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Quality assessment of radiotherapy in the prospective randomized SENOMAC trial

Sara Alkner a,b,*, Elinore Wieslander b, Dan Lundstedt c,d, Martin Berg e, Ingrid Kristensen b, Yvette Andersson f,g, Leif Bergkvist g, Jan Frisell h,i, Roger Olofsson Bagge j,k,l, Malin Sund m,n, Peer Christiansen o,p, Oreste Davide Gentilini q,r, Michalis Kontos s, Thorsten Kühn t,u, Toralf Reimer v, Lisa Rydén a,w, Tove Filtenborg Tvedskov x,y, Birgitte Vrou Offersen z,aa, Henrik Dahl Nissen e, Jana de Boniface b,ab, on behalf of the SENOMAC Trialists’ Group

a Department of Oncology, Faculty of Medicine, Institute of Clinical Sciences Lund, Lund University, Lund, Sweden
b Skåne University Hospital Lund, Department of Hematology, Oncology and Radiation Physics, Lund, Sweden
c Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden
d Department of Oncology at Sahlgrenska University Hospital, Gothenburg, Sweden
e Department of Oncology, Veije Hospital, University Hospital of Southern Denmark, Vejle, Denmark
f Department of Surgery, Vastmanland Hospital Vasteras, Vasteras, Sweden
g Centre for Clinical Research, Uppsala University and Region Vastmanland, Vastmanland Hospital Vasteras, Sweden
h Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden
i Breast Center Karolinska, Karolinska Comprehensive Cancer Center, Karolinska University Hospital, Stockholm, Sweden
j Sahlgrenska Center for Cancer Research, Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
k Department of Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden
l Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, Gothenburg, Sweden
m Department of Surgery, University of Helsinki and Helsinki University Hospital, Finland
n Department of Diagnostics and Intervention/ Surgery, Umeå University, Sweden
o Department of Plastic and Breast Surgery, Aarhus University Hospital, Aarhus, Denmark
p Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
q Breast Surgery, IRCSS Ospedale San Raffaele, Milano, Italy
r Vita-Salute San Raffaele University, Milano, Italy
s Die Filderklinik, Breast Center, Filderstadt, Germany
t Department of Gynecology and Obstetrics, University of Ulm, Germany
e Department of Obstetrics and Gynecology, University of Rostock, Rostock, Germany
f Skåne University Hospital, Department of Gastroenterology and Surgery, Malmö, Sweden
g Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
h Department of Breast Surgery, Gentofte Hospital, Gentofte, Denmark
i Department of Oncology, Aarhus University Hospital, Aarhus, Denmark
j Department of Oncology at Sahlgrenska University Hospital, Gothenburg, Sweden
k Skåne University Hospital, Department of Gastroenterology, Malmö, Sweden
l Department of Clinical Research, Umea University, Sweden
m Department of Oncology, Rostock University, Rostock, Germany
n Department of Clinical Oncology, Danish Center for Particle Therapy, Aarhus, Denmark
o Department of Breast Surgery, Gentofte Hospital, Gentofte, Denmark
p Department of Oncology, Aarhus University Hospital, Aarhus, Denmark
q Department of Experimental Clinical Oncology, Danish Center for Particle Therapy, Aarhus, Denmark
r Department of Surgery, Capio St. Goran’s Hospital, Stockholm, Sweden
s Department of Oncology, University of Gothenburg, Gothenburg, Sweden

* Corresponding author at: Sara Alkner, Clinic of Oncology Lund, Skåne University Hospital, Klinikgatan 5, 22242 Lund, Sweden.
E-mail address: sara.alkner@med.lu.se (S. Alkner).

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ABSTRACT

Background and purpose: Recommendations for regional radiotherapy (RT) of sentinel lymph node (SLN)-positive breast cancer are debated. We here report a RT quality assessment of the SENOMAC trial.

Materials and Methods: The SENOMAC trial randomized clinically node-negative breast cancer patients with 1–2 SLN macrometastases to completion axillary lymph node dissection (cALND) or SLN biopsy only between 2015–2021. Adjuvant RT followed national guidelines. RT plans for patients included in Sweden and Denmark until June 2019 were collected (N = 1176) and compared to case report forms (CRF). Dose to level I (N = 270) and the humeral head (N = 321) was analyzed in detail.

