VIA MEDICA

ORIGINAL ARTICLE

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High-dose adaptive radiotherapy for inoperable breast cancer with skin invasion after failure of chemotherapy

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Oncology in Clinical Practice
DOI: 10.5603/ocp.101271

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Introduction. In patients with inoperable breast cancer and skin invasion, the failure of chemotherapy results in symptoms such as bleeding, discharge, and offensive odor, significantly impacting the patient's quality of life. The purpose of this study was to investigate the feasibility and efficacy of high-dose adaptive radiotherapy for inoperable breast cancer with skin invasion after chemotherapy failure.

Material and methods. In this retrospective study, six consecutive patients diagnosed with inoperable breast cancer, characterized by regional lymph node metastases and, in four cases, oligometastases, were evaluated. All patients showed skin invasion after the failure of chemotherapy. We conducted planned adaptive high-dose radiotherapy using helical tomotherapy to the whole breast and metastatic regional lymph node areas. Subsequently, we administered boost adaptive radiotherapy to the breast cancer and the metastatic lymph nodes. The total doses delivered to the breast cancer and metastatic lymph nodes ranged from 66 to 75 Gy and 60 to 70 Gy, respectively.

Results. After a median follow-up of 18 months, the rates of 2-year local progression-free survival, disease-specific survival, and overall survival were 100%, 62.5%, and 50.0%, respectively. Grade 1 dermatitis was observed in five patients, whereas one patient experienced grade 2 skin edema.

Conclusions. High-dose adaptive radiotherapy may be a feasible and effective treatment option for patients with advanced breast cancer with skin invasion who have failed chemotherapy.

Keywords: breast neoplasms, radiotherapy, palliative therapy

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Introduction

Systemic chemotherapy serves as a primary treatment modality for advanced breast cancer that is not amenable to surgical resection or involves distant metastases [1, 2]. However, the effectiveness of systemic chemotherapy, endocrine therapy, or immunotherapy cannot be universally guaranteed. In cases where these treatments prove ineffective, there exists a risk of tumor infiltration through the skin, resulting in complications such as bleeding, infection, and a significant decline in the patient's quality of life. As a palliative approach, radiotherapy has been acknowledged as an effective method for managing advanced breast cancer with skin invasion, providing relief from symptoms such as bleeding, discharge, and offensive odor [3]. Nevertheless, the use of low radiation doses in this context only offers temporary symptomatic relief and does not yield permanent control. Consequently, the concern of local regrowth of the local-regional tumor emerges, particularly for long-term survivors. Furthermore, there are no reports addressing the optimal dosage and fractionation schedule for radiotherapy in cases of locally advanced inoperable breast cancer with regional lymph node metastases following systemic chemotherapy failure. This article presents our preliminary experience in

Received: 23.06.2024 Accepted: 14.01.2025 Early publication: 25.02.2025

treating advanced breast cancer with cutaneous invasion and regional lymph node metastases through high-dose adaptive radiotherapy employing helical tomotherapy after systemic chemotherapy failure.

Material and methods

Patients

This study was approved by the institutional review board (RO201601), and all procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Over 5 years, a retrospective evaluation was conducted on a cohort of six consecutive patients with locally advanced breast cancer with skin invasion or oligometastatic breast cancer with skin invasion. The latter was defined as the presence of 1–5 metastases. These patients received high-dose adaptive radiotherapy after primary chemotherapy failure. The inclusion criteria for high-dose adaptive radiotherapy in cases of oligometastatic breast cancer required that all metastatic lesions had been controlled either by surgery, stereotactic ablative radiotherapy (SABR), or systemic chemotherapy. Table 1 presents the patient characteristics. Of the six patients, four were diagnosed with stage IV breast cancer, one was diagnosed with stage IIIB breast cancer, and one was diagnosed with stage IIIC breast cancer [American Joint Committee on Cancer (AJCC) 8th ed.]. The Eastern Cooperative Oncology Group (ECOG) performance status in all patients was 0. Systemic therapy was discontinued during radiotherapy. However, following the completion of radiotherapy, four patients received chemotherapy or endocrine therapy, while two patients did not receive any additional treatment (Tab. 1).

