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Radiation therapy volumes after primary systemic therapy in breast cancer patients: an international EUBREAST survey

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Purpose: After primary systemic therapy (PST), agreement on the extent of locoregional therapy is lacking in breast cancer patients who convert from a node-positive to a node-negative status. The aim of this survey was to investigate radiation therapy approaches after PST according to different axillary surgical strategies and disease responses.

Materials and Methods: The European Breast Cancer Research Association of Surgical Trialists developed a web-based survey containing 39 questions on locoregional management based on clinical scenarios in initially node positive breast cancer patients undergoing PST. Twelve international breast cancer societies distributed the link to breast surgeons and radiation oncologists.

Results: Responses from 349 breast specialists were recorded, 72 of whom (20.6%) were radiation oncologists from 17 countries. Nodal status at diagnosis informed the decision for postoperative regional nodal irradiation (RNI) for 44/72 (61.1%) responders. RNI in node positive patients having undergone axillary lymph node dissection (ALND) is delivered in selected cases by 30/72 (41.7%) responders and systemically recommended by 26/72 (36.1%) responders. In case of macrometastases found on ALND, 43/72 (59.7%) responders always deliver RNI. In case of micrometastases in the sentinel lymph node(s) or targeted lymph node(s), 45/72 (62.5%) responders prefer RNI to completion ALND. A majority of responders (59.7%) determine the target volume for RNI according to European Society for Radiotherapy and Oncology guidelines. Significant heterogeneity was observed regarding nodal basins and volumes of interest for dose coverage by RNI.

Conclusions: There is significant heterogeneity in radiation-therapy delivered to the axilla after PST. A more standardized approach engaging both radiation oncologists and breast surgeons will help to optimize the harm-benefit equilibrium of axillary surgery and RNI.

Keywords: Axillary lymph node dissection, Primary systemic therapy, Sentinel lymph node biopsy, Regional nodal irradiation

Introduction

Breast cancer therapy has evolved significantly in the past decades. Early detection and tumor biology-driven systemic therapy has led to improvement in disease control and individualization of locoregional therapies (i.e., surgery and/or radiation therapy) [1,2]. Primary systemic therapy (PST), as opposed to postoperative (i.e., adjuvant) therapy, is recommended to down-stage the in-breast and axillary tumor load to perform less extensive surgery, and to tailor subsequent treatments based on the evaluation of tumor response. For patients with residual disease after PST, new postoperative treatment options emerge, making PST the preferred approach for an increasing number of breast cancer patients [3,4]. Current guidelines recommend PST in subtypes that are highly sensitive to chemotherapy (e.g., highly proliferative, triple negative or human epidermal growth factor receptor 2-positive disease) and in patients with a high tumor load, who might become candidates for de-escalation of surgery [5-7]. However, post-PST locoregional radiation therapy (RT) guidelines are mostly relying on pre-PST disease stage, while meanwhile de-escalation of locoregional therapy upon response is evaluated in clinical trials [1,8]. Even though there is no long-term data from randomized trials, many centers already adopt locoregional therapy to the individual response to PST [8]. The non-for-profit organization, European Breast Cancer Research Association of Surgical Trialists (EUBREAST), has initiated the AXSANA study (EUBREAST03) which aims to evaluate the outcomes of different types of axillary surgery after PST [2]. As part of the EUBREAST effort to improve locoregional therapy for breast cancer, an international survey regarding locoregional treatment approaches after PST was conducted. Since axillary surgery and regional nodal irradiation (RNI) are interchangeable in some cases (as shown in the AMAROS [9] and OTOSOAR [10] trial) or complementary [11], this work aims to explore current practices after PST. In a previous report about surgical management of the axilla, significant heterogeneity in surgical approaches after PST was observed [12]. In this report, survey results regarding RNI practices after PST are summarized and discussed. The clinical scenarios that were described in the survey do not necessarily reflect the recommended standard of care—e.g., sentinel lymph node (SLN) biopsy or targeted axillary dissection (TAD) in case of residual nodal disease at the final histology analysis (ypN+) [6]. Thereby, it aims to demonstrate which nodal basins are targeted for RT according to the type of surgery in real-life circumstances.

Materials and Methods

The survey was designed by a panel of EUBREAST breast cancer experts, comprising two radiation oncologists who serve as faculty of the European Society for Radiotherapy and Oncology (ESTRO) breast cancer course (P.P., O.K.P.), two gynaecologists/breast surgeons (M.L.G., T.K.) one of whom is also on the faculty of the same ESTRO course (T.K.), and two breast surgeons (J.D.B., O.D.G.). The survey was distributed through the networks of 13 international breast cancer societies supporting the initiative (Supplementary Table S1) and was launched online through a Google Form on April 20, 2021 and closed on October 6, 2021. This study does not need an institutional review board review due to the nature of the survey.

