Implementation of Locoregional Adjuvant Radiotherapy for Breast Cancer in a Rural Healthcare Region: Toxicity Outcomes in the Initial Cohort

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Abstract. Background/Aim: The aim of this study was to analyze the toxicity of locoregional adjuvant breast cancer radiotherapy after implementation of this service in a rural healthcare region with long travel distance. Patients and Methods: This was a retrospective single-institution analysis of 87 consecutive female patients (the initial cohort), managed with conventionally fractionated 3-D conformal radiotherapy with or without boost, including both post mastectomy and breast conservation scenarios. Treatment was administered in line with comprehensive national guidelines. Intensity-modulated techniques were not utilized. Results: The median follow-up time was 4 years. None of the patients developed any grade IV side-effects. According to Radiation Therapy Oncology Group (RTOG) criteria, acute grade 2b or 3 skin toxicity was observed in 16%. In addition, 35% developed acute grade 2a skin reactions. A trend was observed regarding grade 2-3 skin toxicities and administration of a boost (p=0.058). There was a significant association between the clinical target volume of the breast and grade 2-3 skin reactions in women who had breast-conserving surgery (p=0.016). Five patients (6%) developed grade 1 pneumonitis, unrelated to dosimetric or other baseline parameters. Conclusion: The toxicity profile after a median follow-up of 4 years was in accordance with published data. Recently, intensity-modulated techniques have been implemented at the study center, which may reduce radiotherapy toxicity in patients with large clinical target volume due to better dose homogeneity.

Locoregional adjuvant radiotherapy is a well-established component of the multimodal treatment concepts currently in use for breast cancer, either after breast conservation therapy or after mastectomy (1-3). In Norway, national guidelines developed by the Norwegian Breast Cancer Group specify the treatment sequence (neoadjuvant systemic therapy, surgery, adjuvant systemic therapy, adjuvant radiotherapy), types of drugs and aspects of radiotherapy, while taking into account the stage and biology of the tumor. Historically, a large region in rural northern Norway had limited access to radiotherapy, leading to the implementation of a radiotherapy unit in the capital of this region, the city of Bodø (4). Before this unit became operational in 2007, the travel distance to other centers exceeded 400 km. As described earlier, the initial purpose of the new unit was to offer palliative radiotherapy (5). However, a gradual expansion of the services in Bodø have allowed for implementation of adjuvant breast cancer treatment. Given that newly established treatment modalities should undergo rigorous quality assurance in order to confirm their clinical safety and to ensure that outcomes resemble those obtained in comparable healthcare settings, the present retrospective study was undertaken. As an indicator of safety, toxicities observed in the first four years were analyzed.

Patients and Methods

All consecutive female patients treated with locoregional adjuvant conventionally fractionated radiotherapy after implementation of this service in 2014 until May 2018 were included in this quality assurance audit. The latter date was chosen to ensure sufficient follow-up of at least 2 years. Male patients and those who received hypofractionated regimens, *e.g.* due to very old age or distant metastatic disease, were excluded. In accordance with the national guidelines (6), the breast or chest wall were treated in 3-

dimensional conformal tangential technique with 25 fractions of 2 Gy (once daily, 5 fractions per week). The use of bolus material was determined on a case-by-case basis. The lymphatic regions received 23 fractions of 2 Gy, typically in an anterior-posterior 3-dimensional conformal technique. Most patients were treated to the lymphatic regions I-IV and interpectoral drainage, as outlined in a European guideline (7). Level I was excluded in the case of previous removal of at least 10 lymph nodes, except for cases with macroscopic perinodal extension or tumor deposits in the axillary fat tissue. This policy was specified in the national guideline. The internal mammary nodes were treated on a case-by-case basis. A boost of 8 fractions of 2 Gy was prescribed for patients ≤50 years of age. A boost of 5 fractions of 2 Gy was prescribed in patients older than 50 years of age when the tumor extended to the resection margin. Typically, a photon boost was given (sometimes electrons). All treatments were discussed in the hospital's weekly Multidisciplinary Breast Cancer Tumor Board. Intensity-modulated techniques were not available. Dosimetric parameters and organ-at-risk constraints were specified in the national guidelines. In March 2016, the deep inspiration breath hold (DIBH) technique was implemented. Before that date, only patients with right-sided tumors were treated in Bodø. Consequently, all study patients with left-sided disease received DIBH radiotherapy. Those with right-sided disease were initially irradiated without DIBH. Adjuvant chemotherapy was given before radiotherapy, whilst human epidermal growth factor receptor 2 (HER2)-directed treatment continued during radiotherapy. Adjuvant endocrine therapy was started before or during radiotherapy, depending on logistic aspects and patient preference. No consistent skin care protocol was applied. Physician-assessed toxicity was registered at the end of radiotherapy using the Radiation Therapy Oncology Group grading system for skin reactions, which features grades 0, 1, 2a, 2b, 3