Abbreviations: cALND, Completion axillary lymph node dissection; cN0, clinically node negative; CTV, clinical target volume; eCRF, electronic case report form, PTY, planning target volume; RT, radiotherapy; SLN, sentinel lymph node.

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Introduction

Appropriate indications for locoregional radiotherapy (RT) in patients with clinically node negative (cN0) breast cancer and 1–2 sentinel lymph node dissection (cALND) in these patients [3–6]. Earlier randomized breast cancer trials showed a benefit of regional RT [7], while more recent studies indicate that it may no longer be necessary in selected node-positive patients when combined with modern systemic therapy [3–5,8]. This has led to discrepancies in RT guidelines, both regarding indications and the inclusion of different nodal levels in the clinical target volume (CTV). The need for RT in regional patients with breast cancer and limited SLN involvement is being investigated in ongoing trials [9–11].

Regional RT and axillary surgery in part treat the same nodal levels in the axilla and are both associated with risk of arm morbidity [12–14]. To correctly interpret the results from clinical trials on axillary surgery, detailed information on RT is crucial. For example, both the AMAROS and ACOZOG Z0011 trial investigate omission of cALND in patients with 1–2 SLN metastases. In the AMAROS trial cALND was replaced by axillary RT [4], while the Z0011 trial protocol instead prohibited axillary RT to patients assigned to omission of cALND [5]. A retrospective analysis of RT plans for 228 patients, however, showed that 19 % had nevertheless received regional RT and in an additional ~ 40 % adjuvant breast RT was given with high tangential fields covering large parts of the axilla [5,15,16]. Thus, Z0011 cannot provide conclusions regarding the omission of both cALND and regional RT. This underlines the importance of a thorough evaluation of adjuvant RT in axillary surgical trials [17,18].

Conventional 3D conformal RT techniques using fixed fields are increasingly replaced by intensity-modulated methods for RT planning such as volumetric arc therapy, increasing conformity of the high dose area. The actual dose to level I, if not intentionally included in the CTV, may thus differ significantly depending on the RT technique used.

Here we report RT quality assessment (QA) of the SENOMAC trial. Adherence to guidelines regarding dose to targets and organs at risk (OAR) was evaluated, as well as fractionation schedule, the use of boost, intended target volumes, and concordance between data reported in the eCRF (electronic case report form) and the actual RT plan. Furthermore, we investigated how dose to level I and the humeral head was affected by whether level I was intentionally included in the target.

Material and methods

Patients

SENOMAC is a prospective multicenter trial which randomized patients with cN0 breast cancer and 1–2 SLN macrometastases 1:1 to cALND or SLN biopsy only during 2015–2021 (ClinicalTrials.gov number, NCT02240472). The trial protocol, early patient-reported outcomes, and recurrence-free survival data have been published [19–22]. Since Sweden and Denmark provided 93 % of the per protocol population (N = 2356/2540), RT QA was restricted to these countries. In 2019, RT plans were collected for patients randomized January 31st 2015 – June 1st 2019 (N = 1176). These data are analyzed in detail and compared with data registered in the eCRF. Inclusion vs. exclusion in the QA cohort is shown in Fig. 1 and treatment characteristics in Table 1.

Guidelines for radiotherapy planning

Radiotherapy in both randomization groups was prescribed according to the Swedish and Danish Breast Cancer Groups guidelines, respectively [23,24]. All patients diagnosed with at least one lymph node macrometastasis had an indication for locoregional RT. Fractionation schedule was 2 Gy x 25 fractions or 2.67 Gy x 15–16 fractions, 5 fractions per week. Hypofractionated treatment was increasingly used during the enrolment period. Patients operated with breast conservation and a margin < 2 mm (Denmark) and/or aged < 41 years (Sweden and Denmark) received a tumor bed boost of 2 Gy x 8 fractions. Patients 41–50 years old (Sweden) and 41–49 years old (Denmark) had a 2 Gy x 5 fractions boost. Boost was most often given sequentially although simultaneous integrated boost was used for some Danish patients.