Each responding healthcare professional agreed explicitly to participate in the study before submitting their form. Participants completed the questionnaire anonymously. No specific requirements were set for physicians participating in the survey. They were asked to complete the questions based on the standard of care at their center. Survey data were collected in a secure and anonymous central database for analysis and reported in aggregate form. For each question, participants selected one or more answers from a list of options.

The survey comprised three sections: a general section directed to all responders regardless of their specialty, one directed to breast surgeons, and one directed to radiation oncologists. The results from the second section have been published before [12]. The list of questions concerning radiation oncology is available in Supplementary Table S2. Statistical analysis was performed with Microsoft Office Excel 365, version 2020 (Microsoft, Redmond, WA, USA) and GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, USA).

Results

A total of 349 breast surgeons and radiation oncologists completed the survey. Of these respondents, 72/349 (20.6%) were radiation oncologists from 17 countries, listed in Supplementary Table S3. Among these, 44/72 (61.1%) worked in university hospitals or hospitals affiliated to universities. The annual hospital caseload exceeded 200 new primary breast cancer patients in the centers of 52/72 (72.2%) responders. A total of 21/72 (29.1%) of responders worked at centers participating in the EUBREAST03/AXSANA study, and 27/72 (37.5%) worked in centers participating in other clinical trials evaluating axillary management after PST.

1. Nodal positive definition

Of all radiation oncologists, 53/72 (73.6%) indicated that histopathological or cytological confirmation was required to classify a patient as nodal positive prior to PST (cN+). Another 17/72 (23.6%) asked for such confirmation only in selected cases, and 2/72 (2.7%)

classify cN+ patients based on clinical and/or radiological suspicion alone. Among those respondents requiring biopsy confirmation, a core needle biopsy was preferred by 30.0% (21/70) and a fine needle aspiration by 22.8% (16/70). For the remainder, it was dependent on the individual case.

2. Influence of nodal status at diagnosis on postoperative RNI

Nodal status at diagnosis informed the decision for postoperative RNI for 44/72 (61.1%) responders, whereas 28/72 (38.8%) responders based RNI on combined pre- and/or post-PST assessment.

3. Post-PST nodal radiation therapy in case of residual disease

RNI in ypN+ patients undergoing axillary lymph node dissection (ALND) is delivered in selected cases by 30/72 (41.7%) responders; systemically recommended by 26/72 (36.1%) responders and not recommended at all by 16/72 (22.2%) responders (Fig. 1A). A majority of responders (43/72; 59.7%) determine the target volume for RNI according to ESTRO guidelines [13], while 24/72 (33.3%) use Radiation Therapy Oncology Group (RTOG) guidelines [14] and another 5/72 (6.9%) do not delineate nodal volumes but use field-based RT (Fig. 1B).

In case of ALND in patients who presented with macrometastases at either upfront staging or upon completion surgery after RNI, 43/72 (59.7%) responders would deliver RNI regardless of the number of macrometastases, 26/72 (36.1%) responders offer RNI in case of >3 macrometastases, and 3/72 (4.1%) responders would not consider RNI in such cases (Fig. 2A).

In case of micrometastases (ypN1mic) in the lymph node(s) retrieved via SLN biopsy or TAD, 45/72 (62.5%) responders prefer RNI rather than completion ALND (Fig. 2B). In case of isolated tumor cells (ypN0(i+)) in the SLNs or targeted lymph nodes, 47/72 (65.3%) responders recommended RNI rather than ALND (Fig. 2C).

