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# Long-term Outcomes of Helical Tomotherapy in Lymph Node-positive Breast Cancer Following Breast-conserving Surgery

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## Abstract

*Background/Aim:* Adjuvant radiotherapy is an integral component of the interdisciplinary curative treatment of lymph node-positive breast cancer. We investigated long-term clinical outcomes of helical tomotherapy following breast-conserving surgery.

*Patients and Methods:* This single-center analysis included 80 female patients with breast cancer stages T1-T4 and lymph node metastasis (N1-N3) who underwent breast-conserving surgery, sentinel node biopsy, and/or axillary lymph node dissection. Patients received adjuvant fractionated radiation therapy to the whole breast and regional lymph node areas using helical tomotherapy. Boost irradiation was delivered sequentially or through the simultaneous integrated boost technique. Local control (LC), metastasis, survival, toxicity, and secondary malignancy rates were retrospectively analyzed.

*Results:* The mean follow-up duration was 75 months. The 5- and 8-year overall survival rates were 89.4% and 87.0%, respectively. LC rates at 5- and 8-year were 98.7%, and metastasis-free survival rates were 91.2% and 85.2%, respectively. Acute erythema occurred in 70% (Grades 1-2) and 26% (Grade 3) of patients. Ipsilateral arm lymphedema of Grade 1 and Grade 2 developed in 10% and 1.3% of the treated patients, respectively. Acute or late toxicities exceeding Grade 3 were not observed.

*Conclusion:* Helical tomotherapy showed excellent long-term results and low toxicity rates as adjuvant radiotherapy in patients with lymph node-positive breast cancer. The incidence of secondary malignancies was relatively low and corresponded to the preexisting records on radiation therapy. Broader clinical implementation of helical tomotherapy could benefit patients.

**Keywords:** Helical tomotherapy, lymph node-positive breast cancer, adjuvant radiotherapy.

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## Introduction

Breast cancer is the most common cancer affecting women (1) and remains a subject of intensive research worldwide (2-4). Anatomically feasible and oncologically justified breast cancer surgery (BCS) combined with adjuvant radiotherapy constitutes the standard curative treatment for lymph node-positive breast cancer. Although mammography screening significantly advances early detection compared to clinical examination, a notable proportion of regional lymph nodes already present with metastasis at diagnosis. In a German screening program, 15% of the detected invasive carcinomas showed lymph node metastases (5).

Additional radiotherapy targeting the whole breast and regional lymph nodes (axillar, supraclavicular, or parasternal regions) significantly improves local control (LC) and overall survival (OS) rates in patients with lymph node positive breast cancer after breast-conserving surgery (BCS) (6-8). Women with only 1-3 positive lymph nodes without additional risk factors particularly benefit from radiation to the breast and regional lymph node. Several randomized studies have confirmed the significant positive effect of adjuvant radiotherapy on local tumor control (8, 9). Even among patients with breast cancer with an extremely favorable prognosis, the omission of adjuvant radiotherapy increases the likelihood of local recurrence over time (1).

A previous population-based analysis showed that adjuvant radiotherapy significantly reduced breast cancer mortality rates among older patients (10). LC rates can be significantly improved by delivering a radiation boost to the tumor bed in conjunction with whole-breast irradiation (11-13). Based on previous guidelines, additional boost irradiation was administered to all patients up to 70 years of age (11). According to current guidelines, boost irradiation should only be applied in patients with pre-menopausal status, poorly differentiated G3 or T2 tumors, human epidermal growth factor receptor (HER2/neu) positivity, or narrow resection margins (11, 13).

The standard radiotherapy technique for whole-breast irradiation is continuous three-dimensional conformal radiation therapy (3D-CRT) (7, 8). Intensity-modulated radiotherapy (IMRT) is an advanced form of radiation therapy. Previous studies have frequently reported the benefits of step-and-shoot IMRT and volumetric arc therapy (VMAT) in adjuvant treatment after BCS in comparison with 3D-CRT (14-16). 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 the heart or parts of the lungs and chest wall with a complex shape, for example, a funnel chest. In cases of complex anatomy, IMRT also facilitates additional radiotherapy to regional lymph nodes after BCS, improving target coverage while reducing dose exposure to organs at risk (OAR) (17-19).

Helical tomotherapy (hT), also known as helical IMRT, is a new approach in the field of photon-IMRT. Compared with other IMRT and rotational techniques, hT offers superior dose homogeneity within the target volume, lowest dose maxima values, and steeper dose gradient, resulting in a conformity index close to one (11, 20, 21).

The technical characteristics of hT have been discussed previously (22-25). The tomotherapy unit is a hybrid imaging tool comprising a 6-MV linear accelerator and helical computed tomography (CT) scanner. Treatments are administered using a rotating fan beam, forming a helical pattern as the patient is moved through the gantry bore (22, 23). This beam is modulated using an extremely fast-moving pneumatically driven binary multileaf collimator (MLC). Through an inverse treatment planning process, the MLC conformation is optimized to deliver highly conformal radiation doses to the target tumor (24). 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 (11, 25).

A recent planning study analyzed several hT-based radiotherapy strategies to investigate different fractionation schemes (normofractionated and hypofractionated) and

boost (sequential and simultaneous integration) application for adjuvant radiotherapy post-BCS (23). Dosimetric analyses revealed no evidence that simultaneous integrated boost or hypofractionation compromises tumor control rates or leads to increased late-onset side effects when using tomotherapy (20). Tomotherapy has shown excellent results in recent clinical studies on adjuvant radiotherapy in patients with breast cancer after BCS. In a retrospective study of 219 female patients with lymph node-negative breast cancer, tomotherapy resulted in high LC rates without severe side effects (11).

However, this retrospective single-center clinical study is the first to examine the long-term results of hT in patients with lymph node-positive breast cancer after BCS in a larger cohort. The study analyzed overall OS, LC, metastasis-free survival (MFS), early and late toxicities, and secondary cancer occurrence rates.

## Patients and Methods

*Patients.* This retrospective single-center clinical study included patients (n=80) with local breast cancer and positive lymph nodes who required adjuvant hT between 2011 and 2020 at the Clinic and Practice of Radiotherapy in Konstanz (Germany). All the patients were women who underwent BCS, with sentinel node biopsy and/or axillary lymph node dissection performed in all cases. Indications for adjuvant radiotherapy were present in all the cases. hT was specifically employed when conventional tangential 3D-RT was insufficient to cover the PTV or when radiation doses delivered to the OARs exceeded tolerable limits. Additional irradiation of lymphatic drainage pathways was particularly challenging in these cases. Patients with synchronous bilateral breast cancer, recurrent cancer, or history of thoracic radiotherapy were excluded. Patients were staged according to the tumor – lymph node – metastasis (TNM) classification system. T describes size or direct extent of the primary tumor, N the degree of spread to regional lymph nodes and M the presence of distant metastasis (26).

The study was conducted 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 Landesärztekammer (State Medical Association) Baden-Württemberg Ethics Committee, Stuttgart, Germany (AZ: F-2021-082). All patients provided written informed consent to undergo the proposed treatment investigated in the study.

Imaging and regions of interest. For radiotherapy planning, all patients underwent CT imaging with a slice thickness of 5 mm. A breast-tilting board (wing step) was used for optimal dorsal positioning, and the upper extremities were secured. Imaging was conducted in the resting expiratory position. The right and left lungs, entire heart, left ventricle, and right breast were delineated on the CT images as organs at risk (OARs) (27). Target volumes were defined according to institutional standards, with the PTV of the treated breast including the entire mammary gland and underlying chest wall. In 72 patients, the ipsilateral axillary and supraclavicular lymph nodes were included in the irradiation field, and the parasternal lymph nodes were treated in cases of central or medial tumor localization. Safety lateral, cranial, and caudal margins of 2 cm, and a safety medial margin of 1 cm were applied. When boost radiation was administered, the PTV of the boost included the tumor bed with a safety margin of 8-mm in all directions.