Planning CTs had target volume delineation prospectively carried out according to the ESTRO consensus or earlier Swedish guidelines [25–27]. The remaining breast/chest wall, nodal levels II–IV, and interpectoral nodes were target in all patients. In Sweden, national guidelines did not advocate inclusion of the internal mammary nodes (IMN) during the early enrolment period (2015–2017). From 2018 onwards, IMN RT was recommended for patients with ≥ 4 macrometastases or 1–3 macrometastases and a centrally or medially located tumor. All Danish patients were recommended IMN RT.

In Sweden, the decision to include level I in the target was site dependent, with the instruction that target volumes should not differ between randomization groups. In Denmark, level I was target in patients with < 10 removed nodes (thus patients in the SLN biopsy only arm) or if ≥ 6 macrometastases were detected regardless of group assignment. Swedish target volumes were often delineated as one CTV or PTV (planning target volume) including both breast/chest wall and nodal volumes [27]. In Denmark the individual nodal levels were delineated separately [25,26].

Swedish guidelines recommended a CTV coverage of the breast/chest wall and regional nodes of V95% ≥ 98 % and a PTV coverage of V95% ≥ 98 %. In case of an unifocal ductal tumor coverage could be reduced to V95% ≥ 90 % (CTV) and V95% ≥ 90 % (PTV). Danish guidelines recommended the breast/thoracic wall CTV to receive 95 %-107 % of the prescribed dose and the nodal CTV 90 %-107 %. Respiratory gating was available at most Swedish sites, but instructions for when it was applied differed. In Denmark, gating was offered to all patients. RT was given with a 3D conformal based photon technique, using tangential fields in combination with periclavicular fields. Mandatory RT data in the SENOMAC eCRF included doses, fractionation, and target volumes.

Evaluation of delivered radiotherapy

Since individual nodal levels were most often delineated as one...
common CTV/PTV in Sweden, and the RT plan generally did not state which lymph node levels were included, this was re-evaluated by experienced radiation oncologists (SA, DL) for all Swedish patients. Levels II-IV were always included in the target volume in Swedish patients and the delineation of these levels uniformly conducted at all Swedish RT sites. The inclusion of level I in the target volume, however, differed between clinics and individual physicians. In several patients parts, but not the whole of this lymph node level, was included in the delineated target, and it was from the RT prescription not possible to determine whether it had been an intended target or not.

Therefore, the proportion of level I included in the target volume (0–25%, 25–50%, 50–75%, or 75–100%) was individually determined by re-assessment of RT plans. For binary analyses, level I was considered to have been included in the RT target if ≥ 50% was included in the delineated target volume (Table 1). In Swedish patients defined as level I included, 74% had ≥ 75% of level I in the delineated target. In those defined as level I not included, 83% had < 25% in the delineated target.

To enable an analysis of dose to individual nodal levels, a new consensus delineation according to ESTRO guidelines was created for a selected number of Swedish patients (N = 60), who were randomly selected and represented 5% of treatment plans or a minimum of three patients at each RT site.

In Denmark, clinical practice was to delineate each nodal CTV separately, and data could readily be extracted from the national Danish national dose plan bank [28]. RT doses were extracted from the treatment plans in both countries.

Ethics approval and informed consent

The trial was approved by the Ethics committee at Karolinska Institute, Stockholm, in 2014 (1165-31-1, amendment regarding the RT QA 2020-00408), and the regional Ethical Review Board in Viborg in 2015 (1-10-72-284-15). All patients signed a written informed consent before trial enrolment and randomization.

Statistics

Descriptive clinical and RT data are summarized in Table 1-3. Categorical variables are presented as frequencies and percentages, and continuous variables as median and interquartile range (IQR) values. Missing observations are presented for each variable. For statistical calculations, the software packages Stata 16.1 (StataCorp, TX, USA) and Medcalc Medcalc® 22.002 (MedCalc, Ostend, Belgium) were used. General comparisons between categorical variables in treatment groups were evaluated with a Chi2 test, while dose coverage in relation to target volumes was evaluated with the Wilcoxon rank sum test.