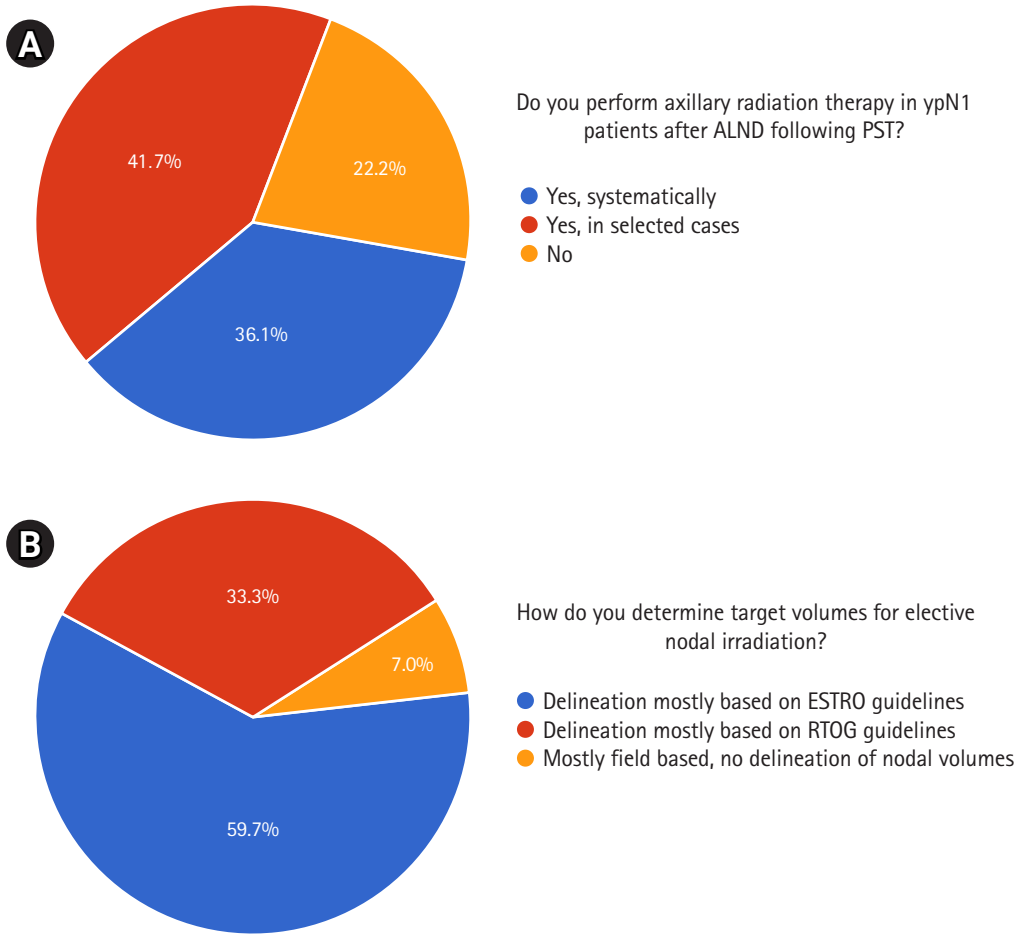

Fig. 1. Regional nodal irradiation after primary systemic treatment (PST); in case of breast cancer patients with positive nodes at final histology (A) and target volumes (B). ALND, axillary lymph node dissection; ESTRO, European Society for Radiotherapy and Oncology; RTOG, Radiation Therapy Oncology Group.

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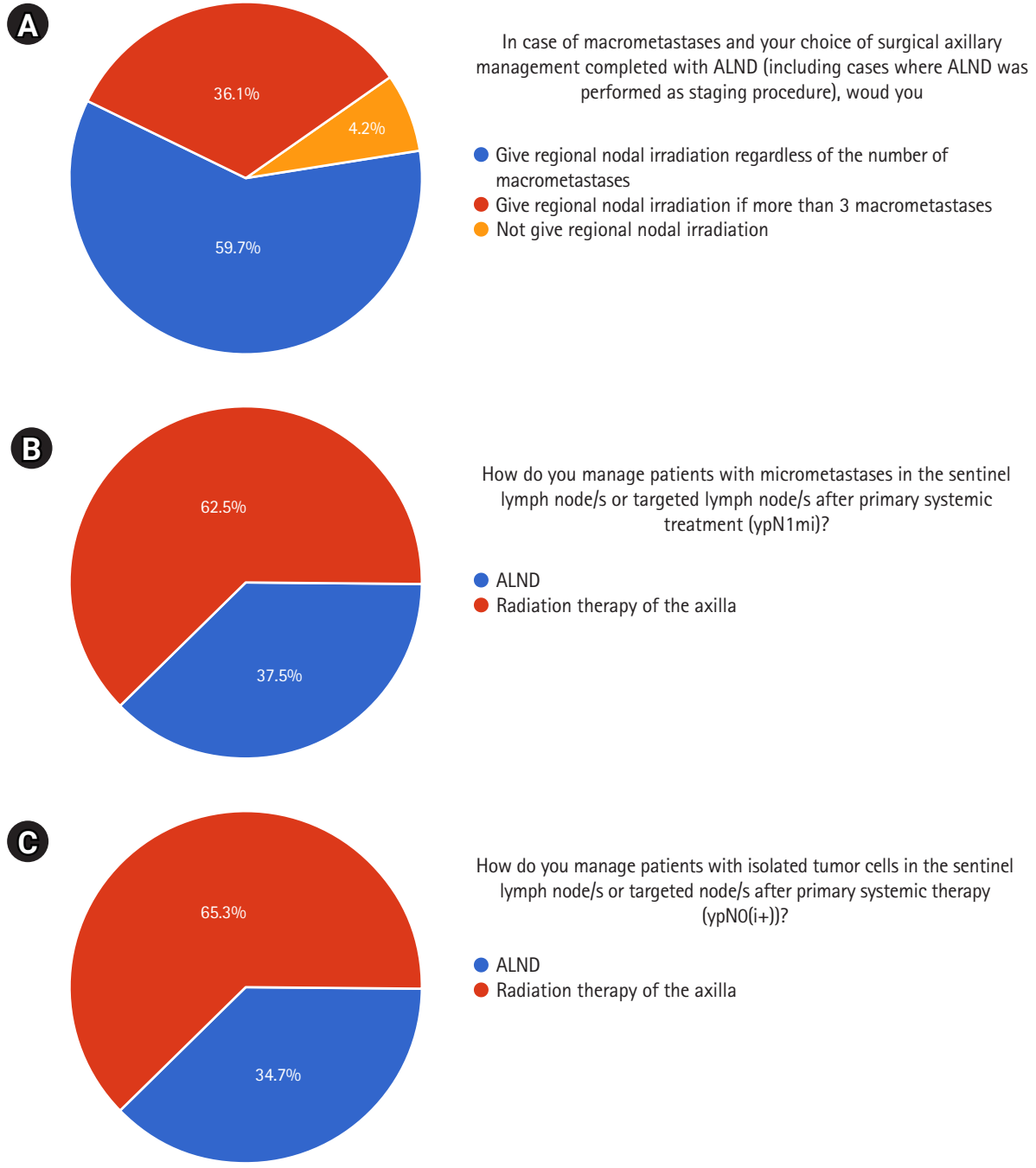

