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DEGRO practical guidelines for radiotherapy of breast cancer IV

Radiotherapy following mastectomy for invasive breast cancer

The term postmastectomy radiotherapy (PMRT) describes adjuvant radiotherapy after mastectomy. Irradiation is typically delivered to the chest wall, including the regional lymphatics.

Since the last recommendations from the Breast Cancer Expert Panel of the German Society for Radiation Oncology (DEGRO) in 2008, evidence for the effectiveness of PMRT has grown and updates of national and international guidelines, including the S3 guidelines of the German Cancer Society (DKG) 2012 [85], those from the National Comprehensive Cancer Network (NCCN) 2013 [63], the Scottish Intercollegiate Guidelines Network (SIGN) 2013 [88], the Federaal Kenniscentrum voor de Gezondheidszorg (KCE, Belgium) 2013 [5] and the National Institute for Health and Care Excellence (NICE) [65]) are available; as are new data and meta-analyses, e.g. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2014 [23]. The authors performed a comprehensive survey of the literature. Data from recently published analyses, trials and guidelines yielding new aspects compared to 2008 were reviewed and discussed. New aspects were included in the current, updated recommendations. In the following section, the statements from the 2012 national S3 guidelines [85] are reported, followed by updated information and a comment from the DEGRO expert panel.

Updated PMRT evidence

PMRT and survival and recurrence

Statement of the German S3 Guidelines 2012 [85]

Statement RT 4a

Postoperative radiotherapy of the chest wall decreases the risk of local recurrence after mastectomy (level of evidence, LOE 1a)

Statement RT 4b

In patients with a high risk of local recurrence, PMRT improves overall survival (LOE 1a)

Evidence that PMRT improves locoregional control and overall survival has grown continuously [19, 20, 23, 24, 26, 29, 33, 42, 51, 52, 62, 64–67, 70, 72, 74, 75, 77, 81, 82, 88, 90, 101, 103, 105]. In almost all of these trials, radiotherapy comprised chest wall irradiation with irradiation of the regional nodes (regional nodal irradiation, RNI; [87]). The known survival benefit and clear reduction in the risk of local recurrence in high-risk patients with T3/T4 tumors or positive resection margins reached a level of evidence (LOE) of 1a, rather than 2a [85]. Therefore, PMRT is highly recommended in these patients (NCCN 2013 [63], NICE 2013 [65]; NZGG 2013 [70] guidelines). In addition, the intermediate risk of local recurrence in T3 N0 tumors with risk factors or T1/2 N1 tumors is increasingly becoming the focus of various reviews and new trials, which consider PMRT to complete treatment in these patients [50, 53, 71]. The recent update of the EBCTCG meta-analysis [23] with extended follow-up un-

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derscores the reduction in risk of local recurrence at 10 years and the risk for breast cancer mortality at 20 years, particularly in patients with positive lymph nodes and even in the presence of systemic therapy. Almost all of these patients received radiotherapy to the supraclavicular/axillary region (>98 %), as well as to the internal mammary chain (IMC; pN0 >80 %, pN+ 95 % of the patients).

PMRT and risk factors

Statement of the German S3 Guidelines 2012 [85]

Statement RT 4c

PMRT of the chest wall is indicated in patients with:

- T3/T4 tumors (LOE 1a, grade of recommendation, (GR A),
- pT3 pN0 R0 tumors and risk factors such as lymphovascular invasion, grade 3, close resection margins, premenopausal women and age < 50 years (LOE 2b, GR B),
- R1/R2 resection without possibility of achieving clear margins (LOE 1a, GR A),
- pN+ (> 3; LOE 1a, GR A).

In the current German S3 guidelines, the recommendations regarding T3 tumors are inconsistent and require further clarification. Firstly, the S3 guidelines state that PMRT is indicated in T3 and T4 tumors, with an LOE of 1a. Furthermore, the guideline separates T3 N0 tumors and recommends PMRT in T3 N0 tumors only when additional risk factors are present. In contrast to the current German S3 guidelines, the NCCN 2013 guidelines recommend PMRT for all T3 N0 patients [63].