Results

A consort diagram for inclusion vs. exclusion in the RT QA cohort is shown in Fig. 1. Three percent of patients (N = 42/1271) did not receive or complete the prescribed RT. For patients receiving a complete RT course, treatment plans were retrievable in 96% (N = 1176/1229, Table 1). Evaluation of target coverage and dose to OAR showed a high concordance with national guidelines. The recommended criteria for target coverage of the breast/chest wall were fulfilled in 94% of patients (N = 1072/1136, 40 RT plans not evaluable), and of the nodes in 97% (N = 1097/1136). Table 2 show doses to OAR.

Target volumes, dose and fractionation extracted from the RT plans are shown in Table 1. The IMN was included in 14% of Swedish and > 99% of Danish patients. Inclusion increased mean dose to the ipsilateral lung from 23.8% to 30.0% (p < 0.001) of the prescribed dose and mean heart dose from 0.6 Gy to 0.9 Gy (p < 0.001) in right-sided treatment. No increase in heart dose was observed for left-sided RT.

eCRF data agreed with the RT plan in 99% (N = 1146/1154) regarding receipt of breast/chest wall RT and in 97% (N = 1115/1154) regarding nodal RT. In Swedish patients, level I was a target in ~ 40% of the RT plans without difference between randomization groups (Table 1). Intentional exclusion of level I from the target volume according to the eCRF was confirmed to agree with the RT plan in 77% (N

Fig. 1. Consort diagram of inclusion vs. exclusion in the radiotherapy quality assessment cohort.
In Danish patients, in accordance with Danish national guidelines, level I was an intended target in patients receiving cALND biopsy only, but only for a minority of patients receiving cALND (Table 1). For the entire RT QA cohort, 31 % (N = 174/565) of the cALND arm had level I as an intended target and 55 % (N = 334/611) of the SLN biopsy only arm (p < 0.001).

The dose to level I was evaluated in detail in the 60 Swedish patients with an ESTRO consensus delineation performed and in 210 Danish patients with delineation of level I (Table 5). When part of the CTV, the median V10% for level I was 100 %, and D95 % 95 % of the prescribed dose. Due to the tangential field technique most often used in breast cancer RT (Supplementary Fig. 1), a high dose coverage of level I was found also in patients where it was not an intended target. The unintentional dose to level I caused a median V10% = 874 % of the prescribed dose, median V20% = 90%, and D95 % for level I was 95 % (IQR 94–95 %) in the SLN biopsy only arm and 89 % (IQR 72–94 %) in the cALND arm.

Inclusion of level I in the target volume significantly increased dose to the humeral head (Table 3). There was however a significant variation between sites in both dose and delineation of the humeral head (data not shown). When level I was not an intentional target, ≥50 % of the humeral head received a median of 6 % of the prescribed dose. With level I included, this dose was increased to 13 %.

**Discussion**

We report quality assessment of RT given within the SENOMAC trial. Concordance between the eCRF and the actual RT plan was high in relation to whether breast/chest wall and regional RT had been given, but lower for detailed information on which individual lymph node levels had been included in the target volume (78 %). This may in part be due to that the lymph node levels were most often not delineated as individual target volumes, but as one common CTV in Sweden. Correspondingly, parts but not the whole of level I was included in the target volume in several patients, and a retrospective cut-off point (50 %) had to be determined to ascertain a binary inclusion status. However, 74 % of Swedish patients defined as level I included had ≥75 % of level I in the delineated target, and 83 % defined as level I not included had <25 % of level I in the delineated target.

Level I was more often part of the target volume in the SLN biopsy only arm. However, since level I received a high dose coverage even when not intentionally included in the target, this should not affect risk of recurrence within the trial. On the other hand, inclusion of level I in the target increased the dose to the humeral head, which may diminish the positive effects of less surgery in the SLN biopsy only arm.

During recent decades the risk of locoregional recurrence following breast cancer treatment has decreased substantially. This is likely caused by early detection, and improved techniques for surgery/pathology.

### Table 1

Prescribed treatment according to the radiotherapy plan.

