were 82.3% and 80.7% in the RNI and control groups, respectively ($p = 0.06$). The benefit was of borderline significance with simultaneous adjustment for the stratification factors ($p = 0.05$). Finally, the number of patients needed to treat to avoid respectively one relapse and one death from BC were 30 and 39 for the entire patient population.

As in the MA20 trial, the EORTC trial suggested that RNI was beneficial for women with early-stage BC with respect to BC-specific outcomes although the difference in OS did not reach statistical significance at 10 years of follow-up. Acute side effects were minimally increased, and the rate of death from causes other than BC was not elevated with RNI. The limitations of this trial as acknowledged by the authors included non-contemporary BC subtype classification and systemic therapy delivery since the study was initiated in the early 1990s, and that individual contribution of IMC-RT compared with SCN-RT in improving outcomes was not measurable. Similar to the MA20 trial, these results are not applicable to patients undergoing SLNB alone, as only 7% underwent SLNB, with the vast majority having undergone the protocol- specified ALND.

3.2.1.3. French trial of IMC-RT. The only multicentre trial investigating the impact of IMC-RT on outcome was reported by Hennequin et al. in patients undergoing total mastectomy and ALND (Hennequin et al., 2013). This trial enrolled 1334 patients undergoing chest wall and SCN-RT randomized to receive IMC-RT (first five intercostals) or no IMC-RT. At 10 years, there was no difference in OS between the 2 study arms (IMC-RT: 62.6% vs. no IMC-RT: 59.3%; $p = 0.8$). The investigators conceded that the results were inconclusive because the study was underpowered. Furthermore, toxicity data were lacking (Hennequin et al., 2013). Therefore, there remains insufficient data to elucidate the effects of individual RT volumes (IMC vs. SC vs. axilla) on disease control and survival.

3.2.1.4. German meta-analysis. Budach et al. (Budach et al., 2013) reported a meta-analysis that included MA20, EORTC 22922 and the IMC-French trials, which suggested that RNI was associated with improved OS with the most significant advantage observed in improved DMFS. Finally this meta-analysis reported similar results as those showed in the MA20 and EORTC trials taken individually (Whelan et al., 2015; Poortmans et al., 2015). RT to the SC/IMC (MA20 and EORTC) was associated with significant improvements in DFS (HR 0.85) and DMFS (HR 0.82). Adding the results of the French trial (Hennequin et al., 2013) and using the random effects model to respect the different design of the French trial, the effect on OS of RNI was still significant (HR 0.88) (Table 3).

Table 4
Regional nodal irradiation indications by nodal site as recommended in published guidelines

Nodal status	National Guidelines	International Guidelines and Consensus
pN0 in SLNB or ALND	RNI is not recommended (Belkacemi et al., 2011; Sautter-Bihl et al., 2014)	- pN0 after TM + ALND: RNI recommended in case of large tumor size (> 5 cm) and/or margins size (Gradishar et al., 2016) Or - RNI not recommended (Senkus et al., 2013)
Micro and Macro metastasis in SLNB without ALND	ALN-RT recommended - 1–2 SLNs + - Micrometastasis - Macrometastases when no ALND (Belkacemi et al., 2011; Sautter-Bihl et al., 2014)	ALN-RT recommended in case of 1–2 positive SLN without ALND and WBI (tangential fields) (Lyman et al., 2014; Gradishar et al., 2016)
1–3 N+ after ALND	- SCN-RT + IMC-RT recommendeded (Belkacemi et al., 2011; Sautter-Bihl et al., 2014) - ALN-RT recommended if nodal involvment ≥3 N+ (Belkacemi et al., 2011)	- SCN-RT+/− IMC-RT recommended (Lyman et al., 2014) - Or - SCN-RT recommended and "consider strongly" IMC-RT (Gradishar et al., 2016)

Abbreviations: ALND: axillary lymph node dissection; TM: total mastectomy; RT: radiotherapy; RNI: regional nodal irradiation; SCN-RT: supraclavicular radiotherapy; IMC-RT: Internal mammary chain radiotherapy; ALN-RT: axillary lymph node radiotherapy; pN: pathologic nodal status; WBI: whole breast irradiation.

