pISSN 2234-1900
eISSN 2234-3156

Radiation Oncology Journal

ROJ

Vol. 41, No. 4, December 2023

www.e-roj.org

The Korean Society for Radiation Oncology

www.e-roj.org

pISSN 2234-1900
eISSN 2234-3156

ROJ Radiation Oncology Journal

Vol. 41, No. 4, December 2023

Aims and Scope

The Radiation Oncology Journal (ROJ) is an official journal of the Korean Society for Radiation Oncology. It was launched in 1983 as the official journal of the Korean Society of Therapeutic Radiology. It was changed in 2000 as the official journal of the Korean Society for Therapeutic Radiology and Oncology and finally in 2011 as ROJ.

The aims of Radiation Oncology Journal are to contribute to the advancements in the fields of radiation oncology through the scientific reviews and interchange of all of radiation oncology. It encompasses all areas of radiation oncology that impacts on the treatment of cancer using radiation as well basic experimental work relating radiation oncology and health policy. It publishes papers describing clinical radiotherapy, combined modality therapy, radiation biology, cancer biology, radiation physics, radiation informatics and new technology including particle therapy.

The ROJ is published quarterly on the last day of March, June, September, and December, one volume per year. Any physicians or researchers throughout the world can submit a manuscript if the scope of the manuscript is appropriate. Articles in the following categories will be published: original articles, invited review articles, case reports, editorials, and letters to the editor related to basic or clinical radiation oncology. All of the manuscripts are peer-reviewed.

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Publisher Hee Chul Park
Editor-in-Chief Sang Min Yoon

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Published on December 31, 2023

ROJ Radiation Oncology Journal

Editorial Board

ROJ Radiation Oncology Journal

Radiat Oncol J
pISSN 2234-1900 eISSN 2234-3156

Vol. 41, No. 4, December 2023

This work was supported by the Korean Federation of Science and Technology Societies Grant funded by the Korean Government (Ministry of Education).

ROJ Radiation Oncology Journal

Editorial

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2023;41(4):223-224
https://doi.org/10.3857/roj.2023.01004

Proton beam therapy as a promising option for high-risk limited stage small cell lung cancer: revealing potential of future novel agents

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Received: November 30, 2023
Revised: December 11, 2023
Accepted: December 12, 2023

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Radiotherapy (RT) is the main local treatment for limited-stage small-cell lung cancer (LS-SCLC). Notably, SCLC is extremely sensitive to radiotherapy. Turrisi et al. [1] demonstrated the oncological benefit of high radiation doses by showing the survival benefit of a 45 Gy/1.5 Gy bid protocol compared to the conventional 45 Gy in 25 fractions treatment. Recently, Faivre-Finn et al. [2] reported that treatment with 66 Gy in 33 fractions could achieve a survival similar to that of the bid regimen. Referencing the literature on non-small cell lung cancer (NSCLC), dose-escalation beyond 60–66 Gy is not always successful and has the potential to increase toxicity [3].

Despite high radiosensitivity, SCLC is prone to systemic recurrence. Considering the studies on NSCLC, whether further escalation of the RT dose can improve the prognosis of SCLC, requires further study. Many patients with SCLC have concomitant diseases and reduced lung function. Therefore, reducing lung exposure using proton beam therapy (PBT) may be a valid option for high-risk patients. In this issue of the *Radiation Oncology Journal*, although Seo et al. [4] applied PBT to a group with significantly poorer lung function, oncological outcomes and toxicity profiles were similar to those of the control group. While the literature on PBT for LS-SCLC is limited, this study is valuable in clinical and research terms.

Welsh et al. [5] conducted a phase I/II study, applying chemoradiation and pembrolizumab for LS-SCLC. Grade ≥ 2 pneumonia occurred in 15%, and median progression-free and overall survival were favorable at 19.75 months and 39.5 months, respectively. Unfortunately, a recent phase II randomized study (STIMULI trial) adding nivolumab and ipilimumab to standard treatment for LS-SCLC failed to demonstrate its benefit, resulting in an increase in grade ≥ 3 toxicities (62% vs. 25%) [6]. Nonetheless, the efficacy of various immunotherapeutic agents is being evaluated for LS-SCLC [7], hopefully achieving encouraging results as in NSCLC. If potential toxicities can be reduced using PBT, the effectiveness of immunotherapy in treating LS-SCLC may be revealed in the future.

Seo et al [4]. reported the safety and efficacy of PBT in patients with high-risk LS-SCLC. These results may expand the role of RT in high-risk groups of LS-SCLC and help demonstrate the effectiveness of novel agents.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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https://doi.org/10.3857/roj.2023.01004

ROJ Radiation Oncology Journal

Review Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2023;41(4):225-236
https://doi.org/10.3857/roj.2023.00290

Dynamic contrast-enhanced magnetic resonance imaging parameter changes as an early biomarker of tumor responses following radiation therapy in patients with spinal metastases: a systematic review

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Received: April 12, 2023
Revised: August 18, 2023
Accepted: August 21, 2023

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Purpose: This systematic review aims to assess and summarize the clinical values of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) parameter changes as early biomarkers of tumor responses following radiation therapy (RT) in patients with spinal metastases.

Materials and Methods: A systematic search was conducted on five electronic databases: PubMed, Scopus, Science Direct, Cochrane, and Embase. Studies were included if they mentioned DCE-MRI parameter changes before and after RT in patients with spinal metastases with a correlation to tumor responses based on clinical and imaging criteria. The Quality Assessment of Diagnostic Accuracy Studies 2 was used to assess study quality.

Results: This systematic review included seven studies involving 107 patients. All seven studies evaluated the transfer constant (Ktrans), six studies evaluated the plasma volume fraction (Vp), three studies evaluated the extravascular extracellular space volume fraction, and two studies evaluated the rate constant. There were variations in the type of primary cancer, RT techniques used, post-treatment scan time, and median follow-up time. Despite the variations, however, the collected evidence generally suggested that significant differences could be detected in DCE-MRI parameters between before and after RT, which might reflect treatment success or failures in long-term follow-up. Responders showed higher reduction and lower values of Ktrans and Vp after RT. DCE-MRI parameters showed changes and detectable recurrences significantly earlier (up to 6 months) than conventional MRI with favorable diagnostic values.

Conclusion: The results of this systematic review suggested that DCE-MRI parameter changes in patients with spinal metastases could be a promising tool for treatment-response assessment following RT. Lower values and higher reduction of Ktrans and Vp after treatment demonstrated good prediction of local control. Compared to conventional MRI, DCE-MRI showed more rapid changes and earlier prediction of treatment failure.

Keywords: Multiparametric magnetic resonance imaging, Spine, Neoplasm metastasis, Radiotherapy

Introduction

With the advancement of cancer treatment regimens, there has been a rise in the survival rates of cancer patients, which has led to a prolonged overall survival and increased incidence of spinal metastasis [1]. As the disease progresses, 40%–70% of advanced can-

cer patients will develop spinal metastases [2], which has become the third most frequent site for metastases following the lungs and liver [3]. Spinal metastases are the leading causes of morbidity in patients with cancer. In addition to being a common cause of cancer pain, spinal metastases frequently result in pathological compression fractures of the vertebrae and metastatic epidural spinal cord compression. Symptoms include pain, paralysis, sensory disturbances, sexual dysfunction, urinary and anal incontinence, decreased quality of life, and death [2,4].

