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Helical Tomotherapy in Local Advanced Breast Cancer Following Mastectomy: Long-term Results and Late Toxicity Analysis

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Abstract

Background/Aim: Adjuvant radiotherapy is a key part of the overall treatment plan for local advanced breast cancer. In this study, we investigated the long-term clinical outcomes of helical tomotherapy (hT) following mastectomy.
Patients and Methods: Female patients (n=38) with locally advanced or lymph node-positive breast cancer who had undergone mastectomy, sentinel-node biopsy, and/or axillary lymph node dissection were included in this single-center analysis. Postmastectomy radiation therapy (PMRT) to involved chest wall was applied by using hT with cumulative dose of 50.4 Gy. Lymphatic drainage pathways were included when they contained tumor cells. Generally, additional mastectomy scar boost irradiation (10 Gy) was applied up to a cumulative dose of 60.4 Gy. Local control (LC), metastasis, survival, toxicity, and secondary malignancy rates were analyzed retrospectively.
Results: The mean follow-up duration was 80 months. LC rates at 5 and 8 years were 97.2%, while metastasis-free survival (MFS) rates were 61.6% and 58%, respectively. Overall survival (OS) rates at 5 and 8 years were 83.9% and 66%, respectively. The occurrence of acute erythema was recorded in 60.5% (grades 1-2) and 23.7% (grade 3) of patients. 18.4% of treated patients developed grade 1 ipsilateral arm lymphedema and 5.3% grade 2. Serious adverse events, higher than grade 3, were not seen. Only one patient showed secondary malignancy 24 months after PMRT.

continued

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Conclusion: Excellent long-term results and low toxicity rates can be achieved in patients with locally advanced breast cancer by applying PMRT using hT. We are the first to report on the very low late toxicity rates and incidence of secondary malignancies. Our data suggests that broader clinical implementation of hT could benefit these patients.

Keywords: Breast cancer, helical tomotherapy, mastectomy, adjuvant radiotherapy, postmastectomy radiation therapy, scar boost radiation.

Introduction

Breast cancer is the most frequently diagnosed malignancy in women worldwide and remains a principal cause of cancer-related mortality (1). Therefore, this disease is still the subject of intensive research (2-5). Mastectomy persists as an essential treatment modality, particularly for locally advanced or multifocal tumors where breast conserving surgery is not possible. Patients with triple-negative and luminal B differentiated breast cancers have a poorer prognosis (6, 7). Among the curative multi-modal treatment approaches available for loco-regional advanced breast cancer, post-mastectomy radiotherapy (PMRT) is a central modality, along with chemotherapy, hormonal therapy, and immunotherapy. Meta-analyses of three randomized clinical studies have shown that PMRT significantly reduces both local recurrence in locally advanced T3 and T4 tumors as well as breast cancer mortality in patients with positive lymph nodes (8-11). Additional irradiation of the regional lymph nodes (axillar, supraclavicular, or parasternal regions) during PMRT can significantly improve local control (LC) as well as overall survival (OS) rates in patients with more than three positive lymph nodes at mastectomy. Patients with one to three positive lymph nodes and premenopausal status or with G2-G3 tumor grading also show significant positive clinical responses (12, 13). Consequently, PMRT is considered a standard treatment modality for locally advanced and/or lymph node-positive breast cancer (12).

The standard technique for PMRT is continuous three-dimensional conformal radiation therapy (3D-CRT) (8, 9, 13-15). While effective in many cases, 3D-CRT may be limited when creating extensive or anatomically challenging volumes adjacent to organs at risk (OARs) such as the heart or lungs.

Intensity-modulated radiotherapy (IMRT) is an advanced form of radiation therapy (16). Previous studies have frequently reported the benefits of step-and-shoot IMRT and volumetric arc therapy (VMAT) in adjuvant radiotherapy of breast cancer in comparison with 3D-CRT (17, 18). IMRT is a useful alternative radiation technique, especially for patients with complex planning target volumes (PTV) or challenging anatomical considerations such as unfavorable positioning of heart or lungs, funnel chest, etc. In cases of complex anatomy, IMRT also facilitates additional radiotherapy after mastectomy and to regional lymph nodes, improving target coverage while reducing dose exposure to OARs (19, 20).

Helical tomotherapy (hT), also known as helical IMRT, is a new treatment approach in the field of photon-IMRT. It offers superior dose homogeneity and conformity within the target volume, lowest maxima dose values, and a steeper dose gradient in comparison to other IMRT and rotational techniques (21, 22).

The technical characteristics of hT have been discussed previously (21, 23-26). The tomotherapy unit is a hybrid therapy/imaging tool comprising a linear accelerator with an energy output of 6 MV and a helical computed tomography (CT) scanner. Irradiation treatments are applied using a rotating fan beam, forming a helical pattern as the patient is moved through the gantry bore (23, 24). An extremely fast-moving pneumatically driven binary multileaf collimator (MLC) modulates the photon beam. During an inverse treatment planning process, the MLC conformation is optimized to deliver highly conformal radiation doses to the PTV (25). TomoEDGE is a recently introduced tomotherapy technique that minimizes the dose penumbra at the cranial and caudal field borders by modulating primary collimators. This shortens the treatment duration by a factor of two without compromising plan quality (21, 26).

Overall, hT has shown excellent results in recent clinical studies in patients with breast cancer after breast conservation surgery (BCS). In retrospective studies of female patients with lymph node-negative and lymph node-positive breast cancer after BCS, adjuvant hT resulted in high LC and survival rates without severe side effects (20, 27). However, clinical data on PMRT using hT in patients with breast cancer remain very limited at present (28).

This retrospective single-center clinical study examined long-term results of PMRT using hT in female patients with locally advanced breast cancer with and without positive lymph nodes. The study analyzed OS, LC, metastasis-free survival (MFS), early and late toxicities, and secondary cancer occurrence rates.

Patients and Methods

Patients. In this retrospective single-center clinical study, 38 female patients with locally advanced breast cancer with and without positive lymph nodes, who required adjuvant hT between 2011 and 2020 at the Clinic and Practice of Radiotherapy in Konstanz (Germany), were included. Mastectomy, sentinel node biopsy, and/or axillary lymph node dissection were performed in all cases. In five cases, immediate breast reconstruction was performed. Two types of implants were used, either permanent silicone gel implants (n=1) or tissue expanders (n=4). Indications for adjuvant radiotherapy were present in all cases. hT was specifically employed when conventional tangential 3D-RT was insufficient to cover the PTV or when radiation doses delivered to OARs exceeded tolerable limits. In these cases, additional irradiation of lymphatic drainage pathways was particularly challenging. Patients with a history of recurrent cancer or who had undergone thoracic radiotherapy were not included in the study. Patients were staged in accordance with the tumor-lymph node-metastasis (TNM) classification system. T describes the size or direct extent of the primary tumor, N describes the degree of spread to regional lymph nodes, and M describes whether the cancer has spread to distant parts of the body (29).

The study was carried out in accordance with the World Medical Association's Declaration of Helsinki and the International Committee of Medical Journal Editors' Recommendations for the Protection of Research Participants.