*Radiotherapy.* All patients were delivered radiation therapy using the TomoTherapy® system (Accuray, Sunnyvale, CA, USA). This linear accelerator is a helical IMRT system with a 6-MV photon beam and integrated planning software. A beam field width of 2.5 cm or 5 cm was applied to all treatment plans, with dose calculations performed using a fine dose grid. The set pitch for each plan was chosen according to previous reports (11, 28), and a modulation factor between 2.4 and 3 was applied. Each radiation plan was optimized to minimize dose exposure to OARs (especially the left lung, heart, and contralateral breast),

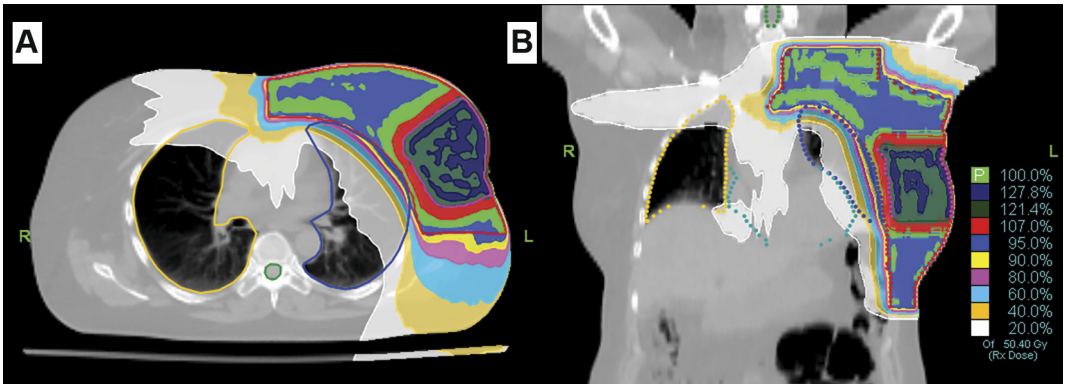


Figure 1. *An example of dose distribution in adjuvant radiotherapy is shown for a female patient with left-sided, lymph node-positive breast cancer following breast-conserving surgery. Treatment includes the whole breast and ipsilateral supraclavicular lymph nodes, with an integrated boost to the tumor bed (50.4/64.4 Gy in 28 fractions), delivered using helical tomotherapy. The dose distribution is illustrated in both the transverse (A) and coronal (B) planes. In the computer-tomography slice, the planning target volume (PTV) of the whole left breast is marked with red outlines and of the boost volume/ tumor bed is marked with violet outlines. The relative isodoses of the described median PTV dose (50.4 Gy) are shown.*

while ensuring at least 95% coverage of the prescribed dose to the PTV of the treated breast and boost volume (Figure 1). Delivery of a maximum dose of >107% was avoided. A normofractionated dose of 50.4 Gy (28×1.8 Gy) was delivered to the whole breast and to the lymphatic drainage pathways. Only one patient was treated with hypofractionated radiotherapy (16×2.65 Gy). When boost radiation was indicated, it was administered sequentially (8×2 Gy, cumulative dose: 50.4 Gy + 16 Gy) in 66% of cases or as a simultaneous integrated boost (28×2.3 Gy, cumulative dose: 64.4 Gy) in 31% of patients (Table I).

*Acute and late toxicities.* Acute and late toxicities were graded according to 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 (29). Severe radiation-related toxicity was defined as >Grade 3 late toxicity. Late toxicities without total loss of function but with significant impact on patients' quality of life were also classified as severe radiation-induced late toxicity. No Grade 4 or 5 toxicities were observed. Changes were determined and documented during the patients' follow-up visits, conducted 6 weeks after radiotherapy and annually thereafter, through a clinical interview. Follow-up examinations included mammography and breast ultrasonography, performed annually.

*Statistical analysis.* The endpoints of this retrospective analysis were LC, distant MFS, disease-free survival (DFS), tumor-specific survival (TSS), and OS. LC following irradiation was defined as the absence of in-field tumor progression or recurrence. All time-to-event data were calculated using the Kaplan–Meier method, with the first day of radiotherapy as starting point until the last follow-up or death. The differences in the Kaplan–Meier curves for subgroups were analyzed using log-rank tests (*e.g.*, G1 *vs.* G2 *vs.* G3), whereas absolute values were compared using Fisher's exact test. A $p$-value of $<0.05$ was considered statistically significant. All statistical analyses and plots were performed using "RStudio" (version 2022.07.01 Build 554) with the "survival" (version 3.3-1) and "survminer" (version 0.4.9) packages, along with additional sub-packages.

## Results

The mean age of the 80 female patients with lymph node-positive breast cancer who underwent BCS was 62 years (range=36-86 years) at the time of adjuvant helical IMRT initiation. The mean follow-up duration was 75

Table I. *Characteristics of the 80 participants in the study.*

| Patient characteristics | Years | |
|---|---|---|
| Age | | |
| Maximum | 86 | |
| Minimum | 36 | |
| Mean | 62 | |
| | Number of patients | Percentage (%) |
| Side | | |
| Left | 40 | 50.00% |
| Right | 40 | 50.00% |
| Histology | | |
| Ductal | 58 | 72.50% |
| Lobular | 13 | 16.25% |
| Tripple | 4 | 5.00% |
| Other | 5 | 6.25% |
| Tumor staging | | |
| T1 | 46 | 57.50% |
| T2 | 30 | 37.50% |
| T3 | 2 | 2.50% |
| T4 | 2 | 2.50% |
| Node staging | | |
| N1 | 63 | 78.75% |
| N2 | 11 | 13.75% |
| N3 | 6 | 7.50% |
| Tumor grading | | |
| G1 | 4 | 5.00% |
| G2 | 51 | 63.75% |
| G3 | 25 | 31.25% |
| RT technique | | |
| NF | 1 | 0.80% |
| NF & SB | 53 | 66.25% |
| NF & SIB | 25 | 31.25% |
| HF | 1 | 0.80% |
| HF & SB | 0 | 0.00% |
| Receptors | | |
| Hormone + | 64 | 80.00% |
| Her 2 + | 18 | 22.50% |
| Her 2 + & Hormone – | 14 | 17.50% |
| Her 2 + & Hormone + | 4 | 5.00% |
| Triple - | 12 | 14.63% |
| Other therapies | | |
| CHT total | 56 | 70.00% |
| Neoadjuvant CHT | 48 | 60.00% |
| Adjuvant CHT | 8 | 10.00% |
| Aduvant & Neoadjuvant CHT | 3 | 3.75% |
| Adjuvant AHT | 68 | 85.00% |

NF: Normal fractionated; HF: hypofractionated; SB: sequential boost; SIB: simultaneously integrated boost; CHT: chemotherapy; AHT: antihormone therapy.

months (standard deviation: ±12 months), with a maximum follow-up of 129 months. Among the 80 patients, 79 received auxiliary boost irradiation, while one patient did not owing to her low-risk profile. Table I provides an overview of the patient characteristics, different fractionation schemata, and boost application techniques used in this study. Additional chemotherapy was administered to 70% of patients: 60% received neoadjuvant chemotherapy, 10% received adjuvant chemotherapy, and 4% received both. Most patients underwent anthracycline- and/or taxane-based chemotherapy. Approximately 80% of the patients showed hormone receptor positivity and received additional adjuvant anti-hormonal therapy. In addition, 22.5% of patients exhibited HER2 overexpression and were treated with trastuzumab for one year.

*Outcomes.* The 5- and 8-year LC rates for the entire cohort were 98.71% [95% confidence interval (CI)=96.3-100%] and 98.71% (95%CI=96.3%-100%), respectively. Local tumor recurrence occurred in only one patient (Figure 2).

Regarding MFS, the 5- and 8-year rates were 91.2% (95%CI=84.6-98.3%) and 85.2% (95%CI=75.4-96.2%), respectively. Patients with T2 tumors showed decreased MFS compared to those with T1 tumors; however, this difference was not considered significant (Figure 3). No significant differences in MFS were identified among subgroups stratified by grades (Grades 1-3) and receptor expression profiles (hormone-positive, HER2-negative, HER2-positive, and triple-negative).

The 5- and 8-year OS rates were 89.4% (95%CI= 82.3%-97.3%) and 87.0% (95%CI=78.7-96.1%), respectively. Patients with T2 tumors exhibited lower OS compared to patients with T1 tumors; however, this difference was not statistically significant. Subgroup analysis revealed no significant differences in OS among patients stratified by tumor grades or receptor expression profiles, although the HER2-positive group showed the highest OS (Figure 4).

The 5- and 8-year TSS rates were 93.7% (95%CI=97.9-99.9%) and 91.1% (95%CI=83.7-99.2%), respectively, whereas no differences were found among groups with different grades or receptor expression profiles (Figure 5).