and 4 (8). Other side effects were assessed according to Common Terminology Criteria for Adverse Events (CTCAE version 4.0 (9). Afterwards, patients who had undergone neoadjuvant treatment were assessed every 6 months; the others had yearly follow-up. Baseline and follow-up data were extracted from electronic health record systems.

Factors predicting for acute toxicity were assessed. Statistical analyses included chi-square or Fisher's exact test and binary logistic regression (SPSS 27; IBM Corp., Armonk, NY, USA). The median follow-up was 4 years. The database created for the purpose of this quality-of-care analysis did not require approval by the local Ethics Committee (REK Nord).

Results

The study included 87 patients, one of whom was treated for bilateral synchronous breast cancer (88 locoregional treatment regions). Most of these 88 regions were treated in postmenopausal women (74%) (Table I). The majority (75%) had stage II disease (T1-2 N1), often grade 2, hormone receptor positive and HER2 negative. As indicated in Table II, 8% were triple-negative and 14% HER2-positive. Post mastectomy radiotherapy was performed in 44%. In 36%, surgery was preceded by neoadjuvant treatment. In 17%, irradiation included a local boost. Further treatment details are summarized in Table III.

None of the patients developed any grade IV side-effects (Table IV). Acute grade 2b or 3 skin toxicity was observed in 16%. In addition, 35% developed acute grade 2a skin reactions. A trend was observed regarding these grade 2-3 skin toxicities and administration of a boost [odds ratio (OR)=3.6, confidence interval (CI)=0.99-12.8; *p*=0.058]. Logistic binary regression showed a significant association between the clinical target volume (CTV) of the breast and grade 2-3 skin reactions in women who had breast-

conserving surgery (OR=1.003, CI=1.001-1.005; *p*=0.016). This was not the case in the post mastectomy subgroup (*p*=0.27) with much smaller CTV; the median CTV was 606 cm^3 after breast-conserving surgery. The other factors displayed in the Tables did not correlate with grade 2-3 skin reactions. Five patients (6%) developed grade 1 pneumonitis, unrelated to dosimetric or other baseline parameters.

Eight patients (9%) developed breast-/shoulder-related late side-effects, mainly fibrosis. These side-effects were less frequently observed in patients older than 60 years, *i.e.* the median age (OR=0.14, CI=0.03-0.655; *p*=0.014). Boost radiotherapy increased the risk of late side effects (OR=6.2, CI=1.3-28.4; *p*=0.027). No cardiac side-effects were reported.

Overall, five patients (6%) developed distant metastases, including the only patient who presented with a locoregional relapse in the irradiated region.

Discussion

After decades of breast cancer therapy improvements, locoregional adjuvant radiotherapy is regarded a safe and effective treatment (1-3, 10). Nevertheless, typical and expected side-effects are often observed, *e.g.* skin reactions, breast edema or pain, pneumonitis, fibrosis or lymphedema (11, 12). Due to technical improvements such as intensity-modulated radiotherapy and DIBH, a better toxicity profile can be achieved in the modern era (13, 14). The purpose of the present study was to evaluate the toxicity of locoregional adjuvant radiotherapy as part of a comprehensive quality assurance project, ensuring that this newly established service at Nordland Hospital provides results comparable to those reported in the literature.