Target volume delineation

We used transverse expiratory-phase non-contrast CT scans with a slice thickness of 2.5 mm for target volume delineation and dose calculation. We constructed five image datasets corresponding to five phases of a breathing cycle (0% to 80% by 20% increments, with 0% representing peak inspiration). We employed gadolinium-enhanced fat-suppressed T1-weighted MRI to demarcate the gross tumor volume (GTV), which encompassed both the primary breast cancer site and the metastatic lymph nodes. Subsequently, we generated fusion images using expiratory phase CT, followed by the generation of internal target volumes (ITVs) within each of the respective GTVs. We delineated the clinical target volume (CTV) to encompass the ipsilateral whole breast as well as the regional lymph node regions where metastases were identified by MRI.

Dose prescription

The radiotherapy treatment for the patients consisted of two stages using helical tomotherapy (Hi·Art® treatment system, Madison, Wisconsin, US). Intensity-modulated radiation therapy (IMRT) was utilized in the initial radiation treatment plan to target the CTV while simultaneously applying an integrated boost to the ITVs. For the initial radiation treatment plan, two planning target volumes (PTVs) were created by adding three-dimensional margins measuring 2 to 3 mm to both the CTVs (PTV1a) and the ITVs (PTV1b). The prescribed dose for PTV1a was 45 Gy in 25 fractions, while the prescribed dose for PTV1b was 50 Gy in 25 fractions. The dose was defined as the minimum dose received by 95% of the volume (D95%). Immediately after completing the initial treatment plan, we performed adaptive radiotherapy treatment planning and administered boost radiotherapy to all ITVs that regenerated through subsequent adaptive radiotherapy planning. To generate the PTVs

Table 1. Characteristics of patients with advanced breast cancer with skin invasion

No.	Age [years]	Pathology	ER/PR/HER2	Stage*	Oligometastasis**	Tx. before RT	Dose***	Tx. after RT
1	46	IDC	+/+/++	T4c N1 M1	Bone #1	TAM, Tmab	70 Gy	PTX
2	72	IDC	–/–/–	T4b N2 M1	Lung #2	PTX	66 Gy	No
3	78	IDC	–/–/++	T4b N1 M1	Bone #1	PTX	70 Gy	No
4	58	ILC	+/+/++	T4b N1 M0	N/A	EC, DOC	70 Gy	LET, Cp
5	52	IDC	+/+/–	T4c N2 M1	Lung #1, Bone #1	TAM, PTX, GEM	66 Gy	Halaven
6	52	IDC	–/–/–	T4c N3 M0	N/A	AC, PTX, Cp	75 Gy	Cp

*American Joint Committee on Cancer (AJCC) 8th ed.; **The number of distant metastases is limited to five or fewer; ***The total dose delivered to the primary lesion; AC — doxorubicin and cyclophosphamide; Cp — capecitabine; DOC — docetaxel; EC — epirubicin and cyclophosphamide; ER — estrogen receptor; GEM — gemcitabine; Halaven — eribulin mesylate; HER2 — human epidermal growth factor receptor 2; IDC — invasive ductal carcinoma; ILC — invasive lobular carcinoma; LET — letrozole; PR — progesterone receptor; PTX — paclitaxel; RT — radiotherapy; TAM — tamoxifen; Tmab — trastuzumab; Tx. — treatment

for the adaptive boost plan, three-dimensional margins ranging from 2 to 3 mm were incorporated to encompass the ITVs. The breast cancer received a prescribed boost radiation dose ranging from 16 to 25 Gy administered over 8 to 10 fractions while the regional lymph nodes, including the axillary, supraclavicular, infraclavicular, and internal mammary lymph nodes, received a prescribed dose of 10 to 16 Gy delivered in 5 to 8 fractions. The total radiation dose administered to the breast cancer ranged from 66 Gy to 75 Gy, while the metastatic lymph nodes received a total dose ranging from 60 Gy to 70 Gy.