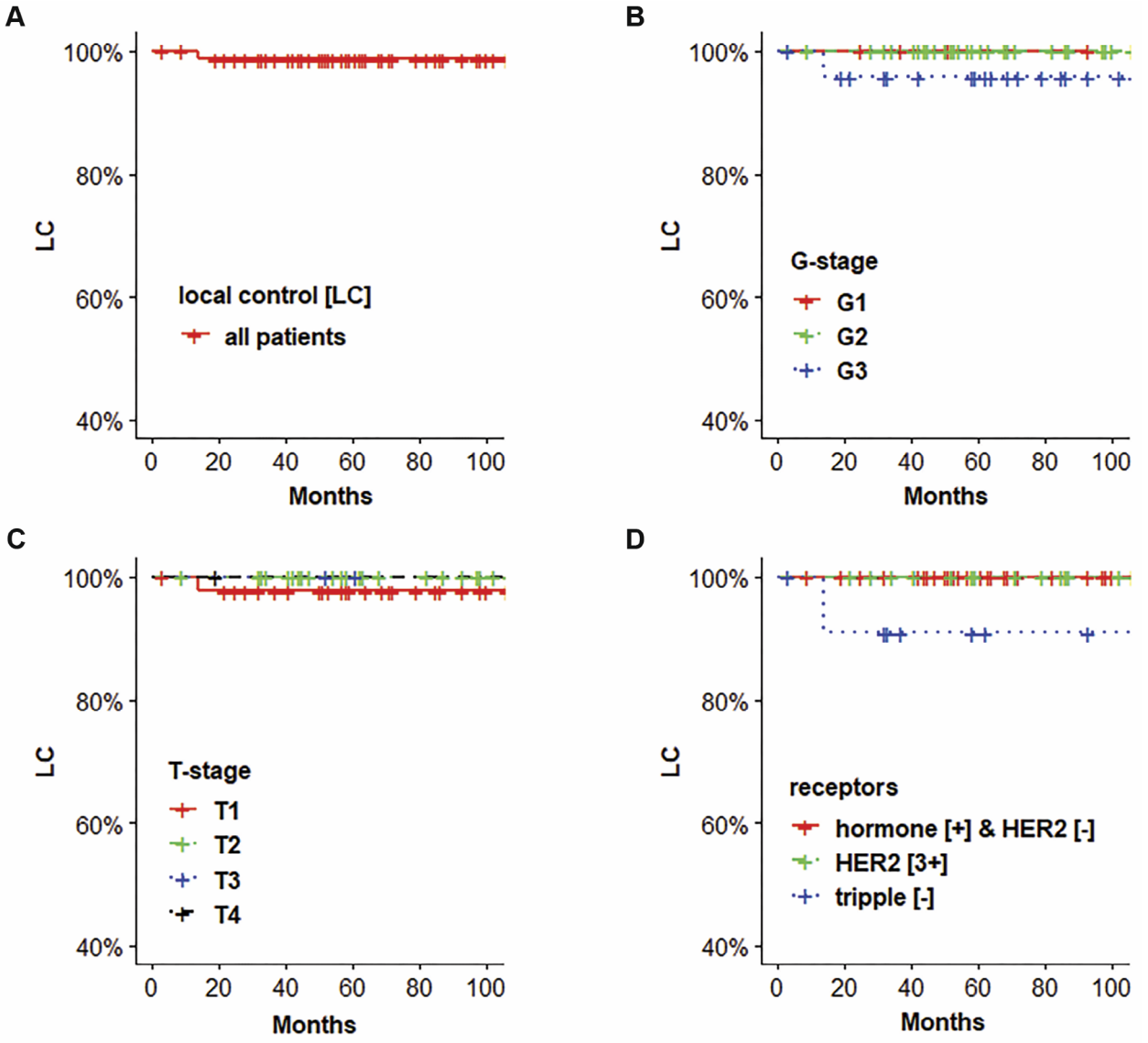


Figure 2. *Kaplan–Meier curve for local control (LC) in all patients (n=80) with lymph node positive breast cancer after breast-conserving surgery using hT (A), or according to grade (G1, G2, G3) (B), tumor stage (T1, T2) (C) and receptor expression [hormone-positive and human epidermal growth factor receptor 2 (HER2)-negative, HER2 positive (3+), and triple negative] (D).*

The 5- and 8-year DFS rates were 89.9% (95%CI=82.9-97.4%) and 80.5% (95%CI=69.3-93.5%), respectively. Patients with T2 tumors showed decreased DFS compared with those with T1 tumors; however, this difference was not statistically significant. Additionally, no significant differences in DFS were identified across subgroups based on tumor grading or receptor expression status.

*Acute toxicity.* Among the 80 female lymph node-positive patients treated with tomotherapy after BCS, 70% experienced mild acute erythema (Grade 1-2, Common Toxicity Criteria), while 26% developed Grade 3 toxicity (epitheliolysis). No severe acute skin toxicities (Grade 4 and 5) were observed. A slight hyperpigmentation of the irradiated skin was observed in 37.5% of patients, with more

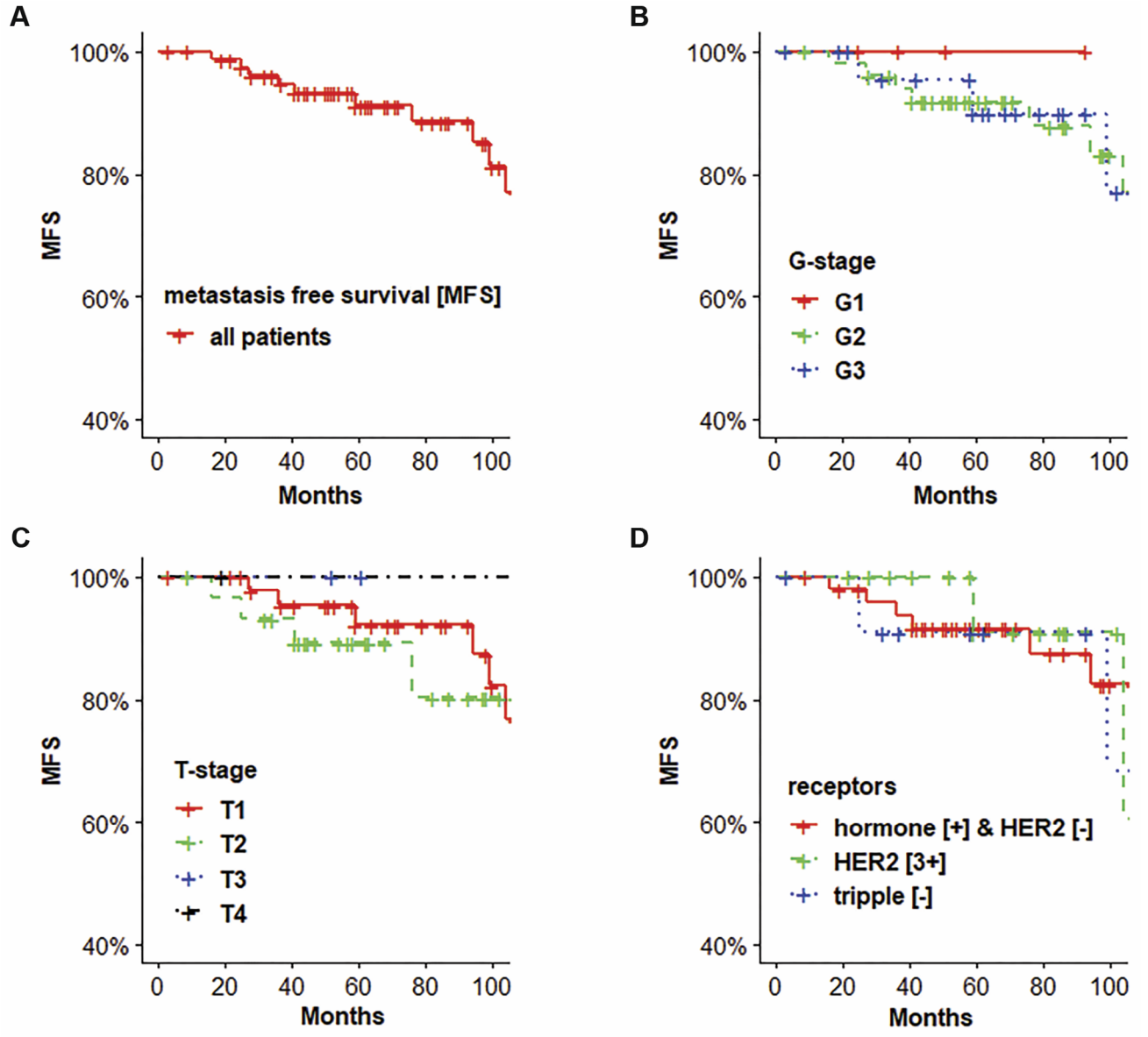


Figure 3. *Kaplan–Meier curve for metastasis free survival (MFS) in all patients (n=80) with lymph node positive breast cancer after breast-conserving surgery using hT (A), or according to grade (G1, G2, G3) (B), tumor stage (T1, T2) (C) and receptor expression [hormone-positive and human epidermal growth factor receptor 2 (HER2)-negative, HER2-positive (3+), and triple negative] (D).*

intense hyperpigmentation in 2.5%. In 1.25% of the treated patients, acute infection of the mammary gland occurred during the course of radiotherapy or after 6 weeks. Signs of mild esophagitis occurred in 15 patients (18.75%) during radiotherapy, resolving shortly after treatment completion. Approximately 27.5% of the patients experienced fatigue during the course of radiotherapy. Six patients developed signs of subacute pneumonitis after radiotherapy, which resolved within several weeks (Table II).