Therefore, a comprehensive review of studies analysing T3 N0 patients with and without risk factors was performed. **Tables 1 and 2** [77] show risk factors and risk categories for local relapse (lymphovascular invasion, blood vessel invasion, positive lymph node ratio >20 %, close resection margins <3 mm, G3 tumor grading, young age/premenopausal status, extracapsular invasion, negative hormone receptor status, invasive lobular cancer, tumor size >2 cm, tumor location or a combination of ≥2 risk factors) and help to identify patients with a high-risk constellation after mastectomy, thus indicating PMRT. Particularly the presence of more than one risk factor seems to have a substantial negative impact on local recurrence rate (LRR; [1, 18, 34, 43, 81, 96, 99, 100]). Rowell showed the risk for local relapse is ≥15 % as soon as two or more risk factors are present [81]. The NCCN guidelines recommend PMRT +/- supra-/infraclavicular fossa + internal mammary nodes in all patients with pN0 and tumor sizes >5 cm or positive margins; however, there is literature available concluding that not all T3 N0 patients should routinely receive PMRT, due to low recurrence rates after a median follow-up time of 15 years [96].

Radiation of internal mammary nodes was described to improve disease-free survival rates in patients with a stage II/III and/or medial tumor location [16].

A review dealing with infiltrating lobular subtype states that in the case of invasive lobular cancer, PMRT is recommended for stage I–III, due to the special biological behavior of this entity [79]. Diepenmaat and colleagues reported a significantly lower recurrence rate for these patients after PMRT, with a hazard ratio for local recurrence of 0.3 compared to patients with invasive lobular cancer without PMRT [21].

The impact of different molecular subtypes of breast cancer on local recurrence or response to radiotherapy is currently unclear and therefore no recommendations are available.

Comments of the DEGRO expert panel

- **PMRT (chest wall + regional lymphatics) has no beneficial effect in patients with negative lymph nodes and tumor sizes < 5 cm and resection margins > 1 mm without risk factors (NCCN 2013 [63], [23]).**
- **The impact of different risk factors (see Table 1) has been better defined in the meantime. Particularly in cases with two or more risk factors, PMRT should be also considered in patients with stage I/II cancers, including T3 N0 (NCCN 2013 [63], Arbeitsgemeinschaft Gynäkologische Onkologie, AGO recommendations [2], French expert review board [6], [94]).**
- **In cases of invasive lobular breast cancer, PMRT might reduce the local recurrence rate (AGO recommendations [2], [79]).**

PMRT for patients with 1–3 positive lymph nodes

Statement of the German S3 Guidelines 2012 [85]

Statement RT 4c

PMRT of the chest wall is indicated in patients with:

- T3/T4 tumors (LOE 1a, GR A)
- pT3 pN0 R0 tumors and risk factors like lymphovascular invasion, grade 3, close resection margins, premenopausal women and age < 50 years (LOE 2b, GR B)
- R1/R2-resection without possibility to achieve clear margins (LOE 1a, GR A)
- pN+ (> 3; LOE 1a, GR A)

Remarkably, there has been an ongoing debate on whether or not PMRT should be given to patients with 1–3 positive axillary lymph nodes, although available evidence has already indicated a likely benefit [23, 53, 57, 72, 78, 80]. The recently published update of the EBCTCG meta-analysis [23] should bring the debate to an end, since it unequivocally demonstrates that patients with 1–3 involved lymph nodes receive the same survival benefit from PMRT as patients with >3 involved lymph nodes.

Importantly, the survival advantage was also present in patients who received systemic treatment and adequate axillary surgery, independent of the number of involved axillary lymph nodes. In 1314 patients with pN+ (1–3 nodes), the risk for local recurrence at 10 years was significantly reduced from 20.3 to 3.8 % and breast cancer mortality decreased significantly by 7.9 % after 20 years. Of these patients, 1133 received systemic therapy. In comparison, the risk for local recurrence in 1772 patients with pN+ (≥4 nodes) at 10 years was significantly reduced from 32.1 to 13.0 % and breast cancer mortality was also reduced by 9.3 % at 20 years [22].