Radiation therapy (RT) is one of the modalities of choice for spinal metastases. RT is applied to relieve pain, control paralysis, and alleviate related symptoms [5]. Initially, conventional external beam radiotherapy (EBRT) was the main type of RT for spinal metastases, but despite its demonstrated efficacy, many patients continue to experience tumor progression following RT [6]. Due to the wide radiation field of EBRT, the radiation dose delivered to the tumor must be kept to a minimum. This limitation of EBRT has led to the development of more advanced RT techniques, such as CyberKnife radiosurgery and stereotactic body radiation therapy (SBRT), which can deliver optimal therapeutic radiation doses while reducing radiation exposure to adjacent structures [7].

Conventional magnetic resonance imaging (MRI) is the gold-standard modality for assessing tumor response in spinal metastases. Local control is described as the absence of progression, which is shown by serial imaging studies as an increase in tumor size in the treated area in 2–3 consecutive MRI scans performed 6–8 weeks apart [8]. While conventional MRI remains the gold standard for therapy evaluation, it provides limited information about the pathogenesis and viability of lesions [6]. The size of a lesion is frequently difficult to assess. Reports claim that in conventional MRI images, nearly half (49.4%) of metastatic spinal tumors exhibit no changes after stereotactic radiosurgery (SRS) [9].

RT can result necrosis and fibrosis in the tumor and surrounding healthy tissues, resulting in tissue alterations following RT. Thus, it is frequently challenging to assess the response of spinal tumors using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, making it difficult to tell whether the disease has progressed [10,11]. Evaluation of the tumor response following radiation has significant consequences for patient care, and early diagnosis of tumor response is mandatory to aid clinicians in determining salvage therapy more promptly and improve clinical outcomes [12].

In recent years, dynamic contrast-enhanced MRI (DCE-MRI) has become more common for assessing spinal metastases [6]. DCE-MRI is superior to conventional MRI for evaluating tumor structures and permeability [13]. Using dynamic T1-weighted gradient-recalled echo sequences, this method measures changes in gadolinium concentrations over time in tissues [6], using a kinetic analysis model with some parameters, namely, the transfer constant (Ktrans), plasma volume fraction (Vp), and extravascular extracellular space volume fraction (Ve) [13], which respectively represent the blood volume, blood flow, vascular permeability, mean transit time, distribution of contrast agent volume, and interstitial space [12]. Malignant tumors undergo neovascularization or angiogenesis, recruitment, synthesis, and vascular tissue formation, which signify tumor development, proliferation, and metastasis [14,15]. DCE-MRI parameters are closely linked to tumor biology and can serve as markers of anti-angiogenic and cytotoxic responses. Furthermore, they are more sensitive than volumetric assessments in the detection of subtle internal tumor responses [16].

DCE-MRI has been reported to be a good predictor of tumor response and post-RT clinical outcomes in various malignancies, including head and neck, cervical, brain, breast, prostate, as well as colon cancers [17-21]. Several studies have reported differences in DCE-MRI parameter changes between responders (treatment success) and non-responders (treatment failure) among patients with spinal metastases undergoing radiation. Changes after RT can be detected significantly earlier with DCE-MRI than with conventional MRI. However, most studies have reported a limited sample size [22-28]. The aim of this systematic review was to examine the available data about the significance of post-radiation DCE-MRI parameter changes as early biomarkers of tumor response following RT in patients with spinal metastases.

Materials and Methods

1. Search strategy

This study followed the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. From December 2022 to January 2023, a comprehensive literature search was conducted using five electronic databases: PubMed, Scopus, Science Direct, Cochrane, and Embase. The goal was to identify all studies relevant to the role of changes in DCE-MRI parameters after RT and their correlation to tumor response evaluation in spinal metastases patients. The search terms included ("dynamic contrast-enhanced magnetic resonance imaging" OR "DCE-MRI") AND ("spinal metastases" OR "spine metastases" OR “bone metastases” OR “bone metastasis” OR “osseous metastases” OR “osseous metastasis”). Considering the scarce availability of study results, we broadened our search terms with “bone metastasis OR bone metastases” and “osseous metastasis” OR “osseous metastases.” Since spinal metastasis responses are essentially analogous to other bone metastasis, the inclusion of broader search terms regarding RT for other bone metastasis would yield helpful information in addition to the small number of available studies. The analysis of the selected articles

https://doi.org/10.3857/roj.2023.00290

and the writing of the systematic review were conducted from February 2023 to June 2023.

2. Eligibility criteria

The included studies fulfilled the following criteria. (1) The population comprised patients with spinal or bone metastases who underwent conventional, stereotactic, CyberKnife, and image-guided radiation therapy (IGRT). (2) The index test involved clinical or imaging follow-up or a combination of both. (3) The reference test involved DCE-MRI parameters assessed before and immediately after RT (6 months). (4) The outcome included the tumor response after RT. The study designs were observational studies (both retrospective and prospective). The search method excluded conference abstracts, letters, editorials, guidelines and consensus, systematic reviews or meta-analyses, case reports, literature reviews, xenograft/animal model studies, trial registries, and unpublished studies. The search strategy imposed no language restrictions.

3. Study selection

Four independent reviewers performed the literature search and study selection. The selection method consisted of scanning titles and abstracts, filtering similar or duplicate articles using the EndNote 20 tool, and reviewing full-text articles. Furthermore, references from selected research were evaluated to identify other eligible studies. Disagreements were settled by discussion among all authors.

4. Data extraction and study-quality assessment

The data obtained included the following. (1) The study characteristics included author information, study year, study duration, the country where the study was conducted, study design, number of patients, and number of lesions. (2) The patient characteristics included age, underlying malignancy, RT used, radiation dose provided, RT site, and median follow-up time. (3) The data from MRI examinations included Tesla MRI power, MRI parameters utilized, processing software, DCE-MRI parameters used, and time of DCE-MRI evaluation before and after RT. (4) Regarding tumor response data, responders were defined as patients with complete or partial responses, whereas non-responders were defined as those with stable disease or progressive disease based on RECIST v1.1 or other clinical/imaging considerations. (5) Other data included the diagnostic properties of DCE-MRI in the evaluation of tumor response.

5. Risk of bias and applicability

The quality and risk of bias of the included studies in this systematic review was evaluated following the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2). Each domain was graded as low risk, unclear/moderate concerns, or high risk. RevMan software (https://revman.cochrane.org) was used to create bias risk graphs. Due to the included studies' diverse results, we could not perform a meta-analysis.

Results

1. Study selection

Seven studies were ultimately included in this systematic review. A total of 359 studies were identified from five databases. After excluding duplicates from the search, 274 studies were further evaluated. After examining the titles and abstracts of the available studies, 256 studies were excluded. In total, the full-text of 18 studies was reviewed. Studies that did not assess changes in DCE-MRI parameters following RT in individuals with spinal or bone metastases were excluded. Ultimately, seven studies met the eligibility requirements. Fig. 1 demonstrates the flow of the making of this systematic review.

2. Quality assessment of the included studies

The quality of the studies was evaluated following the QUADAS-2 checklist. Fig. 2 shows the risk of bias and applicability of the selected studies. Overall, the risk of bias was deemed to be low. Two studies were considered to have a moderate/uncertain risk of bias in the patient-selection domain because they did not specify the methodology of patient selection and whether it was consecutive or not [22,24]. Another study was deemed to have a significant probability of patient-selection bias due to the explicit admission that they did not select participants in a randomized and sequential fashion [23]. In all studies, the reasons for patient exclusion were explicit and appropriate [20,22-24,26-28]. In general, however, the selected individuals were heterogeneous in regard to the primary malignancy and the type of RT techniques applied [22-27].