*Late toxicity.* Nine patients showed lymphedema of the ipsilateral arm: eight patients with Grade 1 and one patient

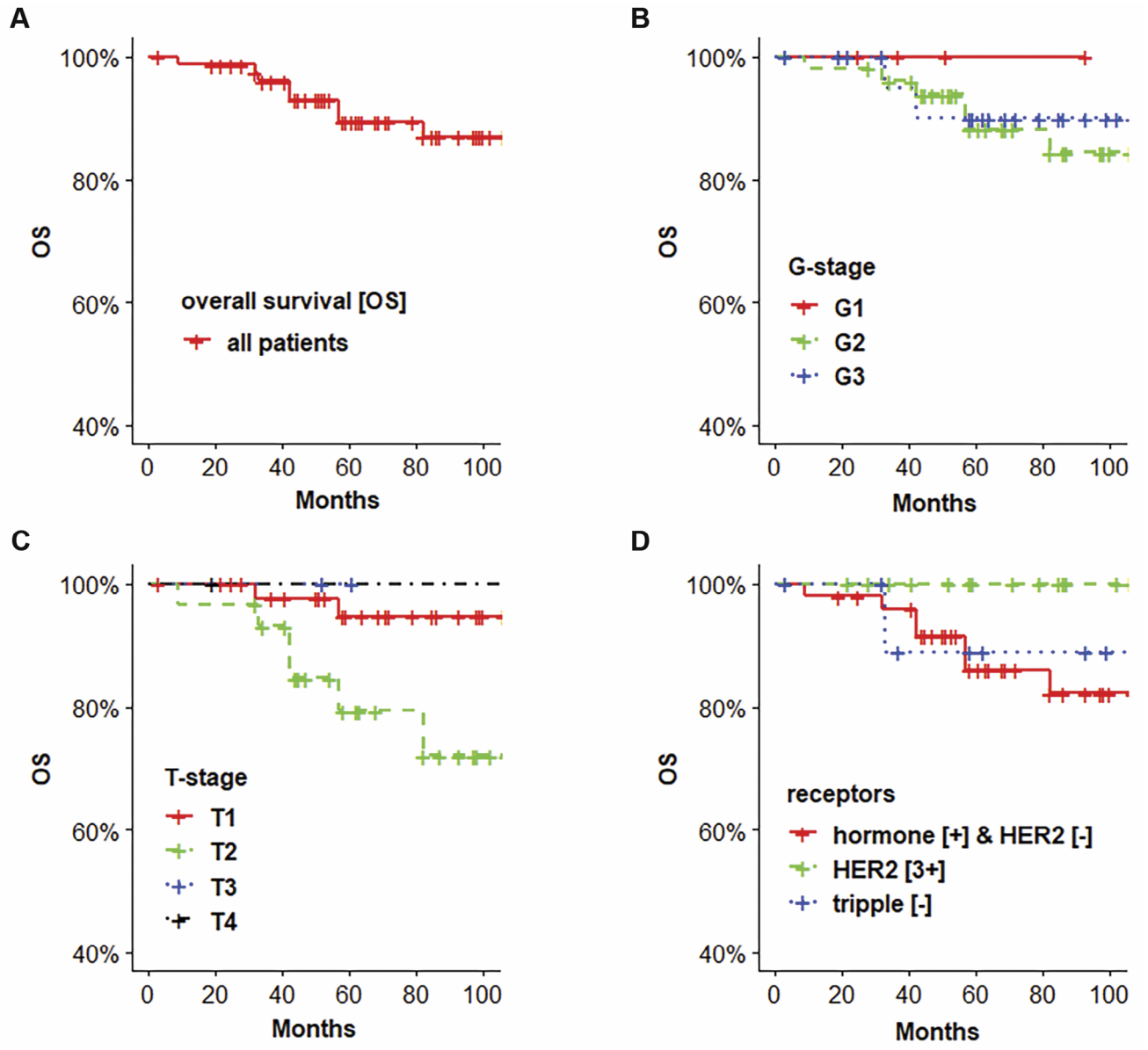


Figure 4. *Kaplan–Meier curve for overall survival (OS) in all patients (n=80) with lymph node positive breast cancer after breast-conserving surgery using hT (A), or according to grade (G1, G2, G3) (B), tumor stage (T1, T2) (C) and to receptor expression [hormone positive and human epidermal growth factor receptor 2 (HER2)-negative, HER2-positive (3+), and triple negative] (D).*

with Grade 2 toxicity. Lymphedema of the treated breast was observed in 17 patients: 15 with Grade 1 and two with Grade 2 toxicity. In two patients, lymphedema developed in the ipsilateral arm and the treated breast. Overall, lymphedema of the ipsilateral arm and/or treated breast was observed in 24 patients, 75% of whom received chemotherapy before or after surgery. Chemotherapy was administer in 66.25% of the 80 patients. Of the 53 patients who received chemotherapy, 18 developed lymphedema, compared to six of the remaining 27 patients who did not

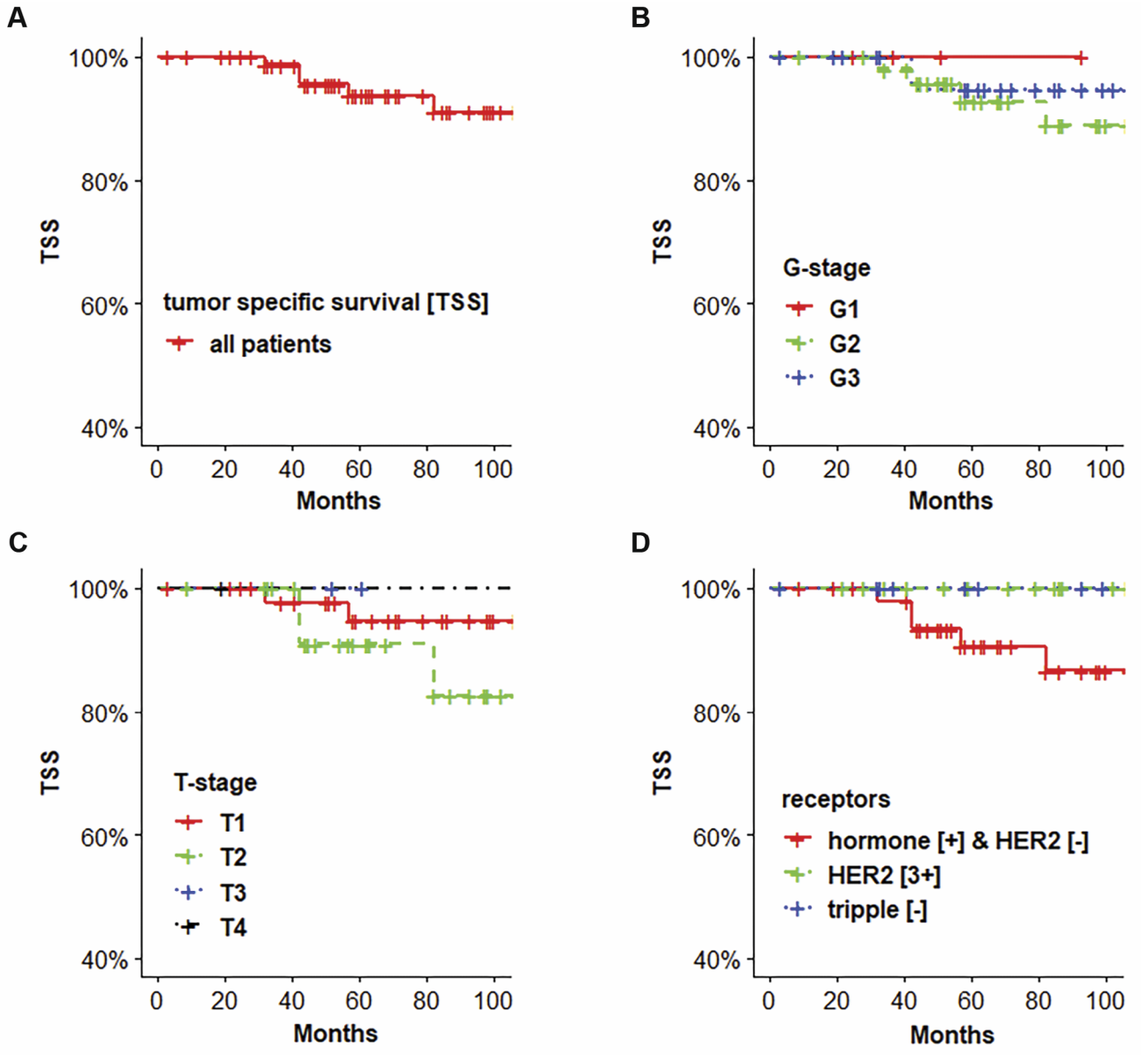


Figure 5. *Kaplan–Meier curve for tumor specific survival (TSS) in all patients (n=80) with lymph node positive breast cancer after breast-conserving surgery using hT (A), or according to grade (G1, G2, G3) (B), tumor stage (T1, T2) (C) and to receptor expression [hormone positive and human epidermal growth factor receptor 2 (HER2) negative, HER2-positive (3+), and triple negative] (D).*

undergo chemotherapy. Fisher's exact test showed no significant differences ($p$>0.05). Fibrosis of the treated mammary gland was noted in 12.5% of the irradiated patients, and mastodynia in 2.5%. Late pulmonary or cardiac toxicities and damage to the brachial plexus were not reported in this cohort.

