What Is the Best Management of cN0pN1(sn) Breast Cancer Patients?

Jana de Boniface^{a,b} Marcus Schmidt^c Jutta Engel^d Marjolein L. Smidt^e
Birgitte Vrou Offersen^f Toralf Reimer^g

^aDepartment of Surgery, Capio St. Göran's Hospital, Stockholm, Sweden;

^bDepartment of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden;

^cDivision of Molecular Medicine, Department of Obstetrics and Gynecology, Comprehensive Cancer Center, University Medical Center Mainz, Mainz, Germany;

^dMunich Cancer Registry (MCR), Institute for Medical Information Processing, Biometry and Epidemiology (IBE) at the University Hospital of Munich, Ludwig Maximilians-University (LMU), Munich, Germany;

^eDivision of Surgical Oncology, Maastricht University Medical Centre, Maastricht, The Netherlands;

^fDepartment of Experimental Clinical Oncology & Department of Oncology, Aarhus University Hospital, Aarhus, Denmark;

^gDepartment of Obstetrics and Gynecology, University of Rostock, Rostock, Germany

Keywords

Breast cancer · Axillary surgery ·
Sentinel lymph node biopsy · Radiotherapy

Summary

Although the majority of breast cancer patients are clinically node-negative (cN0) at diagnosis, 15–20% will have a metastatic sentinel lymph node (SLN, pN1(sn)). While a less radical approach regarding axillary surgery in cN0 patients with a positive SLN biopsy is advocated, the limitations of 5 published trials on axillary management in pN1(sn) are discussed intensely in the literature and support the performance of ongoing validation and extension trials, especially considering the lack of data in the setting of mastectomy. As locoregional radiotherapy has a significant effect on both recurrence and survival, a standardization of locoregional radiotherapy in the situation of SLN biopsy alone in pN1(sn) patients has to be defined in the future, and de-escalation trials should embrace a truly multidisciplinary approach. This is also of utmost importance considering the fact that high-volume nodal disease requires an intensified adjuvant chemotherapy strategy to which patients omitting axillary dissection cannot be stratified. Finally, there is mounting evidence that the therapeutic role of extensive axillary surgery in low-volume nodal disease is negligible, and multidisciplinary and translational efforts must be undertaken to individualize treatment in

order to gain a reasonable balance between necessary staging information and unnecessary treatment-related morbidity.

© 2018 S. Karger GmbH, Freiburg

What is the Best Management of cN0pN1(sn) Breast Cancer Patients from the View of the Epidemiologist?

Jutta Engel

The number of positive lymph nodes is the strongest prognostic factor for survival in invasive breast cancer, supported by data from the Munich Cancer Registry (MCR) [1] (fig. 1). However, the role of diagnostic or even therapeutic lymph node surgery is questionable, since evidence strongly supports the hypothesis that cancer cells that have migrated and already established locoregional metastases no longer metastasize [2, 3]. Improved systemic treatment in recent decades [4] and the increasing impact of molecular (intrinsic) subtypes on systemic treatment decisions [5] are further arguments against surgical treatment of regional lymph nodes. Figure 2 shows that even within the patient group with 1–3 affected lymph nodes, prognosis differs by intrinsic subtypes, in this case distinguished by their immunohistochemical surrogate.

In early breast cancers with clinically uninvolved lymph nodes, findings show that long-term survival does not differ after axillary radiotherapy (RT) and axillary dissection. The only difference is a

Fig. 1. Relative survival ($\approx$ tumor-specific survival) by number of positive lymph nodes based on data from the Munich Cancer Registry (MCR) (M0 at diagnosis, without neoadjuvant therapy).

Fig. 2. Relative survival ($\approx$ tumor-specific survival) by intrinsic (-like) subtype for patients with 1–3 positive lymph nodes based on data from the Munich Cancer Registry (MCR) (M0 at diagnosis, without neoadjuvant therapy).

better axillary control in the group with axillary dissection' [6]. Since several studies have already shown that surgical removal of regional lymph nodes does not translate into a survival benefit, evidence suggesting that irradiation of regional lymph nodes should improve patients' outcome, even if only marginally, is puzzling [7, 8].