In the index test domain, all DCE-MRI parameters were described in detail, by three studies showed a risk of unclear bias because of the unspecified blinding process for the radiologists who assessed the DCE-MRI parameters [22-24]. In the standard reference domain, most studies clearly explained the criteria for evaluating tumor response clinically and radiologically except for one study [23]. Two studies in the flow and timing domain were deemed to have moderate/unclear risks of bias due to heterogeneous follow-up times. The treatment-response evaluation period was generally less than 3 months, indicating an early treatment-response evaluation [22,24].

3. Study characteristics

Seven studies evaluated tumor responses to RT using DCE-MRI pa-

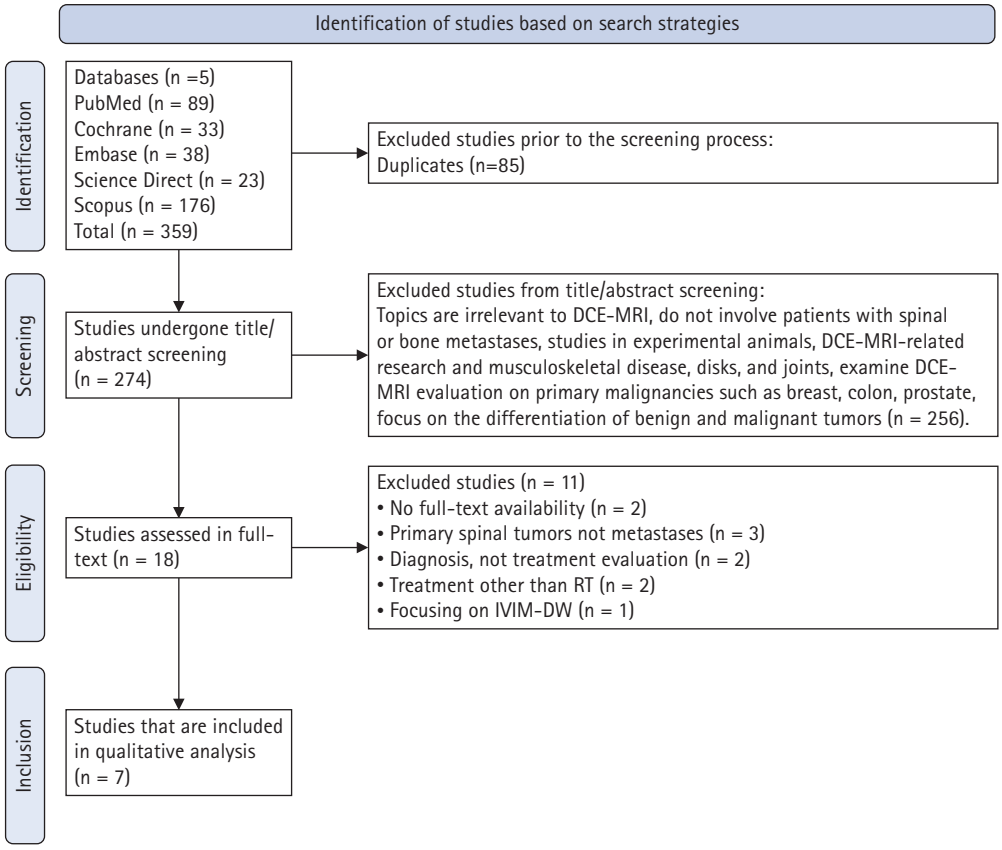

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart. DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; RT, radiation therapy; IVIM, intravoxel incoherent motion; DW, diffusion-weighted.

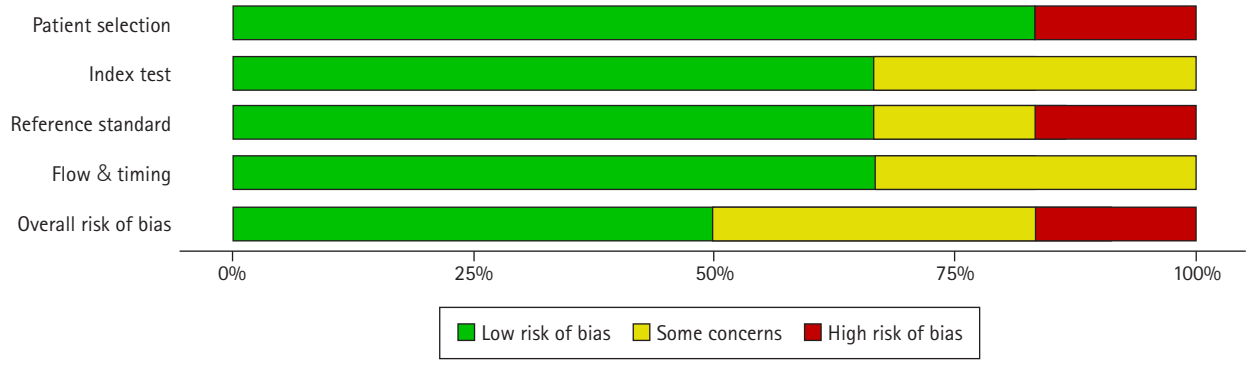

Fig. 2. Assessment of study quality with the Quality Assessment of Diagnostic Accuracy Studies-2.

rameters. These studies included 106 patients with spinal metastases and one patient with pelvic bone metastases. The features of each study are presented in detail in Table 1. All studies were published in four countries between 2013 and 2022: China, Singapore, South Korea, and the United States [22-28]. Four studies were prospective [23,25,27,28], while the others were retrospective [22,24,26].

This systematic review included 107 patients with various primary malignancies, of which the majority were lung, sarcoma, breast, and liver malignancies. Patients with spinal metastases were included in the study based on pathological features and clinical presentation. Due to poor image quality, patients who had undergone surgery and kyphoplasty in the area of metastases to be irradiated were generally excluded from the studies [22,24-27]. All patients in the seven included studies underwent RT, although with varied modalities of radiation delivery. Two studies used SBRT [26,27], two studies used EBRT [22,28], two studies used SRS