Secondary malignancies following adjuvant radiotherapy of the breasts with hT were rarely detected (Figure 6). Only one patient (1.25%) developed dual secondary malignancies simultaneously two years after radiotherapy: carcinoma of the tongue and of the colon. Table II presents radiation-related late-onset toxicities.

Table II. *Side effects (acute and late) experienced by the 80 participants in the study.*

| Side effects | Number of patients | % |
|---|---|---|
| Hyperpigmentation | | |
| None | 48 | 60.00% |
| Slight | 30 | 37.50% |
| Strong | 2 | 2.50% |
| Skin erythema | | |
| None | 3 | 3.75% |
| Grade 1 | 17 | 21.25% |
| Grade 2 | 39 | 48.75% |
| Grade 3 | 21 | 26.25% |
| Infections | | |
| None | 72 | 90.00% |
| Pneumonia | 1 | 1.25% |
| Breast | 1 | 1.25% |
| Other | 4 | 5.00% |
| Cough | 2 | 2.50% |
| Lymphedema arm | | |
| None | 71 | 88.75% |
| Slight | 8 | 10.00% |
| Strong | 1 | 1.25% |
| Lymphedema breast | | |
| None | 63 | 78.75% |
| Slight | 15 | 18.75% |
| Strong | 2 | 2.50% |
| Other | | |
| Fatigue | 22 | 27.50% |
| Mastodynia | 2 | 2.50% |
| Breast shrinkage | 6 | 7.50% |
| Fibrosis/Induration | 10 | 12.50% |
| Adipose tissue necrosis | 0 | 0.00% |
| Pneumonitis | 6 | 7.50% |
| Esophagitis/Dysphagia | 15 | 18.75% |
| Chronic mastitis | 0 | 0.00% |

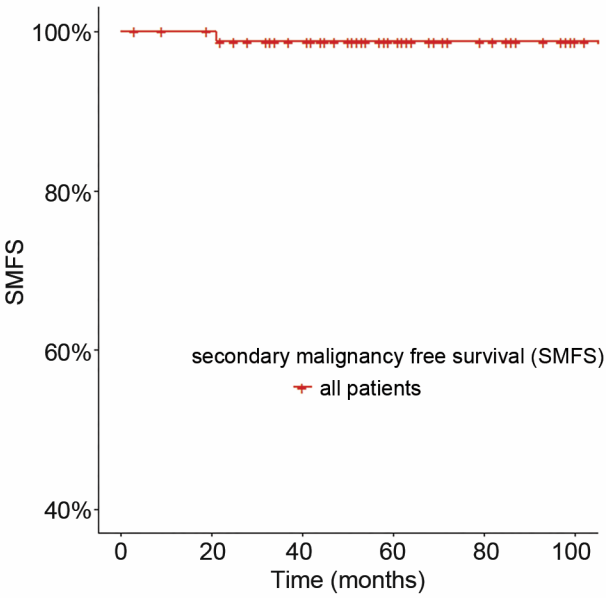


Figure 6. *Kaplan–Meier curve for secondary malignancy free survival (SMFS) regarding to all patients (n=80) with lymph node positive breast cancer after breast-conserving surgery using hT.*

## Discussion

Patients with lymph node-positive breast cancer who underwent BCS showed distinct long-term results following hT. To our knowledge, this study represents the largest cohort (n=80) of patients with lymph node-positive breast cancer treated with hT. Smaller cohorts of 65, 15, and five patients have been described by Arsene-Henry *et al.*, Zolcsak *et al.*, Lee *et al.*, and Joseph *et al.* (30-33). Additionally, two studies with 24 and 20 patients provided data on acute toxicity after shorter follow-up periods (34, 35).

An LC rate of >98% after 5- and 8-year reflected favorable outcomes in this cohort with a mean age of 62 years. OS rates were 89.4% after 5 years and 87% after 8 years, while TSS rates reached 93.7% and 91.1%, respectively. The MFS and DFS rates were 91.2% and 89.9% after 5 years, and 85.2 and 80.5% after 8 years, respectively. Patients with T2-tumours showed a trend towards worse outcomes. Triple-negative breast cancer, normally associated with poor prognosis (36), demonstrated outcomes comparable to the overall cohort. This could be because of the relatively small number of patients (12 of 80 patients) with triple-negative tumors. These findings underscore the importance of breast cancer screening programs to enable early detection of tumors, especially aggressive ones.

Alexandre-Henry *et al.* conducted a retrospective study of hT in patients with breast cancer, including 65, of 179 patients, with initial lymph node involvement and BCS. The 3-year progression-free survival (PFS) of the entire cohort was 96%. Triple-negative patients showed a trend towards reduced PFS. Patients with initial clinical lymph

node involvement who showed negative lymph node status after neoadjuvant chemotherapy had a 3-year PFS of 94.4%, compared to 78.2% for those with persistent lymph node involvement (30). The long-term results of the same study were analyzed by Zolcsak *et al.* The 5-year OS and DFS were 93% and 85%, respectively, for stadium II, and 77% and 73%, for stadium III. Triple-negative patients did not show significantly different results, similar to the cohort of this study, with the same limiting factor being the relatively small number of patients (17% of all) for this subgroup (31). Lee *et al.* retrospectively compared 175 patients treated with step-and-shoot IMRT and 41 patients treated with hT, both with approximately 30% tumor-positive lymph nodes, after BCS. The 5-year OS in the hT group was 95.1% and that in the IMRT group was 94.3%. Interestingly, the 5-year distant MFS was significantly higher in the hT group (100%) in comparison to the IMRT group (91.4%). In the entire cohort, increasing tumor size (T2-T4) correlated significantly with inferior OS, TSS, and MFS rates (32). Joseph *et al.* reported comparable outcomes between hT (n=71) and field-in-field IMRT (n=73), with 5-year OS rates of 97.4% and 96%, respectively (33). However, only 8% of their cohort showed lymph node involvement, limiting comparability with the current study. Notably, MFS rates were relatively high in this cohort (T1-T4 and N1-3), with a 5-year rate of 91.2% and an 8-year rate of 85.2%. This could be explained by the low probability of secondary metastasis due to the prevention of local recurrence after adjuvant radiotherapy. The corresponding studies conducted by Arsene-Henry *et al.*, Zolcsak *et al.*, and Lee *et al.* also achieved 5-year MFS and respective DFS rates higher than 85% (30-32).

Compared with other IMRT techniques, hT provides superior dose homogeneity and coverage in PTV of the breast and boost volume. It effectively prevents dose minima (<95%) and dose maxima (>107%) of the prescribed dose within the PTV in accordance with the International Commission on Radiation Units and Measurements (ICRU) criteria (11, 20, 37, 38). Maintaining a dose range of 95-107% is critical for preventing local tumor relapse while reducing the risk of irradiation-dependent side effects (11). Data from a retrospective study by Lee *et al.* showed significantly improved long-term results using hT compared to that observed in standard IMRT techniques for adjuvant radiotherapy in patients with breast cancer post-BCS (32).

In the present cohort, additional boost radiation was administered to 79 of 80 patients. Additional boost seemed to make an important contribution to the excellent high 8-year LC rates of 98.7%. The literature shows that breast cancer patients across all age groups and T and N states benefit from additional boost radiation in adjuvant radiotherapy post-BCS, leading to significantly reduced local recurrence rates (11, 39). However, the updated guidelines, especially in Germany, only recommend boost radiation for patients with T2 or T1-tumors with G3-grading, HER2 positivity, or premenopausal status. Future studies should be conducted to determine the effect of omitting boost radiation on long-term LC rates in low risk T1-tumors with involved lymph nodes (N+). A recent phase III study by Chua *et al.* demonstrated the benefit of additional boost irradiation in 1,608 patients with ductal carcinoma in situ, significantly improved LC rates (97.1 % *vs.* 92.7%, $p<0.05$) (40).