Fig. 2. Regional nodal irradiation and residual disease in the axillary lymph-node(s). Macro-metastases after ALND (A); micro-metastases after SLNB/TAD (B); isolated tumor cells after SLNB/TAD (C). ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; TAD, targeted axillary dissection.

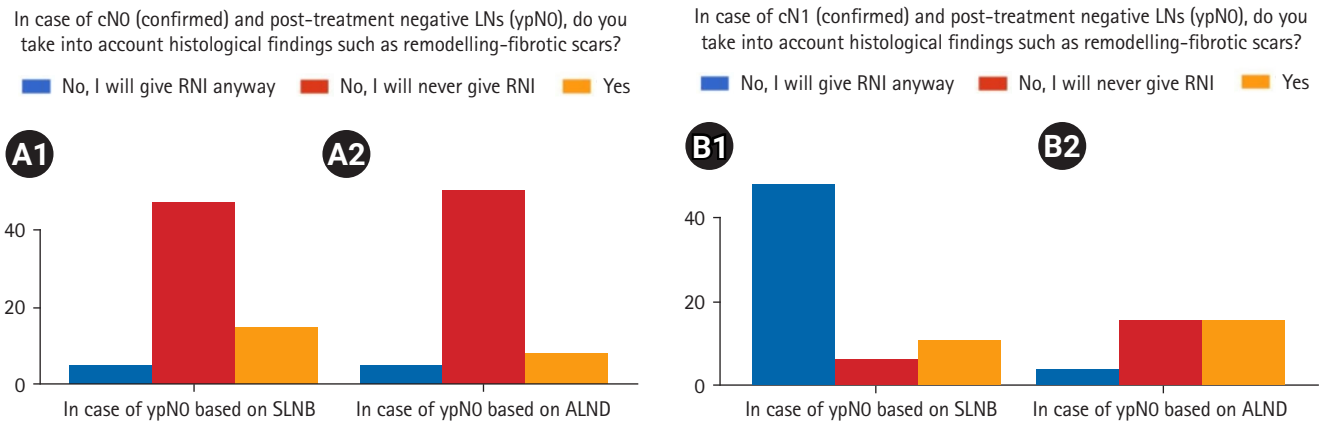

Fig. 3. RNI and remodelling-fibrotic scars: in nodal negative (clinically and pathologically) breast cancer patients after SLNB (A1); in nodal negative (clinically and pathologically) breast cancer patients after ALND (A2); in clinically nodal positive breast cancer patients converted to negative nodal status after primary systemic treatment after SLNB (B1); in clinically nodal positive breast cancer patients converted to negative nodal status after primary systemic treatment after ALND (B2). RNI, regional nodal irradiation; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.