Further elucidation is awaited from the UK Medical Research Council/European Organisation for Research and Treatment of Cancer (EORTC) 22052 – 10051 SUPREMO trial, which recruited patients

Abstract · Zusammenfassung

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DEGRO practical guidelines for radiotherapy of breast cancer IV. Radiotherapy following mastectomy for invasive breast cancer

Abstract

Background and purpose. Since the last recommendations from the Breast Cancer Expert Panel of the German Society for Radiation Oncology (DEGRO) in 2008, evidence for the effectiveness of postmastectomy radiotherapy (PMRT) has grown. This growth is based on updates of the national S3 and international guidelines, as well as on new data and meta-analyses. New aspects were considered when updating the DEGRO recommendations.

Methods. The authors performed a comprehensive survey of the literature. Data from recently published (meta-)analyses, randomized clinical trials and international cancer societies' guidelines yielding new aspects compared to 2008 were reviewed and discussed. New aspects were included in the current guidelines. Specific issues relating to particular PMRT constellations, such as the presence of risk factors (lymphovascular invasion, blood vessel invasion, positive lymph node ratio > 20 %, resection margins < 3 mm, G3 grading, young age/premenopausal status, extracapsular invasion, negative hormone receptor status, invasive lobular cancer, size > 2 cm or a combination of ≥ 2 risk factors) and 1–3 positive lymph nodes are emphasized.

Results. The evidence for improved overall survival and local control following PMRT for T4 tumors, positive resection margins, > 3 positive lymph nodes and in T3 N0 patients with risk factors such as lymphovascular invasion, G3 grading, close margins, and young age has increased. Recently identified risk factors such as invasive lobular subtype and negative hormone receptor status were included. For patients with 1–3 positive lymph nodes, the recommendation for PMRT has reached the 1a level of evidence.

Conclusion. PMRT is mandatory in patients with T4 tumors and/or positive lymph nodes and/or positive resection margins. PMRT should be strongly considered in patients with T3 N0 tumors and risk factors, particularly when two or more risk factors are present.

Keywords

Postmastectomy radiotherapy (PMRT) · Breast cancer · Guideline · Mastectomy · Risk factors

DEGRO Leitlinien für die Radiotherapie des Mammakarzinoms IV. Radiotherapie nach Mastektomie beim invasiven Mammakarzinom

Zusammenfassung

Hintergrund und Ziel. Seit der letzten Aktualisierung der 2008 publizierten Leitlinie der „Expertengruppe Mammakarzinom" der Deutschen Gesellschaft für Radioonkologie (DEGRO) zur Strahlentherapie nach Mastektomie (PMRT) hat sich die Evidenz für die Effektivität der PMRT aufgrund von Überarbeitungen der nationalen S3- und internationaler Leitlinien sowie neuer Daten und Metaanalysen verstärkt. Hieraus resultierende neue Erkenntnisse wurden bei der Aktualisierung der DEGRO-Leitlinien berücksichtigt.

Methode. Die Autoren führten eine umfassende Literaturrecherche durch. Es wurden Daten aktueller (Meta-)Analysen, randomisierter klinischer Studien und Leitlinien internationaler Krebsgesellschaften auf Neuerungen gegenüber 2008 überprüft und diskutiert. Daraus abgeleitete Änderungen wurden in die aktuellen Empfehlungen eingearbeitet. Es wurden spezielle Fragestellungen in Bezug auf eine PMRT bei speziellen Konstellationen wie dem Vorliegen von Risikofaktoren (lymphovaskuläre Invasion, vaskuläre Invasion, positive „lymph node ratio" > 20 %, Resektionsränder < 3 mm, Grading G3, junges Alter/Prämenopausalstatus, extrakapsuläre Invasion, negative Hormonrezeptoren, invasive lobuläre Tumoren, Tumorgröße > 2 cm oder eine Kombination von ≥ 2 Risikofaktoren) und von 1–3 positiven Lymphknoten untersucht.