We evaluated the first 87 patients (88 treatment regions, all treated before intensity-modulated radiotherapy was implemented) with a median follow-up of 4 years. The typical patient was postmenopausal, had stage II hormone receptor-positive breast cancer and was managed with breast-conserving surgery and conventionally fractionated irradiation. However, treatment was tailored to factors such as age and cancer biology, as recommended in the national guidelines. Younger patients (≤50 years) of age received a boost. The use of bolus material was individualized because the current literature and guidelines leave room for diverging opinions and policies (15, 16). This is also true for inclusion of the internal mammary lymph nodes (17). Typically, a bolus was not used and the internal mammary lymph nodes were not included.

The toxicity rates observed in our study, which adhered to treatment planning objectives outlined in national guidelines, correspond well to other reports in the literature (18-20). We found that larger breast CTV and boost administration were associated with worse toxicity. Given that younger patients were selected for a boost, the fact that patients older than 60 years reported fewer and lower-grade late side-effects is understandable. Often, severe acute toxicity translates into chronic skin changes and fibrosis. The latter might compromise breast size and cosmetic appearance beyond surgery-related defects. Some of the previous studies cited above reported that additional factors such as body mass index, smoking or use of bolus material influenced the toxicity outcomes. However, these studies were much larger and thus better suited to address the complete picture of risk factors.

It was reassuring to learn that only one patient developed a locoregional recurrence. In other studies, the prevailing pattern of recurrence was distant metastasis without locoregional component (2, 3, 21). The limited statistical power of the present

evaluations in 87 patients represents the major disadvantage of our study. Furthermore, follow-up was too short to fully address the complete spectrum of late toxicities including cardiac events, which may develop after 10 years or more. Patient-reported outcomes or lymphedema measurements were not included. Moreover, disease relapse is not necessarily expected to occur within the first 5 years in the present era of effective systemic therapy. Even if the radiotherapy concepts were based on national guidelines, heterogeneity existed. Despite such limitations, the data suggest that satisfactory treatment results can be obtained in rural healthcare settings. In the future, shortening of the overall radiotherapy time (5 weeks + boost) by means of hypofractionation or simultaneous integrated boost may be considered, a strategy that was followed during the time period of this study in the oldest patients and when distant metastases were present at first diagnosis of breast cancer.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

References

1 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 and 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 *383(9935):* 2127-2135, 2014. PMID: 24656685. DOI: 10.1016/S0140-6736(14)60488-8

2 Zeidan YH, Habib JG, Ameye L, Paesmans M, de Azambuja E, Gelber RD, Campbell I, Nordenskjöld B, Gutiérez J, Anderson M, Lluch A, Gnant M, Goldhirsch A, Di Leo A, Joseph DJ, Crown J, Piccart-Gebhart M and Francis PA: Postmastectomy radiation therapy in women with T1-T2 tumors and 1 to 3 positive lymph nodes: analysis of the Breast International Group 02-98 trial. Int J Radiat Oncol Biol Phys *101(2):* 316-324, 2018. PMID: 29534902. DOI: 10.1016/j.ijrobp.2018.01.105

3 Hammer J, Geinitz H, Nieder C, Track C, Thames HD, Seewald DH, Petzer AL, Helfgott R, Spiegl KJ, Heck D and Bräutigam E: Risk factors for local relapse and inferior disease-free survival after breast-conserving management of breast cancer: Recursive partitioning analysis of 2161 patients. Clin Breast Cancer *19(1):* 58-62, 2019. PMID: 30197244. DOI: 10.1016/j.clbc.2018.08.001

4 Nieder C, Norum J, Spanne O, Bilberg I, Vagstad G and Dalhaug A: Does distance to treatment centre influence the rate of palliative radiotherapy in adult cancer patients? Anticancer Res *29(7):* 2641-2644, 2009. PMID: 19596940.

