Is radiotherapy after primary chemotherapy (RAPCHEM) on the right path to de-escalation?

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In recent years, advances in early breast cancer diagnosis and treatment have led to improvements in overall prognosis, decreasing locoregional and distant recurrence rates. Improved locoregional disease control, together with the known toxicity of various axillary treatment strategies, generated attempts to de-escalate locoregional treatment, with an intention to improve the patients' quality of life (QoL) without compromising outcomes. This movement first started with trials of sentinel lymph node biopsy (SLNB), which has eventually supplanted axillary lymph node dissection (ALND) in node-negative patients undergoing upfront surgery, whether mastectomy or breast conservation. Subsequent trials have extended the use of SLNB to clinically node-negative patients who have either micrometastatic or low burden of metastatic disease [≤2 pathologically involved sentinel lymph nodes (SLN)], and were treated with tangential breast irradiation and adjuvant systemic therapy (1-3). Finally, the use of regional nodal irradiation (RNI) in lieu of ALND for cT1–2N0 SLN-positive patients, irrespective of the type of breast surgery (breast conservation or mastectomy) has been supported by the results of the AMAROS and OTOASOR trials (4-6), which confirmed non-inferiority of RNI with respect to 10-year long-term overall survival (OS), DFS, and loco-regional control (5) or 8-year disease-free survival (6), and a decrease in lymphoedema and arm morbidity rate in the RNI group (4,6). Based on these results, RNI is now considered the preferred treatment over ALND for this subgroup of patients (5). Of all the axillary management strategies, ALND plus RNI is associated with worst patient reported outcomes, and therefore should be avoided whenever possible, whereas the extent of irradiated target volumes (axillary levels I–II compared to levels I–IV) does not seem to impact the degree of arm morbidity (7). Thus, in the current clinical practice, the preferred direction of the locoregional treatment de-escalation is replacing ALND with RNI.

Whether the same de-escalation approaches are appropriate in the setting of primary systemic treatment is still unclear. In patients with clinically node-negative disease at presentation, surgical trials have demonstrated that SLNB performed after primary systemic treatment provides accurate pathologic information and low false-negative rates (8,9). Following the modern primary systemic treatment in clinically node-positive patients, SLNB has been demonstrated to have satisfactory sensitivity, provided the removal of 3 or more SLN and/or the use of dual tracer (10,11). Currently, ALND is recommended only in patients with residual nodal macrometastases after primary systemic treatment (12). However, the optimal locoregional management for patients achieving good nodal response remains to be established. RNI (with avoidance of operated axilla) is generally indicated, and the attempts for the treatment de-escalation go in the direction of replacing

ALND with RNI. Further evidence for the axillary management is awaited from the ongoing ALLIANCE A011202 trial (NCT01901094), which randomizes patients with a clinically negative axilla (no bulky adenopathy), who proved to be ypN+ on SLNB, to ALND and RNI (standard arm) *vs.* RNI alone (experimental arm). Although there is general agreement on no need for RNI in cN0 patients remaining pathologically node-negative (ypN0) after primary systemic treatment, the role of RNI in those who convert from cN+ to ypN0 and undergo SLNB alone remains controversial, as there is no firm evidence for tailoring RNI by response to primary systemic treatment. Awaiting the results of the ongoing NSAPB B-51 trial (NCT01872975) which randomizes cT1–3pN1 patients who converted to ypN0 into RNI (standard arm) *vs.* no RNI (experimental arm), the current major guidelines recommend against omitting RNI for such patients (12-14). However, some less direct evidence suggests that RNI could be omitted in patients with an estimated low risk of locoregional recurrence. The pooled analysis of NASBP B-18 and NSABP B-27 trials showed that after primary systemic treatment and surgery including ALND, in ypN0 patients who underwent whole breast only radiotherapy after breast conservation, and no locoregional radiotherapy after mastectomy, 10-year locoregional recurrence rates were within the range of 0% to 12.4%, depending on age, tumour size, and primary tumour response (15). Thus, such patient and tumor characteristics can potentially be used to predict risk for locoregional recurrence and to optimize the use of adjuvant radiotherapy in relation to the chest wall and non-operated lymph nodes, although no direct guidance may be gained in relation to the management of the axilla. Additionally, this observation must be interpreted with caution, because in some analyzed subcategories the number of patients who achieved pathologic complete response (pCR) in the breast with pathologically negative nodes was relatively small (15). Several retrospective studies have suggested that in some patients with cT1–2N1 disease (one to three suspicious nodes on imaging before primary systemic treatment), who converted to ypN0, regional radiotherapy and chest wall radiotherapy following ALND could be omitted (16-18). Yet, it was still uncertain how to safely de-escalate locoregional treatment in various patient subgroups, depending on the burden of residual nodal disease. Therefore, a Dutch prospective, registry study [radiotherapy after primary chemotherapy (RAPCHEM), BOOG 2010–03] was developed to evaluate the oncological safety of deescalated radiotherapy, according to a predefined consensusbased study guideline, in patients with cT1–2N1 breast cancer, treated with primary chemotherapy (19).