Ergebnisse. Die Evidenz für verbesserte Überlebenswahrscheinlichkeit und lokoregionale Kontrolle nach PMRT bei T4-Tumoren, positivem Resektionsstatus, > 3 positiven Lymphknoten und zusätzlich bei Patientinnen mit T3 N0-Situation und Risikofaktoren wie lymphovaskulärer Invasion, G3-Tumoren, kleinem Sicherheitssaum und jungem Alter hat sich verstärkt. Neue Risikofaktoren wie invasiver lobulärer Subtyp und negativer Hormonrezeptorstatus wurden eingeschlossen. Für Patientinnen mit 1–3 positiven Lymphknoten hat die PMRT ein Evidenzlevel („level of evidence") 1a erreicht.

Schlussfolgerung. PMRT ist obligat bei Patientinnen mit einem T4-Tumor und/oder positiven Lymphknoten und/oder positiven Schnitträndern. Eine PMRT sollte auch bei Patientinnen mit T3 N0-Tumoren und Risikofaktoren erfolgen, vor allem wenn 2 oder mehr Risikofaktoren vorliegen.

Schlüsselwörter

Postmastektomie Radiotherapie (PMRT) · Mammakarzinom · Leitlinie · Mastektomie · Risikofaktoren

until 2014 [50]. In addition, there are two more retrospective cohort analyses: Tendulkar and colleagues reported an LRR of 8.9 % without PMRT vs. 0 % with PMRT after a median follow-up of 5 years in 271 patients with pN1 stage disease. Grade III and extracapsular extension (ECE) were independent risk factors for the risk of local recurrence [96]. In 318 patients, Huang and colleagues reported a significant reduction of the 11.0 % LRR without PMRT to a 3.1 % LRR with PMRT. In the latter study, median follow-up was > 9 years and the 10-year overall survival rate was 76.1 % vs. 82.1 % (not significant); however, the difference in disease-free survival reached statistical significance (73.8 vs 61.3 %, $p = 0.001$; [37]). High-risk factors were a positive nodal ratio of ≥ 25 % and lymphovascular invasion. A late analysis of the Danish Breast Cancer Group (DBCG) postmastectomy studies (LRR significantly improved with PMRT after 18 years follow-up: 4 % vs. 26 %, $p < 0.001$) and the British Columbia Randomized Trial (overall survival significantly better with PMRT after

Table 1 An overview of risk factors for local recurrence in patients after mastectomy. It is shown that not all risk factors are equally important. Weighting of the risk factors is important for individual treatment decisions