3.2.1.5. Supraclavicular fossa irradiation. In the EORTC 22922 and NCIC MA20 trials, RNI encompassed SC and IMC volumes. In the French post-mastectomy RT (PMRT) trial, all patients had SCN-RT and the randomisation was specifically IMC versus no IMC irradiation. None of these trials could answer to the question of the impact on outcome of elective irradiation of SCN alone vs. IMC alone.

The high risk of recurrence and metastatic spread from residual disease in the SCN is a strong rationale for SCN-RT indication in pN1 patients (Yu et al., 2010). For example, when considering patients with 1–3N+, SCN recurrence is associated with reduced survival of 18% at 10 years. Thus, increased use of SCN-RT in this subgroup of patients has been reported (Yates et al., 2012; Wai et al., 2010; Ragaz et al., 2005).

3.3. Existing published international guidelines (Table 4)

3.3.1. Existing published guidelines for ALN-RT

3.3.1.1. North America. In the SLNB era, the American Society of Clinical Oncology recently published the following recommendations (Lyman et al., 2014): (i) Patients with one or two positive SLN on biopsy who are intending on receiving adjuvant WBI should not undergo additional ALND due to additional morbidity; (ii) Axillary recurrence rates are low following RT without ALND (1.19%). It is important to recognize that while these recommendations, which are based on the aforementioned randomized trials, suggest no difference in outcomes for selected patients when ALND is omitted, they neither guide radiation oncologists in the design of their treatment fields nor help them in determining whether or not to intentionally include axillary levels II and III in the setting where ALND is omitted (Donker et al., 2014).

In the adjuvant setting either after BCS or TM, the recent update of 2016-NCCN guidelines, (Gradishar et al., 2016) states to "strongly consider RT to infraclavicular, supraclavicular area, internal mammary nodes, and any part of the axillary bed at risk" in 1–3 positive patients. However, there are still no NCCN recommendations specifically for ALN-RT.

3.3.1.2. Europe. After ALND, the *French recommendations* were in favor of ALN-RT only for patients with extensive spread of disease to the axilla. This consensus was an expert agreement based on a lower level of evidence, leaving individual physicians to define for themselves what constitutes extensive nodal involvement (eg. 50%-80% positive to excised LNs) (Belkacemi et al., 2011).

In the recent *German Society of Radiation Oncology (DEGRO)* guidelines (Sautter-Bihl et al., 2014), the authors found no basis to systematically deliver adjuvant ALN-RT in patients with only micro-metastatic involvement of one or two resected SLN. Conversely, in the case of macro-metastatic invasion of one or more SLNs, they recommended to consider ALN-RT as an alternative to ALND. For them, specific issues that remain debatable include: i) potential overtreatment in terms of volumes; (ii) unequal distribution of the number of patients with positive SLN in both arms; (iii) 5-year axillary recurrence rates that were lower than expected hypothetical values, (iv) the relatively short follow-up period to obtain the expected number of axillary recurrence events (Sautter-Bihl et al., 2014).

The ESMO guidelines published in 2013 have dedicated a short section to RNI indications, recommending that, the resected part of the axilla should not be irradiated after ALND, except for specific cases of residual disease after surgery. More detailed guidance was not provided in that report (Senkus et al., 2013).

3.4. Published guidelines for IMC-RT

With the exeption of the recent update of the NCCN guidelines, (Gradishar et al., 2016) the majority of national and international published guidelines have been reported before the publication of the recent trials on RNI (Whelan et al., 2015; Poortmans et al., 2015).