Table 1. LN basins of postoperative irradiation in primary nodal positive breast cancer patients undergoing sentinel lymph node biopsy or targeted axillary lymph node dissection

	Level 1-4 Level 1-4 Level 3-4	Level 3-4	IMC Level 3-4 IMC	IMC Level 1-4 Level 1-4 Level 3-4 IMC	Unoperated levels (1-4) upwards[a] Unoperated levels (1-4) upwards[a] Level 1-4 Unoperated levels (1-4) upwards[a] Level 1-4 Level 3-4 Unoperated levels (1-4) upwards[a] Level 3-4	Unoperated levels (1-4) upwards[a] IMC Unoperated levels (1-4) upwards[a] Level 1-4 IMC Unoperated levels (1-4) upwards[a] Level 3-4 IMC Unoperated levels (1-4) upwards[a] Level 1-4 Level 3-4 IMC
ypN0	29 (40)	18 (25)	5 (7)	6 (8)	12 (17)	2 (3)
ypN0(i+)	32 (44)	17 (24)	5 (7)	7 (10)	10 (14)	1 (1)
ypN1(mi)	30 (42)	18 (25)	5 (7)	8 (11)	9 (13)	2 (3)
ypN1	31 (43)	10 (14)	4 (6)	14 (19)	11 (15)	2 (3)
ypN2	24 (33)	5 (7)	3 (4)	29 (40)	6 (8)	6 (8)
ypN3	18 (25)	5 (7)	2 (3)	36 (50)	4 (6)	7 (10)
ypN+ inner and central tumors	5 (7)	4 (6)	12 (17)	37 (51)	7 (10)	9 (13)
ypN+, ECE, < 2 mm	28 (39)	7 (10)	4 (6)	19 (26)	9 (13)	6 (8)
ypN+, ECE, > 2 mm	29 (40)	7 (10)	5 (7)	2 (3)	7 (10)	20 (28)
ypN+, tumor fat deposit, intramammary + LN	16 (22)	2 (3)	4 (6)	35 (49)	9 (13)	5 (7)
cN0 and ypN0 in axilla but internal mammary node avid on PET/CT pre-PST	2 (3)	2 (3)	29 (40)	25 (35)	10 (14)	4 (6)

Values are presented as number (%).
LN, lymph node; ypN, pathology staging after primary systemic therapy; ECE, extracapsular extension; IMC, internal mammary chain, axilla level 1,2,3,4 per European Society for Radiotherapy and Oncology lymph node atlas for breast delineation; PET/CT, positron emission tomography/computed tomography; PST, primary systemic therapy.
[a]Where the axillary surgical changes end on CT-sim, the axillary nodal volume may include all or part of a basin level (example only the upper part of level 1, all level 2, rotter, level 3 & 4).

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Table 2. LN basins of postoperative irradiation in primary nodal positive breast cancer patients undergoing axillary lymph node dissection after PST

	Level 1-4 Level 1-4 Level 3-4	Level 3-4	IMC Level 3-4 IMC	IMC Level 1-4 Level 1-4 Level 3-4 IMC	Unoperated levels (1-4) upwards[a] Unoperated levels (1-4) upwards[a] Level 1-4 Unoperated levels (1-4) upwards[a] Level 1-4 Level 3-4 Unoperated levels (1-4) upwards[a] Level 3-4	Unoperated levels (1-4) upwards[a] IMC Unoperated levels (1-4) upwards[a] Level 1-4 IMC Unoperated levels (1-4) upwards[a] Level 3-4 IMC Unoperated levels (1-4) upwards[a] Level 1-4 Level 3-4 IMC
ypN0	2 (3)	33 (46)	9 (13)	1 (1)	16 (22)	3 (4)
ypN0(i+)	10 (14)	33 (46)	9 (13)	1 (1)	16 (22)	3 (4)
ypN1(mi)	11 (15)	32 (44)	9 (13)	1 (1)	15 (21)	4 (6)
ypN1	12 (17)	29 (40)	9 (13)	1 (1)	13 (18)	8 (11)
ypN2	15 (21)	13 (18)	17 (24)	6 (8)	7 (10)	14 (19)
ypN3	12 (17)	7 (10)	18 (25)	15 (21)	6 (8)	14 (19)
ypN+ inner and central tumors	6 (8)	3 (4)	29 (40)	14 (19)	7 (10)	13 (18)
ypN+, ECE, < 2 mm	1419)	19 (26)	12 (17)	7 (10)	11 (15)	9 (13)
ypN+, ECE, > 2 mm	18 (25)	14 (19)	13 (18)	10 (14)	11 (15)	6 (8)
ypN+, tumor fat deposit, intramammary + LN	10 (14)	6 (8)	20 (28)	16 (22)	8 (11)	9 (13)
cN0 and ypN0 in axilla but internal mammary node avid on PET/CT pre-PST	3 (4)	1 (1)	41 (57)	10 (14)	8 (11)	9 (13)