Patient evaluation and follow-up

Before the initiation of radiotherapy, a comprehensive pre-treatment evaluation was performed in all patients, encompassing physical assessment, complete blood counts, blood chemical analyses to assess renal and hepatic function, as well as multiparametric MRI scans, including diffusion-weighted imaging (DWI) and gadolinium-enhanced fat-suppressed T1-weighted imaging. During radiotherapy, patients were assessed weekly for adverse events. Physical assessment and MRI were performed every 2–3 months after radiotherapy until progression of the irradiated tumor. Adverse events were assessed and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The response was assessed on gadolinium-enhanced fat-suppressed T1-weighted imaging with the use of serial measures of the product of the two largest cross-sectional diameters. Local progression was defined as either an increase in tumor size by at least 25% or the development of a new lesion within the radiation field.

Statistical analysis

The primary endpoint was local progression-free survival (PFS), measured from the last date of radiotherapy until disease progression within the PTV or death or the last evaluation date. Disease-specific survival (DSS) was measured from the date of the last radiotherapy until the date of death attributed to breast cancer or the last day that the patient was known to be alive (censoring date). Overall survival (OS) was also measured from the last date of radiotherapy until death or censoring on the last day that the patient was known to be alive. The Kaplan-Meier curves were generated for local PFS, DSS, and OS.

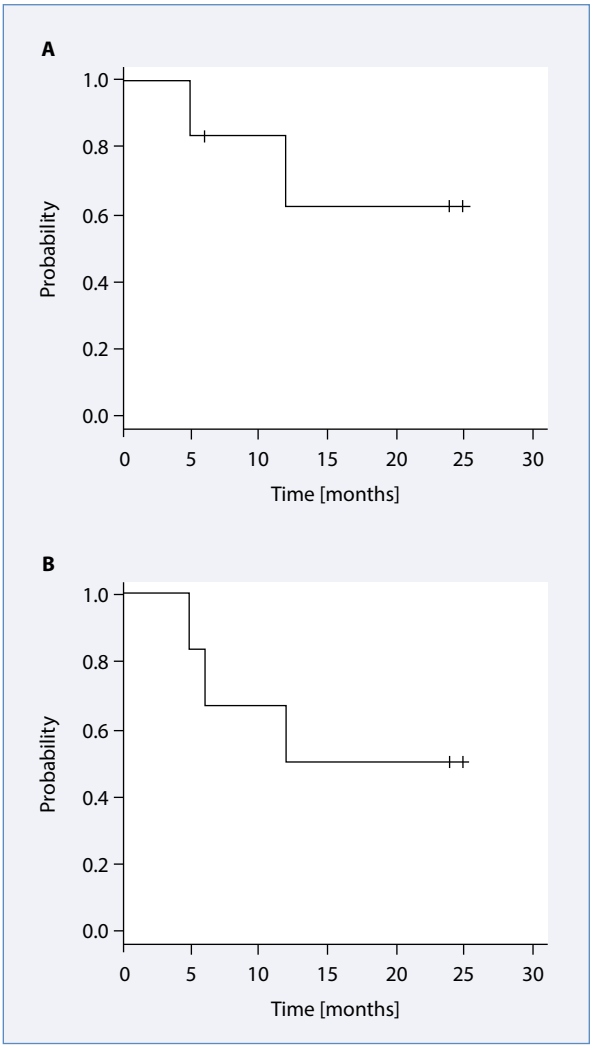

Figure 1. Kaplan-Meier curves of patients with inoperable breast cancer with skin invasion after chemotherapy failure; **A**. Disease-specific survival was 62.5% at 2 years; **B**. Overall survival was 50.0% at 2 years