The tailored approach evaluated in the RAPCHEM study comprised three risk groups for locoregional recurrence, based on ypN-status following ALND, with corresponding locoregional radiotherapy recommendations: no chest wall radiotherapy and no RNI in the low-risk group (i.e., ypN0), only local radiotherapy in the intermediate-risk group (i.e., ypN1, one to three positive nodes in surgical specimen after primary chemotherapy), and local radiotherapy plus RNI in the high-risk group (i.e., ypN2–3, four or more positive nodes in surgical specimen after primary chemotherapy) (19). The protocol amendment in 2013 allowed less invasive axillary staging procedures, i.e., SLNB before primary chemotherapy, or SLNB and/or MARIprocedure (marking the axilla with radioactive iodine seed), after primary chemotherapy. Patients who did not undergo ALND were assigned to the risk groups based on the pathology outcomes of the less invasive staging procedure and the presence or absence of the following risk factors: grade 3, lymphovascular invasion, and tumour size of more than 3 cm, and generally presented with lower N-stage than patients in the ALND group (19). It was hypothesized that the 5-year locoregional recurrence rate (primary outcome) would be less than 4% if the study guideline was followed. The results showed that for the whole cohort (N=838), 5-year locoregional recurrence rate was 2.2% [95% confidence interval (CI): 1.4–3.4%], and did not significantly differ between the three risk groups, nor according to whether the study guideline was followed or not (*Table 1*). The no-ALND group had better 5-year recurrence-free interval (91.7%, 95% CI: 86.1–95.1%) than the ALND group (85.2%, 95% CI: 82.3–87.7%), P=0.032, but the no-ALND group had generally more favourable ypN status compared with the ALND group, which might have positively affected prognosis (19). These results, interpreted as paving the way to safely de-escalate locoregional radiotherapy in the absence of evidence from randomized trials, generated understandable enthusiasm (21). However, there are some pitfalls and concerns to be aware of when trying to apply the results of the RAPCHEM study into the current clinical practice.

A major problem in the interpretation of RAPCHEM results, in particular in the SLNB subpopulation is related to completely different criteria of risk definition for the ALND and SLNB subgroups, which precludes joint interpretation of these results. Additionally, more than half of SLNB were performed before chemotherapy, which precludes inclusion of therapy response in the decision on

Table 1 RAPCHEM outcomes per risk and treatment subgroups

Risk group	RAPCHEM approach	Treatment subgroup†					
		Per protocol		Protocol deviations—less than per protocol		Protocol deviations—more than per protocol	
		Recurrence rate (%)	Number of patients	Recurrence rate (%)	Number of patients	Recurrence rate (%)	Number of patients
Low risk (N=291)	ALND ± RNI‡	2.3	162	NR	2	1.9	73
	SLNB ± RNI		19		0		36
Intermediate risk (N=370)	ALND ± RNI‡	1.0	174	3.2	54	3.8	94
	SLNB ± RNI		30		10		12
High risk (N=177)	ALND + RNI‡	1.4	125	8.4	7	N/A	–
	SLNB + RNI		32		18		–

†, number of patients in each subgroup is taken from Boersma *et al.* (20); ‡, with omission of the operated part of the axilla. RAPCHEM, radiotherapy after primary chemotherapy study (19); ALND, axillary lymph node dissection; N/A, not applicable; RNI, regional nodal irradiation; SLNB, sentinel lymph node biopsy; NR, not reported.

locoregional radiotherapy.