According to recent evidence, irradiation of lymph nodes reduces regional recurrence [7, 8], an effect limited to the hormone receptor-negative subgroup [8]. The reason for this is currently inadequately explored and could be further questioned. Whether an immune reaction is triggered by the irradiation of lymph nodes with a subsequent effect on distant metastases remains to be discussed, especially with regard to increasingly better systemic immunotherapy. In addition, there is no evidence supporting an early effect of regional radiation on the prevention of distant metastases [8], while the median growth time from initiation of distant metastases to their diagnosis is about 5 years or even more [9].

In summary, surgical removal of regional lymph nodes seems unreasonable, even in patients with 1–3 positive lymph nodes. Regarding the irradiation of regional lymph nodes, too many open questions remain. If any implications for medical practice could be derived from the evidence presented, one could consider and further discuss regional irradiation in the subgroup of hormone receptor-negative tumors until causality is clarified.

What is the Best Management of cN0pN1(sn) Breast Cancer Patients from the View of the Surgeon?

Jana de Boniface, Toralf Reimer, Marjolein L. Smidt

Sentinel lymph node (SLN) biopsy is the standard axillary staging procedure in clinically node-negative (cN0) breast cancer. Further axillary treatment in the case of SLN metastases (pN1(sn)) was

investigated in 5 randomized controlled trials, recently reviewed by Schmidt-Hansen et al. [10]. In summary, no differences in survival or recurrence rates were observed between SLN biopsy alone, SLN biopsy followed by axillary radiotherapy (ART), and SLN biopsy followed by completion axillary lymph node dissection (cALND). Morbidity, however, increases in the case of ART and especially cALND when compared to SLN biopsy alone.

Previous Clinical Trials for cN0pN1(sn) Patients

The ACOSOG Z0011 trial randomized nearly 900 patients with cT1–2 cN0 cM0 breast cancer and 1–2 metastatic SLNs treated with breast-conserving surgery (BCS) to either no further axillary surgery or cALND. No differences in recurrence or survival rates were detected. Target enrolment was 1,900 women, but the trial closed early due to lower than expected accrual and event rates [11–13]. Because a significant proportion of patients were treated with high tangents or direct nodal irradiation via a third field, a local effect on the axilla through RT could not be excluded; however, protocol violations were balanced between the 2 study arms [14].

The randomized non-inferiority trial IBCSG 23-01 compared cALND versus SLN biopsy alone in patients with one or more micrometastatic SLNs [15]. This trial did not meet its accrual goal either (target: $n = 1,960$; reported: $n = 934$), but its results do not support cALND in the case of SLN micrometastases [16].

Analogous to IBCSG 23-01, the small multicenter AATRM 048/13/2000 trial compared cALND with SLN biopsy alone in the case of SLN micrometastases ($n = 233$). No differences in survival were reported [17].

Importantly, all 3 trials randomized patients only after the results of SLN biopsy were known, which puts these trials at risk of recruitment bias such that patients perceived to be at higher risk may not have been invited to participate.

In the EORTC 10981-22023 AMAROS trial, patients with early-stage breast cancer and positive SLN biopsy were randomized between cALND and ART ($n = 1,425$) [18]. Owing to the equal survival outcome in both groups, irradiation of axillary nodes is considered a valid alternative to cALND in SLN-positive cases.

The smaller single-center OTOASOR (Optimal Treatment Of the Axilla – Surgery Or Radiotherapy) trial, randomizing between cALND and regional nodal irradiation (RNI) in patients with SLN metastasis, reached similar results [19].

In the 2 latter trials, randomization was performed before SLN biopsy so that the risk of recruitment bias was significantly reduced.

Proportion of Micro- and Macrometastases

Those trials comparing cALND versus SLN biopsy alone recruited mainly patients with SLN micrometastases: in AATRM and IBCSG, only micrometastases were allowed, and in ACOSOG Z0011, the rate of SLN micrometastatic disease was considerable (44.8% for SLN biopsy alone vs. 37.5% for cALND; $p = 0.05$).