 https://doi.org/10.3857/roj.2023.00290

https://doi.org/10.3857/roj.2023.00290

Table 1. Study characteristics of the included studies

Study, year	Country	Study design	Number of patients	Age (yr)	Lesions	Primary malignancy	RT and doses administered	RT location	Clinical outcome	Follow-up time (mo)
Chu et al. [22], 2013	USA	Retrospective	15	N/R	19	Liver (1), leiomyosarcoma (1), tonsil (3), renal (5), thyroid (1), prostate (2), breast (2), colon (2), NS-GTC (1), unknown (1)	External beam radiotherapy, doses and fractions not stated.	Lumbar (10), thoracal (6), sacrum (3)	R: 17 lesions NR: 2 lesions	≥ 11
Spratt et al. [26], 2016	USA	Retrospective	9	61 (range 33–77)	12	Sarcoma (9)	Hypofractionated and single-fraction SBRT 24 Gy in a single fraction, 27 Gy (9 Gy × 3 fractions), and 30 Gy (10 Gy × 3 fractions)	Thoracal, lumbar, sacrum	R: 11 lesions NR: 1 lesion	11.2 (range 5.1–31.1)
Kumar et al. [24], 2017	USA	Retrospective	30	65 (range 40–89)	N/R	Thyroid (5), colon (4), breast (4), prostate (4), renal (4), sarcoma (3), lung (2), other (4)	Single-fraction SRS 24 Gy on 20 patients and hypo fractionated SRS 27–30 Gy on 10 patients	Thoracal, lumbar	R: 25 patients NR: 5 patients	20 (range 5–40)
Lis et al. [7], 2017	USA	Prospective	6	60	8	Prostate (4), thyroid (1), renal (1)	HD IGRT 24 Gy and 9 Gy (×3 fractions)	Thoracal, lumbar	R: 6 NR: 0	1.8–27.5 months
Chen et al. [25], 2021	China	Prospective	27	53 ± 13	39	Lung (6), breast (4), thyroid (4), renal (3), sarcoma (5), liver cancer (8), colon (1), bile duct (1), melanoma (3), lymphoma (1)	CyberKnife SRS, hypofractionated SRS 4–10 Gy per fraction, total doses 25–40 Gy	Cervical (13), thoracic (12), lumbar (11), sacral (3)	R: 27 lesions NR: 12 lesions	18.6 (range 6.2–36.4) Mean: 18.5
Vellayappan et al. [27], 2022	Singapore	Prospectives	10	62 (range 51–75)	13	Renal (4), lung (5), prostate (2), breast (1), colon (1)	SBRT Median SBRT dose was 27 Gy (range 24–27) over 3 fractions (range 2–3)	Cervical, lumbar, thoracal	R: 9 NR: 1	42 (range 22.3–54.3)
Lee et al. [28], 2021	South Korea	Prospectives	10	63 (range 43–73)	N/R	Liver (10)	RT with 30 Gy in ten fractions (X-ray beam and proton beam)	Thoracal, lumbar, sacral, ilium	R: 6 NR: 4	6 (range 3–7)

RT, radiation therapy; NS-GCT, non-seminomatous germ cell tumors; R, responders; NR, non-responsders; SBRT, stereotactic body radiation therapy; N/R, not reported; SRS, stereotactic radiosurgery; HD IGRT, high-dose image-guided radiation therapy.

[24,25], and one study used high-dose (HD) IGRT [23].

The tumor response to RT was evaluated using clinical and imaging criteria. Responder criteria were generally identical among the included studies with few differences [22-24,26,28]. Chu et al. [22] defined responders or treatment success based on evidence of tumor contraction (shrinking size of the outer borders of the abnormal signal lesion), negative results on positron emission tomographic-computed tomographic scans, or tumor stability in a long-term (more than 11 months without change). Post-treatment evaluation point was non-uniform, ranging from 10–187 days. Spratt et al. [26] described non-responders as a progressive radiographic size enlargement of the treated lesion and a persistent progression in more than one post-treatment scan with consideration of clinical features such as the progression of neurologic symptoms related to the treated site. The median time from SBRT completion to post-treatment DCE-MRI evaluation was 57 days (interquartile range, 51 to 62 days; range, 42 to 79 days). The study used a median follow-up time of 11.2 months to decide treatment failure/success.

Kumar et al. [24] described responders as those with no radiographic evidence of tumor recurrence in MRI and positron emission tomography (PET). Recurrent cases were defined as patients that showed progressive increase in the size of the treated lesion with consideration of the clinical scenario at a median follow-up time of 21 months. They did not clearly state the evaluation time-point after RT, however they did mention their earliest post-RT scan was 1 month, which did predict recurrence. Chen et al. [25] evaluated the tumor response using RECIST v1.1. The first post-RT evaluation was conducted 3 months after CyberKnife radiosurgery, followed by a 3-month cycle of follow-up examinations. In a median follow-up time of 18.6 months (range, 6.2 to 36.4 months) with a mean of 18.5 months, the patients were grouped in accordance with the evaluation results. Those patients with complete response (CR), partial responses (PR), or stable diseases (SD) were grouped into responders or non-progressive disease (non-PD). Patients with an increase in the sum of diameters of target lesions were grouped into non-responders or PD.

Vellayappan et al. [27] evaluated tumor response following the MD Anderson criteria at 3 months. Patients were subsequently divided into PD, CR, PR, and SD. Local recurrence was assessed in the median follow-up time of 42 months (range, 22.3 to 54.3 months) based on available clinical imaging at the last follow-up. Lis et al. [23] evaluated the tumor changes in spinal metastases patients undergoing HD IGRT immediately one hour after RT, which was then compared to the imaging results in long-term follow-up to further confirm the treatment response. The longest follow-up was 27.9 months. Lee et al. [28] evaluated the local tumor response based on MD Anderson criteria. The first evaluation time point was 1 month after RT (first post-RT; range, 15 to 45 days). The median follow-up time of 6 months (range, 3 to 7 months).

DCE-MRI parameters evaluation before and after therapy were performed on all the patients enrolled in the included studies. The first post-treatment DCE-MRI scan was generally conducted less than three months after the completion of RT [22-26,28]. A total of four studies used MRI with a magnetic strength of 1.5 T [22-24,26], and the three other studies used MRI at 3 T [25,27,28]. Detailed characteristics of the DCE-MRI parameters are shown in Table 2. All studies evaluated the Ktrans parameter [22-28], and five studies evaluated Vp [22-24,26-28]. Other parameters included Ve and Kep.

The DCE-MRI protocol was similar in all studies. Gadolinium contrast was given at a rate of 2–3 mL/s and a dose of 0.1–0.2 mmol/kg. Image processing software was used to obtain pre- and post-processing data. Background noise was removed, spatial and temporal filtering was applied, and the aorta's automatic arterial input function (AIF) was detected. Each patient's AIF was calculated individually. Before proceeding with the next processing steps, the shape of the AIF curve was visually verified [22-28]. In five studies, DCE-MRI parameters were measured using the Tofts 2-compartment pharmacokinetic model [22-26,28], and only one study used distributed parameters (DP) [27].

4. Changes in DCE-MRI parameters and evaluation of tumor response after RT

1) Ktrans

This systematic review included all studies that examined changes in Ktrans after RT. Spratt et al. [26] demonstrated that around 2 months after SBRT, the DCE-MRI evaluation revealed a reduction in the mean Ktrans by up to 59% and a reduction in the maximum Ktrans by up to 55.2%. As much as 75% of lesions had a decrease in the mean Ktrans, and 92% of patients had a reduction in the maximum Ktrans. The mean and maximum Ktrans increased after SBRT in one patient with local recurrences (by 83.4%, and 9.5%, respectively). All patients with a 50% reduction in mean and maximum Ktrans after SBRT showed no local progression (median follow-up of 11.2 months; range, 5.1 to 31.1 months). However, this study did not compare the changes in responders and non-responders because of the small number of samples, so statistical significance was not obtained [26].