Ethical approval was obtained from the Medical Chamber (Landesärztekammer) of Baden-Wuerttemberg Ethics Committee, Stuttgart, Germany (file number F-2021-082). All patients provided written informed consent to undergo the proposed treatment investigated in the study.

Imaging and regions of interest. All study participants underwent CT imaging for radiotherapy planning, with a slice thickness of 5 mm. A breast-tilting board (wing step) was used to optimize dorsal positioning while the upper extremities were secured. CT-imaging was carried out in the neutral airway position. The right and left lungs, entire heart, left ventricle, and contralateral breast were delineated on the CT images as OARs (30). Target volumes were defined according to institutional standards. Chest wall, subcutaneous tissue and the scar of the tumor affected side was included into the PTV. In case of tumor-positive lymph nodes, the ipsilateral axillary and supraclavicular lymphatic drainage pathways were included in the irradiation field, and the parasternal lymph nodes were treated in cases of central or medial tumor localization. In total, 32 patients (84%) showed tumor-involved lymph nodes. Safety lateral, cranial, and caudal margins of 2 cm, and a safety medial margin of 1 cm were applied.

Radiotherapy. The TomoTherapy® system (Accuray, Sunnyvale, CA, USA) was used to deliver radiation therapy to all patients. This linear accelerator is a helical intensity-modulated radiation therapy (IMRT) system with a 6-MV photon beam and integrated planning software. All treatment plans were applied with a beam field width of 2.5/5 cm, and dose calculations were performed using a fine dose grid. The pitch value for each plan was selected

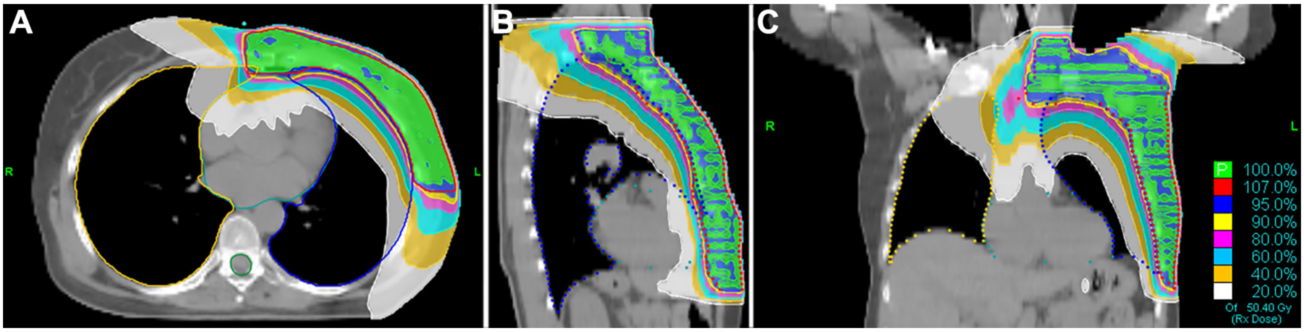

Figure 1. *An example of the dose distribution in postmastectomy radiation therapy (PMRT) (ventral thorax wall and the ipsilateral regional/supraclavicular lymph nodes; 50.4 Gy in 28 fractions) of a female patient with left-sided lymph node positive breast cancer after mastectomy using helical tomotherapy is shown in transversal (A), sagittal (B) and coronal (C) section planes. In the computer-tomography slice, the planning target volume (PTV) of the ventral thorax wall and the lymphatic drainage pathway is marked with red outlines. The relative isodoses of the described median PTV dose (50.4 Gy) are shown.*

based on previous reports (27, 31), with a modulation factor ranging from 2.4-3. The objective of optimizing each radiation plan was to minimize dose exposure to OARs, especially the right and left lung, heart, and contralateral breast, while ensuring at least 95% coverage of the prescribed dose to the PTV (Figure 1). Delivery of a maximum dose of >107% was avoided. A normo-fractionated dose of 50.4 Gy (28×1.8 Gy) was administered. This was delivered to the chest wall and to the lymphatic drainage pathways. Additional mastectomy scar boost irradiation (5×2 Gy) was applied sequentially to a cumulative dose of 60.4 Gy to the mastectomy scar with a 2.5 cm edge margin. In two cases scar boost was applied by integrated boost irradiation (28×2.3 Gy) to a cumulative dose of 64.4 Gy.

Acute and late toxicities. The Common Terminology Criteria for Adverse Events, Version 5, published by the Radiation Therapy Oncology Group and European Organization for Research and Treatment of Cancer, was used to grade acute and late toxicities (32). Severe radiation-related toxicity was defined as higher than grade 3 late toxicity. Toxicities with significant impact on patients' quality of life but without total loss of function were also classified as severe radiation-induced late toxicities. Clinical interviews were used to determine and document changes during the patients' follow-up visits, conducted 6 weeks after radiotherapy and annually thereafter. No grade 4 or 5 toxicities were observed. Ultrasonography of the thorax wall and the regional lymphatic drainage pathways as well as mammography of the contralateral breast were included in the follow-up examinations, which were carried out annually.

Statistical analysis. The key outcomes evaluated in this retrospective study included LC, tumor-specific survival (TSS), disease-free survival (DFS), distant MFS, and OS. The Kaplan-Meier method was used to calculate all time to event data. The starting point was the first day of radiotherapy until the last follow-up or death. Statistical analyses and plots were carried out using R-Studio (version 2022.07.01) with the "survminer" (version 0.4.9) and "survival" (version 3.3-1). The log-rank test was the primary method used to compare differences between Kaplan-Meier curves for subgroups, while absolute values were compared using Fisher's exact test.

Results

The mean age of the 38 female patients with locally advanced breast cancer who underwent mastectomy, sentinel-node biopsy, and/or axillary lymph node dissection, was 58 years (range=36-91 years) at the time of adjuvant helical IMRT initiation. The mean follow-up duration was 80 months (standard deviation: ±13.0 months), with a maximum follow-up of 154 months. Among the cohort, 65.8% of patients received neoadjuvant chemotherapy, while 18.4% received adjuvant chemotherapy. In both cases, chemotherapy was anthracycline- and/or taxane-based. A total of 78.9% of patients underwent additional anti-hormonal therapy, while 28.9% showed HER2 overexpression and were treated with trastuzumab for one year (Table I).

Outcomes. The 5- and 8-year OS rates were 83.9% [95% confidence interval (CI)=72.9-96.6%) and 66.0% (95% CI=51.1-96.2%), respectively. Subgroup analysis revealed no significant differences in OS among patients stratified by tumor grades. Compared to the HER2-positive group and to the hormone receptor positive group triple negative patients showed the significant lowest OS (p<0.05), (Figure 2).

The 5- and 8-year TSS were 90.6% (95% CI=80.8-100%) and 86.3% (95% CI=74.3-100%), respectively. Patients with G1 tumors exhibited higher TSS when compared to patients with G2/ G3 by trend; however, this difference was not statistically significant. Subgroup analysis revealed no significant differences in TSS among patients stratified by hormone receptor or HER2 status (Figure 3).

LC rates were 97.2% at both five and eight years (95% CI=92.0-100%). During the observation period local recurrence occurred in one patient (2.6%), whose tumor showed a G3 grading without expressing either hormone or HER2 receptors (Figure 4).

