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Original Article

Validation of the ESTRO target volume consensus guideline for early-stage breast cancer in the DBCG Skagen Trial 1

Kristine Wiborg Høgsbjerg [a,b,*], Mette Skovhus Thomsen [c], Else Maae [d], Ingvil Mjaaland [e], Mette Holck Nielsen [f], Maja Vestmø Maraldo [g,h], Carine Kirkove [i], Tamaz Lörincz [j], Sami Aziz-Jowad Al-Rawi [k], Egil S Blix [l], Andreas Schreiber [m], Mechthild Krause [n,o], Unn-Miriam Kasti [p], Louise Wichmann Matthiessen [q], Stine Elleberg Petersen [r], Jens Overgaard [a,b], Birgitte Vrou Offersen [a,b,r]

[a] Dept. of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark
[b] The Faculty of Health, Aarhus University, Aarhus, Denmark
[c] Dept. of Medical Physics, Aarhus University Hospital, Aarhus, Denmark
[d] Dept. of Oncology, Vejle Hospital, University Hospital of Southern Denmark, Vejle, Denmark
[e] Dept. of Oncology, Stavanger University Hospital, Stavanger, Norway
[f] Dept. of Oncology, Odense University Hospital, Odense, Denmark
[g] Dept. of Clinical Oncology, Center for Cancer and Organ Diseases, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark
[h] Dept of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[i] Division of Radiation Oncology, Cliniques Universitaires Saint-Luc, Belgium
[j] Dept. of Oncology, Aalborg University Hospital, Aalborg, Denmark
[k] Dept. of Oncology, Zealand University Hospital, Næstved, Denmark
[l] Dept. of Oncology, University Hospital of North Norway, Tromsø, Norway
[m] Praxis für Strahlentherapie, Dresden, Germany
[n] Dept. of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[o] National Center for Tumor Diseases (NCT), Dresden-Rossendorf, Germany
[p] Dept. of Oncology, Kristiansand Hospital, Kristiansand, Norway
[q] Dept. of Oncology, Copenhagen University Hospital – Herlev and Gentofte, Herlev, Denmark
[r] Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark

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ABSTRACT

Background and purpose: Adjuvant loco-regional radiotherapy reduces recurrence risk and enhances survival in early-stage breast cancer. The ESTRO consensus guideline on target volume delineation for elective radiotherapy of early-stage breast cancer, published in 2015, sought to standardise contouring practices. In the DBCG Skagen Trial 1, all clinical target volume (CTV) delineations followed the ESTRO guideline, allowing pre-planned prospective validation. This study aimed to characterise the loco-regional recurrence (LRR) pattern in accordance with target delineation as per the ESTRO guideline.

Materials and methods: DBCG Skagen Trial 1 enrolled 2,963 patients (2,908 in the intention-to-treat cohort). LRR, with or without concurrent distant recurrence, were identified from imaging and medical records, and categorised as inside the CTV, marginal miss, or distant recurrence relative to the ESTRO-defined CTVs.

Results: At median follow-up of 5.2 years (IQR 4.1–6.7), 78 patients developed LRR: 41 isolated LRR and 37 with concurrent distant recurrence. Among the 78 patients with LRR, 74 (95%) had recurrences located within the ESTRO-defined CTVs and were planned to receive the full prescribed dose. All local recurrences were within the CTVp, and all but three patients had regional recurrences within the CTVn. Only three marginal misses were identified.

* Corresponding author at: Dept. of Experimental Clinical Oncology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark.
E-mail address: kwh@oncology.au.dk (K.W. Høgsbjerg).

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Conclusion: LRR in the DBCG Skagen Trial 1 occurred almost exclusively within the ESTRO-defined CTVs, providing prospective validation of the guideline, without evidence suggesting a need for modification of target volumes.