Kumar et al. [24] discovered a significant difference in post-SRS changes in Ktrans parameters between responders and non-responders (-66% vs. -7%; $p = 0.01$). At a median follow-up of 21 months (range, 5 to 40 months), no local recurrences were found in patients with a reduced post-SRS Ktrans by up to 66% (25 patients). Patients with local recurrences (five patients) showed only

 https://doi.org/10.3857/roj.2023.00290

Table 2. DCE-MRI parameter characteristics

Study, year	Tesla MRI	Contrast agent	Post-processing	Quantitative analysis	Evaluated DCE-MRI parameters	DCE-MRI parameters time evaluation
Chu et al. [22], 2013	1.5 T	Gd-DTPA 0.1 mmol/kg at flow rate of 2.5 mL/s	NordicICE version 2.3 (NordicNeuroLab)	The Tofts 2-compartment pharmacokinetic model	Vp, Ktrans, AUC, PE	Pre-therapy 2–115 days; post-treatment 0–187 days
Spratt et al. [26], 2016	1.5 T	Gd-DTPA 0.1 mmol/kg at flow rate of 2–3 mL/s	NordicICE (NordicNeuroLab)	Tofts 2-compartment pharmacokinetic model	Ktrans, Vp	57 days post-therapy (IQR, 51–62 days; range 42–79 days)
Kumar et al. [24], 2017	1.5 T	Gd-DTPA 0.1 mmol/kg at flow rate of 2–3 mL/s	NordicICE version 2.3 (NordicNeuroLab)	Extended Tofts' 2-compartment pharmacokinetic model	Vp, Ktrans	Before and after not specified.
Lis et al. [7], 2017	1.5 T	Gd-DTPA 0.1 mmol/kg at flow rate of 2.5 mL/s	NordicICE (NordicNeuroLab) and MATLAB (MathWorks)	Toft's pharmacokinetic model analysis	Vp, Ktrans	1 hour before and after therapy, compared to subsequent follow-up (range, 51–504 days)
Chen et al. [25], 2021	3T	Gadopentetate dimeglumine 0.1 mmol/kg at flow rate of 2 mL/s	GE ADW4.6 workstation and GenIQ software	Extended Tofts 2-compartment pharmacokinetic model	Ktrans, Kep, Ve	1 week pre-therapy; 1/3 months post-therapy
Vellayappan et al. [27], 2022	3T	Dotarem (gadoterate meglumine) 0.2 mL/kgBB at flow rate of 3 mL/s	MATLAB (MathWorks)	Distributed parameter	Ktrans, PS, Vp, Ve,	At time of CT simulation; 1-week and 3-month post-radiation therapy
Lee et al. [28], 2021	3T	Gadoterate meglumine (Dotarem) at a rate of 3 mL/s	IntelliSpace Portal version 10.0 (Philips)	Extended Tofts 2-compartment pharmacokinetic model	Ktrans, Ve, Vp, Kep	Before (baseline) and 1 month after completing RT (first post-RT; range 15–45 days)

DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; Gd-DTPA, gadolinium-diethylenetriamine pentaacetic acid; Vp, plasma volume fraction; Ktrans, transfer constant; AUC, area under the curve; PE, peak enhancement; IQR, inter quartile range; Ve, extravascular extracellular space volume fraction; PS, permeability surface area product; CT, computed tomography; RT, radiation therapy.

a 7% reduction in Ktrans (median follow-up of 14; range, 7 to 20 months).

Lis et al. [23] studied the early response after HD IGRT in six patients with spinal metastases. DCE-MRI parameters were assessed one hour before and after HD IGRT, and the results were compared. DCE-MRI parameters from 1 hour after HD IGRT were also compared to parameters at the first follow-up. The Ktrans parameter decreased at 1 hour after HD IGRT (median pre-therapy Ktrans of 4.84; median post-therapy Ktrans of 2.3; $p = 0.06$). There were no significant changes in the Ktrans parameter ($p = 0.1$) when comparing the first and subsequent follow-ups (range, 51 to 504 days), which was consistent with the evidence of no tumor growth found in imaging. In conventional MRI, all six tumors showed no local recurrence after up to 839 days of follow-up.

Chen et al. [25] reported similar findings. The responder group had a decrease in Ktrans parameters (-32.6%; range, -76% to -83.3%), whereas the non-responder group had an increase (Ktrans of 20.4%; range, -64.8% to 338%) in three months following RT. Statistically significant changes in Ktrans were noted ($p = 0.001$). Vellayappan et al. [27] assessed Ktrans levels at baseline, week 1, and week 12 following SBRT. Although not statistically significant ($p > 0.05$), the mean and median values of Ktrans after SBRT were subsequently reduced (mean baseline values of 12.08 and 3.65 [range, 0.03 to 62.49]; at week 1 of 3.10 and 2.66 [range, 0.01 to 10.55]; at week 12 of 1.30 and 0.92 [range 0.001 to 4.60], respectively). The study did not report a comparison of DCE-MRI parameters between responders and non-responders group since only one patient experienced local recurrence at 54 months of follow-up.

Chu et al. [22] investigated the use of DCE-MRI in predicting the response to therapy after RT. However, they did not specify the type of RT administered to patients (conventional or fractional RT or SBRT). The baseline evaluation time for DCE-MRI parameter values was 2–115 days, and the post-RT evaluation time was 10–187 days. There was no significant difference in Ktrans parameters before and after RT ($p = 0.48$).

Lee et al. [28] assessed changes in DCE-MRI parameters and their prognostic value after EBRT. The median time interval between the first DCE-MRI evaluation and the last RT was 30 days (range, 23 to 34 days). They found a decrease in Ktrans by -16.16% ± 45.60% (pre-RT of 135.38 [range, 43.51 to 346.0]; first post-RT DCE-MRI of 100.08 [range, 38.62 to 257.49]). However, the changes were not statistically significant. The median follow-up time was

6 months (range, 3 to 7 months). They found no significant differences in Ktrans (responders of 152.20 [range, 107.47 to 228.01]; non-responders of 96.94 [range, 43.51 to 346.04]) and ΔKtrans% between the PD and non-PD group (responders of -11.31 [range, -75.51 to 75.54]; non-responders of -30.74 [range, -72.97 to 31.48]), respectively.

2) Vp

A total of five studies evaluated changes in Vp parameters after RT [22–24,26,27]. Spratt et al. [26] reported that after SBRT, 92% of the 11 lesions in nine patients with spinal sarcoma showed a significant decrease in the mean Vp value by 58.7% and in the Vp maximum value by 63.2%. One lesion showed an increase in the mean and maximum Vp, but there was no local failure or progression of the lesion.

Chu et al. [22] found that the parameter Vp best predicts therapy response. There was a significant difference in Vp values after RT between tumor responders and non-responders ($p = 0.01$). Vp decreased by -65.66% (range, -21.31% to -99.26%) in 17 tumors that showed successful therapy, while Vp increased in two cases that did not (Vp of 145.27% and 206.79%). Kumar et al. [24] obtained comparable results. Tumor responders and non-responders showed a statistically significant difference in Vp values (-76% vs. +30%, $p = 0.01$).

Lis et al. [23] found a rapid and significant decrease by up to 65.2% in the Vp parameter 1 hour after HD IGRT (median Vp pre-SBRT of 15.14; median post-SBRT of 3.94). The perfusion parameters decreased at the subsequent follow-up, although the Vp reduction was not as dramatic as at 1 hour after SBRT. At 51–504 days, all patients had no tumor recurrence. Vellayappan et al. [27] reported no statistically significant change ($p > 0.05$) between mean and median Vp levels at baseline, 1 week after SBRT, and 12 weeks after SBRT (11.04 and 4.03 [range, 0.29 to 43.46]; 18.88 and 5.92 [range, 0.06 to 22.44]; 6.01 and 5.86 [range, 0.65 to 13.51], respectively). Lee et al. [28] reported that Vp changed by -49.74% ± 191.81% 1 month following EBRT (at baseline of 4.93 [range, 0.38 to 24.52]; 1 month of 2.86 [range, 0.21 to 33.35]). However, in a median follow-up time of 6 months, they found no significant differences in Vp between responders and non-responders (4.93 [range, 0.38 to 8.46] vs. 5.53 [range, 2.38 to 24.52]). Assessment of ΔVp% also showed similar results with no significant differences: -11.51 (ragne, -97.55 to 520.64) vs. -38.44 (range, -83.39 to 64.20) [28].