<table>
<thead>
<tr>
<th>Intended RT targets</th>
<th>All Swedish patients N = 874</th>
<th>cALND arm SE N = 420</th>
<th>SLN only arm SE N = 454</th>
<th>P-value</th>
<th>All Danish patients N = 302</th>
<th>cALND arm DK N = 145</th>
<th>SLN only arm DK N = 157</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast/Chest Wall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (0 %)</td>
<td>0 (0 %)</td>
<td>1 (0 %)</td>
<td>0 (0 %)</td>
<td>0 (0 %)</td>
<td>1 (0 %)</td>
<td>1 (0 %)</td>
<td>0 (0 %)</td>
</tr>
<tr>
<td>Yes</td>
<td>873 (100 %)</td>
<td>420 (100 %)</td>
<td>453 (100 %)</td>
<td>302 (100 %)</td>
<td>145 (100 %)</td>
<td>157 (100 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level I ***</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>539 (62 %)</td>
<td>266 (63 %)</td>
<td>273 (60 %)</td>
<td>129 (43 %)</td>
<td>125 (86 %)</td>
<td>4 (3 %)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>335 (38 %)</td>
<td>154 (37 %)</td>
<td>181 (40 %)</td>
<td>173 (57 %)</td>
<td>20 (14 %)</td>
<td>153 (97 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level II-IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>35 (4 %)</td>
<td>15 (4 %)</td>
<td>20 (4 %)</td>
<td>0 (0 %)</td>
<td>0 (0 %)</td>
<td>0 (0 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>839 (96 %)</td>
<td>405 (96 %)</td>
<td>434 (96 %)</td>
<td>302 (100 %)</td>
<td>145 (100 %)</td>
<td>157 (100 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>753 (86 %)</td>
<td>359 (85 %)</td>
<td>394 (87 %)</td>
<td>1 (1 %)</td>
<td>0 (0 %)</td>
<td>0 (0 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>121 (14 %)</td>
<td>61 (15 %)</td>
<td>60 (13 %)</td>
<td>301 (100 %)</td>
<td>144 (99 %)</td>
<td>157 (100 %)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** cALND completion axillary lymph node dissection DK Denmark, Gy gray, IMN internal mammary nodes, RT radiotherapy, SE Sweden, SLN sentinel lymph node.

* Chi² test for difference between randomization groups.
** Or corresponding dose given as simultaneous integrated boost (SIB).
*** See text for definition of when level I is considered an intended target.
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radiotherapy and oncology differ among these trials. RT as well as surgery may optimize RT in accordance with surgical technique, a detailed description of RT planning within the trial is of utmost importance [30].

As expected, there was a systematic difference in inclusion of level I between randomization arms in Danish SENOMAC patients due to national guidelines. However, even when not intentionally included in the target, most of level I received a therapeutic dose. Hence, the difference in intended target between treatment arms affected the actual RT dose delivered to the nodes to a limited extent. In addition, patient anatomy significantly affects dose to both level I and the humeral head (Supplementary Fig. 1), emphasizing that modern treatment of level I is more fifty shades of grey, than a black or white situation.

The unintentional dose to level I is often due to the field arrangement in 3D conformal RT [16], with dose from tangential fields to the breast/chest wall and adjacent fields to the axilla. In line with our results, RT QA in the Skagen trial 1 (investigating moderate hypofractionation in regional BC RT) showed that for patients receiving regional RT, dose coverage of level I was high even when level I was not an intentional target [34]. In median, 58 % of level I received 95% of the prescribed dose (V95% = 58%), and in 12.5 % (N = 8/64) level I received a full dose coverage (D95% > 90 %) even if not an intended target. The BOOG 2013–08 trial randomizes cN0 BC patients between SLN biopsy or its omission, with 98.5 % of patients in the no-SLN arm receiving only whole breast RT. The unintentional dose to level I was on average 60 % of the prescribed dose [35], which is similar to what was found in the RT QA for the INSEMA trial [36].

Modern RT techniques may increase conformity of the high dose volume. Although we show that nodes within level I receive a high dose

Table 2

Dose parameters for organs at risk.