The 5- and 8-year MFS rates were 61.6% (95% CI=47.6-79.8%) and 58.0% (95% CI=43.6-77.1%), respectively. Patients with T1/T2 tumors exhibited higher MFS by trend when compared to patients with T3/T4 tumors; however, this difference was not statistically significant. Subgroup analysis revealed no significant differences in MFS among patients stratified by tumor grades, in which patients with G1-tumors demonstrated the highest MFS of 75% after eight years. Patients with HER2-positive and hormone receptor negative tumors presented a significantly higher 8-year MFS-rate compared to hormone receptor positive or triple negative tumors within the cohort (p<0.05), (Figure 5).

Table I. *Characteristics of the participants in the study.*

Patient characteristics	
Age, years	
Range	36-91
Mean	58
Median	55
Side	n (%)
Left	16 (42.1%)
Right	22 (57.9%)
Histology	n (%)
Ductal	25 (65.8%)
Lobular	10 (26.3%)
Tripple	2 (5.3%)
Other	1 (2.6%)
Tumor staging	n (%)
T1	10 (26.3%)
T2	10 (26.3%)
T3	2 (5.3%)
T4	16 (42.1%)
Node staging	n (%)
N0	6 (15.8%)
N1	13 (34.2%)
N2	7 (18.4%)
N3	12 (31.6%)
Tumor grading	n (%)
G1	4 (10.5%)
G2	18 (47.4%)
G3	16 (42.1%)
Receptors	n (%)
$Hormone^+$ & $Her2^-$	15 (39.5%)
$Her2^+$ & $Hormone^-$	7 (18.4%)
$Her2^+$ & $Hormone^+$	4 (10.5%)
$Triple^-$	12 (31.6%)
Other therapies	n (%)
CHT total	25 (65.8%)
Neoadjuvant CHT	25 (65.8%)
Adjuvant CHT	7 (18.4%)
Neoadjavant + Adjuvant CHT	7 (18.4%)
Adjuvant AHT	30 (78.9%)

CHT: Chemotherapy; AHT: anti-hormone therapy.

DFS was 58.8% (95% CI= 44.7-77.5%) at five years and 55.2% (95% CI=40.8-74.7%) at eight years. Subgroup analysis revealed no significant differences in DFS among patients stratified by tumor grades, in which patients with G1-tumors demonstrated highest MFS with 75% after five and eight years. Patients with HER2-positive and hormone receptor negative tumors presented a significantly higher 8-year DFS-rate compared to hormone receptor positive or triple negative tumors within the cohort (p<0.05) (Figure 6).

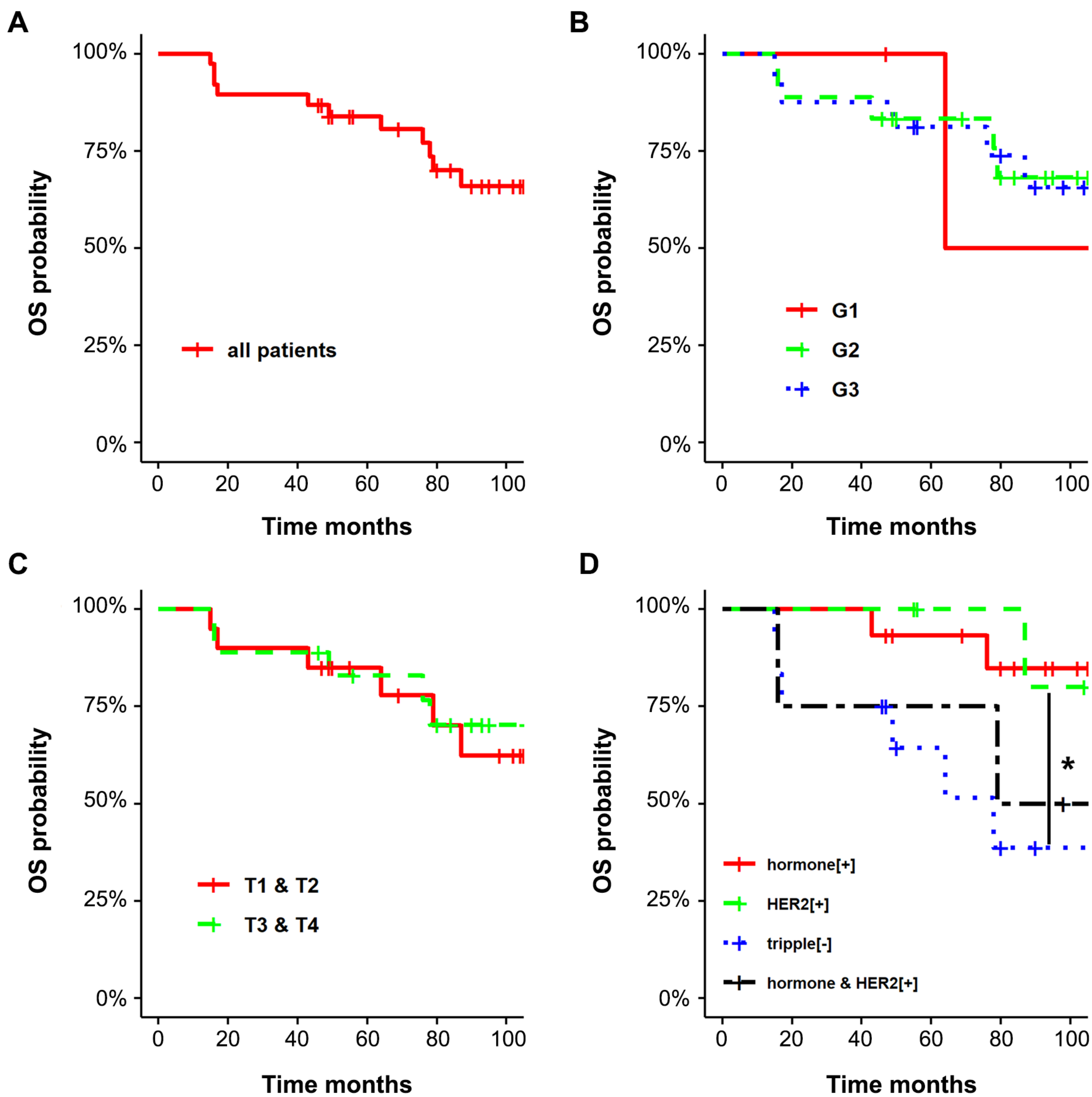

Figure 2. *Kaplan-Meier curve for overall survival (OS) in all female patients with breast cancer (n=38) after postmastectomy radiation therapy (PMRT) using helical tomotherapy (hT) (A), or according to grade (G1, G2, G3) (B), tumor stage (T1, T2) (C) and to receptor expression [hormone positive and human epidermal growth factor receptor 2 (HER2)-negative, HER2-positive (3+), triple negative, hormone-positive and HER2-positive] (D). Asterisk (*) indicates significance at p<0.05.*

Acute toxicity. In total, 15.8% of patients developed no acute erythema, while grade 1 and 2 erythema were observed in 15.8% and 44.7% of patients, respectively. Grade 3 skin reactions (epitheliolysis) occurred in 23.7% of the cohort. Slight hyperpigmentation was present in 34.2% of cases, while strong pigmentation occurred in 13.2%. Fatigue was reported by 34.2% of patients during radiotherapy, and signs of esophagitis or dysphagia were documented in 31.6%. Hematologic toxicity was rare: only 7.9% developed grade 1 leukopenia, and no cases of grade 2 or higher were observed (Table II).