3.5. North America

In the 2016 NCCN guidelines, RNI is defined as RT to both the SC and IMC regions (Gradishar et al., 2016). After BCS, NCCN recommendations are mainly similar for all N+ patients: RT to the breast and infra/supraclavicular area, with a recent change to "strongly consider IMC-RT" in patients with positive nodes. After mastectomy, NCCN strongly recommends RNI for patients with ≥ 4N+, 1-–3N+ and pN0 with large tumors (> 5 cm) or positive margins. Conversely, RNI was not recommended in pT1-2pN0 disease after either BCS or mastectomy.

3.6. Europe

The French group (Belkacemi et al., 2011) recommends IMC-RT and SCN-RT for all patients with pN1 disease and/or inner/central tumors after either BCS or mastectomy. For pN0 patients with

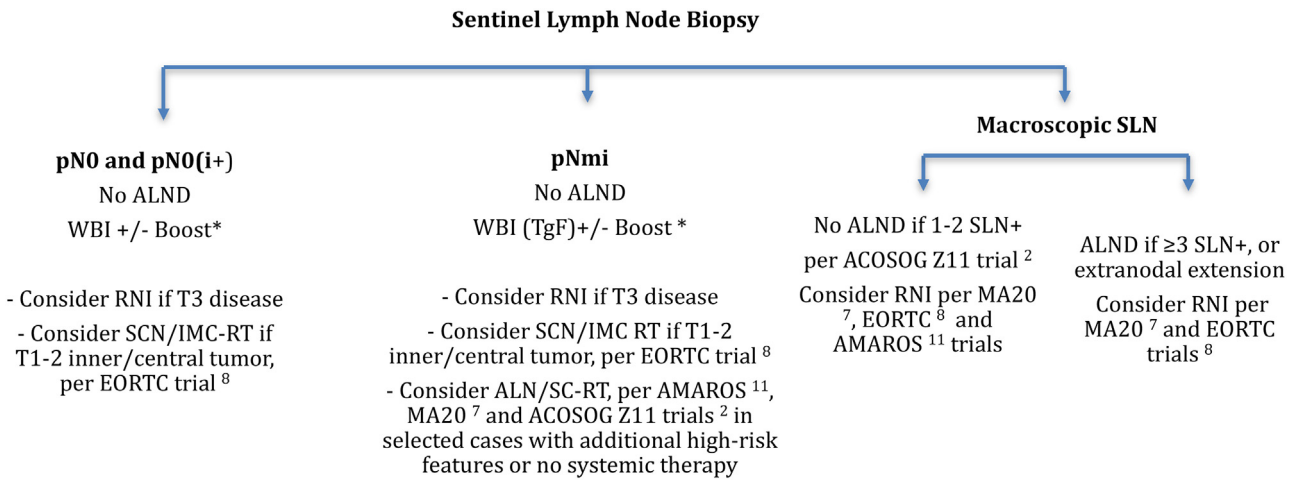

Fig. 1. Represents the main options and indications according to nodal involvement and data reported in surgical and radiotherapy randomized trials.
ALND: axillary lymph node dissection; SLN: sentinel lymph node; RNI: regional nodal irradiation; pN: pathologic nodal status; WBI: whole breast irradiation; TgF: tangential fields; ST: systemic therapy; SCN-RT: supraclavicular nodal radiotherapy; IMC-RT: Internal mammary chain radiotherapy, ALN/SC-RT: axillary node radiotherapy (including undissected axilla level III).
*Chest wall irradiation indications should be discussed with consideration of individual patients' clinical and pathologic prognostic factors. 2: Giuliano, A.E., Ann. Surg.; 7: Whelan, T., N. Engl. J. Med.; 8: Poortmans, P., N. Engl. J. Med.; 9: Budach, W., Radiother. Oncol.; 11: Donker, M., Lancet Oncol.

outer tumors, no RT is recommended. In contrast, the DEGRO panel (Sautter-Bihl et al., 2014) concludes that until further follow-up and subgroup analyses from trials are available, IMC-RT should not be used, as the specific contribution of IMC-RT to improved outcome is unclear. In light of new evidence from recent randomized trials and population-based studies suggesting medial tumor location and node positive disease should be considered for IMC-RT as part of RNI (Poortmans et al., 2015; Belkacemi et al., 2011), these recommendations have been debated.