Introduction

Adjuvant loco-regional radiotherapy (RT) reduces the risk of recurrence and improves overall survival in early-stage breast cancer patients [1]. Advances in RT planning, including CT-based simulation, respiratory gating, and intensity-modulated RT (IMRT), have enabled more conformal dose delivery with steeper dose gradients between clinical target volumes (CTVs) and organs of interest [2,3]. The transition from 2D bone-based to 3D CT-based planning took place in many centres after the turn of the millennium. At the ESTRO teaching courses on multidisciplinary management of breast cancer, substantial international variation in delineation practices was identified, underscoring the need for harmonised, consensus-based guidelines. In response, the ESTRO consensus guideline on target volume delineation for RT in early-stage breast cancer was developed and published in 2015 [4,5]. The guideline was based on contemporary knowledge of lymphatic drainage, the fact that lymph nodes are mostly located along veins, recurrence patterns, and advances in RT technology [6–8]. Compared to contemporaneous guidelines, such as the RTOG and RADCOMP Breast Cancer Atlases, the ESTRO guideline defined smaller CTVs to balance adequate target coverage with minimisation of doses to organs of interest [9]. While this approach has been investigated in a few retrospective studies, prospective clinical validation remains to be explored [10–13].

In the same year as the publication of the ESTRO consensus guideline, the Danish Breast Cancer Group (DBCG) initiated the phase III randomised Skagen Trial 1, enrolling nearly 3000 patients with an indication for loco-regional RT [14]. As pre-planned in the protocol, all target volumes were delineated according to the newly developed ESTRO consensus guideline. As a prospectively designed trial that adheres to the protocol-mandated ESTRO guideline, the DBCG Skagen Trial 1 provides a unique opportunity to assess the adequacy of the defined CTVs in a contemporary high-risk breast cancer population. The present study aims to evaluate the pattern of loco-regional recurrences (LRR) and thereby provide the first prospective clinical validation of the ESTRO consensus guideline.

Methods

Study design

The DBCG Skagen Trial 1, conducted from 2015 to 2021, randomised 2,963 patients (2,908 in the intention–to–treat cohort) with invasive breast cancer and an indication for loco-regional RT across seven countries to receive either 50 Gy in 25 fractions (fx) (2 Gy fx) or 40 Gy in 15 fx (2.67 Gy fx). A simultaneous integrated tumour bed boost (SIB) was optional in both groups. Patients were randomised 1:1 and stratified by surgery type and treating institution. The primary endpoint was ipsilateral arm lymphoedema at 3 years. Details regarding the overall study design, patient characteristics, and primary outcomes are reported elsewhere [14].

Study population

Eligible patients were women aged ≥18 years with histologically confirmed invasive breast cancer (T1–4, pN0–3, M0) who had undergone either mastectomy or breast-conserving surgery (BCS) and had an indication for loco-regional RT. Indications included the presence of at least one macroscopic nodal metastasis (≥N1) or pT3–4 N0 tumours; pT4 tumours were only eligible if they became operable following neoadjuvant chemotherapy (NACT). Eligibility was independent of tumour type and grade, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status. Both NACT and adjuvant systemic therapies (chemotherapy, endocrine therapy, and anti-HER2 treatment) were permitted. Sentinel node procedures and/or axillary lymph node dissection (ALND) were allowed according to institutional, national, or other trial guidelines.

Exclusion criteria were, among others, previous breast cancer or ductal carcinoma in situ (DCIS), bilateral breast cancer, an indication for nodal boost, and prior RT to the chest region [14].

Treatment planning

All target volumes were delineated according to the ESTRO consensus guideline for early-stage breast cancer, as specified in the trial protocol. CT simulation was performed with a maximum slice thickness of 3 mm. Inter-centre consistency in delineation was high and satisfactory, as previously demonstrated [15,16].

Patients with an indication for a tumour bed boost received SIB, equal to 10 Gy/5 fx or 16 Gy/8 fx, as per protocol and DBCG guidelines [14,17,19]. The boost was incorporated into the respective fractionation arm, resulting in four distinct dose regimens: 57 Gy/50 Gy/25 fx (50 Gy + 10 Gy boost), 63 Gy/51.5 Gy/28 fx (50 Gy + 16 Gy boost), 45.75 Gy/40 Gy/15 fx (40 Gy + 10 Gy boost), or 52.2 Gy/42.3 Gy/18 fx (40Gy + 16 Gy boost) [14,16]. As nodal boosts were not allowed, no patients had visible macroscopic nodal disease at the time of RT.

To achieve the prescribed coverage and maintain dose homogeneity, three-dimensional conformal RT (3D-CRT) was recommended using a single isocentre with tangential fields and parallel posterior edges to cover CTVp. For the nodal CTV (CTVn), an anterior periclavicular field was applied, with an optional posterior opposing field to improve dose homogeneity within the target. If required, intensity-modulated RT techniques, including Volumetric Modulated Arc Therapy (VMAT) or tomotherapy, were permitted [14,16].