5 Nieder C, Haukland E, Mannsåker B, Pawinski A and Dalhaug A: Early palliative radiation therapy in patients with newly diagnosed cancer: Reasons, clinical practice, and survival. Pract Radiat Oncol *5(5):* e537-e542, 2015. PMID: 25823382. DOI: 10.1016/j.prro.2015.02.008

6 Norwegian Breast Cancer Group (NBCG) guidelines, available online, https://nbcg.no/retningslinjer/

7 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 and Poortmans P: ESTRO consensus guideline on target volume delineation for elective radiation therapy of

early-stage breast cancer. Radiother Oncol *114(1):* 3-10, 2015. PMID: 25630428. DOI: 10.1016/j.radonc.2014.11.030

8 Fisher J, Scott C, Stevens R, Marconi B, Champion L, Freedman GM, Asrari F, Pilepich MV, Gagnon JD and Wong G: Randomized phase III study comparing best supportive care to Biafine as a prophylactic agent for radiation-induced skin toxicity for women undergoing breast irradiation: Radiation Therapy Oncology Group (RTOG) 97-13. Int J Radiat Oncol Biol Phys *48(5):* 1307-1310, 2000. PMID: 11121627. DOI: 10.1016/s0360-3016(00)00782-3

9 Common Terminology Criteria for Adverse Events, available online, https://www.eortc.be/services/doc/ctc/ctcae_4.03_2010-06-14_quickreference_5x7.pdf

10 Gitt A, Böse-Ribeiro H, Nieder C, Kup PG, Hermani H, Bühler H, Ergönenç HY, Drüppel D, Adamietz IA and Fakhrian K: Treatment results of MammoSite catheter in combination with whole-breast irradiation. Anticancer Res *36(1):* 355-360, 2016. PMID: 26722065.

11 Yee C, Wang K, Asthana R, Drost L, Lam H, Lee J, Vesprini D, Leung E, DeAngelis C and Chow E: Radiation-induced skin toxicity in breast cancer patients: A systematic review of randomized trials. Clin Breast Cancer *18(5):* e825-e840, 2018. PMID: 30072193. DOI: 10.1016/j.clbc.2018.06.015

12 Werner EM, Eggert MC, Bohnet S and Rades D: Prevalence and characteristics of pneumonitis following irradiation of breast cancer. Anticancer Res *39(11):* 6355-6358, 2019. PMID: 31704867. DOI: 10.21873/anticanres.13847

13 Jensen KE, Soril LJJ, Stelfox HT, Clement FM, Lin Y and Marshall DA: Side-effects associated with the use of intensity-modulated radiation therapy in breast cancer

patients undergoing adjuvant radiation therapy: A systematic review and meta-analysis. J Med Imaging Radiat Sci *48(4):* 402-413, 2017. PMID: 31047476. DOI: 10.1016/j.jmir.2017.09.002

14 Kim K, Chun M, Jin H, Jung W, Shin KH, Shin SS, Kim YJ, Park SH, Kim JH, Kim YH, Shin HS, Kim H, Kim SS, Lee JH, Kim YB, Lee SY, Choi J, Oh DH, Kang KM, Kwon J, Kim MY, Koo T, Park HJ and Ahn SJ: Inter-institutional variation in intensity-modulated radiotherapy for breast cancer in Korea (KROG 19-01). Anticancer Res *41(6):* 3145-3152, 2021. PMID: 34083309. DOI: 10.21873/anticanres.15100

15 Dahn HM, Boersma LJ, de Ruysscher D, Meattini I, Offersen BV, Pignol JP, Aristei C, Belkacemi Y, Benjamin D, Bese N, Coles CE, Franco P, Ho A, Hol S, Jagsi R, Kirby AM, Marrazzo L, Marta GN, Moran MS, Nichol AM, Nissen HD, Strnad V, Zissiadis YE, Poortmans P and Kaidar-Person O: The use of bolus in postmastectomy radiation therapy for breast cancer: A systematic review. Crit Rev Oncol Hematol *163:* 103391, 2021. PMID: 34102286. DOI: 10.1016/j.critrevonc.2021.103391

16 Nuzzo M, Ursini LA, Patani F, Rosa C, Trignani M, DI Tommaso M, Meattini I, Gregucci F, Ciabattoni A, Genovesi D and Caravatta L: Using the bolus in post-mastectomy radiation therapy (PMRT): A national survey on behalf of the Italian Association of Radiotherapy and Clinical Oncology (AIRO) breast cancer group. Anticancer Res *40(11):* 6505-6511, 2020. PMID: 33109590. DOI: 10.21873/anticanres.14673