Regarding the effects of toxicities in patients with breast cancer, including the lymph nodes, previous clinical studies comparing IMRT (different IMRT techniques were grouped together) to traditional 3D- or 2D-techniques reported reduced rates of late-onset fibrosis (41) and telangiectasia (42) with IMRT. IMRT also improved the lungs and heart protection compared to conventional radiation techniques (43). Data on acute toxicity following adjuvant breast radiotherapy using hT are derived mainly from retrospective collectives involving up to 179 patients, though lymph node-positive subgroups were not investigated separately (30, 32-35). In summary, these data show a very low incidence of higher-grade acute side effects, such as erythema, infections, or mastalgia (30, 32-35).

In the cohort studied by Joseph *et al.*, dry desquamation of the skin (Grade 3) was reported in 87% of the patients (33). In the present study cohort, Grade-3 side effects of the

skin occurred in 26% of the cases, with no cases of severe acute skin toxicities (Grade 4 and 5). Cutaneous hyperpigmentation displays harmless side effects after radiotherapy but represents a cosmetic problem. Normally, the hyperpigmentation is mild and disappears after several weeks or months (11). A radiogenic hyperpigmentation rate of 63% was described by Joseph *et al.* after adjuvant hT (33), while the current cohort showed mild hyperpigmentation in 37.5% and pronounced hyperpigmentation in 2.5% of the patients. Fatigue occurred in 27.5% of patients, and this effect is comparable to data provided by Van Parijs *et al.*, in which 25% of the patients were affected post-radiotherapy of the breast (44). In the present cohort, none of the patients developed leukopenia, anemia or thrombocytopenia >Grade 2 during radiotherapy. During radiotherapy hemogram changes are possible and depend on the irradiated volume (45). The volume of the breast is relatively small compared to the overall volume of the body. Additional irradiation of lymph node areas could increase the risk of the incidence of hemogram changes. In a prospective study, 85 patients (24 with regional lymph node involvement) were treated with hT post-BCS. Grade 2 leukopenia occurred in 11% of all cases, with larger PTVs identified as a potential risk factor (34). Mild clinical symptoms of radiation-induced pneumonitis occurred in six patients in our cohort, which was confirmed by CT examination of the thorax and successfully treated with oral cortisone administered over several weeks, resulting in complete regression. This incidence of pneumonitis is comparable to the results obtained by Arsene-Henry *et al.*, who reported no relevant lung damage after 38 months (30). Lymphedema of the ipsilateral arm occurred in 11% of all patients; eight patients had Grade 1 and one patient had Grade 2. Chemotherapy is another risk factor for radiation-induced lymphedema (11). In the literature, the reported incidence of lymphedema caused by sentinel node biopsy and adjuvant radiotherapy is 11% (46). In this collective, fibrosis of the irradiated breast occurred in 12.5% of patients. The study performed by Joseph *et al.* reported a fibrosis incidence of 13.8% in the patients treated with hT (33).

For curative breast cancer therapy, standard adjuvant radiotherapy after BCS was previously performed using a normofractionated dose application. Current substantial randomized studies conducted in >7,000 patients with breast cancer showed that equally high tumor control and low toxicity rates were achieved when treatment was performed with moderate hypofractionation. The overall treatment duration is considerably shortened by hypofractionated radiotherapy (47-49). This cohort included 79 of 80 patients who received normo-fractionated (cumulative dose: 50.4 Gy; single dose: 1.8 Gy) radiation because additional hypofractionated radiation of the regional lymph node regions with involvement of the axilla and plexus brachialis was not initially tested in studies. Only one patient was treated with hypo-fractionated radiotherapy. Retrospective studies have suggested that hypofractionated radiotherapy can also be executed safely as adjuvant radiotherapy after BCS in patients with breast cancer, even with regional lymph node involvement, providing adequate tumor control and toxicity rates (50, 51). Long-term results of the current prospective phase III studies are expected in the near future (52).

Prior studies reported an incidence of secondary malignancies in 1-2% of patients with cancer following radiotherapy. More recent data showed that <10% of the secondary malignancies are caused by radiotherapy (53, 54). Information on the occurrence of secondary malignancies in patients with breast cancer after radiotherapy is also available (11). An analysis of 375,000 patients demonstrated a significantly higher incidence of secondary malignancies in those who received radiotherapy compared to those who did not (1.33% *vs.* 1.2%) after a median follow-up of 8.9 years. Approximately 3.4% of secondary malignancies in this population are due to irradiation treatment (55). In a French study of 17,745 patients with breast cancer, the 15-year cumulative incidence of secondary malignancies was 1.807 per 100,000 individuals after a median follow-up of 13.4 years (56). In both the groups, irradiation was performed using 3D-conformal techniques.

To evaluate the influence of irradiation technique on secondary cancer risk, treatment planning studies have estimated a higher radiation-induced cancer risk due to breast radiation therapy using multibeam IMRT or VMAT compared with 3D-CRT (57, 58). Clinical breast data regarding secondary cancer rates following IMRT are limited. In terms of helical IMRT/ hT, only the studies by Zolcsak *et al.* and Zwicker *et al.* were published and showed secondary cancer rates of 3% and 1.8%, respectively (11, 31). In the present study, a collective of 80 patients having breast cancer with lymph node involvement, who underwent hT, exhibited a secondary cancer rate of 1.25% after a mean follow-up of 75 months. This result also indicates that adjuvant radiotherapy *via* hT induces a radiation-induced cancer risk similar to that of 3D-conformal irradiation technique.

## Conclusion

hT for lymph-positive breast cancer post-BCS has exhibited excellent long-term tumor control, survival, and low toxicity rates. Similar to other radiation techniques, the rate of secondary cancers were low. The findings of this study indicate that hT as an adjuvant radiotherapy can benefit patients with breast cancer with lymph node involvement.

## Conflicts of Interest

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

## Authors' Contributions

F.Z., M.S. and R.K. initiated and supervised the project. F.Z., L.R. 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.

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## References

1 Ghoncheh M, Pournamdar Z, Salehiniya H: Incidence and mortality and epidemiology of breast cancer in the world. Asian Pac J Cancer Prev 17(sup3): 43-46, 2016. DOI: 10.7314/apjcp.2016.17.s3.43
2 Park JH, Lim JH, Kim S, Heo J: A multi-label artificial intelligence approach for improving breast cancer detection with mammographic image analysis. In Vivo 38(6): 2864-2872, 2024. DOI: 10.21873/invivo.13767
3 Seki H, Ishiguro Y, Makino A, Yamaguchi K, Imoto S: Nomogram predicting axillary lymph node dissection omission after neoadjuvant chemotherapy for node-positive breast cancer. Anticancer Res 44(11): 5131-5138, 2024. DOI: 10.21873/anticanres.17338
4 Silva J, Oliveira PA, Duarte JA, Faustino-Rocha AI: Mammary cancer models: an overview from the past to the future. In Vivo 39(1): 1-16, 2025. DOI: 10.21873/invivo.13800
5 Jahresbericht Evaluation 2020. Deutsches Mammographie-Screening-Programm. Kooperationsgemeinschaft Mammographie, Berlin, Dezember 2022. Available at: https://fachservice.mammo-programm.de/download/evaluationsberichte/Jahresbericht-Evaluation-2020.pdf [Last accessed on April 2, 2025]
6 Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Radiotherapy to regional nodes in early breast cancer: an individual patient data meta-analysis of 14 324 women in 16 trials. Lancet 402(10416): 1991-2003, 2023. DOI: 10.1016/S0140-6736(23)01082-6
7 Thorsen LBJ, Overgaard J, Matthiessen LW, Berg M, Stenbygaard L, Pedersen AN, Nielsen MH, Overgaard M, Offersen BV, DBCG Radiotherapy Committee: Internal mammary node irradiation in patients with node-positive early breast cancer: fifteen-year results from the Danish Breast Cancer Group internal mammary node study. J Clin Oncol 40(36): 4198-4206, 2022. DOI: 10.1200/JCO.22.00044
8 Danish Breast Cancer Cooperative Group, Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J: Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol 24(15): 2268-2275, 2006. DOI: 10.1200/JCO.2005.02.8738
9 Katz A, Strom EA, Buchholz TA, Thames HD, Smith CD, Jhingran A, Hortobagyi G, Buzdar AU, Theriault R, Singletary SE, McNeese MD: Locoregional recurrence patterns after

mastectomy and doxorubicin-based chemotherapy: implications for postoperative irradiation. J Clin Oncol 18(15): 2817-2827, 2000. DOI: 10.1200/JCO.2000.18.15.2817

10 Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM, PRIME II investigators: Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. Lancet Oncol 16(3): 266-273, 2015. DOI: 10.1016/S1470-2045(14)71221-5