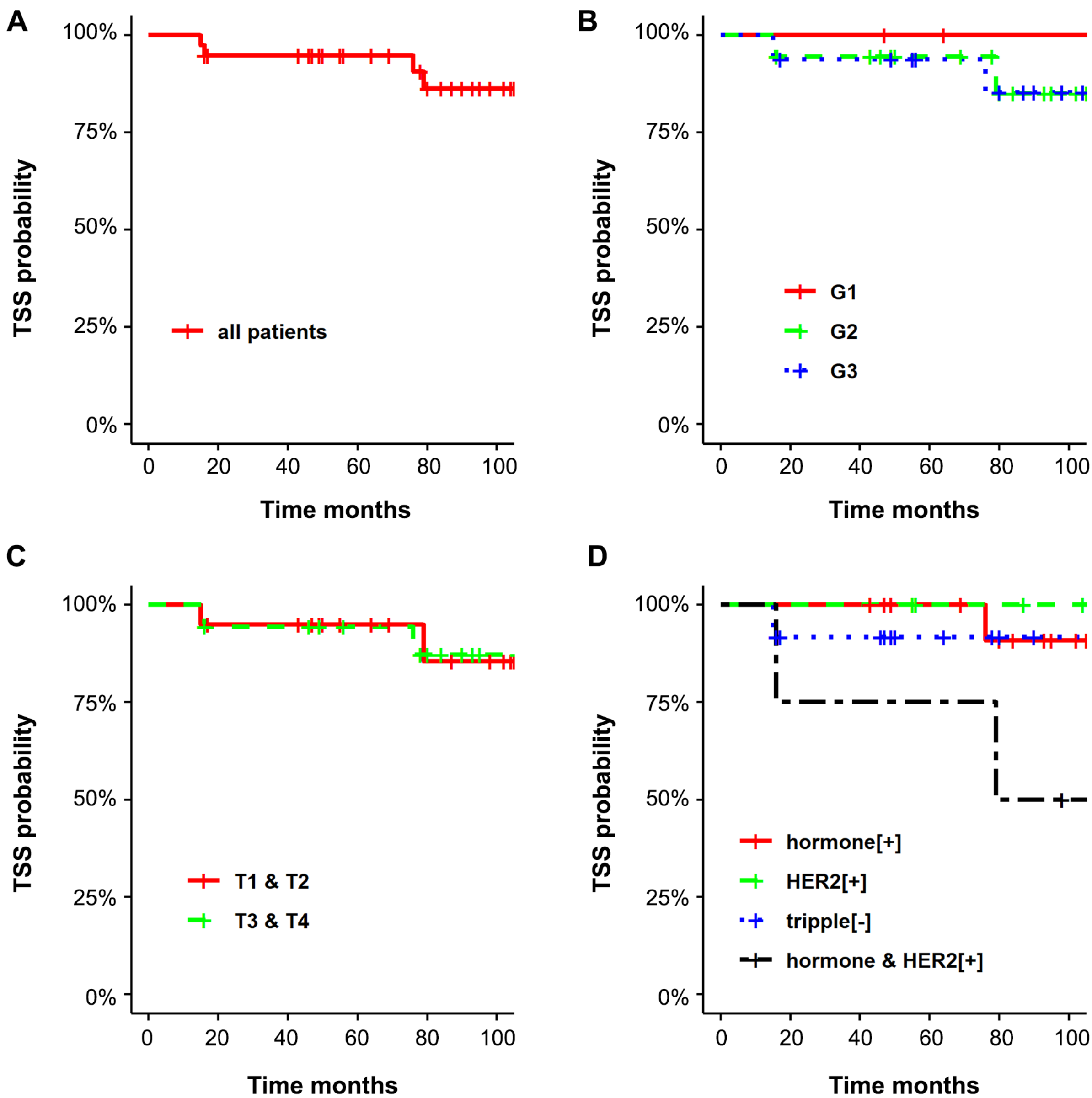

Figure 3. *Kaplan-Meier curve for tumor specific survival (TSS) in all female patients with breast cancer (n=38) after postmastectomy radiation therapy (PMRT) using helical tomotherapy (hT) (A), or according to grade (G1, G2, G3) (B), tumor stage (T1/T2, T3/T4) (C) and receptor expression [hormone-positive and human epidermal growth factor receptor 2 (HER2)-negative, HER2-positive, triple negative, hormone-positive and HER2-positive] (D).*

Late toxicity. Ipsilateral arm lymphedema was observed in 23.7% of patients (grade 1: 18.4%, grade 2: 5.3%). Lymphedema of the irradiated chest wall was documented in 10.5% of the cohort. Tissue induration was reported in 7.9%, while no cases of pain, adipose tissue necrosis, or infections were reported. Late pulmonary or cardiac toxicities and brachial plexus injury were not observed. No cases of osteonecrosis of the sternum or ribs were observed (Table III).

After a follow-up of 80 months, one patient (2.6%) developed secondary malignancies after hT PMRT of the left sided thorax wall, including the supraclavicular