	Trial/stage	No. of patients (N)	RT	Endpoint	Median FU	L1	V1	N1	R+	G3	Young age < 45 years	Tumor size > 2 cm	Tumor location	ECE	1. HR-2Her-2neu+3. Triple -	ILC	≥ 2 RF
Randomized controlled trials																	
Kyndi 2008 [51]	DBCG 82b+c	1000	PMRT[a]	OS+	17 years	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.+2.+3.+	NA	NA
Reviews																	
Rowell 2009 [81]	Different trials and reports N0		PMRT	LRR+	NA	+	NA	NA	+	+	+	+	NA	NA	–	NA	+
	Meta-Analysis of three RCTs	667	PMRT	LRR+; OS+	NA	+	NA	NA	+	+	+	+	NA	NA	–	NA	+
Offersen 2011 [71]	DBCG 82b+c	1152	PMRTIMMS	LRR+OS+	18 years	NA	NA	+	NA	+	NA	NA	NA	NA	1.+2.+3. NA	NA	NA
	British Columbia Randomized Trial	318	PMRTIMMS	LRR+OS+	20 years	NA	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA
	British Columbia Cohort treated outside trial	2768	PMRT+/– RNI	LRR+	10 years	NA	NA	+	NA	NA	NA	NA	Medial-Central	NA	NA	NA	NA
Poortmans 2013 [79]	Invasive lobular cancers	NA	PMRT[a]	LRR+	NA	NA	+	+	NA	+	NA	+	NA	–	NA	+	NA
Retrospective analyses of large cohorts (>300 patients)																	
Jagsi 2005 [43]	N0, no T4	877	–	LRR+	100 months	+	NA	NA	+	NA	+	+	NA	NA	1.+(sub-analysis)2. NA 3. NA	NA	+
Truong 2005 [98]	T1–2, N0British Columbia	1505	–	LRR+	7 years	+	NA	NA	NA	+	–	+	NA	NA	1.+2. NA 3. NA	–	+
Truong 2005 [99]	T1–2, N1British Columbia	821	–	LRR+	7.7 years	NA	NA	+#	+	+	+	+	medial	NA	1.+2. NA 3. NA	NA	+
Diepenmaat 2009 [21]	Invasive lobular cancer	383	PMRT+/–RNI	LRR+	7.2 years	NA	NA	–	NA	NA	–	–	NA	NA	NA	+	NA
Abi-Raad 2011 [1]	T1/2 N0	1136	–	LRR	9 years	+	NA	NA	+	+	+	+	NA	NA	1.–2. NA 3. NA	NA	+
Tendulkar 2012 [95]	N1	369	PMRT+/–Boost+MS+/–IM	LRR+	5.2 years	+	NA	+#	–	+	–	–	NA	+	1.+2. NA 3. NA	NA	+
Geng 2013 [30]	N+	1220	PMRT+ Boost MS	LRR+OS+	156 months	NA	NA	NA	NA	NA	NA	+	NA	+	NA	NA	NA
Hastings 2013 [34]	T1 N0	1259	–	LRR+	8.15 years	–	NA	NA	+	+	NA	NA	–	NA	1.+2.–3. NA	–	+
Cheng 2013 [18]		1545	PMRTIMMS	LRR	61 months	+	NA	–	NA	+	–	+	–	+	1.+2.–3. NA	NA	+
Kim 2013 [46]	T1/2 N1Korean Breast Cancer Registry	3477	PMRT+MS+/-MS	OS+	3.3 years	NA	NA	#	NA	+	+	+	NA	NA	1.+2.3.	NA	NA

RT radiotherapy, **FU** follow up, **L1** lymphovascular invasion, **V1** blood vessel invasion, **N+** one or more positive lymphnodes, **#** positive node ratio > 20%, **R+** close resection margins (< 3 mm), **G3** tumor grading 3, young age = < 45 years/premenopausal, **ECE** extracapsular invasion, **HR-** negative hormone receptor status, **Triple-** triple negative receptor status, **ILC** invasive lobular cancer, **≥ 2 RF** two or more risk factors in combination, **+** risk factor, **RCT** randomized controlled trial, **PMRT** postmastectomy radiotherapy, **MS** medial supraclavicular irradiation, **IM** internal mammary chain irradiation, **LRR** local recurrence rate, **OS** overall survival, **+** risk factor, **-** no risk factor, **NA** not available

[a]PMRT not further described in detail

Table 2 Risk categories for locoregional relapse after mastectomy and axillary clearance

Risk category	Low	Intermediate	High
Risk	< 10 %	10–20 %	> 20 %
Tumor stage	T1–2	T1–2	T3–4
Number of Ax LK+	0	1–3	> 3
Grade	1–2	3	
Vascular invasion (V1, L1)	–	+	
Histology	Ductal	Lobular	

Ax LK+ involved axillary lymph nodes Modified from Poortmans P: Evidence based radiation oncology: Breast cancer [77]

20 years follow-up: 47 % vs. 37 %, $p = 0.03$) clearly show the benefit of PMRT and irradiation of the regional lymphatics in patients with 1–3 positive axillary lymph nodes [71].