Values are presented as number (%).
LN, lymph node; ypN, pathology staging after primary systemic therapy; ECE, extracapsular extension; IMC, internal mammary chain, axilla level 1,2,3,4 per European Society for Radiotherapy and Oncology lymph node atlas for breast delineation; PET/CT, positron emission tomography/computed tomography; PST, primary systemic therapy.
[a]Where the axillary surgical changes end on CT-sim, the axillary nodal volume may include all or part of a basin level (example only the upper part of level 1, all level 2, rotter, level 3 & 4).

4. Significance of remodelling fibrotic scars after PST

After a negative SLN biopsy, histological findings suggesting a complete response of a previous nodal metastases, such as remodelling-fibrotic scars, are considered by 15/67 (22.3%) responders as an indication to recommend RNI in case of initially node negative status (cN0), and by 11/66 (16.6%) only in case of initially nodal positive status. Among the 52 responders not taking scars into account, 5/52 (9.6%) give RNI anyway in case of initially cN0 and 2/55 (3.6%) in case of cN1. In initially cN0, 47/52 (90.3%) would not recommend RNI despite fibrotic changes, while only 6/55 (10.9%) would abstain RNI in initially nodal positive breast cancer patients (Fig. 3A.1 and 3B.1).

In case of no residual nodal disease (ypN0) after ALND, above-described histological findings are considered by 8/65 (12.3%) responders to recommend RNI in case of cN0 status, and by 16/36 (44.4%) in case of nodal positive breast cancer patients. Among the 57 responders not taking scars it into account, 5/57 (8.7%) give RNI also in case of cN0 and 4/57 (7.0%) only in case of cN+ (Fig. 3A.2 and 3B.2).

5. Lymph node basins of RT in selected conditions

The lymph node basins of RNI in primary cN+ breast cancer patients undergoing PST and SLN/TAD or ALND differ according to the residual tumor burden. The responders were given different cases, according to the tumor response to PST, axillary surgery (ALND, TAD, SLN biopsy), the total number of axillary lymph nodes resected, and the patient's arm morbidity. For each case, the responder was allowed to choose several answers, which reflected the nodal basins and volumes of interest for dose coverage by RNI.

The different scenarios and replies are fully represented in the supplement (Supplementary Table S4–S8). A summary of the different selection options from the survey in selected conditions is reported in Tables 1–3.

Table 3. LN basins of postoperative irradiation in primary nodal positive breast cancer patients undergoing axillary lymph node dissection after PST, in case of postoperative arm lymphedema

	Level 1-4 Level 1-4 Level 3-4	Level 3-4	IMC Level 3-4 IMC	IMC Level 1-4 Level 1-4 Level 3-4 IMC	Unoperated levels (1-4) upwards[a] Unoperated levels (1-4) upwards[a] Level 1-4 Unoperated levels (1-4) upwards[a] Level 1-4 Level 3-4 Unoperated levels (1-4) upwards[a] Level 3-4	Unoperated levels (1-4) upwards[a] IMC Unoperated levels (1-4) upwards[a] Level 1-4 IMC Unoperated levels (1-4) upwards[a] Level 3-4 IMC Unoperated levels (1-4) upwards[a] Level 1-4 Level 3-4 IMC
ypN0	5 (7)	39 (54)	8 (11)	1 (1)	16,22)	3 (4)
ypN0(i+)	5 (7)	39 (54)	8 (11)	1 (1)	16 (22)	3 (4)
ypN1(mi)	5 (7)	38 (53)	9 (13)	1 (1)	16 (22)	3 (4)
ypN1	10 (14)	32 (44)	11 (15)	1 (1)	12 (17)	6 (8)
ypN2	13 (18)	15 (21)	16 (22)	7 (10)	7 (10)	14 (19)
ypN3	12 (17)	9 (13)	16 (22)	14 (19)	6 (8)	15 (21)
ypN+ inner and central tumors	3 (4)	5 (7)	29 (40)	11 (15)	9 (13)	15 (21)
ypN+, ECE, < 2 mm	12 (17)	24 (33)	12 (17)	7 (10)	9 (13)	9 (13)
ypN+, ECE, > 2 mm	15 (21)	18 (25)	13 (18)	9 (13)	9 (13)	9 (13)
ypN+, tumor fat deposit, intramammary + LN	9 (13)	11 (15)	21 (29)	14 (19)	7 (10)	10 (14)
cN0 and ypN0 in axilla but internal mammary node avid on PET/CT pre-PST	4 (6)	4 (6)	41 (57)	7 (10)	5 (7)	11 (15)