3) Ve

Chen et al. [25] found significant differences in Ve and ΔVe between responders and non-responders (0.22 [range, 0.08 to 0.44] vs. 0.17 [range, 0.10 to 0.27]; 27.8% [range, -31.6% to 282.2%] vs. -13.5% [range, -38.5% to 220.9%]). Vellayappan et al. [27] reported no statistically significant change between the mean and median Ve at baseline, 1 week after SBRT, and 12 weeks after SBRT (11.04 and 4.03 [range, 0.29 to 43.46]; 18.88 and 5.92 [range, 0.65 to 13.51]; 6.01 and 5.86 [range, 0.65 to 13.51], respectively). Lee at al. [28] reported significant increases of Ve by +161.9% ± 198.5% 1 month following RT (pre 161.54 [range, 128.38 to 410.13] vs. post 273.99 [range, 181.39 to 1,216.95]). Similar to Vp and Ktrans, in a median follow-up time of 6 months, Ve did not demonstrate significant increases between responders and non-responders group (195.00 [range, 135.30 to 368.89] vs. 148.30 [range, 128.38 to 410.13]), respectively. Assessment of ΔVe% yielded similar results (122.14 [range, 5.17 to 440.48] vs. 57.46 [range, -39.27 to 410.41]).

4) Other parameters

Chen et al. [25] reported that responders had considerably lower post-therapy Kep than non-responders ($p = 0.024$ and $p = 0.001$; -41.1% [range, -86.2% to 38.3%] vs. -6% [range, -42.8 to 68.4%]). Lee et al. [28] evaluated the changes in Kep 1 month following RT, which showed a significant decrease by -54.70% ± 32.21%. At a median follow-up of 6 months, there was no significant difference in Kep values between responders and non-responders (836.33 [628.82 to 1,082.32] vs. 741.29 [301.41 to 956.28], respectively). ΔKep values also did not show significant differences (-50.11 [range, -97.54 to -7.29] vs. -63.20 [range, -64.85 to -41.27]). Other metrics that can be determined from the SI curve include peak enhancement (PE) and area under the curve (AUC). According to Chu et al. [22], there was a substantial difference between the PE and AUC groups and between treatment failures and successes.

5. DCE-MRI parameters as an early predictor of tumor recurrence compared to conventional MRI

Kumar et al. [24] studied the difference in time to recurrence detection between conventional MRI and DCE-MRI. DCE-MRI detected local recurrences up to 18 months earlier than conventional MRI in five cases of recurrence (mean ± standard deviation, 6.6 ± 6.8 months) [24]. Chu et al. [22] demonstrated that the Vp parameter could detect a positive response to therapy within 10 days after treatment, which was significantly earlier than conventional MRI. DCE-MRI changes following RT could predict tumor response in less than 6 months, which is almost half the time required by conventional MRI to determine the outcome of therapy or tumor stability.

6. Diagnostic properties of DCE-MRI parameter changes in treatment response evaluation

Kumar et al. [24] analyzed the diagnostic properties of DCE-MRI

https://doi.org/10.3857/roj.2023.00290

parameters for detecting the recurrence of tumors. Ktrans and Vp had exceptionally high AUC values of 0.866 and 0.998, respectively. With a cutoff value of -50%, the Ktrans parameter demonstrated a good sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)—80%, 76%, 44%, and 94% respectively. In diagnosing local recurrence of cancers, the Vp parameter changes demonstrated a sensitivity of 100%, specificity of 98%, PPV of 91%, and NPV of 100% with a cutoff value of -20%.

Chen et al. [25] reported that Ktrans, Kep, and Ve metrics had relatively good diagnostic value. Ktrans had an AUC of up to 0.821 with a sensitivity of 83.3%, a specificity of 77.8%, and a cutoff value of 15.2%. Kep had an AUC of 0.818, a cutoff of -23.8%, a sensitivity of 91.7%, and a specificity of 70.4%. Ve was reported to have an AUC of 0.753 with a -11.2% cutoff, 66.7% sensitivity, and 88.9% specificity. Spratt et al. [26] examined a uniform cohort of 12 metastatic sarcoid spinal lesions undergoing SBRT. They reported that combining the perfusion changes of Ktrans and Vp could increase the accuracy up to 100% in predicting local recurrence in comparison to subjective assessments of tumor size and neuroradiological impressions using conventional MRI [26].

Discussion and Conclusion

Early detection of tumor response by noninvasive approaches is crucial, particularly in cases of spinal metastases, with which a delay in management may result in serious complications such as paralysis [26]. This systematic review highlights the current evidence regarding changes in DCE-MRI parameters as an early indicator of spinal metastatic tumor response following RT. The current evidence suggests that considerable changes in DCE-MRI parameters occur immediately after RT. These initial tumor changes are associated with the tumor response to therapy, as demonstrated by long-term clinical and imaging follow-up.

Compared to standard MRI techniques, DCE-MRI can yield helpful information regarding vascularity, tumor microenvironment, and tumor hemodynamics [23]. A quantitative evaluation of vascular characteristics can be derived using pharmacokinetic models of contrast uptake and measurements of signal intensity changes over time [23,29]. DCE-MRI metrics can detect changes in blood flow in lesions before and after therapy and signify a curative impact depending on the magnitude of changes in parameters before and after therapy. Ktrans, Vp, and Ve are the most typically evaluated parameters [25], with Ktrans representing contrast-agent transfer from the extravascular extracellular space (EES) to the vascular space, Vp reflecting intravascular volume, and Ve representing EES volume [30].

Ktrans can be used to determine the transfer rate of contrast agents from blood plasma to the extravascular-extracellular region, which is valuable for monitoring tumor response [31]. Unlike normal blood vessels, tumor blood vessels display elevated Ktrans and Kep values due to their elevated permeability and perfusion [32]. In most studies, there was a substantial difference between the post-radiation Ktrans values of responders and non-responders. Even though not all research achieved statistical significance, they all demonstrated the same tendency. Lower Ktrans levels and a substantial decrease in Ktrans were linked with treatment success [23-26].

The calculated intravascular volume is represented by Vp, and reductions in Vp values following RT suggest a decline in vascularity in lesions that respond favorably to therapy, whereas an increase in Vp values is observed in cases of treatment failure [22]. Ve is the EES volume per unit of tissue volume [30], and in contrast to Ktrans and Vp, which show an increase in the responder group, the included studies generally revealed a rise in Ve values in the responder group and a decrease in Ve values in the non-responder group [25].

Radiation can trigger the breakdown of tumor vascularization, thrombosis, fibrosis, and medial necrosis, which might disrupt the intratumor microenvironment and indirectly result in the death of tumor cells [33,34]. Decreased Vp and Ktrans values and increased Ve values in cases of successful treatment may be associated with the destruction of tumor vascularization [26], and reduced angiogenic activity due to large areas of post-RT fibrosis [35]. In the responder group, radiation damages the blood arteries of the tumor tissue, leading to a reduction in intravascular space volume and an increase in EES. This could account for the rise in Ve [30].