In the ESMO guidelines, the indications for utilization of IMC-RT are not specifically addressed. They suggested that "until the results from recent trials become available, RNI remains indicated for only patients with involved LNs" (Senkus et al., 2013).

3.7. Review of the published guidelines for SCN-RT

3.7.1. North America

In the NCCN guidelines, (Gradishar et al., 2016) SCN-RT was recommended after BCS or mastectomy for ≥ 4N+ and 1–3N+ patients and pN0 and tumors > 5 cm or positive margins after mastectomy.

3.7.2. Europe

The ESMO guidelines do not specify treatment to the SCN-region but include this region with comprehensive RNI when advocating for N+ patients to have regional nodes treated (Senkus et al., 2013). While the older DEGRO guidelines were more restrictive regarding SCN-RT indications, (Sautter-Bihl et al., 2008) in the French guidelines (Belkacemi et al., 2011) and the recent update of the DEGRO guidelines, (Sautter-Bihl et al., 2014) SCN-RT and IMC-RT were recommended for all patients with 1–3N+ and > 4N+. They also recommended that the risk-to-benefit ratio of adding IMC-RT to the SCN-RT be discussed with patients individually, particularly intermediate risk patients (1–3N+) as currently, data are lacking to distinguish the specific contribution of SCN-RT versus IMC-RT on outcomes.

4. Discussion

The recent evolution in breast cancer including sentinel SLNB, modern radiotherapy techniques and the use of molecular subtyping to guide systemic and targeted agents have considerably contributed for a more tailored approach in the new era of personalized medicine. In terms of RT, there have been recent landmark studies that reported a significant impact clinical practice of the regional nodal management of breast cancer (Hafty and Mahmoud, 2015). Considerations of RNI indications and volumes in the era of positive SLNB should take into account several parameters including: (i) the number of SLN involved ii) number of nodes harvested (iii) tumor location (inner/central tumors for IMC-RT) and (iv) the degree of nodal involvement (focal vs. extensive extranodal extension). In the interpretation of data from the available trials, it is important to note that patients treated with breast conserving surgery received adjuvant RT to the whole breast, which may also encompass the low axilla in the TgF. However, as some trials lack RT quality assurance, the ability to draw conclusions about which nodal regions require treatment when axillary dissection is omitted remains unclear. This is especially relevant in light of data suggesting that TgF RT does not provide adequate axillary RT dose coverage (Belkacemi et al., 2014; Karam et al., 2013).

Ultimately, the application of available data requires carefully balancing the perceived risks of recurrence versus the concerns for treatment-related toxicity and recognizing that prospective data that define the benefits of irradiating individual nodal regions in isolation remain lacking. Acknowledging that there remain unanswered questions and variations in practice, we suggest that RNI indications and volumes be selected based on existing data and the degree of nodal involvement in the axilla as illustrated in Fig. 1.

4.1. RNI in pN0(i+) disease

While there is currently no level I evidence specific to the pN0(i+) population, available published data have reported excellent outcome among patients with pN0(i+) disease, similar to that seen in patients with node negative disease (Karam et al., 2013). Specifically, locoregional recurrence risk of pN0(i+) is comparable to pN0 disease, thus indications for RNI should also be similar among these two groups of patients. As in pN0 disease, decisions for RNI for pN0(i+) that are based on tumor size and location (inner and central) are supported by the results of the EORTC 22922 trial (Poortmans et al., 2015). Currently, there appears to be no strong rationale to advocate systematic RNI in pN0/pN0(i+) tumors in the outer quadrants, even those that are ≥ 5 cm, (Taghian et al., 2004)

but RNI may be considered for select pN0 cases based on individualized assessment of other prognostic factors, such as grade, Her2 positive, TN, LVI, proliferative index, and probability of IMC drainage (Sautter-Bihl and Sedlmayer, 2015; Caudle et al., 2015).