11 Zwicker F, Klepper R, Hauswald H, Hoefel S, Raether L, Huber PE, Debus J, Schempp M: Helical tomotherapy of lymph node-negative early-stage breast cancer after breast-conserving surgery: long-term results. Anticancer Res 43(5): 2041-2053, 2023. DOI: 10.21873/anticanres.16365

12 Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, Schinagl D, Oei B, Rodenhuis C, Horiot JC, Struikmans H, Van Limbergen E, Kirova Y, Elkhuizen P, Bongartz R, Miralbell R, Morgan D, Dubois JB, Remouchamps V, Mirimanoff RO, Collette S, Collette L, European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups: Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol 16(1): 47-56, 2015. DOI: 10.1016/S1470-2045(14)71156-8

13 Vrieling C, van Werkhoven E, Maingon P, Poortmans P, Weltens C, Fourquet A, Schinagl D, Oei B, Rodenhuis CC, Horiot JC, Struikmans H, Van Limbergen E, Kirova Y, Elkhuizen P, Bongartz R, Miralbell R, Morgan DA, Dubois JB, Remouchamps V, Mirimanoff RO, Hart G, Collette S, Collette L, Bartelink H, European Organisation for Research and Treatment of Cancer, Radiation Oncology and Breast Cancer Groups: Prognostic factors for local control in breast cancer after long-term follow-up in the EORTC boost *vs* no boost trial. JAMA Oncol 3(1): 42, 2017. DOI: 10.1001/jamaoncol.2016.3031

14 Jagsi R, Griffith KA, Moran JM, Matuszak MM, Marsh R, Grubb M, Abu-Isa E, Dilworth JT, Dominello MM, Heimburger D, Lack D, Walker EM, Hayman JA, Vicini F, Pierce LJ, Michigan Radiation Oncology Quality Consortium: Comparative effectiveness analysis of 3D-conformal radiation therapy versus intensity modulated radiation therapy (IMRT) in a prospective multicenter cohort of patients with breast cancer. Int J Radiat Oncol Biol Phys 112(3): 643-653, 2022. DOI: 10.1016/j.ijrobp.2021.09.053

15 Choi KH, Ahn SJ, Jeong JU, Yu M, Kim JH, Jeong BK, Lee JH, Kim SH, Lee JH: Postoperative radiotherapy with intensity-modulated radiation therapy versus 3-dimensional conformal radiotherapy in early breast cancer: A randomized clinical trial of KROG 15-03. Radiother Oncol 154: 179-186, 2021. DOI: 10.1016/j.radonc.2020.09.043

16 Piras A, Menna S, D'Aviero A, Marazzi F, Mazzini A, Cusumano D, Massaccesi M, Mattiucci GC, Daidone A, Valentini V, Boldrini L: New fractionations in breast cancer: a dosimetric study of 3D-CRT versus VMAT. J Med Radiat Sci 69(2): 227-235, 2022. DOI: 10.1002/jmrs.530

17 Dogan N, Cuttino L, Lloyd R, Bump EA, Arthur DW: Optimized dose coverage of regional lymph nodes in breast cancer: the role of intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2007 68(4): 1238-1250, 2007. DOI: 10.1016/j.ijrobp.2007.03.059

18 Gupte A, Sasidharan A, Kunheri B, Kumar AN, Reddy S, Nair H, Pushpaja KU, Anoop R, Dutta D: Dosimetric comparison of four different radiotherapy planning techniques for adjuvant radiotherapy of left-sided breast, axilla, and supraclavicular fossa. J Med Phys 46(4): 308-314, 2021. DOI: 10.4103/jmp.JMP_54_21

19 Huang Y, Gong C, Luo M, Yuan X, Ding S, Wang X, Zhang Y: Comparative dosimetric and radiobiological assessment of left-sided whole breast and regional nodes with advanced radiotherapy techniques. J Radiat Res 64(4): 677-684, 2023. DOI: 10.1093/jrr/rrad045

20 Zwicker F, Hoefel S, Kirchner C, Huber PE, Debus J, Schempp M: Hypofractionated radiotherapy with simultaneous-integrated boost after breast-conserving surgery compared to standard boost-applications using helical tomotherapy with TomoEdge. Anticancer Res 41(4): 1909-1920, 2021. DOI: 10.21873/anticanres.14957

21 Altinok P, Tekçe E, Karaköse F, Berk K, Kalafat Ü, Kiziltan HS, Akgün Z, Mayadagli A: Dosimetric comparison of modern radiotherapy techniques for gastric cancer after total gastrectomy. J Cancer Res Ther 16(8): 133, 2020. DOI: 10.4103/jcrt.JCRT_548_18

22 Krause S, Beck S, Schramm O, Schubert K, Hauswald H, Zabel-du Bois A, Herfarth K, Debus J, Sterzing F: Tomotherapy radiosurgery for arteriovenous malformations—current possibilities and future options with helical tomotherapy dynamic jaws? Technol Cancer Res Treat 12(5): 421-428, 2013. DOI: 10.7785/tcrt.2012.500335

23 Welsh JS, Patel RR, Ritter MA, Harari PM, Mackie TR, Mehta MP: Helical tomotherapy: an innovative technology and approach to radiation therapy. Technol Cancer Res Treat 1(4): 311-316, 2002. DOI: 10.1177/153303460200100413

24 Shepard DM, Olivera GH, Reckwerdt PJ, Mackie TR: Iterative approaches to dose optimization in tomotherapy. Phys Med Biol 45(1): 69-90, 2000. DOI: 10.1088/0031-9155/45/1/306

25 Katayama S, Haefner MF, Mohr A, Schubert K, Oetzel D, Debus J, Sterzing F: Accelerated tomotherapy delivery with TomoEdge technique. J Appl Clin Med Phys 16(2): 4964, 2015. DOI: 10.1120/jacmp.v16i2.4964

26 Edge SB, Compton CC: The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 17(6): 1471-1474, 2010. DOI: 10.1245/s10434-010-0985-4