17 Haussmann J, Budach W, Tamaskovics B, Bölke E, Corradini S, Djiepmo-Njanang FJ, Kammers K and Matuschek C: Which target volume should be considered when irradiating the regional nodes in breast cancer? Results of a network-meta-analysis. Radiat Oncol *14(1):* 102, 2019. PMID: 31186015. DOI: 10.1186/s13014-019-1280-6

18 Wright JL, Takita C, Reis IM, Zhao W, Lee E, Nelson OL and Hu JJ: Prospective evaluation of radiation-induced skin toxicity in a race/ethnically diverse breast cancer population. Cancer Med *5(3):* 454-464, 2016. PMID: 26763411. DOI: 10.1002/cam4.608

19 De Langhe S, Mulliez T, Veldeman L, Remouchamps V, van Greveling A and Gilsoul M: Factors modifying the risk for developing acute skin toxicity after whole-breast intensity modulated radiotherapy. BMC Cancer *14(1):* 711, 2014. PMID: 25252713. DOI: 10.1186/1471-2407-14-711

20 Kraus-Tiefenbacher U, Sfintizky A, Welzel G, Simeonova A, Sperk E, Siebenlist K, Mai S and Wenz F: Factors of influence on acute skin toxicity of breast cancer patients treated with standard three-dimensional conformal radiotherapy (3D-CRT) after breast-conserving surgery (BCS). Radiat Oncol *7(1):* 1-9, 2012. PMID: 23249653. DOI: 10.1186/1748-717X-7-217

21 Nichol A, Narinesingh D, Raman S, Germain F, Chan EK, Tran E, Gondara L, Speers C, Lohrisch CA and Truong P: The effect of bolus on local control for patients treated with mastectomy and radiation therapy. Int J Radiat Oncol Biol Phys *110(5):* 1360-1369, 2021. PMID: 33485893. DOI: 10.1016/j.ijrobp.2021.01.019

Table I. Patient characteristics (N=88).

Parameter	Subgroup	Number (%)
Age	≤60 Years	45 (51)
	>60 Years	43 (49)
	Median (min-max)	60 (33-85)
Body mass index	<18.5 kg/m^2	0 (0)
	18.5-25 kg/m^2	32 (36)
	≥25-35 kg/m^2	49 (56)
	≥35 kg/m^2	7 (8)
Menopausal status	Pre	14 (16)
	Peri	5 (6)
	Post	65 (74)
	Not documented	4 (5)
Comorbidity	Chronic obstructive pulmonary disease	4 (5)
	Cardiac disease	4 (5)
	Hypertension	23 (26)
	Diabetes mellitus	4 (5)
	Hypercholesterolemia	17 (19)
	Autoimmune disease excluding thyroid	10 (11)
	Autoimmune disease including thyroid	20 (22)
Smoking habit	Yes	14 (16)
	No	42 (48)
	E-cigarette	2 (2)
	Not documented	30 (34)

Table II. Tumor characteristics (N=88).

Parameter	Subgroup	Frequency, n (%)
Histology	Ductal carcinoma	72 (82)
	Lobular carcinoma	11 (13)
	Both components	1 (1)
	Not specified	4 (5)
TNM stage	Stage 2	66 (75)
	Stage 3	22 (25)
pT stage	T0/complete response	11 (13)
	T1	35 (40)
	T2	35 (40)
	T3	4 (5)
	T4	2 (2)
	Not documented	1 (1)
pN stage	N0	18 (20)
	N1	64 (73)
	N2	5 (6)
	Not documented	1 (1)
Number of positive lymph nodes	0	18 (20)
	1	47 (53)
	2	11 (13)
	3-5	8 (8)
	6-9	5 (6)
Positive nodes after axillary dissection	0-10%	16 (36)
	11-50%	24 (53)
	≥51%	5 (11)
Multiple tumors	Ipsilateral	15 (17)
	Bilateral tumor(s)	3 (3)
Perinodal tumor extension	Yes	36 (41)
	No	52 (59)
Primary tumor size	≤20 mm	47 (53)
	>20 mm	41 (47)
Histological grade	1	14 (16)
	2	47 (53)
	3	14 (16)
	Not documented	13 (15)
Ki-67	≤30%	41 (47)
	31-60%	26 (30)
	>60%	4 (5)
	Not documented	17 (19)
Blood vessel invasion	Yes	16 (18)
	No	31 (35)
	Possible	2 (2)
	Not documented	39 (44)
Lymphatic vessel invasion	Yes	9 (10)