Treatment planning aimed to ensure adequate coverage and dose homogeneity within all CTVs. The dose was prescribed to the CTV and not the planning target volume (PTV), as per the DBCG guidelines. As specified in the protocol, CTVp (breast or chest wall) was to receive 95–107% (50 Gy/25 fx) or 95–105% (40 Gy/15 fx) of the prescribed dose. Regional nodal RT included levels (I), II–IV, interpectoral, and internal mammary nodes (IMN). CTVn were to receive 90–107% and 90–105% of the prescribed dose for 50 Gy/25 fx and 40 Gy/15 fx, respectively. Quality assurance (QA) of the planned RT was performed retrospectively and confirmed adherence to the protocol, with V95% of 98% for CTVp and 95–100% for CTVn [16].

Surgical treatment

Surgery was performed as either mastectomy or BCS, as decided by the operating surgeon and patient. Axillary staging was performed with ALND unless patients were clinically node-negative on palpation and/or ultrasound and had a sentinel node biopsy (SNB). Patients with 1–2 macro metastases on SNB generally received Level 1 nodal (CTVn_L1) irradiation; in Denmark, such patients could be enrolled in the SENOMAC trial and randomised between SNB only versus ALND, whereas in Norway, several patients received SNB with CTVn_L1 irradiation outside of the trial [20].

Loco-regional recurrence

The primary endpoint in the present study was LRR, with or without

concurrent distant recurrence (DR), identified on available diagnostic imaging and in electronic medical files.

Local recurrence was defined as any recurrent tumour, thus as the presence of DCIS or invasive carcinoma within the ipsilateral mammary region, including the skin, surgical scar, subcutaneous tissue, breast, or chest wall. Regional recurrence was defined as nodal relapse within the ipsilateral nodal regions, as defined in the ESTRO consensus guideline. Each recurrence was categorised on anatomical location, and dose coverage was investigated. Recurrences were defined as inside the CTV if they were located within the ESTRO-defined CTVs. Recurrences in the surgical scar were classified as inside the CTV if the CTVp received the full prescribed dose, even when the recurrence site itself received less than 95% due to build-up effects. This approach was justified by the fact that the primary tumour had been removed radically. Marginal misses were defined as recurrences located outside the ESTRO-defined CTV, but still within the 50% isodose line. The remaining recurrences were defined as DR.

To ensure a comprehensive assessment of LRR, all recurrences were reviewed on all available imaging to determine the anatomical extent of disease. In the Danish cohort (70.2% of the study population), imaging from patients registered with DR or who had died without reported LRR was reviewed to identify any unrecorded LRRs and ensure data completeness. The extent of LRR was then compared with the RT planning CT to assess whether the recurrence was located inside the ESTRO CTVs and to determine the dose delivered to the recurrence. For patients with nodal recurrence, imaging was further evaluated to determine whether nodal disease had been retrospectively visible on the planning CT. Patients presented with isolated LRR or recurrences adjacent to the loco-regional target area were subsequently evaluated to determine whether the recurrence was located within or outside the delineations specified by the ESTRO, RTOG, and RADCOMP guidelines [9,21]. In cases of uncertainty regarding the anatomical classification of the LRR, the case was discussed within the research group, with additional input from a radiologist or nuclear medicine specialist when required.

Ethical considerations

This study is a preplanned sub study of the main trial, which was conducted in accordance with the Declaration of Helsinki (5th revision) and approved by the Regional Ethics Committee (approval no. 1-10-72-409-14).

Statistical analyses

Median follow-up was estimated using the reverse Kaplan-Meier method, where the status indicator is reversed so that the event of interest (local-regional recurrence) becomes the censor, and the censor becomes the event. The cumulative incidence of LRR in the entire DBCG Skagen Trial 1 cohort was estimated using the Aalen-Johansen method, with contralateral cancer, distant recurrence, other malignancy, or death as competing events.

Results

At a median follow-up of 5.2 years (IQR 4.1–6.7 years), LRR was identified in 78 patients, comprising 64 with local and 23 with regional recurrences. Of these, 41 patients had isolated LRR (iLRR) and 37 had LRR concurrent with DR (cLRR). The cumulative risk of loco-regional recurrence at 5 years was 2.7% (95% CI 2.1-3.4%).