In the OTOASOR trial, the mean number of removed positive SLNs was significantly different between study groups (1.36 for cALND vs. 1.17 for RNI; $p = 0.001$), and the axillary tumor burden in the cALND arm was extensive compared with AATRM, IBCSG

23-01, or Z0011 (25% pN1mi, 53% pN1a, 17% pN2a, and 5% pN3a). Surprisingly, the proportion of largest SLN metastasis in AMAROS is comparable to the Z0011 population: 59–62% macro-metastasis, 29% micrometastasis, and 10–12% isolated tumor cells.

Proportion of Breast-Conserving Therapy versus Mastectomy

A major remaining question is axillary management in cN0 pN1(sn) patients undergoing mastectomy. While ACOSOG Z0011 did not allow inclusion of mastectomy patients, IBCSG 23-01 was open for inclusion of both BCS and mastectomy. Interestingly, the rate of mastectomy patients remained at a low 9% (86 patients overall). Likewise, AATRM 048/13/2000 included only 18 (7.7%) mastectomy patients. AMAROS reached the highest proportion of mastectomy patients yet with 248 (17.4%) cases, tightly followed by OTOASOR with 15.6% (74 cases only). Partly, this skewed representation of mastectomy patients in trials allowing for their inclusion may be explained by selection bias, but eligible tumor diameter certainly also played a significant role. This could explain low mastectomy rates in the 2 trials with an upper eligible tumor size of 3 cm (OTOASOR) and 3.5 cm (AATRM 048/13/2000) but leaves some doubt about selection bias in the AMAROS and IBCSG 23-01 trials, both allowing tumor sizes of up to 5 cm in diameter. Thus, ongoing trials that do include mastectomy patients are important to guide future axillary management in this subgroup.

Significance of Unintentional Radiotherapy to Axillary Lymph Nodes

In the context of BCS, axillary recurrence is reduced by postoperative whole breast irradiation (WBI) even in patients with pN0(sn) [20]. In practice, there is significant unintentional irradiation at least to level I of the ipsilateral axilla even with standard tangents [21]. This might contribute to the unexpectedly low axillary recurrence rate after SLNB alone in the ACOSOG Z0011 trial despite a 27% rate of non-SLN metastasis in the control arm [14].

Z0011 results for patients with 1–2 positive SLNs in the case of BCS were accepted postulating postoperative conventionally fractionated WBI [22]. Current 3-dimensional RT shows a similar overlap with axillary fields [23], while intraoperative partial irradiation seems to lack the protective effect that WBI can offer [24]. There are no data available for SLN biopsy alone in pN1(sn) and hypofractionated RT. Likewise, the development of modern RT techniques may reduce unintentional irradiation of the axilla with unclear consequences.

In various ongoing studies (e.g., POSNOC, SENOMAC, IN-SEMA), ascertainment of the actually administered RT dose to each axillary level and a central review of radiation treatment plans are integrated into the study protocols. Little data exists regarding incidental doses delivered by tangents to the axilla in patients undergoing post-mastectomy RT in the era of modern techniques. POSNOC and SENOMAC should give an answer to this open question.

Should Axillary Management Options Consider Tumor Molecular Subtypes?

The human epidermal growth factor receptor 2 (HER2)-overexpressing and triple-negative molecular subtypes pose a higher risk

for locoregional recurrence [25]. Triple-negative breast tumors, however, have the lowest risk of high-volume nodal involvement of all molecular subtypes [26]. It is a significant clinical question whether specific subtypes may need differential consideration when deciding on axillary management in pN1(sn) cases. In order to guide axillary treatment decisions in this scenario, several nomograms have been developed to predict the status of non-SLN. One of these is the Memorial Sloan Kettering nomogram [27], taking into consideration all known risk factors for non-SLN metastases: tumor characteristics such as size, type, grade, estrogen receptor (ER) status, and lymphovascular invasion, SLN characteristics (size, method of detection, number of positive SLNs, extracapsular invasion), and the number of negative SLN removed. The accuracy of most nomograms to identify cases with non-SLN metastases, however, is judged to be 70–80%, and they can therefore only be seen as supportive information in a multivariable setting. Likewise, even if molecular subtypes are an integral part of predictive tools, they cannot by themselves serve to guide axillary treatment decisions.