27 Knöchelmann AC, Ceylan N, Bremer M: Left-sided breast cancer irradiation with deep inspiration breath-hold:

changes in heart and lung dose in two periods. In Vivo 36(1): 314-324, 2022. DOI: 10.21873/invivo.12704
28 Chen M, Chen Y, Chen Q, Lu W: Theoretical analysis of the thread effect in helical TomoTherapy. Med Phys 38(11): 5945-5960, 2011. DOI: 10.1118/1.3644842
29 National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf [Last accessed on March 16, 2023]
30 Arsene-Henry A, Foy JP, Robilliard M, Xu HP, Bazire L, Peurien D, Poortmans P, Fourquet A, Kirova YM: The use of helical tomotherapy in the treatment of early stage breast cancer: indications, tolerance, efficacy-a single center experience. Oncotarget 9(34): 23608-23619, 2018. DOI: 10.18632/oncotarget.25286
31 Zolcsak Z, Loap P, Fourquet A, Kirova YM: Long-term follow-up results of intensity-modulated radiotherapy with helicoïdal tomotherapy for non-metastatic breast cancers: Single centre experience. Cancer Radiother 26(5): 654-662, 2022. DOI: 10.1016/j.canrad.2021.12.002
32 Lee HH, Chen CH, Luo KH, Chuang HY, Huang CJ, Cheng YK, Chen F, Kuo SH, Huang MY: Five-year survival outcomes of intensity-modulated radiotherapy with simultaneous integrated boost (IMRT-SIB) using forward IMRT or Tomotherapy for breast cancer. Sci Rep 10(1): 4342, 2020. DOI: 10.1038/s41598-020-61403-6
33 Joseph K, Vos LJ, Gabos Z, Pervez N, Chafe S, Tankel K, Warkentin H, Ghosh S, Amanie J, Powell K, Polkosnik LA, Horsman S, MacKenzie M, Sabri S, Parliament MB, Mackey J, Abdulkarim B: Skin toxicity in early breast cancer patients treated with field-in-field breast intensity-modulated radiotherapy *versus* helical inverse breast intensity-modulated radiotherapy: results of a phase III randomised controlled trial. ClinOncol (R CollRadiol) 33(1): 30-39, 2021. DOI: 10.1016/j.clon.2020.07.005
34 Chitapanarux I, Nobnop W, Onchan W, Klunklin P, Nanna T, Sitathanee C, Kulpisitthicharoen S, Sripan P: Hypofractionated whole breast irradiation with simultaneous integrated boost in breast cancer using helical tomotherapy with or without regional nodal irradiation: A report of acute toxicities. Front Oncol 13: 1122093, 2023. DOI: 10.3389/fonc.2023.1122093
35 İnan GA, Aral IP, Arslan A, Celik TO, Ozturk HF, Arslan SA, Tezcan Y: Helical tomotherapy experience in breast cancer adjuvant radiotherapy and acute toxicity results. Rep Pract Oncol Radiother 27(6): 973-981, 2022. DOI: 10.5603/RPOR.a2022.0121
36 Chu J, Yeo MK, Lee SH, Lee MY, Chae SW, Kim HS, DO SI: Clinicopathological and prognostic significance of programmed death ligand-1 SP142 expression in 132 patients with triple-negative breast cancer. In Vivo 36(6): 2890-2898, 2022. DOI: 10.21873/invivo.13030
37 Zwicker F, Swartman B, Roeder F, Sterzing F, Hauswald H, Thieke C, Weber KJ, Huber PE, Schubert K, Debus J, Herfarth K: *In vivo* measurement of dose distribution in patients' lymphocytes: helical tomotherapy versus step-and-shoot IMRT in prostate cancer. J Radiat Res 56(2): 239-247, 2015. DOI: 10.1093/jrr/rru096
38 Bortfeld T, Webb S: Single-Arc IMRT? Phys Med Biol 54(1): N9-N20, 2009. DOI: 10.1088/0031-9155/54/1/N02
39 Bartelink H, Horiot JC, Poortmans PM, Struikmans H, Van den Bogaert W, Fourquet A, Jager JJ, Hoogenraad WJ, Oei SB, Wárlám-Rodenhuis CC, Pierart M, Collette L: Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. J Clin Oncol 25(22): 3259-3265, 2007. DOI: 10.1200/JCO.2007.11.4991
40 Chua BH, Link EK, Kunkler IH, Whelan TJ, Westenberg AH, Gruber G, Bryant G, Ahern V, Purohit K, Graham PH, Akra M, McArdle O, O'Brien P, Harvey JA, Kirkove C, Maduro JH, Campbell ID, Delaney GP, Martin JD, Vu TTT, Muanza TM, Neal A, Olivotto IA, BIG 3–07/TROG 07.01 trial investigators: Radiation doses and fractionation schedules in non-low-risk ductal carcinoma in situ in the breast (BIG 3–07/TROG 07.01): a randomised, factorial, multicentre, open-label, phase 3 study. Lancet 400(10350): 431-440, 2022. DOI: 10.1016/S0140-6736(22)01246-6
41 Donovan E, Bleakley N, Denholm E, Evans P, Gothard L, Hanson J, Peckitt C, Reise S, Ross G, Sharp G, Symonds-Tayler R, Tait D, Yarnold J, Breast Technology Group: Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. Radiother Oncol 82(3): 254-264, 2007. DOI: 10.1016/j.radonc.2006.12.008
42 Mukesh MB, Barnett GC, Wilkinson JS, Moody AM, Wilson C, Dorling L, Chan Wah Hak C, Qian W, Twyman N, Burnet NG, Wishart GC, Coles CE: Randomized controlled trial of intensity-modulated radiotherapy for early breast cancer: 5-year results confirm superior overall cosmesis. J Clin Oncol 31(36): 4488-4495, 2013. DOI: 10.1200/JCO.2013.49.7842
43 Staffurth J, Radiotherapy Development Board: A review of the clinical evidence for intensity-modulated radiotherapy. Clin Oncol (R Coll Radiol) 22(8): 643-657, 2010. DOI: 10.1016/j.clon.2010.06.013
44 van Parijs H, Vinh-Hung V, Fontaine C, Storme G, Verschraegen C, Nguyen DM, Adriaenssens N, Nguyen NP, Gorobets O, De Ridder M: Cardiopulmonary-related patient-reported outcomes in a randomized clinical trial of radiation therapy for breast cancer. BMC Cancer 21(1): 1177, 2021. DOI: 10.1186/s12885-021-08916-z
45 Zwicker F, Swartman B, Huber PE, Herfarth K, Debus J, Hauswald H: Lack of relevant haemogram changes during percutaneous radiotherapy of localised prostate cancer. In Vivo 34(3): 1555-1563, 2020. DOI: 10.21873/invivo.11945
46 Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, Yiangou C, Horgan K, Bundred N, Monypenny I,

England D, Sibbering M, Abdullah TI, Barr L, Chetty U, Sinnett DH, Fleissig A, Clarke D, Ell PJ: Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC trial. J Natl Cancer Inst 98(9): 599-609, 2006. DOI: 10.1093/jnci/djj158

47 Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, Dobbs HJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Simmons S, Sydenham MA, Venables K, Bliss JM, Yarnold JR, START Trialists' Group: The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 14(11): 1086-1094, 2013. DOI: 10.1016/S1470-2045(13)70386-3

48 Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, Shelley W, Grimard L, Bowen J, Lukka H, Perera F, Fyles A, Schneider K, Gulavita S, Freeman C: Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 362(6): 513-520, 2010. DOI: 10.1056/NEJMoa0906260

49 Shaitelman SF, Schlembach PJ, Arzu I, Ballo M, Bloom ES, Buchholz D, Chronowski GM, Dvorak T, Grade E, Hoffman KE, Kelly P, Ludwig M, Perkins GH, Reed V, Shah S, Stauder MC, Strom EA, Tereffe W, Woodward WA, Ensor J, Baumann D, Thompson AM, Amaya D, Davis T, Guerra W, Hamblin L, Hortobagyi G, Hunt KK, Buchholz TA, Smith BD: Acute and short-term toxic effects of conventionally fractionated vs hypofractionated whole-breast irradiation: a randomized clinical trial. JAMA Oncol 1(7): 931-941, 2015. DOI: 10.1001/jamaoncol.2015.2666

50 Koukourakis IM, Panteliadou M, Giakzidis AG, Nanos C, Abatzoglou I, Giatromanolaki A, Koukourakis MI: Long-term results of postoperative hypofractionated accelerated breast and lymph node radiotherapy (HypoAR) with hypofractionated boost. Curr Oncol 28(5): 3474-3487, 2021. DOI: 10.3390/curroncol28050300

51 Bellefqih S, Elmajjaoui S, Aarab J, Khalil J, Afif M, Lachgar A, El Kacemi H, Kebdani T, Benjaafar N: Hypofractionated regional nodal irradiation for women with node-positive breast cancer. Int J Radiat Oncol Biol Phys 97(3): 563-570, 2017. DOI: 10.1016/j.ijrobp.2016.11.010

52 Krug D, Vonthein R, Schreiber A, Boicev AD, Zimmer J, Laubach R, Weidner N, Dinges S, Hipp M, Schneider R, Weinstrauch E, Martin T, Hörner-Rieber J, Olbrich D, Illen A, Heßler N, König IR, Dellas K, Dunst J: Impact of guideline changes on adoption of hypofractionation and breast cancer patient characteristics in the randomized controlled HYPOSIB trial. Strahlenther Onkol 197(9): 802-811, 2021. DOI: 10.1007/s00066-020-01730-9

53 Berrington de Gonzalez A, Curtis RE, Kry SF, Gilbert E, Lamart S, Berg CD, Stovall M, Ron E: Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries. Lancet Oncol 12(4): 353-360, 2011. DOI: 10.1016/S1470-2045(11)70061-4

54 Wiltink LM, Nout RA, Fiocco M, Meershoek-Klein Kranenbarg E, Jürgenliemk-Schulz IM, Jobsen JJ, Nagtegaal ID, Rutten HJ, van de Velde CJ, Creutzberg CL, Marijnen CA: No increased risk of second cancer after radiotherapy in patients treated for rectal or endometrial cancer in the randomized TME, PORTEC-1, and PORTEC-2 trials. J Clin Oncol 33(15): 1640-1646, 2015. DOI: 10.1200/JCO.2014.58.6693

55 Burt LM, Ying J, Poppe MM, Suneja G, Gaffney DK: Risk of secondary malignancies after radiation therapy for breast cancer: Comprehensive results. Breast 35: 122-129, 2017. DOI: 10.1016/j.breast.2017.07.004

56 Bazire L, De Rycke Y, Asselain B, Fourquet A, Kirova YM: Risks of second malignancies after breast cancer treatment: Long-term results. Cancer Radiother 21(1): 10-15, 2017. DOI: 10.1016/j.canrad.2016.07.101

57 Abo-Madyan Y, Aziz MH, Aly MM, Schneider F, Sperk E, Clausen S, Giordano FA, Herskind C, Steil V, Wenz F, Glatting G: Second cancer risk after 3D-CRT, IMRT and VMAT for breast cancer. Radiother Oncol 110(3): 471-476, 2014. DOI: 10.1016/j.radonc.2013.12.002

58 Lee B, Lee S, Sung J, Yoon M: Radiotherapy-induced secondary cancer risk for breast cancer: 3D conformal therapy versus IMRT *versus* VMAT. J Radiol Prot 34(2): 325-331, 2014. DOI: 10.1088/0952-4746/34/2/325