Among the 41 patients with iLRR, 37 (90%) presented with isolated local recurrence within the CTVp, 3 (7%) with both local and regional recurrence, and 1 (6%) with isolated regional recurrence. Regional recurrences were limited, with involvement of CTVn_L1 in three patients and ventral to CTVn_L3 in one patient (Fig. 1A, Table 2).

Among the 37 patients with cLRR, 18 (49%) had local and DR, but no regional recurrence, 13 (35%) had regional and DR, and 6 (16%) had both local, regional and DR. Overall, 24 of the 37 patients had recurrence within the CTVp, while regional recurrence involved various nodal sites: CTVn_L1 (13/37), CTVn_L2 (11/37), CTVn_L3 (9/37), CTVn_L4 (9/37), CTVn_interpectoral (7/37), and CTVn_IMN (7/37) (Fig. 1B, Table 2).

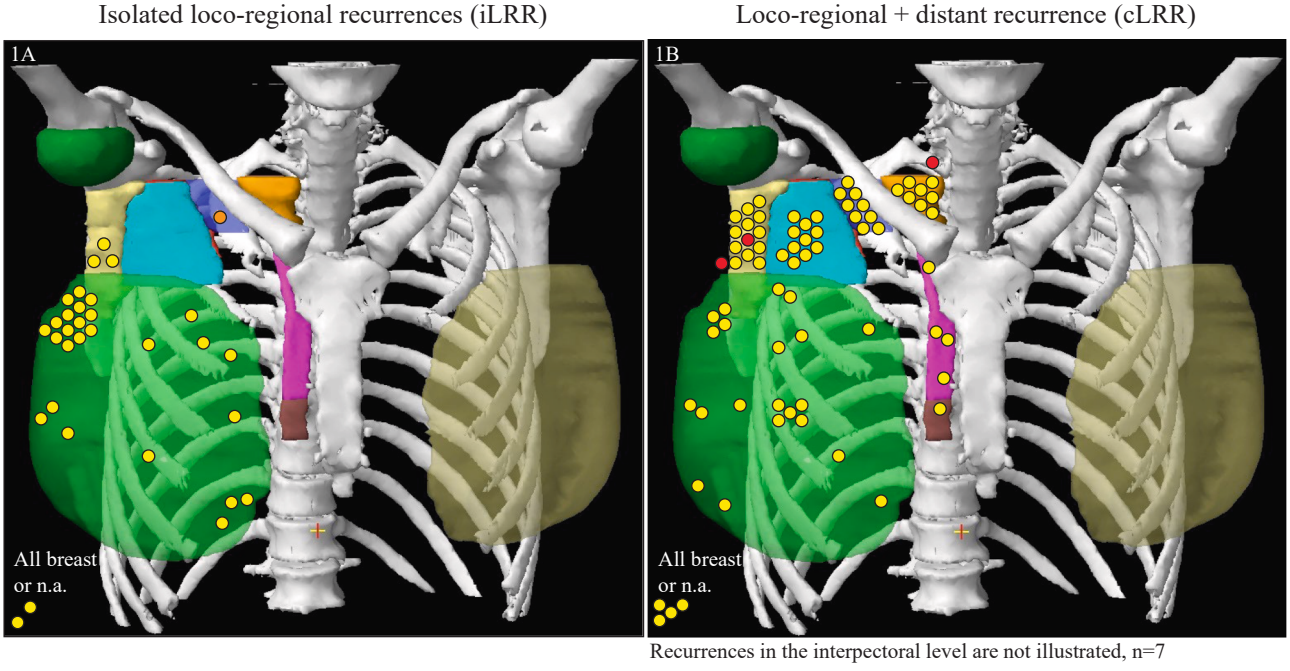


Fig. 1. Localisation of loco-regional recurrences. (A) Isolated loco-regional recurrences (iLRR; n = 41 patients). (B) Loco-regional recurrences with synchronous distant recurrence (cLRR; n = 37 patients). Yellow markers indicate recurrences within the CTV; orange markers indicate recurrences outside the CTV but receiving the full prescribed dose; red markers indicate marginal misses (50–90% dose). Each marker represents one patient per involved volume (see Table 2 for no. of patients). N.a., information regarding the localisation of the local recurrence was not available.