Current Trials

Four ongoing randomized trials assessing axillary management in cN0 pN1(sn) were discussed in a recent review [28]. Despite their different designs and target populations, these trials (POSNO [29], INSEMA [30], SENOMAC [31], and SINODAR ONE [32]) should be able to answer whether omission of cALND is oncologically safe even in larger tumors (T3, SENOMAC), in the presence of more than 2 SLN metastases (INSEMA), in mastectomy patients (SENOMAC, POSNO, SINODAR ONE), and in the case of extranodal extension. Significant heterogeneity in proposed RT may call for a pooled analysis in a larger setting in order to define the impact of unintentional and intentional axillary irradiation.

What is the Best Management of cN0pN1(sn) Breast Cancer Patients from the View of the Medical Oncologist?

Marcus Schmidt

From the viewpoint of a medical oncologist, knowing the extent of axillary involvement is crucial. Clearly, the most obvious distinction is between node-negative and node-positive. However, the number of involved lymph nodes is also important when considering the most appropriate therapy.

In order to avoid over- as well as under-treatment, it is advisable to select the appropriate treatment strategy on the basis of a careful risk assessment for each individual patient. Even though adjuvant therapeutic strategies rely on ER and HER2, the number of involved lymph nodes is still important for clinical decision making. ER-positive/HER2-negative patients with limited involvement of axillary lymph nodes, for example, might be spared adjuvant chemotherapy if the tumor biology is favorable [33]. Conversely, in ER-positive patients with limited involvement of lymph nodes but either an adverse tumor biology or more than 3 involved axillary lymph nodes, adjuvant chemotherapy is indicated. Regard-

less of the ER status, the number of involved lymph nodes is important to tailor chemotherapy appropriately.

Based on the concept of dose-dense and sequential chemotherapy, node-positive breast cancer patients were randomly assigned in a 2×2 factorial design [34]. At a median follow-up of 36 months, dose-dense treatment with granulocyte-colony stimulating factor (G-CSF) support significantly improved both disease-free survival (DFS) and overall survival (OS). Utilizing an intense dose-dense sequential adjuvant chemotherapy, Möbus et al. [35] conducted a clinical trial in high-risk breast cancer patients with 4 or more involved axillary lymph nodes (median number of positive lymph nodes: $n = 8$). Patients were randomly assigned to receive intense dose-dense (idd) sequential epirubicin (E), paclitaxel (T), and cyclophosphamide (C) every 2 weeks, or conventionally dosed and scheduled EC followed by paclitaxel every 3 weeks. Recently, the results of this trial were updated. The authors confirmed that the previously reported survival benefit of iddETC was further increased and achieved an absolute difference of 10% after 10 years of follow-up. A further study reporting a significant advantage for dose-dense chemotherapy in comparison to conventionally dosed chemotherapy was conducted by the Gruppo Italiano Mammella (GIM), enrolling node-positive (median number of positive lymph nodes: $n = 5$) breast cancer patients. In the GIM-2 study, a significant survival advantage of dose-dense chemotherapy using EC followed by paclitaxel in terms of DFS and OS was found after a follow-up of 7 years [36]. Conversely, other trials in early breast cancer with fewer lymph nodes involved (median number of positive lymph nodes: $n = 1$ and 2, respectively) failed to show a significant survival advantage for dose-dense chemotherapy [37, 38]. A major difference between those dose-dense trials was the level of risk of the patients enrolled. Only trials enrolling patients with a high number of involved lymph nodes showed superiority of dose-dense regimens.

In conclusion, to better individualize adjuvant therapy in early breast cancer, a thorough understanding of the individual risk of a patient is necessary. Because of this, knowing just the nodal status (i.e., positive vs. negative) is not sufficient. The extent of axillary involvement should not be disregarded. This calls for an axillary dissection in patients with involved SLNs.

What is the Best Management of cN0pN1(sn) Breast Cancer Patients from the View of the Radiooncologist?