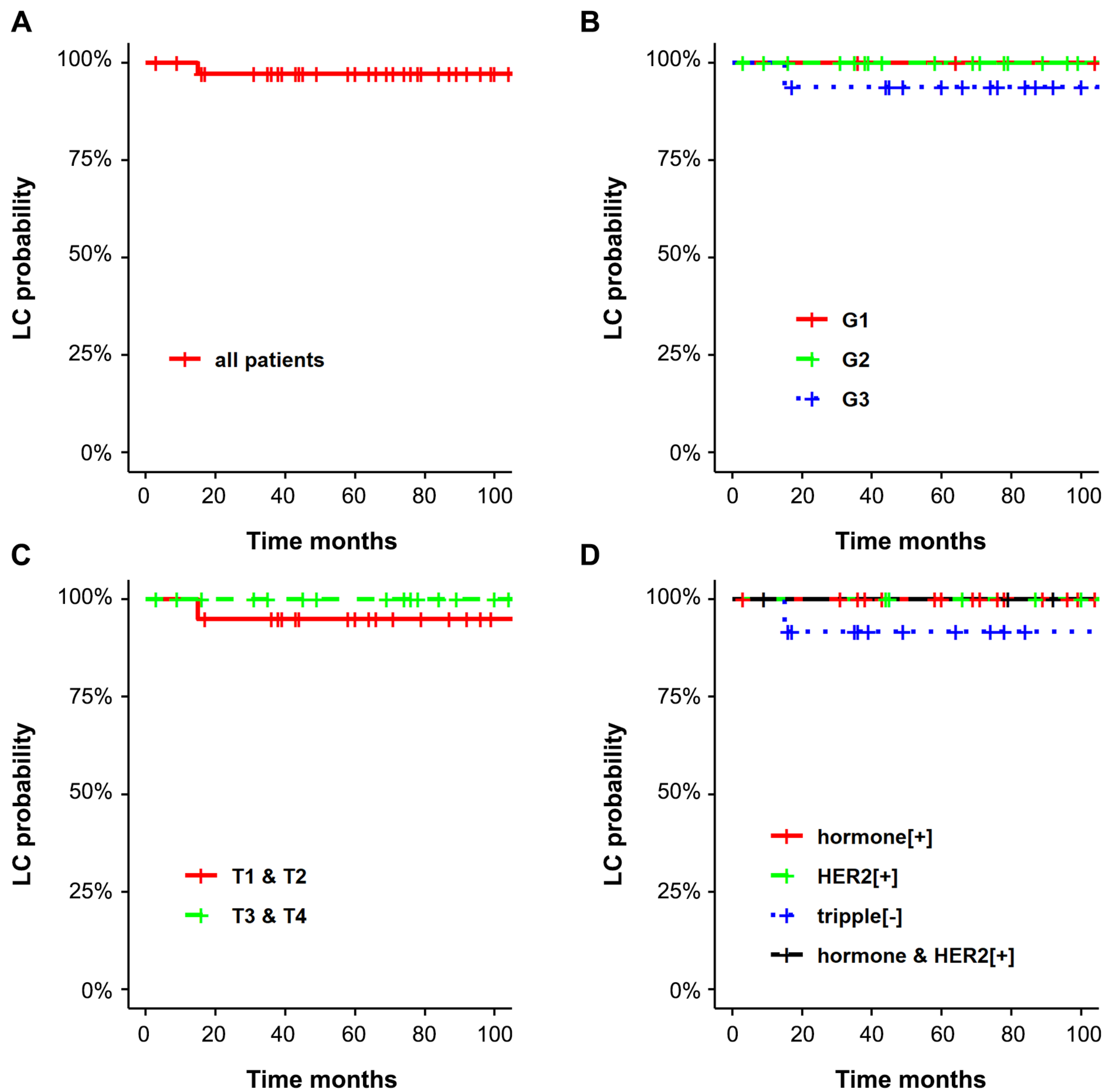

Figure 4. *Kaplan-Meier curve for local control (LC) in all female patients with breast cancer (n=38) after postmastectomy radiation therapy (PMRT) using helical tomotherapy (hT) (A), or according to grade (G1, G2, G3) (B), tumor stage (T1/T2, T3/T4) (C) and receptor expression [hormone-positive and human epidermal growth factor receptor 2 (HER2)-negative, HER2-positive, triple negative, hormone-positive and HER2-positive] (D).*

lymphatic drainage pathways leading to a secondary malignancy free survival (SMFS) of 97.4% (Figure 7). Histologically confirmed carcinoma of the floor of the mouth was located outside of the PTV 24 months after PMRT and was treated successfully by curative tumor resection.

Discussion

This single-institution retrospective study analyzed long term results of women with locally advanced breast cancer with and without positive lymph nodes who received PMRT with hT. Most patients underwent comprehensive regional

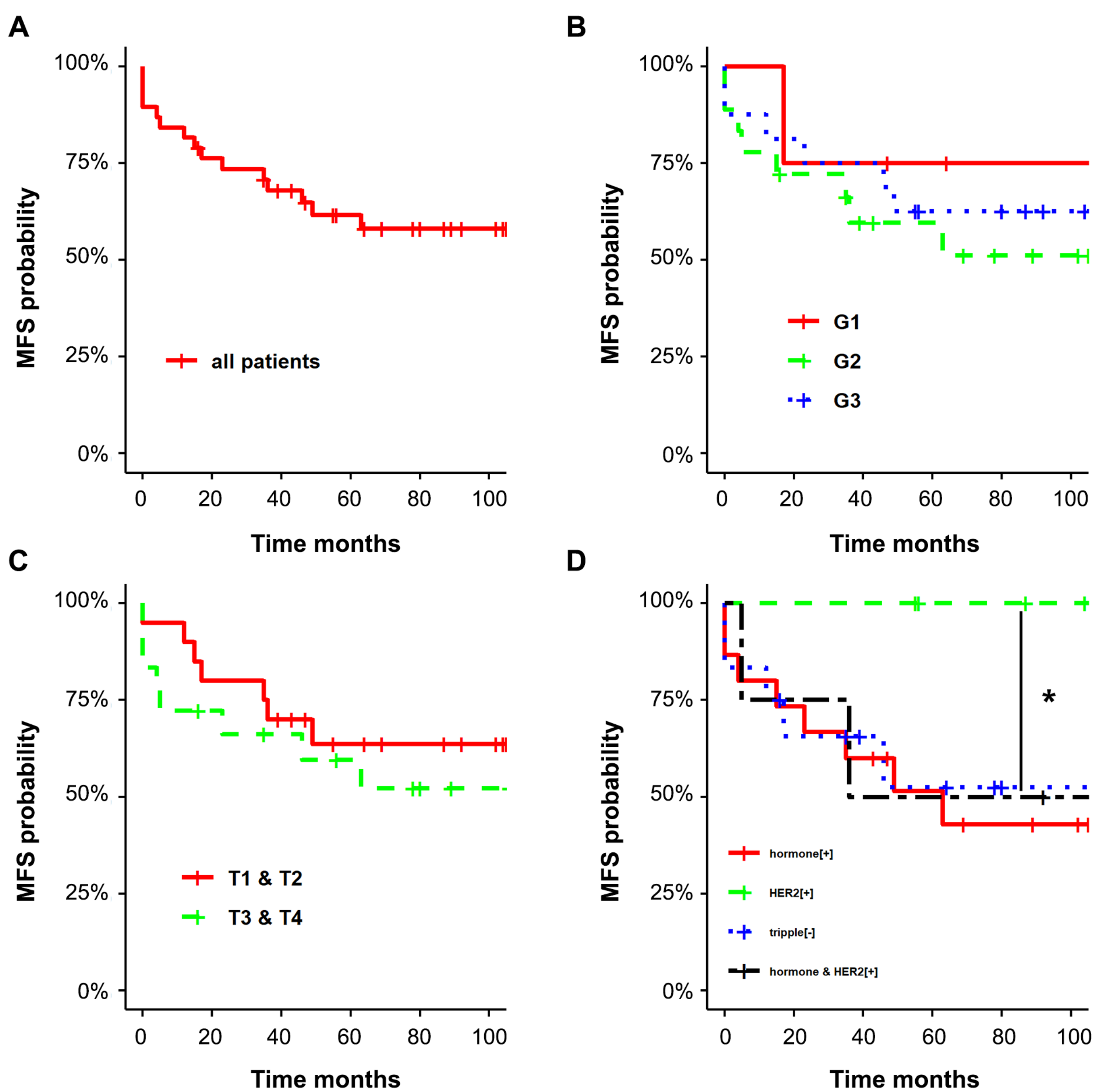

Figure 5. *Kaplan-Meier curve for metastasis free survival (MFS) in all female patients with breast cancer (n=38) after postmastectomy radiation therapy (PMRT) using helical tomotherapy (hT) (A), or according to grade (G1, G2, G3) (B), tumor stage (T1/T2, T3/T4) (C) and receptor expression [hormone-positive and human epidermal growth factor receptor 2 (HER2)-negative, HER2-positive, triple negative, hormone-positive and HER2-positive] (D). *significance at p<0.05.*

nodal irradiation (92%). In this cohort, disease control was high with favorable tolerability. At a mean follow-up of 80 months, we observed: a) excellent LC of 97% at five and eight years, b) MFS of 62% at five years and 58% at eight years, c) TSS of 91% at five years and 86% at eight years, and d) OS of 84% at five years and 66% at eight years. Acute toxicity was dominated by grade 1-2 dermatitis, hyperpigmentation of irradiated skin, mild esophagitis, and fatigue. Late toxicity such as clinically significant lymphedema (≥ grade 2) of the ipsilateral arm/ thorax wall occurred in 5.3% of treated