Comments of the DEGRO expert panel

- **In contrast to the current German S3 guidelines, the DEGRO panel regards PMRT as mandatory in patients with positive axillary lymph nodes, irrespective of the number of involved lymph nodes (LOE 1a; [94])**

Patient age and the implications for PMRT

Due to various reasons, omission of radiotherapy in elderly patients is still common [86], but this is also a topic of debate in young patients [102]. Smith and colleagues described omission of radiotherapy in elderly women in 50 % of cases, even in high-risk constellations [93]. At the same time, it is also known that patients who are not treated according to radiotherapy guidelines have a worse outcome, particularly in terms of significantly decreased overall and disease-free survival [32]. In 2012, the International Society of Geriatric Oncology (SIOG) and the European Society of Breast Cancer Specialists (EUSOMA) published their recommendations for the management of elderly patients with breast cancer [8]. They recommend PMRT for elderly patients with more than three positive axillary lymph nodes and/or a pT3/4 tumor. Even though the absolute risk reduction for elderly patients is somewhat smaller than for younger patients, the benefit received from PMRT is still substantial.

EUSOMA recommendations are also available for young patients [13]. Varga et al. showed that young patients < 40 years are not treated according to the standard of care in more than 50 % of cases. This resulted in a significantly reduced overall survival [102]. Although high-level evidence is only available following breast conserving surgery, it is obvious that tamoxifen alone cannot substitute for postoperative radiotherapy without a substantial increase in LRR, as exemplified by the results of Hughes et al., who observed a four-fold increase in the 10-year LRR [41].

Comments of the DEGRO expert panel

- **Patients should not be precluded from PMRT on the basis of formal age criteria alone.**
- **Where PMRT is indicated, it should only be omitted in case of poor clinical condition or comorbidities substantially reducing life expectancy.**

PMRT and breast reconstruction

Reconstruction with autologous flaps or implants is possible in combination with PMRT [47, 48]. In a systematic review, autologous reconstructions represented 20 vs. 80 % of expander-implant reconstructions after mastectomy [91].The same group describes that 20–30 % of patients may require some type of revision/replacement, with long-term follow-up based on large series from the Memorial Sloan Kettering Cancer Center and the Cleveland Clinic [91]. Autologous reconstruction seems to be better than permanent implant (LOE 1b; [4, 47, 48]). Expander placement prior to PMRT has a superior cosmetic outcome with no difference in LRR compared to autologous reconstruction without expander [47]. Immediate reconstruction with expander/implant and PMRT followed by definitive allogeneic breast reconstruction results in acceptable morbidity and patient satisfaction [76]. Favorable replacement and removal rates were shown in a large cohort from the Memorial Sloan Kettering Cancer Center who received PMRT after implantation of a tissue expander and then a permanent implant after PMRT [35].

In a prospective analysis, delaying the expander-implant exchange for at least 6 months after the completion of PMRT significantly reduced expander-implant failure [73]. However, the optimal timing of PMRT is controversially discussed [15, 47, 48]. Regarding the irradiation technique, no significant differences were found for dose inhomogeneity during the treatment planning with an opposed pair of beams [97]. To increase the skin dose, bolus material might be used. However, Chawla et al. showed an impairment of cosmesis using bolus material [17].

Comments of the DEGRO expert panel

- **Evidence is accumulating that following PMRT with modern radiotherapy techniques, reconstruction using autologous material or implants or both are options.**
- **Implanting expanders before definitive reconstruction and finished skin expansion prior to starting PMRT seems to be feasible and result in good patient satisfaction. Physicians and patients should be aware of a reasonable implant removal rate and toxicities such as fibrosis.**

PMRT and primary systemic therapy

Statement of the German S3 Guidelines 2012 [85]

Statement RT 4d

After primary (neoadjuvant) systemic therapy (PST), the indication for adjuvant radiotherapy follows pretherapeutic TN categories, irrespective of response to the primary systemic treatment (LOE 2 A, GR A).