Results

At a median follow-up of 18 months, the 2-year local PFS, DSS, and OS rates were 100%, 62.5% (Fig. 1A), and 50.0% (Fig. 1B), respectively. No local or regional recurrences were observed during the follow-up period (Fig. 2A–D). One patient experienced a fatal duodenal perforation six months following radiotherapy; however, no tumor recurrence was observed either within the radiation field or in areas outside the radiation fields. During radiotherapy, five (83%) patients developed grade 1 dermatitis. However, it resolved spontaneously without therapy. One (17%) patient (#2) exhibited grade 2 skin edema (Fig. 3A and B), which was successfully alleviated with the application of topical steroid ointment.

Discussion

This study demonstrates the feasibility and potential efficacy of high-dose adaptive radiotherapy using helical tomotherapy for inoperable breast cancer with skin

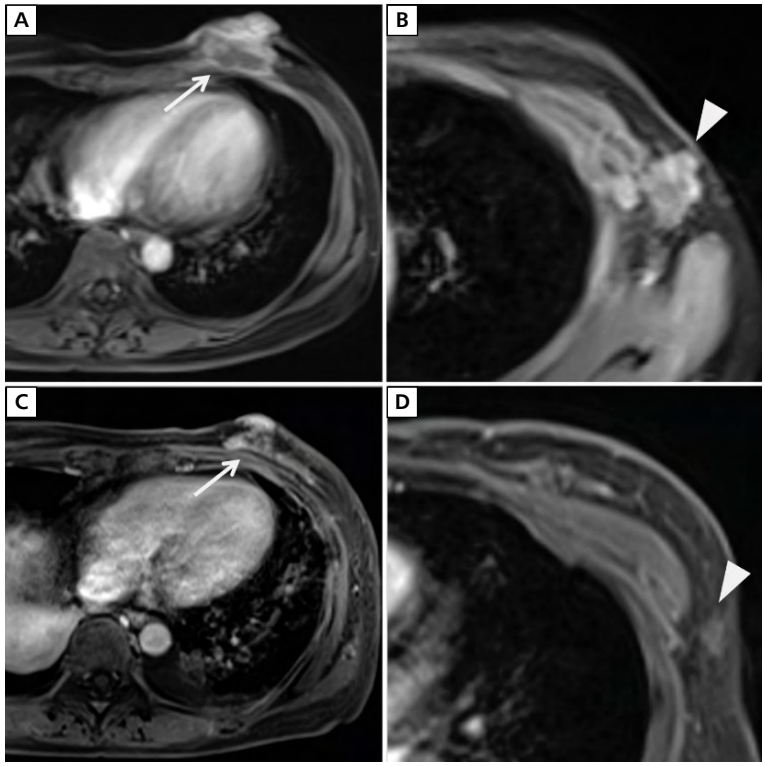

Figure 2. A representative case of locally advanced breast cancer with skin invasion after the failure of second-line chemotherapy (case #6); **A, B.** Before radiotherapy, the breast cancer (arrow) showed invasion to both the skin and the chest wall, as well as regional lymph node metastases (arrowhead); **C, D.** At six-month follow-up after radiotherapy, complete regression of both the breast cancer (arrow) and the lymph node metastases (arrowhead) was observed