Full planned CTV coverage, as prescribed, was achieved in nearly all patients with LRR. All 64 local recurrences were located within the CTVp and had received the full prescribed dose. Among patients with regional recurrence, one patient had a recurrence ventral to the musculus pectoralis major at the level of CTVn_L3; despite the atypical localisation, the area had received the full prescribed dose and was therefore not categorised as a marginal miss. Three patients were identified as having marginal misses (Figs. 1 and 2, Table 2): one recurrence within CTVn_L1 in a patient for whom this level was not included in the treatment volume; one recurrence lateral to CTVn_L1; and one patient with multiple recurrences in the neck, including a lesion located cranial to CTVn_L4. The two patients with marginal misses, defined as outside the ESTRO CTVs, both achieved a non-pathologic complete response (non-pCR) following NACT, with minimal to no treatment effect on the primary tumour and regional lymph nodes. Both patients initially had ER-negative/HER2-negative tumours (for one patient, the tumour converted to ER-positive status at surgery), and both patients subsequently developed extensive distant disease. The nodal sites corresponding to the marginal misses were not identifiable on diagnostic imaging of the primary tumour.

The median age of patients with LRR was 53 years (range, 28–82 years). BCS was performed in 47 of 78 patients (60%), with a higher proportion in the iLRR group (33 of 41 patients, 80%) compared with the cLRR group (14 of 37 patients, 38%). ALND was performed in 87% of patients (Table 1).

Most patients had T2 (21-50 mm) tumours (47%). T3 tumours (>50 mm) were more common in patients with cLRR (14 of 37 patients; 38%) compared to those with iLRR (7 of 41 patients; 17%). Accordingly, a higher proportion of patients in the cLRR group received bolus. All patients received contemporary systemic therapy according to menopausal status, tumour subtype, including chemotherapy, endocrine therapy, and HER2-targeted therapy; immunotherapy was not standard at the time of inclusion. NACT was administered to 45 patients (58%), with pathological response assessed according to standard protocols [22] Pathological complete response (pCR) was less frequently observed in patients with cLRR than in those with iLRR. Extensive residual nodal disease (≥4 positive nodes) was observed more often in patients with cLRR (16 of 37 patients; 43%) than in patients with iLRR (2 of 41 patients; 11%). Molecular subtype using immunohistochemistry of ER and HER2 status on tumour samples from the 78 patients was 36 (46%) ER+/HER2–, 30 (38%) ER–/HER2–, 7 (9%) ER–/HER2+, and 5 (6%) ER+/HER2+. The distribution was comparable between groups. (Table 1).

Among the 78 patients with LRR, 55 (71%) retained the same histological subtype, ER and HER2 status at recurrence as in the primary tumour. Among these, 40 patients (51% of the patients with LRR) were considered true recurrences, because the recurrent tumour occurred in the same quadrant as the primary tumour and showed an identical histological and molecular subtype. In addition, 6 patients (8%) had recurrences with the same subtype but in a different localisation within the CTVp, while 9 patients (12%) had the same subtype, but the recurrence was not located in the CTVp.

Overall, among 78 patients with LRR, 74 (95%) had the recurrence located within the ESTRO-defined CTVs, and the recurrence volume was planned to receive the full prescribed dose. Only in four of the 2,908 patients in the intention-to-treat cohort did a recurrence occur close to, but outside, the ESTRO CTVs planned to receive full dose. Of these four patients, one patient had a recurrence within CTVn_L1; however, this volume was not planned for dose delivery.

Following a systematic assessment of patients with recurrence, no recurrences were identified medial to CTVn_L4, nor in cervical regions that would be included in the RTOG or RADCOMP volumes but fall outside the ESTRO-CTVs.

Discussion

This study presents, to the best of our knowledge, the first prospective assessment of recurrence patterns in patients with high-risk breast cancer who were irradiated using the ESTRO target definition guideline. Our analysis offers detailed insights into the pattern and localisation of LRRs and shows that, iLRR predominantly occurred within the CTVp_breast following BCS, whereas cLRR was more common among patients with extensive nodal involvement and higher initial stage. In addition, pCR following NACT was less common in patients with cLRR, suggesting a less chemosensitive tumour phenotype and contributing to the poorer prognosis [23].