Values are presented as number (%).
LN, lymph node; ypN, pathology staging after primary systemic therapy; ECE, extracapsular extension; IMC, internal mammary chain, axilla level 1,2,3,4 per European Society for Radiotherapy and Oncology lymph node atlas for breast delineation; PET/CT, positron emission tomography/computed tomography; PST, primary systemic therapy.
[a]Where the axillary surgical changes end on CT-sim, the axillary nodal volume may include all or part of a basin level (example only the upper part of level 1, all level 2, rotter, level 3 & 4).

Discussion and Conclusion

Herein we present the results of an international EUBREAST survey exploring RNI practices after PST. Similar to our previous report, reflecting the practices of axillary surgery after PST, our results show that there is some extent of heterogeneity in radiation practices [11]. For the purpose of the discussion, Supplementary Fig. S1 summarizes the different types of axillary procedures to allow a comprehensive understanding of the nodal basins that are treated by surgery.

In our survey, a large fraction of responders would not consider RNI even in case of residual nodal disease after PST if an ALND had been performed. This most probably reflects differences in current practices between centers and countries in upfront surgery as well. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analyses [15,16] show a clear benefit in disease outcomes when giving RNI after ALND to nodal basins that were not resected during ALND (axilla levels 2–4 and the internal mammary node chain). This benefit was also demonstrated in patients with no or limited nodal involvement (1–3 metastatic nodes and even in high-risk medial/central tumors without axillary nodal involvement) [11,15-17]. Likely, the observed differences in practices reflect poor understanding and lack of acceptance regarding the contribution of RNI on disease outcomes combined with a fear of toxicity reported only in some older trials (initiated before 1989), indicating that radiation resulted in increased morbidity and mortality mostly from cardiac events [18,19]. This is now, based on the most recent EBCTCG publication, clearly related to older treatment regimens and should not further influence contemporary decision-making [16]. Indeed, there is a high level of evidence, even from the two dimensional (2D)-RT era and with long-term follow-up, showing that if RT is applied with appropriate quality assurance measures, the benefit in disease control is indeed significant with limited tox-

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icity and without increasing cardiac mortality [20-22]. The reduction in the odds of breast cancer death following RNI appears larger after less extensive surgery (e.g., breast conserving surgery or axillary sampling) [23]. More contemporary radiation techniques allow to further significantly reduce heart and lung doses even in challenging cases [24], thereby sharply reducing risks of RT-related morbidity.

Nowadays, breast cancer patients with a larger tumor burden (e.g., T3, cN+) are often offered PST to downstage the disease, which leads to less extensive surgery. Thus, similar to what was discussed above [23], the nodal basins at risk should be covered to achieve the maximum benefit of therapy.

The majority of responders in the present report recommended pathological confirmation of nodal involvement in patients with clinically suspicious nodes. Suspicious nodes on imaging or palpation are not necessarily truly positive and should be biopsied to guide both systemic and locoregional therapy. In the NSABP-B04 trial, only 75% out of those clinically node-positive on palpation had positive nodes on histopathological evaluation after ALND [25]. Therefore, suspicious nodes should be confirmed by fine needle aspiration or core needle biopsy. While core needle biopsy may provide more detailed information, it is not mandatory if the aim is only to confirm nodal involvement [26-28].

The large majority of responders indicated that the clinical pre-PST stage is important for identification of the nodal volumes to be targeted after PST and a not negligible number of responders take into account the scarring and fibrotic changes for selecting patients to RNI. In case of initial nodal involvement that becomes ypN0 at the SLN biopsy and ALND, RNI is administered by the 16% and 44% of the responders, respectively, based on the scarring and fibrotic changes of the node(s) on final pathology. However, such nodal changes can be noted even in a healthy population, due to chronic disease or as a reaction to nodal clip placement or biopsy of the node [29]. Therefore, such changes are no reliable indicators for previous tumor involvement and should not pose an indication for RNI in the absence of other risk factors.

According to ESTRO breast cancer faculty recommendations [30], the radiation oncologist must review and take into account pre-PST images to plan RT. This allows a comprehensive estimation of the disease extent and volumes that are at high risk of locoregional recurrence. Thus, pre-PST nodal stage and the level of nodal involvement need to be considered for planning RNI to assure that nodal basins at high risk for residual tumor will be covered, especially if nodal basins that might initially have been involved by tumor are not dissected, taking into account the extend of axillary surgery.