Second, the RAPCHEM strategy basically de-escalated RNI rather than ALND, which goes in the opposite direction to what is currently being pursued according to the evidence on less arm morbidity with RNI compared to ALND (5,7). Currently, in the ypN0 patients ALND is being widely replaced by SLNB, and although the RAPCHEM protocol was amended to include patients in whom ALND was omitted, the size of the no ALND group was small, precluding any conclusions regarding such patients (19), which limits the practical application of the results. In the low-risk group there were 57 patients treated with SLNB, performed before primary chemotherapy in 16, and after primary chemotherapy in 41 patients (19). Despite recommendation of the study protocol, only 20 of these 57 patients were not given RNI, including six patients treated with no radiotherapy at all after mastectomy (20). As opposed to what is being suggested (21), this is definitely not sufficient to conclude that based on the RAPCHEM results the patients with pCR on SLNB could be safely treated without any further axillary management. For the cN1/ypN1 patients (intermediate-risk group) the current major guidelines recommend ALND and RNI with avoidance of operated axilla (12-14). In the RAPCHEM protocol, only local radiotherapy without RNI was recommended for this group, provided the patients underwent ALND. Overall, 228 ypN1 patients (61% of the intermediate-risk group), were treated with ALND without RNI (20), thus having been subjected to the de-escalated approach, though pointed in the opposite direction compared to the current tendencies of replacing ALND with RNI, allowing for drawing a conclusion that irradiation of nodal groups III and IV may probably safely be omitted in this population. Additionally, in the intermediate-risk group there were 44 patients who underwent SLNB and RNI (20). Virtually all had SLNB before chemotherapy (19), so the final axillary status was unknown and some of them might have actually converted to ypN0, which would classify them as low, not intermediate risk, thus precluding any reliable conclusions. No treatment de-escalation was scheduled for the high-risk group, and eventually only single cases were treated against the study protocol, i.e., with less than full RNI (i.e., levels I–IV) (20).

Third, locoregional recurrences occurring concurrently with distant metastases were excluded from the locoregional recurrence rate (19). Should they be included, the locoregional recurrence rate more than doubled, being 5.2% (95% CI: 4.9–6.9%) at 5 years in the whole cohort (19). This alone might have had a big impact on the results, especially in the so called low-risk group (ypN0), which was enriched for patients with aggressive phenotypes [triple negative and human epidermal growth factor receptor 2 (HER2)-positive] due to their stronger association with axillary pCR. In the multivariate analysis the triple negative disease was significantly associated with worse recurrence-free interval (19). This urges caution in translating the results into clinical practice, as the risk of underestimation of the locoregional recurrence rate among theoretically "low risk" patients (ypN0) is tangible, at least for some patient

subpopulations.

Fourth, the only risk factors besides ypN status, considered as related to locoregional recurrence for the purpose of risk groups definition, were grade 3 disease, lymphovascular invasion, and tumour size of more than 3 cm. Molecular subtypes were not taken into account as criteria for the assignment of the patients to the risk groups (19), nor were tested as possible risk factors for non-compliance with the study guidelines (20). An interesting insight can be drawn from the analysis of the outcomes when adherence to the study guidelines is considered. Although the differences were not statistically significant, the patients who received more radiotherapy than prescribed by the study guidelines, have consistently worse OS, shorter recurrence-free interval, and in the intermediate-risk group also worse locoregional control (19). This may reflect a selection of patients with worse prognosis within the broadly defined risk groups for more radiation. Among the tested risk factors (type of breast and axillary surgery, extent of cN+ disease, i.e., palpable or not, age, lymph-vascular invasion, grade, tumour size and pathologic response) only type of breast and axillary surgery seemed to be related to receiving less or more radiotherapy than recommended (20), and this factor has not been associated with worse prognosis (19). Therefore, another widely recognised adverse prognostic factor or a combination of factors must have been taken into account by treating radiation oncologists. Although the reasons for non-adherence to the study guidelines, nor for the possibly worse prognosis in the patients who received more radiation than recommended remain speculative, non-considering molecular subtypes in the definition of the risk-groups is one of the main pitfalls of this study, especially that triple negative disease was a negative predictor of recurrencefree interval in the multivariate analysis (19).