<table>
<thead>
<tr>
<th></th>
<th>All Swedish patients</th>
<th>ALND arm SE</th>
<th>SLN only arm SE</th>
<th>All Danish patients</th>
<th>ALND arm DK</th>
<th>SLN only arm DK</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td><strong>Ipsilateral lung</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>847</td>
<td>408</td>
<td>439</td>
<td>302</td>
<td>145</td>
<td>157</td>
</tr>
<tr>
<td>D50% (%</td>
<td>24.6 (20.7–28.6)</td>
<td>24.6 (20.8–28.8)</td>
<td>24.6 (20.7–28.5)</td>
<td>30.9 (27.1–33.3)</td>
<td>30.0 (27.0–33.2)</td>
<td>31.5 (27.7–33.5)</td>
</tr>
<tr>
<td>V90% (%)</td>
<td>23.0 (18.5–28.4)</td>
<td>22.9 (18.5–28.3)</td>
<td>23.3 (18.5–28.4)</td>
<td>31.0 (27.1–34.4)</td>
<td>30.4 (27.1–34.3)</td>
<td>31.9 (27.2–34.5)</td>
</tr>
<tr>
<td>V100% (%)</td>
<td>5.6 (2.7–10.0)</td>
<td>6.1 (2.8–10.1)</td>
<td>5.3 (2.7–9.8)</td>
<td>7.6 (5.6–10.1)</td>
<td>7.5 (5.4–9.8)</td>
<td>8.0 (5.7–10.3)</td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Right-sided tumor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>115</td>
<td>54</td>
<td>61</td>
<td>140</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>586 (512–645)</td>
<td>579 (511–647)</td>
<td>588 (519–640)</td>
<td>675 (610–753)</td>
<td>690 (599–752)</td>
<td>656 (615–760)</td>
</tr>
<tr>
<td>D50% (%</td>
<td>0.7 (0.5–0.9)</td>
<td>0.6 (0.5–0.8)</td>
<td>0.8 (0.6–1.1)</td>
<td>1.0 (0.8–1.2)</td>
<td>1.0 (0.8–1.2)</td>
<td>1.0 (0.8–1.3)</td>
</tr>
<tr>
<td>V90% (%)</td>
<td>0.0 (0.0–0.0)</td>
<td>0.0 (0.0–0.0)</td>
<td>0.0 (0.0–0.0)</td>
<td>0.0 (0.0–0.0)</td>
<td>0.0 (0.0–0.0)</td>
<td>0.0 (0.0–0.0)</td>
</tr>
<tr>
<td><strong>Left sided tumor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>452</td>
<td>218</td>
<td>234</td>
<td>147</td>
<td>70</td>
<td>77</td>
</tr>
<tr>
<td>D50% (%</td>
<td>1.9 (1.3–3.1)</td>
<td>2.0 (1.4–3.1)</td>
<td>1.8 (1.3–3.0)</td>
<td>2.1 (1.7–3.4)</td>
<td>2.3 (1.7–3.5)</td>
<td>2.0 (1.7–3.1)</td>
</tr>
<tr>
<td>V90% (%)</td>
<td>0.8 (0.0–2.7)</td>
<td>0.9 (0.0–2.6)</td>
<td>0.7 (0.0–2.8)</td>
<td>0.6 (0.0–3.2)</td>
<td>1.0 (0.0–3.8)</td>
<td>0.5 (0.0–2.8)</td>
</tr>
<tr>
<td><strong>Humeral head</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>142</td>
<td>179</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D50% (%</td>
<td>5.6 (4.3–9.7)</td>
<td>12.6 (6.5–51.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V90% (%)</td>
<td>0.0 (0.0–1.5)</td>
<td>6.2 (0.0–28.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V100% (%)</td>
<td>0.0 (0.0–0.0)</td>
<td>0.3 (0.0–10.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All doses are given as percentage of the prescribed dose to the breast/chest wall, except for D50% heart, as fraction doses are always very small.

Abbreviations: CTV clinical target volume, DK Denmark, IQR interquartile range, SE Sweden.

For all variables except number of patients the median value is reported.
Hence, an analysis of dose to OAR in relation to IMN-RT includes a bias symptoms from the arm and shoulder. Investigated in SENOMAC using information on patient reported intra-site variability in treatment planning. Still, inclusion of the IMN comes, but not bias the results in favor of the intervention SLN biopsy technique, this may no longer be the case with inversely optimized intensity modulated RT. This must be taken into consideration when introducing new RT planning techniques into clinical routine.