A majority of responders indicated that the ESTRO guidelines [31] are used to define nodal volumes while the remainder used RTOG guidelines or indicated that a field-based planning (i.e., similar to 2D era, based on bony landmarks) is performed. It is an important achievement for the radiation oncology community that delineation of nodal basins has been now quite broadly accepted for RNI planning, however, our survey clearly shows we should strive for further implementation of this essential component of anatomy-based RT preparation and delivery. Breast cancer represents approximately 30%–40% of all radiation therapy unit workload [32], and nodal delineation is time consuming and mandates practice. Field-based 2D planning based on bony landmarks has governed breast radiation planning for decades. It is relatively easy and less time consuming, and is in some centers performed by the non-medical radiation planning team. Delineation of nodal basins mandates an understanding of the concept of the nodal atlas and the anatomy shown on the planning computed tomography (CT) scan and requires a lot of practice. Professional courses such as provided by Fellowship in Anatomic Delineation and Contouring (FALCON) [30] are extremely valuable, as is experience and training that allow to identify potential residual disease after PST and axillary surgery [33]. Relying on bony landmarks can result in under-coverage of the levels of the axilla that did not undergo lymphadenectomy, especially as these bony landmarks are based on extensive ALND that include also full dissection of level 2 (behind the pectoralis muscle up to the axillary vessels) which is sometimes not routinely done nowadays (Supplementary Fig. S2).

Surgical changes in the axillary levels such as clips (often applied at the superior border of the dissection), seroma, and inflammatory changes and other post-surgical effects can be noted on the RT planning CT scan. Our survey show that many radiation oncologists take these surgical changes into account for planning RNI, understanding that even if an ALND was performed, such surgical changes may only be observed in level 1 (partial ALND). In such cases, level 2, retropectoral nodes and levels 3–4 should be targeted if RNI is indicated. However, some radiation oncologists stated that only levels 3–4 will be targeted after ALND, suggesting that either they have full confidence in the ALND procedure (which includes levels 1–2) or the volumes are according to the concept of the 2D era [33] where only a medial supra-clavicular field is applied after ALND.

A common quality indicator of ALND used to be the removal of at least 10 lymph nodes [34]. The results show that to some extent, the radiation oncologist decides on the nodal levels to target according to the number of nodes that were examined. In addition, the number of nodes retrieved in the setting of PST is often lower than in the setting of upfront surgery in case of ALND. Surprisingly, the survey shows that not all radiation oncologists consider the type of axillary surgical procedure (e.g., SLN biopsy, TAD, ALND) after PST and pay more attention to the number of nodes to decide

on the RNI volumes, suggesting that in part there might be a lack of familiarity with the differences in these procedures or, alternatively, a lack in confidence with the extent of nowadays ALND. Remarkably, some will not target the lower levels of the axilla in case SLN biopsy or TAD was performed and target levels 3–4 and/or internal mammary chain (IMC) drainage. SLN biopsy or TAD are surgical staging methods to evaluate the lower axillary levels and not anatomic procedures like ALND. Therefore, levels 1–2, Rotter, with/without IMC are considered not covered by the ALND and should be irradiated in case there is an indication for RNI.

Our study holds several limitations. The survey was conducted not to achieve a consensus but to reflect current practices. Therefore, in some of the questions the responders were given different options or could choose several options simultaneously, limiting our ability to inform the reader of a straightforward level of agreement. Moreover, in case of 2D planning, the radiation oncologist might not be familiar with the axillary levels of the delineation atlases, therefore some of the responses might not reflect actual practices.

In conclusion, this survey shows heterogeneity in clinical practices of RNI, but also underlines the tremendous progress made since the 20th century's 2D era. We discuss the use of delineation guidelines for RNI and highlight the importance of understanding new axillary procedures applied after PST, supporting multidisciplinary team efforts such as the Toolbox [8], Oncoplastic Breast Consortium, and EUBREAST initiatives. Surgery and radiation for breast cancer are at times exchangeable and at times complementary. A comprehensive collaboration between disciplines that allows for in-depth mutual understanding will further improve the therapeutic benefit of locoregional therapies.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Author Contributions

Conceptualization, MLG, OKP, ODG, JDB, TK, PP; Investigation and methodology, MLG, OKP, JDB; Writing of the original draft, MLG, OKP, JDB; Writing of the review and editing, TK, PP; Formal analysis, MLG, OKP, JDB; Data curation, MLG, OKP, JDB; Visualization, TK, PP.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2024.00248.

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