	No	54 (61)
	Possible	4 (5)
	Not documented	21 (24)
Margin	Involved	9 (10)
	Free margin 0-1 mm	17 (19)
	Free margin >1mm	52 (69)
	Not specified free margin	10 (2)
Estrogen receptor status	Positive	75 (85)
	Negative	13 (15)
Progesterone receptor status	Positive	63 (72)
	Negative	25 (28)
HER2 status	Positive	12 (14)
	Negative	76 (86)
Triple-negative		7 (8)
BRCA mutation	*BRCA1*	1 (1)
	BRCA2	2 (2)
	BRCA-mutation negative	43 (49)
	Not tested	42 (48)
DCIS component	Yes	37 (42)
	No	48 (55)
	Not specified	3 (3)

TNM: Tumor, Node, Metastases
HER: human epidermal growth factor receptor
BRCA: breast cancer gene
DCIS: ductal carcinoma in situ

Table III. Therapeutic parameters (N=88).

Parameter	Subgroup	Value
Breast surgery, n (%)	Conservative	47 (53)
	Ablation	39 (44)
	Oncoplastic	2 (2)
Axillary surgery, n (%)	Dissection	45 (51)
	Sentinel node	42 (48)
	None	1 (1)
Neoadjuvant treatment, n (%)	None	56 (64)
	Endocrine	2 (2)
	Chemotherapy	26 (30)
	Endocrine + chemotherapy	1 (1)
	HER2 + chemotherapy	3 (3)
Adjuvant treatment, n (%)	None	4 (5)
	Endocrine	43 (49)
	Chemotherapy	7 (8)
	Endocrine + chemotherapy	22 (25)
	Chemotherapy + HER2	1 (1)
	Chemotherapy + endocrine + HER2	3 (3)
	Endocrine + HER2	2 (2)
	HER2	6 (7)
Diagnostic setting, n (%)	Screening	23 (26)
	Palpable mass	51 (58)
	Other symptomatic complaints	8 (9)
	Other settings	6 (7)
Volume of breast or thoracic wall, n (%)	<250 cm^3	17 (19)
	250-499 cm^3	27 (31)
	500-999 cm^3	36 (41)
	≥1,000 cm^3	8 (9)
Boost, n (%)	Yes	15 (17)
Inclusion of internal mammary nodes, n (%)	Yes	4 (5)
Bolus, n (%)	Thoracic wall	19 (21)
Prothesis, n (%)	Yes	3 (3)
D_{max} (%), N=88	Median (range)	108, 103-111
D_{98} CTV (%), N=88	Median (range)	94, 91-97
D_2 CTV (%), N=88	Median (range)	106, 101-108
Heart Dmean (Gy), N=45	Median (range)	1.4, 0.3-2.8
Lung V20 (%), N=88	Median (range)	27, 13-36

CTV: clinical target volume

HER: human epidermal growth factor receptor
Dmax: maximum dose
D_{98}: dose to 98% of the CTV
D_2: dose to 2% of the CTV
Dmean: mean dose
Gy: Gray
V20: lung volume exposed to 20 Gy

Table IV. Toxicity outcomes (N=88).

Toxicity type	Grade	Number (%)
RTOG acute skin reaction	0-1 2a 2b-3 4	43 (49) 31 (35) 14 (16) 0 (0)
CTCAE pneumonitis	0 1 >1	83 (94) 5 (6) 0 (0)
CTCAE skin changes, fibrosis, pain (breast/thoracic wall/shoulder)	0 1-2 >2	80 (91) 8 (9) 0 (0)

RTOG: Radiation Therapy Oncology Group

CTCAE: Common Terminology Criteria for Adverse Events (version 4.0)