In the SENOMAC trial, the median dose to the humeral head was generally higher in patients with level I intentionally included. Since level I was more frequently a part of the RT target in the SLN biopsy only arm, these patients received a higher median dose to the humeral head. At the same time, this is the trial arm with less arm morbidity as a result of reduced surgery [21]. If anything, this dose difference may therefore diminish the positive effects of less surgery on patient-reported outcomes, but not bias the results in favor of the intervention SLN biopsy only. Publications regarding a correlation between dose to the humeral head and arm morbidity are sparse [37–39]. This will be further investigated in SENOMAC using information on patient reported symptoms from the arm and shoulder.

During the trial period, recommendations on whether the IMN should be included in the target varied between and within countries. Hence, an analysis of dose to OAR in relation to IMN-RT includes a bias of intra-site variability in treatment planning. Still, inclusion of the IMN increased mean lung dose and to a lesser extent also mean heart dose in right-sided RT. A corresponding increase in heart dose was not seen for left-sided RT, possibly due to a choice of reduced IMN coverage rather than an increased heart dose.

This review includes only patients randomized in the SENOMAC trial before June 2019. While this selection had practical reasons, there is no indication to believe that results for patients included later should differ from those presented. On the contrary, feed-back information to sites with focus on RT planning during the QA process, could have increased awareness and thus improved concordance to the study protocol and eCRF RT documentation.

Finally, this report focuses on target volumes and doses in the RT plan. There is no guarantee that what is planned is also what is delivered [40]. However, since all RT departments involved in the SENOMAC trial used image guidance and continuous quality control, it is expected that RT was delivered in accordance with RT plans.

In conclusion, this report confirms the importance of detailed RT QA in adjuvant breast cancer trials, using the actual RT plans rather than only eCRF data. In 3D-conformal treatment planning a significant dose is given to level I even if not being intentionally included in the target. Although there was an imbalance between study arms in whether level I was as an intended target, this should hence not significantly affect recurrence data within the SENOMAC trial. When introducing newer intensity modulated RT techniques, unintentional dose to the axilla should however be taken into consideration, since it may then be substantially reduced by increased conformity of the high dose area. The question of dose to the humeral head in relation to side effects from the arm and shoulder is important and will be further investigated.

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**CRediT authorship contribution statement**

Sara Alkner: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. Elinore Wieslander: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. Dan Lundstedt: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Martin Berg: Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. Ingrid Kristensen: Writing – review & editing, Methodology, Investigation, Conceptualization. Leif Bergkvist: Writing – review & editing, Methodology, Investigation, Conceptualization. Yvette Andersson: Writing – review & editing, Methodology, Investigation, Conceptualization. Roger Olofsson Bagge: Writing – review & editing, Methodology, Investigation, Conceptualization. Jan Frisell: Writing – review & editing, Methodology, Investigation, Conceptualization. Malin Sund: Writing – review & editing, Methodology, Investigation, Conceptualization. Peer Christiansen: Writing – review & editing, Methodology, Investigation, Conceptualization.
Conceptualization. Oreste Davide Gentilini: Writing – review & editing, Methodology, Investigation, Conceptualization. Michalis Kontos: Writing – review & editing, Methodology, Investigation, Conceptualization. Thorsten Kühn: Writing – review & editing, Methodology, Investigation, Conceptualization. Toralf Reimer: Writing – review & editing, Methodology, Investigation, Conceptualization. Lisa Rydén: Writing – review & editing, Methodology, Investigation, Conceptualization. Tove Filtenborg Tvedskov: Writing – review & editing, Methodology, Investigation, Conceptualization. }

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Roger Olofsson Bagge has received institutional research grants from Bristol-Myers Squibb (BMS), Endomagnetics Ltd (Endomag), SkylineDx and NeraCare GmbH, speaker honorarium from Roche, Pfizer and Pierre-Fabre, and has served on advisory boards for Amgen, BD/BARD, NeraCare GmbH, speaker honorarium from Roche, Pfizer and Bayer, Eli-Lilly. None of the other authors declare any conflict of interest.]

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110372.

References