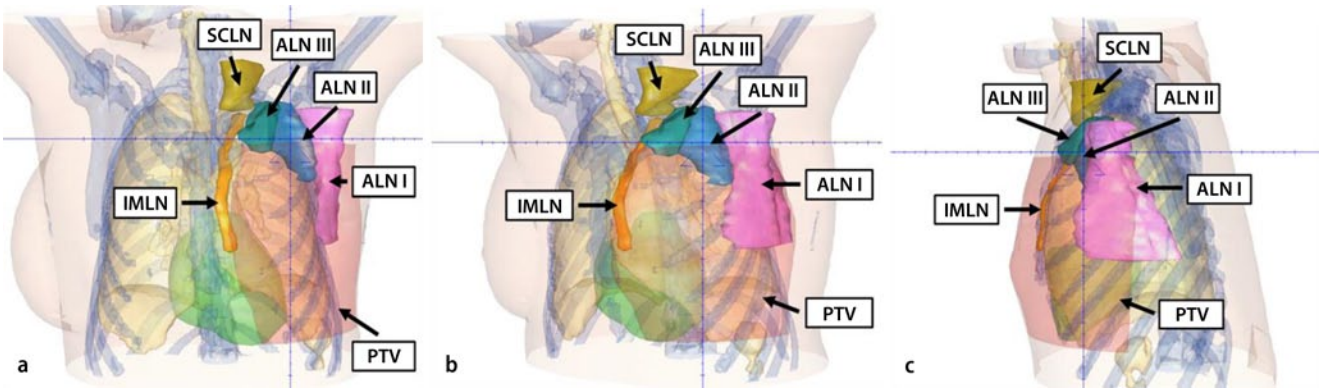

Fig. 1 ▲ Target volume definition for postmastectomy radiotherapy (PMRT) including the regional lymphatics (supraclavicular/axillary + internal mammary chain, IMC). Regional lymph node projections in a postmastectomy setting: **a** frontal projection (0°) **b** oblique projection (30°), **c** lateral projection (90°) *ALN I* axillary lymph nodes level I (*pink*), *ALN II* axillary lymph nodes level II (*blue*), *ALN III* axillary lymph nodes level III (*turquoise*), *IMLN* internal mammary lymph nodes (*orange*), *SCLN* supraclavicular lymph nodes (*ocher*), *PTV* postmastectomy planning target volume (*transparent red*), heart (*green*), lungs and airway (*yellow*), bony structures (*transparent blue*)

PMRT after primary systemic therapy (PST) is recommended in patients with a risk of relapse ≥10 % [7]. PMRT is therefore recommended in any pretherapeutic stage III disease and in stage I or II with residual disease in lymph nodes. PMRT is controversially discussed for patients with stage I or II and residual disease in the breast but not in lymph nodes [7], and also for patients with complete pathological response after PST [7, 36, 38, 59, 92]. After a complete response, it is discussed that PMRT might be omitted in stage I/II or even stage III (KROG 12-05 study) cancers [7, 36, 92]. These findings have to be interpreted with caution, as radiotherapy was not subject to randomization in these studies. Others have shown a benefit of PMRT in patients with complete response after PST [38, 59]. Marks et al. recently suggested that the indication for PMRT should be based on prechemotherapy positive axillary nodal metastases and not postchemotherapy axillary nodal metastases, since this results in better breast cancer mortality rates [56].

In the future, the RAPCHEM (NCT01279304) trial at the Netherland Cancer Institute Amsterdam/Maastricht (inclusion of ypT0–2 ypN0 patients with and without PMRT) and The Alliance for Clinical Trials in Oncology trial (inclusion of ypT0–3 ypN0 patients with and without PMRT) might provide answers to these questions. Further trials include the NSABP B-51/RTOG trial, where patients with initially confirmed axillary metastases converting to pathologically negative nodes after PST will be randomized after neoadjuvant chemotherapy for PMRT to the chest wall and the regional lymphatics [56]. In general, the risk factors for LRR are the same as for patients without PST [36, 107]. Again, the presence of several risk factors leads to a significantly higher LRR [39].