Whereas earlier guidelines, such as the RADCOMP and RTOG Breast Cancer Atlas, recommended relatively large nodal volumes, the ESTRO consensus guideline suggests a more anatomically confined target definition. In the DBCG Skagen Trial 1 cohort of 2,908 patients, LRRs were uncommon at a median follow-up of 5.2 years. However, among those who experienced LRRs, 96% (75/78) were located inside the ESTRO CTVs. For patients with recurrences close to the loco-regional target volumes, treatment plans were reviewed, and no patients were identified for whom a recurrence would have been included by the RTOG consensus delineation but missed by the ESTRO CTVs. Prior retrospective mapping studies reported that local recurrences outside the ESTRO-CTV but within RTOG volumes occurred in approximately 10% of cases, primarily in the pectoralis muscle and more frequently after mastectomy than BCS. In contrast, we observed a higher proportion of local

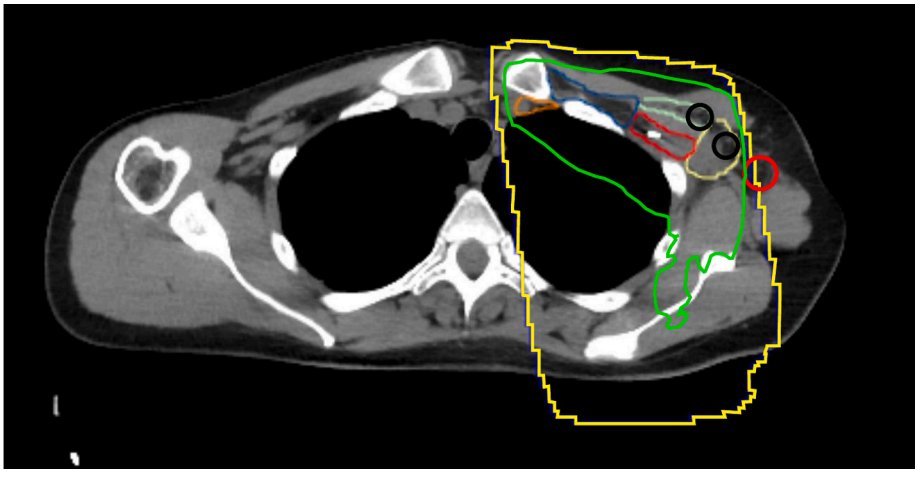


Fig. 2. Example of a marginal miss. Planning CT scan illustrating a marginal miss with recurrence localisation and 50% and 90% isodose curves. The yellow line represents the 50% isodose, the green line the 90% isodose, the red circle the marginal miss, and the black circle the recurrence within the CTV.

Table 1
Patients' characteristics. iLRR, isolated locoregional recurrence; cLRR, concurrent loco-regional and distant recurrence; NACT, neoadjuvant chemotherapy; ER, estrogen receptor; HER2, Human epidermal growth factor receptor 2; SIB, simultaneous integrated boost; BCS, breast-conserving surgery.