Birgitte Vrou Offersen

The status of the axilla in early breast cancer patients is of utmost importance. It is a strong prognostic factor and guides optimal locoregional and systemic therapy. From a radiation oncologist's perspective, there is currently a trend towards extending the indication of locoregional RT from patients with high nodal burden (>3 positive lymph nodes) to patients with only 1–3 positive lymph nodes [7, 8, 39, 40]. There is Level 1A evidence of a 2.3 versus 17.8% locoregional recurrence risk at 10 years for patients with 1 macrometastasis randomized between locoregional RT versus no

RT, and of a reduced overall recurrence risk (rate ratio 0.60, 95% confidence interval 0.39–0.92) [39]. Importantly, this risk reduction was seen independently of systemic therapy. More recent trials addressing the effect of locoregional RT including the internal mammary nodes (IMN) identified a spectrum of patients with medially located breast cancers (44% of the 4,004 patients included in the EORTC trial) or node-negative patients with high-risk features (the DBCG-IMN study) that demonstrated a benefit from RT even in the case of low nodal burden [7, 8, 40]. In the DBCG-IMN study of more than 3,000 patients all of whom were at high risk and had locoregional RT, patients with right-sided breast cancer received RT to the IMN, whilst left-sided patients did not. A significant OS gain of 3.7% was demonstrated at 8.9 years median follow-up for patients with RT to the IMN. A subgroup analysis explored if IMN RT could be safely omitted in any subgroups, but even in laterally positioned pN1 disease it could not be demonstrated that IMN RT was inefficient using OS as endpoint. Thus, even in low nodal burden, comprehensive locoregional RT is highly relevant. In the most recent St. Gallen consensus guideline, locoregional RT is therefore recommended if there is macrometastatic nodal involvement, although ‘several Panel members’ suggested during post-meeting discussions that adverse pathology should identify those patients with lower nodal burden requiring RT [41].

It is very likely that certain subgroups of breast cancer patients with low nodal burden and no or few adverse risk features do not benefit from locoregional RT; these groups, however, must be identified through prospective randomized trials, some of them being already active. It is likely that cN0 pN1(sn) patients can be spared from axillary dissection. Among 17,265 breast cancer patients treated in Denmark between 2010 and 2015, SLN biopsy was performed nationwide as part of the Danish Breast Cancer Group (DBCG) standard procedure which includes preoperative ultrasound [42]. Among these cN0 patients, 21% had one or more macrometastases in the SLN and therefore underwent axillary dissection. In 1.4% of the patients, macrometastasis was identified in non-SLN during SLN biopsy, indicating good performance of the technique. Among those patients with SLN macrometastases, 80%

had 1–3, 14% had 4–9, and 6% had 10 or more macrometastases. High nodal burden was associated with lobular cancer, age > 50 years, large tumor size, and grade 2–3, whereas ER and HER2 status were of no importance. This high rate of residual nodal burden is a strong indicator that results from high-quality randomized trials are strongly needed. In the DBCG guidelines, the nodal burden is important not only for the decision on locoregional RT but also for offering chemotherapy. Thus, if the axilla is misclassified as pN1 in 20% of patients with macrometastases in the SLN (because they truly are pN2–3), a proportion of these patients will not be offered relevant chemotherapy.

To provide the best management of patients with pN1 disease, comprehensive locoregional RT is recommended [43]. This includes using modern radiation facilities to obtain a homogeneous dose distribution in the target volumes that are clearly defined and delineated according to the ESTRO target volume consensus, respiratory control during RT, and informing the patient about the risks from continuing smoking if she is a smoker [44–46]. The risk of late radiation-induced morbidity after modern RT is no doubt less than described in previous reports from patients treated decades ago. Certainly, there is still a risk of serious late effects like heart disease and secondary lung cancer. These morbidities, however, occur late, and are only possible if the patient has survived the breast cancer. Therefore, life-saving RT should always focus on limiting dose to organs at risk including heart and lungs.

The dream scenario is to predict benefit from locoregional RT based on the biology of the primary tumor, and potentially be able to identify up to 25% of a high-risk cohort where locoregional RT can safely be omitted irrespective of nodal status [47]. However, until further evidence supports this strategy, comprehensive locoregional RT is recommended in all node-positive breast cancer patients, including those with cN0pN1(sn).