Comments of the DEGRO expert panel

- **PMRT after PST is recommended in patients with an intermediate or high risk for locoregional relapse, i.e. the indication for PMRT should be based on pretreatment staging analogous to the adjuvant situation (see above), irrespective of response to PST, until data from prospective trials are available.**

PMRT and breast cancer in males

Whether breast cancer in males has a different biological behavior is still a matter of debate [60, 69]. For breast cancer in males, it is recommended to follow the guidelines for PMRT for women (SIOG and EUSOMA; [8]). In the review by Ruddy and colleagues, an improvement in LRR but not in overall survival after PMRT is described [83]. These authors recommend always administering PMRT in high-risk male breast cancer patients and optionally in intermediate risk patients. In a further population-based study ($n = 664$), an overall survival benefit was seen with PMRT in stage II (trend) and stage III (significant) male breast cancer. In stage I, patients appeared not to benefit from PMRT (LOE3a; [25]).

Comments of the DEGRO expert panel

- **The indication for PMRT in male patients following mastectomy should follow the guidelines for women.**

PMRT target volume, dose and technique

The PMRT target volume generally includes the chest wall and the regional lymphatics. The specific role of IMC irradiation has been discussed previously [87]. There is evidence from prospective studies [50, 71] and a recent meta-analysis [23] that inclusion of the IMC lymphatics in PMRT should be strongly considered, particularly in pN+ patients (see ◘ **Fig. 1**). No systematic data on the influence of trastuzumab on cardiac toxicity in combination with concurrent radiotherapy to the IMC have been published up to date.

The PMRT dose is 50–50.4 Gy, given in 1.8–2.0 Gy fractions. Optionally, a scar boost can be applied at 2 Gy per fraction to a total dose of approximately 60 Gy, particularly in the case of close margins. All dose schedules are given 5 days per

week [14]. In the UK Standardization of Breast Radiotherapy (START) studies, about 7–14 % of the total patients received hypofractionated radiotherapy following mastectomy, but none did in the Canadian trial. Hypofractionation to the chest wall may therefore be an option for selected patients, analogous to the DEGRO recommendation for patients after breast conserving surgery [87, 89]. No relevant clinical evidence on the role of hypofractionation following PST is currently available.

A recent meta-analysis of three randomized trials showed that additional regional radiotherapy to the internal mammary and medial supraclavicular lymph nodes significantly improves disease-free, distant metastasis-free and overall survival in stage I-III breast cancer [12]. Regarding the technique, three-dimensional treatment planning is usually used for photon beams irradiating the chest wall and/or regional lymph nodes. Additionally, electrons can be used to cover the medial part of the chest wall and to improve doses to organs at risk. To define the field borders for radiotherapy of the chest wall the RTOG contouring atlas (available at http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx) or the Danish recommendations [68] can be used. New treatment techniques such as intensity-modulated radiotherapy (IMRT) or proton therapy are currently under investigation [54, 55].

Summary of the DEGRO expert panel

- **PMRT including the chest wall and regional lymphatics is mandatory following mastectomy in patients with T4 tumors or (any) positive lymph nodes or R1/R2 resection. Radiotherapy to the IMC in node-positive patients should be strongly considered.**
- **PMRT should be strongly considered in T3 N0 patients with two or more risk factors (see ◘ Table 1).**
- **PMRT should only be omitted in elderly patients in cases of poor clinical condition or comorbidities substantially reducing life expectancy.**
- **Breast reconstruction using autologous materials or implants or both are options following PMRT with modern radiotherapy techniques.**
- **The indication for PMRT after PST should be based on pretreatment staging, analogous to the adjuvant situation, irrespective of response to PST, until data from prospective trials are available.**

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Compliance with ethical guidelines

Conflict of interest. F. Wenz, E. Sperk, W. Budach, J. Dunst, P. Feyer, R. Fietkau, W. Haase, W. Harms, M. D. Piroth, M.-L. Sautter-Bihl, F. Sedlmayer, R. Souchon, C. Fussl, and R. Sauer state that there are no conflicts of interest.

The accompanying manuscript does not include studies on humans or animals.

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