This systematic review reveals that patients with treatment failure generally exhibit a rise in Vp and Ktrans levels. The rise in perfusion parameters in cases of treatment failure could be related to the ability of viable and progressing tumors to emit angiogenesis-inducing substances such as vascular endothelial growth factor, which provide the essential vascularity for tumor growth [36]. Radiation-resistant cancers sustain less damage to the structure and function of tumor vascularization than radiation-sensitive tumors [25], which leads to fewer perfusion parameter changes among non-responders.

It is essential to decide the point at which DCE-MRI can be performed to provide the most accurate RT response and recurrence prediction. Lis et al. [23] reported the earliest time of post-treatment scans. Changes after RT could be detected as early as 1 hour after RT, showing a significant reduction in Vp values of up to 65.2% after RT. Ktrans also decreased, but not as drastically as Vp. Subsequent follow-up scans showed a continued decrease in perfusion (51–839 days after), but the decline in Vp was far less in subsequent follow-up studies. These significant changes in DCE-MRI parameters within 1 hour were reported to reflect treatment success in long-term follow-ups in the six patients.

Chu et al. [22] reported a positive treatment response of ΔVp values that could be detected within 10 days, which is much earlier than the report of stable disease with conventional imaging. Data on perfusion changes for other cases were obtained within 31–187 days after RT. Spratt et al. [26] found that changes in DCE-MRI values within 2 months post-SBRT could predict treatment success. Kumar et al. [24] reported that the earliest recurrence could be detected within 1 month in a group of patients with local recurrences. It may be possible to predict local recurrence at this early time interval and perhaps even earlier.

Kumar et al. [24] also compared the time interval between the first detection of tumor recurrences by Vp versus standard imaging. Vp could predict local recurrences up to 18 months earlier than standard MRI. Interestingly, they compared the time after RT to the percentage change in Vp, which showed no correlation in the local control group, but there was a trend toward a significantly positive correlation in the local recurrence group. This hinted at a plausible link between time and an increase in perfusion parameters for tumors that locally recur, which would be expected as tumors continue to grow over time.

Vellayappan et al. [27] reported that changes in Ktrans, PS, Vp, and Ve parameters could be detected in 1 week at the earliest, but they demonstrated changes in parameters that were more continuous and sustainable within 12 weeks. Similar to that report, Chen et al. [25] found that changes in parameters can be detected within 3 months with significant differences in ΔKtrans, ΔKep, and ΔVe between the groups of responders and non-responders. Lee et al. [28] reported that changes in DCE-MRI parameters could be detected in one month after the completion of RT. However, in a median follow-up time of 6 months, these parameters did not show distinctions between responders and non-responders, which could have been due to the method of region-of-interest placement.

Based on this data synthesis, we hypothesize that post-RT changes can be detected within 1 hour after RT at the earliest, but they could show changes that are more continuous and sustained in the following weeks. Nevertheless, these data show that changes in perfusion parameters could be used to predict treatment success or failure earlier than 6 months after RT, which is nearly half the follow-up time required to determine successful treatment of a stable tumor using conventional MRI. This demonstrates that functional changes occur significantly earlier than structural alterations.

In clinical practice, early detection of response to therapy has numerous advantages. Patients with a poor response who are identified early might receive therapeutic adjustments immediately, thus optimizing their clinical outcome. Alternatively, rapid early recognition of a favorable response to therapy can lessen the stress and costs suffered by patients whose therapy is successful [22]. Several studies have reported the diagnostic accuracy of DCE-MRI parameters in predicting local tumor response, which all demonstrate a strong diagnostic value with an AUC value of around 0.753–0.998, a sensitivity of 80%–100%, and a specificity of 70%–98% [22,24-26]. Although both Vp and Ktrans were shown to have good diagnostic value in predicting response to therapy, Kumar et al. [24] demonstrated that Vp was more accurate than Ktrans.

It is worth noting that there could be distinctions in how different RT methods could influence response evaluation using DCE-MRI. As we know, the limitation of EBRT has led to the development of more advanced and precise RT techniques [37,38]. Recently, emerging evidence has strongly implied a different mechanism of SBRT and SRS in the process of killing tumor cells, compared to the conventionally fractionated RT. SBRT and SRS not only directly kill tumor cells, but also destroy the tumor vascular beds, leading to a deteriorated intratumor microenvironment and subsequently indirect tumor cell death [37]. This theory is backed by considerable preclinical data [37,39,40]. A novel vascular-mediated cell-killing method via the ceramide pathway is associated with the mechanism of action of SBRT and SRS in killing tumor cells [38]. A radiation dose more than 8 Gy per fraction can trigger secretory ASMase translocation from the cytosol to the glycosphingolipid contained in the outer leaflet of the plasma membrane. In turn, this can hydrolyze sphingomyelin into ceramide, which is a pro-apoptotic second messenger molecule. Endothelial cells contain a large amount of secretory ASMase (nearly 20 times more than any other cell in the body), so they are more susceptible and sensitive to ceramide-mediated and radiation-induced apoptosis [39,40]. Consequently, in tumor response evaluation to RT, it is not farfetched to conclude that DCE-MRI evaluation using perfusion metrics can be more biologically relevant when judging treatment response to SBRT in comparison to conventionally fractionated RT.

This systematic review has several drawbacks. Only a small number of studies are included in systematic reviews, and this one included only six papers with small sample sizes. The subjects included in the study generally had heterogeneous primary tumors and were treated with various RT techniques and radiation doses, which could influence the outcomes of DCE-MRI parameter measurements. In addition, we could not avoid the heterogeneity of tumor histology and inconsistent follow-up MRI examinations. There are also some technical considerations in interpreting the study results, which could also be potential factors for the different study results, such as scanners, software, or operator-dependent variabilities, which are known constraints in DCE-MRI application. In addition, to achieve a correct quantitative analysis using DCE-MRI, pre-contrast T1 and AIF must be evaluated accurately. This must be acknowledged when interpreting these studies. In DCE-MRI parame-

 https://doi.org/10.3857/roj.2023.00290

ter acquisition, high temporal resolution, coverage, and signal-to-noise ratio frequently result in insufficient temporal resolution for accurately calculating AIF. Due to low temporal resolution, a low sample rate can impact the AIF time and the early wash-in process of the contrast agent [22,23].

Nonetheless, this systematic review also has several strengths. This is the first systematic review to synthesize the current evidence regarding DCE-MRI parameters for evaluating the tumor response in patients with spinal metastases after RT. Despite the study's limited capability, the results are noteworthy because they show the potential of DCE-MRI characteristics as early non-invasive markers of response to treatment, which are useful much earlier than the current standard evaluation method using conventional MRI.

In conclusion, despite the diversity of available studies, this systematic review highlighted that most DCE-MRI studies indicate a role for changes in DCE-MRI parameters as biomarkers of early tumor response following RT in patients with spinal metastases. Responders show lower values and higher reduction of Ktrans and Vp after therapy, demonstrating that these values are good predictors of local control. Long-term prospective studies with larger study samples, more homogeneous primary tumors, and more uniform DCE techniques are still needed to provide further evidence of DCE-MRI's significance as a predictor of post-RT spinal metastatic tumor response.