	All		**iLRR**		**cLRR**	
	n=	78	n=	41	n=	37
Age						
Median (min, max)	53	(28–82)	53	(29–77)	53	(28–82)
Laterality						
Right	38	49%	18	44%	20	54%
Left	40	51%	23	56%	17	46%
Surgery						
Breast-conserving surgery (BCS)	47	60%	33	80%	14	38%
Mastectomy	31	40%	8	20%	23	62%
Axillary lymph node dissection						
ALND	68	87%	33	80%	35	95%
No ALND	10	13%	8	20%	2	5%
T-size						
1–20 mm	20	26%	15	37%	5	14%
21–50 mm	37	47%	19	46%	18	49%
>50 mm	21	27%	7	17%	14	38%
Positive lymph nodes (clinical). Before NACT, n = 45						
Negative	4	9%	3	16%	1	4%
Positive (macro)	30	67%	10	53%	20	77%
Missing	11	24%	6	32%	5	19%
Positive lymph nodes (pathological), after NACT, n = 45						
0	12	27%	7	37%	5	19%
1–3	15	33%	10	53%	5	19%
4–9	9	20%	2	11%	7	27%
>9	9	20%	–	–	9	35%
Positive lymph nodes (pathological), no NACT, n = 33						
0	1	3%	0	0%	1	9%
1–3	22	67%	18	82%	4	36%
4–9	8	24%	3	14%	5	45%
>9	2	6%	1	5%	1	9%
Neoadjuvant chemotherapy (NACT)						
+ NACT, pCR	5	6%	5	12%	0	0%
+ NACT, non pCR	40	51%	14	34%	26	70%
− NACT	33	42%	22	54%	11	30%
Histology						
Ductal carcinoma	68	87%	38	93%	30	81%
Lobular carcinoma	4	5%	0	0%	4	11%
Other	6	8%	3	7%	3	8%
Grade						
Grade 1	2	3%	1	2%	1	3%
Grade 2	25	32%	13	32%	12	32%
Grade 3	46	59%	24	59%	22	59%
Missing/not usable	5	6%	3	7%	2	5%
ER/HER2-defined subtypes						
ER-/HER2-	30	38%	13	32%	17	46%
ER-/HER2+	7	9%	5	12%	2	5%
ER+/HER2-	36	46%	18	44%	18	49%
ER+/HER2+	5	6%	5	12%	0	0%
Smoking						
Never/prior	69	88%	37	90%	32	86%
Current	9	12%	4	10%	5	14%
Radiotherapy*						
40 Gy/15 fx	38	49%	20	49%	18	49%
50 Gy/25 fx	40	51%	21	51%	19	51%
Bolus						
Yes	16	21%	4	15%	12	25%
No	62	79%	37	85%	25	75%
SIB (BCS only), n = 47						
Yes	16	34%	8	24%	8	57%
No	31	66%	25	76%	6	43%

recurrences following BCS, typically located near the primary tumour site within the CTVp [13]. Similarly, whereas previous studies identified CTV_L4 as the most common site of regional recurrence, our cohort showed a predominance of recurrences in axillary CTV_L1, followed by CTV_L2 and CTV_L3, with comparatively fewer events in CTV_L4. Notably, regional recurrences in our cohort were largely confined to irradiated volumes, with the majority receiving ≥90% of the prescribed dose across all nodal levels, supporting the adequacy of ESTRO-based target delineation even in patients with advanced nodal disease. One patient had a marginal miss within CTVn_L1, a region that was not included in the planned treatment field. In some countries, CTVn_L1 would routinely be included in the target volume, reflecting the considerable international variation in nodal irradiation practices for breast cancer [24]. In addition, no recurrences were observed medial to CTVn_L4. These findings confirm that the smaller ESTRO volumes specify an adequate target volume, and routine expansion of nodal volumes beyond these recommendations may not be necessary in early-stage breast cancer with no residual lymph node involvement. This interpretation, however, should be considered in the context of the treatment techniques applied.

Table 2
Anatomical localisation of loco-regional recurrences (LRR) stratified by recurrence type: isolated loco-regional recurrence (iLRR) and concurrent loco-regional and distant recurrence (cLRR). Values are presented as the number of patients with a recurrence within the specified clinical target volume (CTV), and percentages represent the proportion of the relevant cohort (overall, iLRR, or cLRR). Marginal misses were classified according to the nearest ESTRO-defined nodal level. *Recurrence anterior for CTVn_L3 classified as CTVn_L3.

	All		**iLRR**		**cLRR**	
	n=	78	n=	41	n=	37
Recurrence in CTVp	64	(82%)	40	(98%)	24	(65%)
≥ 95% dose	64		32		32	
50–95% dose						
Recurrence in CTVn_L1	16	(21%)	3	(2%)	13	(35%)
≥ 90% dose	14		2		12	
50–90% dose	2		–		2	
Recurrence in CTVn_L2	11	(14%)	–		11	(30%)
≥ 90% dose	11		–		11	
50–90% dose	–		–		–	
Recurrence in CTVn_L3*	10	(13%)	1	(2%)	9	(24%)
≥ 90% dose	10		–		9	
50–90% dose	–		–		–	
Recurrence in CTVn_L4	9	(12%)	–		9	(24%)
≥ 90% dose	8		–		8	
50–90% dose	1		–		1	
Recurrence in CTVn_interpectoral	7	(9%)	–		7	(19%)
≥ 90% dose	7		–		7	
50–90% dose	–		–		–	
Recurrence in CTVn_IMN	7	(9%)	–		7	(19%)
≥ 90% dose	7		–		7	
50–90% dose	–		–		–	