4.2. RNI in micrometastatic SLN involvement

In micrometastatic disease involving SLN without additional ALND, the risk of axillary recurrence is low in patients who receive RT and systemic therapy as shown by both the ACOSOG-Z0011 and IBCSG-2301 trials (Giuliano et al., 2010; Galimberti et al., 2013). Again, with the exception of larger lesions involving the inner and central breast, (Poortmans et al., 2015) a strong rationale to advocate routine RNI is lacking for this patient population. Moreover, while the number of harvested LNs seems to be less important to consider for RNI, it is an important factor for residual disease in the axilla, and a high TgF may be considered to cover axilla level I and II to treat the potential residual disease in the remaining non-sentinel nodes (Belkacemi et al., 2013; Belkacemi et al., 2014). In patients without adjuvant systemic treatment, RNI use should be discussed individually within a multidisciplinary board taking into consideration patient and disease-specific factors to estimate the risks of non-SLN involvement and nodal recurrence (Pepels et al., 2013).

4.3. RNI in macrometastatic SLN involvement

Current standard of care in pN1 disease after SLNB remains controversial. After total mastectomy, the current published clinical trials do not support to omit further therapy of axilla in case of macrometastases in 1–2 SLNs. In patients with 1–2 positive SLNs who meet the ACOSOG Z0011 criteria, ALND may be omitted but adjuvant RT should be considered. As ACOSOG Z0011 included patients with only 1 or 2 SLN+ (and no gross extranodal extension), ALND remains the standard of care for patients with > 2 positive SLN or gross extranodal extension. Similarly, as the AMAROS trial included predominantly patients with low-volume nodal disease (77% of patients having only one positive SLN and 40% having micrometastatic disease or isolated tumor cells), the AMAROS trial data do not justify omitting ALND in patients with > 2 positive nodes. For cN0, pN1 patients with 1–2+ nodes on SLNB not meeting the inclusion criteria of Z-0011, the axilla should be treated with either ALND or ALN-RT. If ALND is not performed, contouring of the axillary levels and directed radiation is indicated to therapeutically treat the axilla, as tangential fields alone do not fully cover potential residual disease in the axilla in all patients (Belkacemi et al., 2013; Belkacemi et al., 2014).

4.4. RNI in macrometastatic SLN involvement with ALND

There are now level 1 of evidence data supporting the use of RNI directed to both SCN and IMN areas in pN1 or pN0, central/medially located tumors. In routine practice, available data are in favor of including the SCN volume when treating patients with 1 or more positive lymph nodes (Ragaz et al., 2005; Gradishar et al., 2016). Though randomized data are lacking to guide decisions to utilize SCN-RT *or* IMC-RT fields in isolation (one without the other), consideration of using SCN-RT (without axilla I/II level coverage) and IMC-RT should be based on patient and tumor related factors which incorporate the longevity of the patient, since the gains in breast cancer specific outcomes with RNI are long-term benefits that are appreciable over a decade or longer.

5. Conclusion

The evolution from ALND to SLNB staging has led to complex clinical implications for radiation oncologists/surgeons who are faced with challenging scenarios for locoregional management, including cases of SLN-positive disease without ALND. With prospective trials reporting improved DMFS with RNI use, RNI is increasingly considered for patients with node-positive and selected patients with high-risk node-negative disease. The outcomes of ALND and RT directed to the axilla appear to be equivalent for patients with cN0 disease with 1–2 positive SLN, with less lymphedema experienced with radiation, therefore, radiation is a viable alternative to ALND. While the individual contributions of RT to each nodal basin on long-term outcomes remains to be defined, it appears consistent across studies that RNI in general improves breast cancer specific outcomes and distant metastasis free survival. Moreover, these recent level I data support the consideration of RNI in high-risk pN0 central/medial tumors and node-positive patients.

Author contributions

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