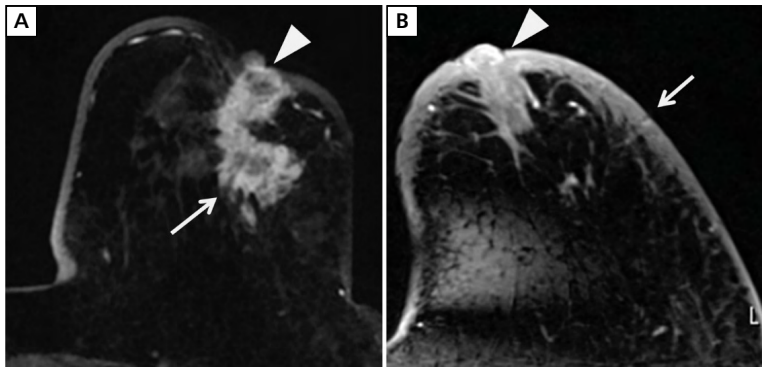

Figure 3. A 72-year-old woman with triple-negative breast cancer with skin invasion after first-line chemotherapy failure using paclitaxel (case #2); **A.** Before radiotherapy, the subareolar breast cancer (arrow) showed invasion to the skin and nipple (arrowhead), resulting in complications such as bleeding, infection, and nipple retraction attributed to the nipple invasion; **B.** Six months after radiotherapy, the breast cancer was found to have regressed completely and the nipple retraction was relieved (arrowhead). The skin exhibited thickening (arrow) as a consequence of grade 2 skin edema

invasion after failure of chemotherapy. We found no reports on applying definitive radiotherapy to primary breast cancer sites and sites of lymph node metastases in this scenario. According to reports, patients with bone-only oligometastases had 5- and 10-year overall survival rates of 83% and 75%, respectively [4]. Patients with non-bone oligometastases had 5- and 10-year overall survival rates of 31% and 17%, respectively. In another study, mean overall survival was 28 months in the control group and 41 months in the SABR group [5].

Despite the presence of distant metastases, patients diagnosed with oligometastasis can anticipate favorable long-term survival rates. Consequently, the management of primary tumor and regional lymph node metastases assumes crucial significance in preserving the quality of life for both locally advanced breast cancer patients and those with oligometastatic breast cancer.

This study has several strengths. First, this study provides evidence that high-dose adaptive radiotherapy effectively controls primary tumors and lymph node metastases, even in cases where initial chemotherapy fails to achieve desired outcomes. Previous research indicated the potential benefits of SABR in treating operable early breast cancer [6]. However, there are no published data regarding definitive radiotherapy for inoperable breast cancer with skin invasion and regional lymph node metastases that do not respond to first-line chemotherapy. Second, the initial radiotherapy treatment plan, which treated the whole breast and metastatic lymph node areas, resulted in a reduction in tumor size. This reduction enabled adaptive radiotherapy to deliver high-dose radiation to the smaller GTV that had existed before the initial radiotherapy treatment planning. By reducing the GTV during initial radiotherapy planning, it was possible to administer a high-dose radiation boost without increasing adverse events.

This study has also several limitations that need to be addressed. First, the sample size was relatively small, and the follow-up period was limited. However, for the first proof of principle of high-dose adaptive radiotherapy for inoperable advanced breast cancer with skin invasion and regional lymph node involvement, we believe that even a small number of cases and a short follow-up period are not critical limitations. Second, the entire radiotherapy treatment period was lengthy, typically lasting from 6 to 7 weeks. Although hypofractionated radiotherapy for the whole breast and metastatic lymph node areas might be feasible [**7**], we did not apply it to shorten the treatment period due to using simultaneous integrated boost radiotherapy in the initial radiotherapy treatment planning.

Conclusions

In conclusion, our findings, from a single retrospective cohort study, require further scientific validation. However, our study provides evidence to support the potential efficacy of high-dose adaptive radiotherapy using helical tomotherapy in the treatment of inoperable advanced breast cancer with regional lymph node metastases, even in situations where initial chemotherapy regimens have been ineffective. Moreover, our results demonstrate a low incidence of significant adverse events associated with this treatment approach.

Article Information and Declarations

Data availability statement

The data that support the findings of this study are available from the corresponding author but restrictions apply to the availability of these data, which were used under license for this study.

Ethics statement

This study was approved by the institutional review board (RO201601), and all procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Author contributions

Y.H., E.T.: conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing.

Funding

This publication was prepared without any external source of funding.

Acknowledgments

None.

Conflict of interest

The authors declare no conflict of interest.

Supplementary material:

None.

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