The ESTRO consensus guideline was originally developed to support RT planning in patients with early-stage breast cancer. If applied to patients with more advanced disease, individual adjustments may be required to ensure appropriate target coverage, as acknowledged within the guideline itself. This validation was performed in a cohort of high-risk patients who were considered radically operated without evident postoperative pathological lymph node involvement; patients with an indication for nodal boost were therefore not included. Some patients had locoregionally advanced disease, including those who became operable following NACT for cT4 tumours. As diagnostic ^{18}F-FDG PET/CT was not standard during the inclusion period, the extent of disease may have been underestimated in some patients relative to current staging practices [25,26]. Consequently, the reported patterns of loco-regional control may partly reflect unintended nodal coverage, and caution is warranted when extrapolating these results to contemporary treatment settings. Notably, in the two patients with marginal misses outside the CTV and the patient with a recurrence ventral to CTV_L3, no pathologic lymph nodes were detectable on their diagnostic CT scans. If these patients had more extensive disease at the time of diagnosis than was evident on CT, such involvement might have been identifiable with ^{18}F-FDG PET/CT, which was not part of the diagnostic work-up at that time. The present validation is primarily based on conventional 3D-CRT planning [16]. Particular attention should be paid to anatomical regions typically covered by tangential and anterior–posterior fields in conventional techniques, as these may not be adequately covered with more conformal modalities, such as VMAT and proton therapy. With highly conformal techniques, there is a risk of reduced dose coverage in regions between adjacent CTVs, resulting in low-dose volumes ("gaps") that are less common in conventional approaches. These can be mitigated by expanding target volumes as in the RadComp trial; however, this must be balanced the potential increase in side effects [27]. A similar consideration has been addressed in the DBCG Proton Trial (NCT04291378), where the ESTRO guideline is applied, and the DBCG RT committee has acknowledged the presence of such dose gaps. Ongoing evaluation is therefore required to determine whether these dosimetric features translate into an increased risk of recurrence in patients treated with contemporary techniques.

The strengths of this study include that the DBCG Skagen trial 1 was a large randomised controlled trial covering a wide range of patient and tumour characteristics and stages, all RT plans were prospectively delineated according to the ESTRO consensus guidelines. All cases with recurrence were individually reviewed through a detailed review of their recurrence imaging, and the median follow-up was 5.2 years. This analysis should be regarded as an early validation, and longer-term outcomes, including a planned 10-year follow-up, will provide further insight. A limitation of the study is the relatively small number of LRRs for the validation of the ESTRO guideline; however, this reflects the outcome of contemporary treatments and the relatively short follow-up. Precise localisation would ideally rely on high-quality imaging in treatment position at recurrence; however, this was not routinely performed, particularly in patients with concomitant DR, where it was not clinically indicated. Consequently, localisation was based on available clinical and imaging information, with uncertain cases discussed within a multidisciplinary setting.

Conclusion

In high-risk breast cancer patients treated with adjuvant RT according to the ESTRO consensus guideline, more than 96 % of LRRs occurred within the ESTRO CTVs. This validation supports the clinical feasibility of the ESTRO consensus guideline and, consequently, routine expansion of the clinical target volumes beyond the ESTRO volumes does not appear to be necessary in early-stage breast cancer.

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CRediT authorship contribution statement

Kristine Wiborg Høgsbjerg: Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mette Skovhus Thomsen:** Writing – review & editing, Supervision, Methodology. **Else Maae:** Writing – review & editing, Investigation. **Ingvil Mjaaland:** Writing – review & editing, Investigation. **Mette Holck Nielsen:** Writing – review & editing, Investigation. **Maja Vestmø Maraldo:** Writing – review & editing, Investigation. **Carine Kirkove:** Writing – review & editing, Investigation. **Tamás Lörincz:** Writing – review & editing, Investigation. **Sami**

Aziz-Jowad Al-Rawi: Writing – review & editing, Investigation. **Egil S Blix: . Andreas Schreiber:** Writing – review & editing, Investigation. **Mechthild Krause:** Writing – review & editing, Investigation. **Unn-Miriam Kasti:** Writing – review & editing, Investigation. **Louise Wichmann Matthiessen:** Writing – review & editing, Investigation. **Stine Elleberg Petersen:** Writing – review & editing, Investigation. **Jens Overgaard:** Writing – review & editing, Conceptualization. **Birgitte Vrou Offersen:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Further reading

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