Fifth, two-thirds of the patients in the RAPCHEM study had hormone-receptor (HR) positive, HER2-negative molecular subtype. The vast majority of these patients must have been on adjuvant endocrine therapy for the entire duration of the 5-year follow-up. Despite the adjuvant endocrine therapy, HR-positive tumours retain a substantial risk of late recurrence, and there are more recurrences after 5 years than in the first 5 years after diagnosis (22). Thus, longer follow-up is needed to confirm safety and applicability of the RAPCHEM de-escalation approach, especially that the intermediate-risk group, largely subjected to the de-escalation of RNI, contained 75% of such patients.

An additional concern regards the potential wide-scale overtreatment with neoadjuvant chemotherapy, if the RAPCHEM de-escalation approach were to be incorporated in the routine clinical practice. Neoadjuvant chemotherapy is the first step in this approach, and in the RAPCHEM study it was applied to the cohort of patients containing two-thirds of HR-positive, HER2-negative tumours. Following upfront surgery, post-menopausal women with HR-positive, HER2-negative tumour, one to three positive axillary lymph nodes (pN1), and a low/intermediate recurrence score based on the 21-gene breast cancer assay (Oncotype DX), which constitute >85% of pN1 patients, derive no benefit from chemotherapy (23). For these women, cumulative and potentially irreversible toxicities of unnecessary neoadjuvant chemotherapy, including cardiotoxicity (anthracyclines), long term disabling neuropathies (taxanes), secondary malignancies, cognitive symptoms, and thromboembolic events, potentially outweigh any benefit they could gain from the subsequent locoregional de-escalation, especially taking into account, that a large percentage of cN1 patients undergoing upfront surgery can actually be spared ALND, following the results of Z0011 and AMAROS studies (13).

Lastly, as the least aggressive and associated with the best overall prognosis luminal A subtype of breast cancer is associated with the lowest pCR rate, including conversion to ypN0 status, selecting the volume of residual disease in the axilla as a criterion to define the risk of relapse might have not been the best choice.

In summary, the RAPCHEM prospective registry study provides important data on contemporary rates of locoregional recurrences in patients with cT1–2N1 breast cancer, treated with primary chemotherapy and ALND, with or without RNI based on ypN status. Although the results are encouraging, extrapolating the RAPCHEM strategy to modern practice encounters significant difficulties (*Table 2*). Delivering ALND in lieu of RNI would be a step back in cN1/ypN0 patients, for whom SLNB with RNI is the recommended option, resulting in better functional outcomes (10,11). The next step would be the omission of RNI, and there is already a fully accrued phase III trial, NSAPB B-51 (NCT01872975), investigating this option, awaiting results. The data on 20 patients with low risk and no postoperative RNI following SLNB (some of which would not have been candidates for radiotherapy according to current standards) from the prospective registry study is not enough to change the practice from now on. In cN1/ypN1 patients, again, the RAPCHEM de-escalation approach of ALND alone instead of SLNB with

Table 2 Current treatment recommendations for cT1–2N1 breast cancer (one to three suspicious nodes on imaging), and directions of the locoregional treatment de-escalation attempts in the setting of primary systemic treatment, in comparison to the RAPCHEM strategy

Clinical scenario	RAPCHEM approach	RAPCHEM-based conclusion on de-escalation	Current guidelines	Current directions of the locoregional treatment de-escalation
Low risk	ALND, no RNI (N=181)†	Omission of chest wall/RNI safe	SLNB + RNI	SLNB, no RNI
	SLNB, no RNI (N=20)†	None possible		
Intermediate risk	ALND, no RNI (N=228)†	Omission of RT to LN groups III and IV safe	ALND + RNI‡	SLNB + RNI
	SLNB + RNI (N=44)†	None possible		
High risk	ALND + RNI‡ (N=128)†	None	ALND + RNI‡	No de-escalation

†, number of patients in each subgroup is taken from Boersma *et al.* (20); ‡, with omission of the operated part of the axilla. RAPCHEM, radiotherapy after primary chemotherapy study (19); ALND, axillary lymph node dissection; RNI, regional nodal irradiation; SLNB, sentinel lymph node biopsy; RT, radiotherapy; LN, lymph node.

RNI, is not in line with the current tendencies. The latter strategy is being prospectively investigated in the ongoing ALLIANCE A011202 trial (NCT01901094) against the standard approach of ALND and RNI.

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Footnote

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