Disclosure Statement

The authors declare no conflicts of interest.

References

- 1 Munich Cancer Registry: Catchment area and cancer statistics. 2018. www.tumorregister-muenchen.de/en/facts/specific_analysis.php.
- 2 Engel J, Emeny RT, Holzel D: Positive lymph nodes do not metastasize. *Cancer Metastasis Rev* 2012;31:235–246.
- 3 Holzel D, Emeny RT, Engel J: True local recurrences do not metastasize. *Cancer Metastasis Rev* 2011;30:161–176.
- 4 Holzel D, Eckel R, Bauerfeind I, Baier B, Beck T, Braun M, Ettl J, Hamann U, Kiechle M, Mahner S, Schindlbeck C, de Waal J, Harbeck N, Engel J: Improved systemic treatment for early breast cancer improves cure rates, modifies metastatic pattern and shortens post-metastatic survival: 35-year results from the Munich Cancer Registry. *J Cancer Res Clin Oncol* 2017;143:1701–1712.
- 5 Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lonning PE, Borresen-Dale AL, Brown PO, Botstein D: Molecular portraits of human breast tumours. *Nature* 2000;406:747–752.
- 6 Louis-Sylvestre C, Clough K, Asselain B, Vilcoq JR, Salmon RJ, Campana F, Fourquet A: Axillary treatment in conservative management of operable breast cancer: dissection or radiotherapy? Results of a randomized study with 15 years of follow-up. *J Clin Oncol* 2004;22:97–101.
- 7 Poortmans PM, Collette S, Kirkove C, et al.; EORTC Radiation Oncology and Breast Cancer Groups: Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med* 2015;373:317–327.
- 8 Whelan TJ, Olivetto IA, Levine MN: Regional nodal irradiation in early-stage breast cancer. *N Engl J Med* 2015;373:1878–1879.
- 9 Engel J, Eckel R, Kerr J, Schmidt M, Furstenberger G, Richter R, Sauer H, Senn HJ, Holzel D: The process of metastasisation for breast cancer. *Eur J Cancer* 2003;39:1794–1806.
- 10 Schmidt-Hansen M, Bromham N, Hasler E, Reed MW: Axillary surgery in women with sentinel node-positive operable breast cancer: a systematic review with meta-analyses. *Springerplus* 2016;5:85.
- 11 Giuliano AE, Ballman KV, McCall L, Beitsch PD, Brennan MB, Kelemen PR, Ollila DW, Hansen NM, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, Hunt KK, Morrow M: Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial. *JAMA* 2017;318:918–926.