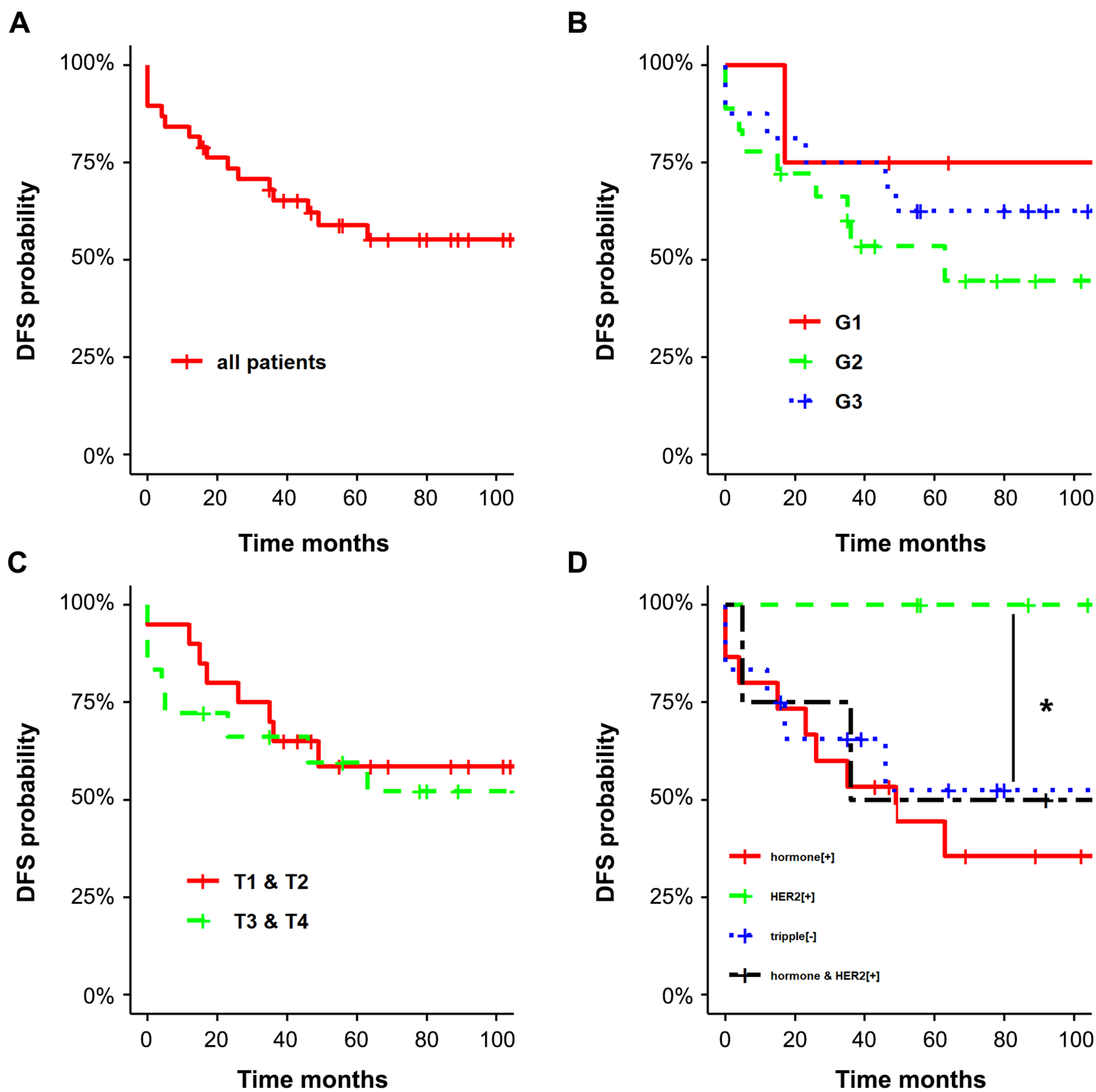

Figure 6. *Kaplan-Meier curve for disease free survival (DFS) in all female patients with breast cancer (n=38) after postmastectomy radiation therapy (PMRT) using helical tomotherapy (hT) (A), or according to grade (G1, G2, G3) (B), tumor stage (T1/T2, T3/T4) (C) and receptor expression [hormone-positive and human epidermal growth factor receptor 2 (HER2)-negative, HER2-positive, triple negative, hormone-positive and HER2-positive] (D). *significance at p<0.05.*

patients. No cases of symptomatic pneumonitis or brachial plexus complications were seen. Collectively, these outcomes align with the expected benefits of PMRT while underscoring the dosimetric and clinical advantages of hT for complex chest-wall and nodal targets.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis established that PMRT to the chest wall and regional lymph nodes reduces 10-year recurrence and 20-year breast cancer mortality for node-positive disease, including in women with one to three positive

Table II. *Acute side effects experienced by the participants in the study.*

Early side effects	n (%)
Hyperpigmentation	
None	20 (60.0%)
Slight	13 (37.5%)
Strong	5 (2.5%)
Skin erythema	
None	6 (3.8%)
Grade 1	6 (21.3%)
Grade 2	17 (48.8%)
Oesophagitis	
None	26 (64.4%)
Grade 1	12 (31.6%)
Grade 2	0 (0.00%)
Grade 3	0 (0.0%)
Blood count changes (leukopenia)	
None	35 (92.1%)
Grade 1	3 (7.9%)
Grade 2	0 (0.0%)
Grade 3	0 (0.0%)
Infections	
None	34 (89.5%)
Pneumonia	0 (0.0%)
Mastitis	0 (0.0%)
Bronchitis	1 (2.6%)
Cough	1 (2.6%)
Hoarseness	1 (2.6%)
Fatigue	13 (34.2%)

Table III. *Late side effects experienced by the participants in the study.*

Late side effects	n (%)
Lymphedema ipsilateral arm	
None	29 (76.3%)
Slight	7 (18.4%)
Strong	2 (5.3%)
Lymphedema thorax wall	
None	34 (89.5%)
Slight	4 (10.5%)
Strong	0 (0.0%)
Other	
Thorax wall pain	0 (0.0%)
Fibrosis/ induration	3 (7.9%)
Adipose tissue necrotis	0 (0.0%)
Esophageal stenosis	0 (0.0%)
Pneumonitis	0 (0.0%)
Lung fibrosis	0 (0.0%)
Heart damage	0 (0.0%)

nodes. Additional PMRT significantly reduces the loco-regional recurrence rate from 26% to 8.1% after 10 years and the breast cancer mortality rate from 66.4% to 58.3% after 20 years (10). Our LC-, MFS-, and OS-rate estimates fit within these proven proportional benefits and suggest that modern delivery of radiotherapy with hT can maintain treatment efficacy while improving normal tissue sparing.

Data with clinical long-term results in cases of breast cancer after PMRT by hT are very rare. To our knowledge, this study is the first to present a cohort of female breast cancer patients (n=38) with a follow-up of 80 months after PMRT, which includes long term data regarding late toxicities and secondary cancer induction.

A study by Orecchia *et al.* evaluated acute and intermediate toxicity after PMRT by hT, with a median follow-up of 13 months in 120 patients (33). Another study (n=173) with clinical long-term results was published by Dejean *et al.* with a median follow-up of 65 months and a focus on implant security after PMRT, without reporting systematic data about other late toxicities (28).

A LC of 97.2% after eight years in this study compares favorably with five-year local recurrence rates of 3.4% in patients after PMRT and breast reconstruction, and 5.8% in patients after PMRT without reconstruction, as described by Dejean *et al.* The latter study did not find any negative effects after PMRT on local recurrence after implant-based breast reconstruction (28). Although Dejean *et al*. did not provide actuarial LC curves, the absolute number of failures was small, including in cases of additional irradiation of the lymphatic drainage pathways (28). Both sets of data show that hT achieves excellent local tumor control due to its very high dose homogeneity and coverage to complex PTV of PMRT in patients with locally advanced breast cancer.

In the study by Dejean *et al.,* metastatic recurrence rate was 14.8% after five years (28). In this study, MFS was 62% after five years and 58% after eight years. A plausible reason for this obvious difference of approximately 20% is that the percentage of initial lymph node-positive patients was 84% in this study compared to 70.5% in Dejean *et al*.'s cohort. Distant metastasis can occur for two reasons. First, an initial occult spread of tumor cells can lead to detectable metastasis during follow-up. Second, local tumor recurrence after primary treatment can cause new secondary metastasis. In

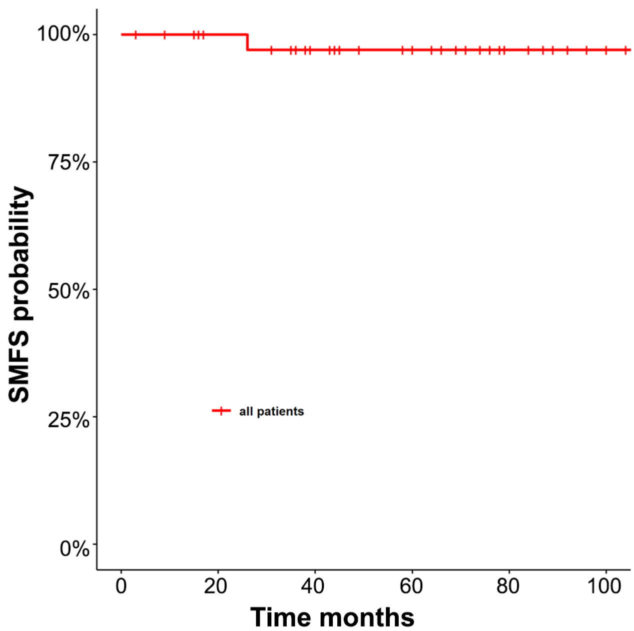

Figure 7. *Kaplan-Meier curve for secondary malignancy free survival (SMFS) regarding to all female patients with breast cancer (n=38) with local advanced breast cancer after mastectomy and postmastectomy radiation therapy (PMRT) using helical tomotherapy (hT).*

both patient cohorts, LC rates after PMRT were very high (>96%) and metastasis rates depended on initial occult tumor spread, which correlates with the percentage of initial lymph node-positive patients (10).

Similar correlations can be observed between the Dejeans' and our study when considering OS rates. The percentage of patients alive at their latest follow-up was 94% in the cohort of Dejean *et al.* (28). In this study OS after five and eight years was 84% and 66%, respectively.

These findings align with the results of a meta-analysis by the EBCTCG, which showed that any first recurrence rate and breast cancer mortality rate after PMRT depended on the number of initial tumor-affected lymph nodes. Patients with one to three tumor-affected lymph nodes show a first recurrence rate and a breast cancer mortality rate of 24.8% and 18.1%, respectively, after five years. In the case of ≥4 affected lymph nodes, these values increased to 57.6% and 46.3% respectively (10). The percentage of patients with ≥4 affected lymph nodes was 50% in this study. However, Dejean *et al*. reported no differentiated information according to the number of tumor-affected lymph nodes (28).

In the present study, we analyzed for the first time the impact of receptor status on long-term outcomes in patients with breast cancer treated with PMRT using hT. In this subgroup analysis, patients with HER2-positive and hormone receptor-negative tumors demonstrated improved 8-year MFS and DFS. Congruent, patients with triple-negative breast cancer showed a significantly lower 8-year OS rate. In this context, Schramm *et al*. reported in their systematic review that HER2-targeted therapies, such as trastuzumab, have led to a substantial improvement in prognosis, with marked gains in both PFS and OS (34).

Early toxicity. In our cohort, grade 3 dermatitis occurred in 23.7% of the cohort, although no cases of higher than grade 3 were observed. In our earlier study, the rate of grade 3 dermatitis was 26% in patients with breast cancer treated with adjuvant hT after BCS, although the surgical settings were different (20). Similarly, Orecchia *et al*. reported mild acute skin toxicities after hypofractionated PMRT by hT, with a grade 2 dermatitis rate of 37% (33).

When considering early cutaneous skin reactions after radiotherapy, cosmetic aspects must also be addressed. Irradiation-induced hyperpigmentation can occur during or shortly after radiotherapy, although it has no pathological significance. However, hyperpigmentation can be associated with patient discomfort and reduce patients' quality of life.

In the literature, radiogenic hyperpigmentation rates of 63% and 40% were described after adjuvant radiotherapy by hT in cases of BCS (20, 35). Overall, 34% of the present cohort showed slight hyperpigmentation, while 13% showed pronounced hyperpigmentation, adding up to a total of 47%.

Fatigue occurred in 34% of patients. Comparable data on fatigue during adjuvant radiotherapy using hT after BCS, reported by Van Parijs *et al*. and Zwicker *et al.*, showed rates of 25% and 27.5%, respectively (20, 36). Additional irradiation of the lymphatic drainage pathways may further increase rates of fatigue symptoms (37, 38).

Hematologic toxicity was rare in the present cohort. Only 8% of all patients developed grade 1 leukopenia. None of the patients showed grade 2/3 leukopenia, anemia, or thrombocytopenia. In the literature, larger PTVs were identified as a potential risk factor for hematologic toxicity in radiotherapy (39).

Late toxicity. To our knowledge the present retrospective study is the first to report data on late toxicity after PMRT using hT in patients with locally advanced breast cancer. Late occurring side effects of PMRT that result in nerve damage, especially of the ipsilateral plexus brachialis, must be considered particularly when clavicular lymphatic drainage pathways are involved in the target volume. Older data report a risk of developing late complications after conventional fractionated megavolt radiotherapy below 1%. However, single radiation doses >2.5 Gy with a total dose >40 Gy results in a significantly greater risk of plexus injury (40).