- 12 Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall LM, Morrow M: Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* 2011;305:569–575.
- 13 Giuliano AE, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, Saha S, Hunt KK, Morrow M, Ballman K: Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg* 2010;252:426–432; discussion 432–433.
- 14 Jaggi R, Chadha M, Moni J, Ballman K, Laurie F, Buchholz TA, Giuliano A, Haffty BG: Radiation field design in the ACOSOG Z0011 (Alliance) Trial. *J Clin Oncol* 2014;32:3600–3666.
- 15 Galimberti V, Cole BF, Zurrada S, et al.; International Breast Cancer Study Group Trial 23-01 investigators: Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncology* 2013;14:297–305.
- 16 Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thurlimann B, Senn HJ; Panel members: Strategies for subtypes – dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol* 2011;22:1736–1747.
- 17 Sola M, Alberro JA, Fraile M, Santesteban P, Ramos M, Fabregas R, Moral A, Ballester B, Vidal S: Complete axillary lymph node dissection versus clinical follow-up in breast cancer patients with sentinel node micrometastasis: final results from the multicenter clinical trial AATRM 048/13/2000. *Ann Surg Oncol* 2013;20:120–127.
- 18 Donker M, van Tienhoven G, Straver ME, et al: Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014;15:1303–1310.
- 19 Savolt A, Peley G, Polgar C, Udvarhelyi N, Rubovszky G, Kovacs E, Gyorffy B, Kasler M, Matrai Z: Eight-year follow up result of the OTOASOR trial: the Optimal Treatment Of the Axilla – Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: a randomized, single centre, phase III, non-inferiority trial. *Eur J Surg Oncol* 2017;43:672–679.
- 20 Van Wely BJ, Teerenstra S, Schinagel DA, Aufenacker TJ, de Wilt JH, Strobbe LJ: Systematic review of the effect of external beam radiation therapy to the breast on axillary recurrence after negative sentinel lymph node biopsy. *Br J Surg* 2011;98:326–333.
- 21 Belkacemi Y, Allab-Pan Q, Bigorie V, Khodari W, Beaussart P, Totobenzazara JL, Mege JP, Caillet P, Pigneur F, Dao TH, Salmon R, Calitchi E, Bosc R: The standard tangential fields used for breast irradiation do not allow optimal coverage and dose distribution in axillary levels I–II and the sentinel node area. *Ann Oncol* 2013;24:2023–2028.
- 22 Lyman GH, Somerfield MR, Bosserman LD, Perkins CL, Weaver DL, Giuliano AE: Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2017;35:561–564.
- 23 Van Roozendaal LM, Schipper RJ, Smit LH, Brans BT, Beets-Tan RG, Lobbens MB, Boersma LJ, Smidt ML: Three-dimensional breast radiotherapy and the elective radiation dose at the sentinel lymph node site in breast cancer. *Ann Surg Oncol* 2015;22:3824–3830.
- 24 Gentilini O, Botteri E, Leonardi MC, Rotmensz N, Vila J, Peradze N, Thomazini MV, Jereczek BA, Galimberti V, Luini A, Veronesi P, Orecchia R: Ipsilateral axillary recurrence after breast conservative surgery: the protective effect of whole breast radiotherapy. *Radiother Oncol* 2017;122:37–44.
- 25 Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ: Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. *Breast Cancer Res Treat* 2012;133:831–841.
- 26 Ugras S, Stempel M, Patil S, Morrow M: Estrogen receptor, progesterone receptor, and HER2 status predict lymphovascular invasion and lymph node involvement. *Ann Surg Oncol* 2014;21:3780–3786.
- 27 Van Zee KJ, Manasseh DM, Bevilacqua JL, Boolbol SK, Fey JV, Tan LK, Borgen PI, Cody HS 3rd, Kattan MW: A nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy. *Ann Surg Oncol* 2003;10:1140–1151.
- 28 Esposito E, Di Micco R, Gentilini OD: Sentinel node biopsy in early breast cancer. A review on recent and ongoing randomized trials. *Breast* 2017;36:14–19.
- 29 Goyal A, Dodwell D: POSNOC: a randomised trial looking at axillary treatment in women with one or two sentinel nodes with macrometastases. *Clin Oncol (R Coll Radiol)* 2015;27:692–695.
- 30 Reimer T, Stachs A, Nekljudova V, Loibl S, Hartmann S, Wolter K, Hildebrandt G, Gerber B: Restricted axillary staging in clinically and sonographically node-negative early invasive breast cancer (c/iT1–2) in the context of breast conserving therapy: first results following commencement of the Intergroup-Sentinel-Mamma (INSEMA) trial. *Geburtshilfe Frauenheilkd* 2017;77:149–157.