Studies reviewing long term clinical results of adjuvant hT for lymph node-positive patients with breast cancer after BCS did not report any cases of severe damage to the brachial plexus, when a slight hypofractionated or normofractionated technique was used. In very rare cases, mild paresthesia occurs temporarily (20, 41). In the cohort presented here with normofractionated hT-PMRT, no case of any ipsilateral brachial plexus injury was observed during the follow-up period of 80 months. The advantage of hT is that it avoids maximum doses over 107% of the described target dose and regularly stays under 105% (42). Therefore, hT helps to avoid damage to the brachial plexus after PMRT in patients with breast cancer.

In the literature, the reported incidence of lymphedema caused by sentinel node biopsy and adjuvant radiotherapy after BCS is 11% (20, 43). In cases of locally advanced tumors with tumor-positive lymph nodes, axilla dissection and PMRT rates of ipsilateral arm lymphedema increases to 20-30% (44, 45). In this study, mild lymphedema (grade 1) of the ipsilateral arm was observed in 18.4%, while severe lymphedema (grade 2) was observed in 5.3% of the patient cohort. The risk of lymphedema after PMRT depends on the existence of tumor involved lymph nodes and on whether lymph node dissection was performed. Overall, 84% of the patients in the present cohort showed tumor-positive lymph nodes, with 50% presenting with more than three involved lymph nodes (46). In contrast, additional chemotherapy is a risk factor for radiation-induced lymphedema of the ipsilateral arm (27). A total of 66% of the patients in this cohort were additionally treated with neoadjuvant chemotherapy, while 18% of the patients were treated with adjuvant chemotherapy. When considering these circumstances, PMRT using hT shows lymphedema rates at the lower end of the expected range.

Radiogenic pneumonitis and late onset consecutive lung fibrosis must be considered when observing late toxicities after adjuvant radiotherapy in patients with breast cancer. Radiogenic pneumonitis rates of 7-24% have previously been described in BCS cases (20, 27, 47). Karlsen *et al.* reported a clinical pneumonitis rate of 16% within 12 months after postoperative radiotherapy, including PMRT (48). However, reports of pneumonitis rates after PMRT using hT are rare. No case of pneumonitis was observed by Dejean *et al.* after PMRT using hT (28). Long-term data on clinically relevant lung fibrosis after PMRT is rare. To our knowledge, there is no data regarding cases of breast cancer treated with PMRT using hT in the literature. In the present study, no cases of clinical pneumonitis or lung fibrosis occurred. These findings underline the great potential of hT to achieve high dose-gradients for maximal dose reduction in organs at risk.

Following radiotherapy, the incidence of secondary malignancies is 1-2% in patients with breast cancer. More recent data indicate that <10% of the secondary malignancies are generated after radiotherapy (49, 50).

An examination of 375,000 patients showed a significantly higher incidence of secondary malignancies in those who sustained irradiation treatment compared to those who did not (1.33% *vs*. 1.2%) after a median follow-up of 8.9 years. In this population almost 3.4% of secondary malignancies were due to radiation therapy (51). Bazire *et al.* reported on a French study of 17,745 patients with breast cancer, where the 15-year cumulative incidence of secondary malignancies was 1.8% after a median follow-up of 13.4 years (52). Radiotherapy was conducted using 3D-conformal techniques in both groups.

Different treatment planning studies estimated a higher radiation-induced cancer risk, when adjuvant breast irradiation is performed with IMRT or VMAT compared with 3D-CRT (53, 54). Clinical data regarding the incidence of secondary cancer following IMRT of patients with breast cancer is rare. Concerning helical IMRT/hT, only the studies by Zwicker *et al.* and Zolcsak *et al.* were published and showed secondary cancer rates of 1.25%, 1.8%, and 3%, respectively (20, 27, 55).

Long-term data on secondary cancer induction after PMRT is rare. There is no long-term data available in cases of PMRT using hT to our knowledge. In the present study, only one patient (2.6%) developed a secondary malignancy two years after PMRT of the left sided thorax wall, including the supraclavicular lymphatic drainage pathways. Histologically confirmed carcinoma of the floor of the mouth was outside of the PTV of PMRT. The relatively short time after PMRT using hT pointed to a non-radiation induced secondary cancer. This result also indicates that adjuvant radiotherapy *via* PMRT using hT shows similar incidence of secondary malignancies to that of 3D-conformal radiation techniques. So far, there is no indication that the use of hT increases induction of secondary cancer after radiotherapy.

Technique. Previous clinical studies comparing IMRT to traditional 3D- or 2D-techniques have reported reduced rates of late-onset fibrosis (56) and telangiectasia (57) in patients with breast cancer, including the lymph nodes. Lung and heart protection is also enhanced by IMRT compared to conventional radiation techniques (58).

hT provides superior dose homogeneity and coverage in PTV in comparison to other IMRT techniques. In accordance with the International Commission on Radiation Units and Measurements (ICRU) criteria, it effectively prevents dose minima (<95%) and dose maxima (>107%) of the prescribed dose within the PTV (16, 20, 27, 42). In adjuvant radiotherapy of breast cancer, maintaining a dose range of 95-107% is critical for preventing local tumor recurrence, while decreasing risk of radiation-induced side effects (20, 27). Data from a retrospective study by Lee *et al*. showed significantly improved long-term results using hT compared to standard IMRT techniques for adjuvant radiotherapy in patients with breast cancer post-BCS (59). Nichols *et al*. reported that both IMRT techniques (hT and VMAT) matched the ICRU criteria and were superior compared to 3D-CRT. hT achieved better dose homogeneity in PTV and showed better OAR sparing at higher doses (60).

In the present study, scar boost radiation in addition to the irradiation of the chest wall was performed in 34 of 38 patients (89.5%). This additional boost appears to have contributed to the high 8-year LC rates of 97%. Patients with breast cancer across all age groups and tumor size have been shown to benefit from additional boost radiation in adjuvant radiotherapy post-BCS, leading to significantly increased LC rates (20, 27, 61). Additional scar boost radiation is also a common method in the clinical practice of PMRT to avoid local tumor recurrence, with LC rates up to 95% (62).

Conclusion

PMRT using hT including lymph draining pathways and scar boost irradiation exhibited excellent long-term local tumor control and low toxicity rates. Patients with HER2-positive and hormone receptor-negative tumors demonstrated excellent MFS and DFS. Overall survival rates and incidences of secondary malignancies are similar to other radiation techniques. The results of this clinical study indicate that PMRT using hT can benefit patients with locally advanced breast cancer.

Conflicts of Interest

The Authors declare that there are no conflicts of interest in relation to this study.

Authors' Contributions

F.Z., and L.R. initiated and supervised the project. L.R., F.Z. and R.K. collected the data. M.S., L.R., F.Z. and S.H. performed the data analysis. M.S., F.Z., H.H, P.H., J.D. and L.R. interpreted the experimental data and prepared figures. F.Z. and L.R. wrote the manuscript with input from all Authors. All Authors have been involved in Manuscript´s revisions.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis or representation of this manuscript.

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