- 31 De Boniface J, Frisell J, Andersson Y, Bergkvist L, Ahlgren J, Ryden L, Olofsson Bagge R, Sund M, Johansson H, Lundstedt D; SENOMAC Trialists' Group: Survival and axillary recurrence following sentinel node-positive breast cancer without completion axillary lymph node dissection: the randomized controlled SENOMAC trial. *BMC Cancer* 2017;17:379.
- 32 Tinterri C, Canavese G, Bruzzi P, Dozin B: SINODAR ONE, an ongoing randomized clinical trial to assess the role of axillary surgery in breast cancer patients with one or two macrometastatic sentinel nodes. *Breast* 2016;30:197–200.
- 33 Curigliano G, Burstein HJ, Winer EP, et al: De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. *Ann Oncol* 2017;28:1700–1712.
- 34 Citron ML, Berry DA, Cirincione C, et al: Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* 2003;21:1431–1439.
- 35 Möbus V, Jackisch C, Luck HJ, du Bois A, Thomssen C, Kuhn N, Nitz U, Schneeweiss A, Huober J, Harbeck N, von Minckwitz G, Runnebaum IB, Hinke A, Konecny GE, Untch M, Kurbacher C; AGO Breast Study Group (AGO-B): Ten-year results of intense dose-dense chemotherapy show superior survival compared with a conventional schedule in high-risk primary breast cancer: final results of AGO phase III iddEPC trial. *Ann Oncol* 2018;29:178–185.
- 36 Del Mastro L, De Placido S, Bruzzi P, et al.; Gruppo Italiano Mammella (GIM) investigators: Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2 × 2 factorial, randomised phase 3 trial. *Lancet* 2015;385:1863–1872.
- 37 Swain SM, Tang G, Geyer CE Jr, Rastogi P, Atkins JN, Donnellan JP, Fehrenbacher L, Azar CA, Robidoux A, Polikoff JA, Brufsky AM, Biggs DD, Levine EA, Zapas JL, Provencher L, Northfelt DW, Paik S, Costantino JP, Mamounas EP, Wolmark N: Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial. *J Clin Oncol* 2013;31:3197–3204.
- 38 Cameron D, Morden JP, Canney P, et al.; TACT2 Investigators: Accelerated versus standard epirubicin followed by cyclophosphamide, methotrexate, and fluorouracil or capecitabine as adjuvant therapy for breast cancer in the randomised UK TACT2 trial (CRUK/05/19): a multicentre, phase 3, open-label, randomised, controlled trial. *Lancet Oncol* 2017;18:929–945.
- 39 EBCTCG (Early Breast Cancer Trialists' Collaborative Group); McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z, Darby S: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014;383:2127–2135.
- 40 Thorsen LB, Offersen BV, Dano H, Berg M, Jensen I, Pedersen AN, Zimmermann SJ, Brodersen HJ, Overgaard M, Overgaard J: DBCG-IMN: a population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. *J Clin Oncol* 2016;34:314–320.
- 41 Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, Thurlimann B, Senn HJ; Panel Members: Tailoring therapies – improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol* 2015;26:1533–1546.
- 42 Jessing C, Langhans L, Jensen MB, Talman ML, Tvedskov TF, Kroman N: Axillary lymph node dissection in breast cancer patients after sentinel node biopsy. *Acta Oncol* 2018;57:166–169.
- 43 Poortmans PM, Coles C, Bernier J: Treatment of regional lymph nodes in breast cancer – evidence in favor of radiation therapy. *JAMA Oncol* 2016;2:989–990.
- 44 Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Biete Sola A, Kirova YM, Pignol JP, Remouchamps V, Verhoeven K, Weltens C, Arenas M, Gabrys D, Kopek N, Krause M, Lundstedt D, Marinko T, Montero A, Yarnold J, Poortmans P: ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. *Radiother Oncol* 2015;114:3–10.
- 45 Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Sola A, Kirova YM, Pignol JP, Remouchamps V, Verhoeven K, Weltens C, Arenas M, Gabrys D, Kopek N, Krause M, Lundstedt D, Marinko T, Montero A, Yarnold J, Poortmans P: ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer, version 1.1. *Radiother Oncol* 2016;118:205–208.
- 46 Taylor C, Correa C, Duane FK, Aznar MC, Anderson SJ, Bergh J, Dodwell D, Ewertz M, Gray R, Jaggi R, Pierce L, Pritchard KI, Swain S, Wang Z, Wang Y, Whelan T, Peto R, McGale P; Early Breast Cancer Trialists' Collaborative Group: Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J Clin Oncol* 2017;35:1641–1649.
- 47 Tramm T, Mohammed H, Myhre S, Kyndi M, Alsner J, Borresen-Dale AL, Sorlie T, Frigessi A, Overgaard J: Development and validation of a gene profile predicting benefit of postmastectomy radiotherapy in patients with high-risk breast cancer: a study of gene expression in the DBCG82bc cohort. *Clin Cancer Res* 2014;20:5272–5280.