Statement of Ethics

As this study did not involve any human subjects, Institutional Review Board approval and informed consent were not required.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Author Contributions

Conceptualization, Mulyadi R. Investigation and methodology, Mulyadi R, Putri PP, Handoko, Zairinal RA, Prihartono J. Writing of the original draft, Mulyadi R, Putri PP, Handoko, Zairinal RA, Prihartono J. Writing of the review and editing, Mulyadi R, Putri PP, Handoko, Zairinal RA, Prihartono J.

Data Availability Statement

Data availability statements provide a statement about where data supporting the results reported in a published article can be found.

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ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2023;41(4):237-247
https://doi.org/10.3857/roj.2023.00339

Radiotherapy dose de-escalation in patients with high grade non-Hodgkin lymphoma in a real-world clinical practice

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Received: May 15, 2023
Revised: July 24, 2023
Accepted: August 8, 2023

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Purpose: The standard treatment of non-Hodgkin lymphoma (NHL) comprises combined modality treatment, radiotherapy (RT), and chemotherapy with rituximab which has significantly improved both disease-free survival (DFS) and overall survival (OS). However, there is no uniformity in radiation dose usage in these patients. In this retrospective study, we compared lower radiation dose with higher in patients with aggressive NHL.

Materials and Methods: From 2007 to 2017, treatment records of all high-grade NHL or diffuse large B-cell lymphoma and non-central nervous system NHL were included. We compared response rates, OS and DFS of patients who received ≤30 Gy RT to those with >30 Gy. Univariate and multivariate analyses were done to determine factors affecting prognosis, i.e., age, sex, stage, International Prognostic Index (IPI), adding rituximab, and radiation dose.

Results: A total of 184 NHL patients treated with combined modality or radiation alone having complete follow-up details were analyzed. At median follow-up of 66.8 months, 5-year OS was 72.8% in high-dose group versus 69.9% in low-dose group ($p = 0.772$) and 5-year DFS 64.7% versus 64.1% ($p = 0.871$). Patients having early-stage disease receiving low dose and those with advanced disease treated with >30 Gy had better OS and DFS though not statistically significant. Adding rituximab was associated with significantly better OS and DFS irrespective of radiation dose delivered. High IPI score and omitting rituximab were the only factors that significantly worsened both OS and DFS. Acute radiation toxicities were comparable in both groups ($p = 0.82$). Among late toxicities, no patient developed a second malignancy and 5% died due to cardiovascular complications ($p = 0.595$) though only two patients (1.1%) had received thoracic radiation.

Conclusion: The two groups had comparable response rates, acute toxicities, DFS and OS. This study suggests that RT dose reduction may be possible in high-grade NHL without compromising the DFS and OS.

Keywords: Non-Hodgkin lymphoma, Radiotherapy, Late effects, Radiation dose de-escalation

Introduction

Non-Hodgkin lymphoma (NHL) is the 12th most common cancer in the world as per GLOBOCAN 2020 statistics, accounting for 2.8% of all newly diagnosed cancer cases and 2.6% of cancer related deaths [1]. The standard treatment comprises of chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) along with rituximab, anti CD20 antibody. The addition of rituximab has shown improvement in disease-free survival (DFS) and overall survival (OS) in NHL patients [2]. Involved-field radiotherapy (IFRT) is considered for bulky disease and in patients with partial response. Randomized trials by Aviles et al. [3,4] have shown

significantly better DFS and OS with combined modality treatment in patients having bulky disease with complete response post chemotherapy and in those with residual disease (< 5 cm). Even in the rituximab era, same results were also seen in a retrospective analysis from MD Anderson Cancer Center where addition of radiotherapy (RT) significantly improved OS and DFS in both limited and advanced stage disease with no local relapse within the irradiated field [5]. However, there is no uniformity in the radiation dose, with doses ranging from 30–55 Gy.

NHLs are considered to be radiosensitive tumors requiring much lesser radiation dose as compared to epithelial malignancies. In aggressive NHL, no dose response was seen across 20-50 Gy in an analysis from Stanford University [6]. However, in early-stage NHL, dose dependent response was observed in an analysis from the British National Lymphoma Investigation, with compete response noted at ≥ 45 Gy [7]. Similarly, the European Organisation for. Research and Treatment of Cancer data showed that risk of local relapse is almost doubled in patients receiving < 45 Gy radiation [8]. But, most of these patients did not receive chemotherapy. Hence, in this era of combined modality treatment, the RT dose needs to be carefully evaluated specially in patients who received rituximab. Our aim should be to deliver the lowest compatible dose to achieve optimal efficacy.

The 5-year survival in aggressive NHL was reported to be 58% [9]. Due to their long survival, apart from disease control, treatment related toxicities also are a serious matter of concern. Both acute and late radiation toxicities are dose dependent. Acute reactions depend on the total dose delivered whereas late reactions depend on the total dose as well as the dose per fraction. A retrospective analysis on high-grade NHL patients revealed significantly higher rates of stroke and myocardial infarction in patients receiving ≥ 40 Gy [10]. Also, delivering a low RT dose comes with logistic benefits, like fewer patient visits, more treatment slots, etc. However, most of the data available is retrospective in nature. There is only one prospective trial by Lowry et al. [11] which highlights dose reduction in both indolent and aggressive NHL does not worsen disease control. In this retrospective analysis, we wanted to see if radiation dose de-escalation is feasible in aggressive NHL treated in the rituximab era.

Materials and Methods

From 2007 to 2017, available treatment records of all NHL patients were scrutinised. Of them, only patients with high-grade NHL or diffuse large B-cell lymphoma and those with non-central nervous system primaries were included in the analysis. Written consent was obtained from all the patients. A complete history including comorbidities was noted along with clinical examination. Baseline investigations such as complete blood count, renal and liver function test, lactate dehydrogenase, and histopathology were recorded. All patients underwent computed tomography (CT) of neck, chest, abdomen, and pelvis along with bone marrow biopsy for staging or positron emission tomography (PET)-CT whenever feasible. All of them underwent IFRT with or without chemotherapy. The International Prognostic Index (IPI) was calculated according to the description by the International Non-Hodgkin's Prognostic Factors Project for patients with all required parameters present and staging as per Ann Arbor classification.

We compared outcome of patients who received ≤ 30 Gy RT dose (low dose) to those with > 30 Gy (high dose). Outcomes compared were response rate, DFS, and OS. The response to treatment was defined as per international workshop criteria [12]. Complete response (CR) was defined as "disappearance of all detectable clinical and radiographic evidence of disease."

Partial response (PR) was defined as "a ≥ 50% reduction in all measurable tumors." Progressive disease (PD) was defined as "≥ 50% increase in the size of previously involved sites or appearance of new lesions despite treatment." Stable disease (SD) was defined as a response lesser than PR, but not fulfilling the PD criteria.

Toxicities were assessed using the Radiation Therapy Oncology Group grading scale. Acute toxicities were those which occurred within 3 months and late toxicities were those which occurred after 3 months of treatment completion. Acute toxicity was assessed at 1 month of treatment completion. Late toxicities were reported as cumulative events till last follow-up.

Baseline patient and disease characteristics were compared between two groups using chi-square test. OS was calculated from the date of diagnosis till death (due to any cause) or last follow-up and DFS till recurrence, death or last follow-up. DFS and OS were estimated using Kaplan-Meier method with log-rank test. Univariate and multivariate analyses were done to determine the factors affecting disease outcomes, i.e., age, sex stage, IPI, addition of rituximab, and radiation doses delivered. A p-value of < 0.05 was considered statistically significant.

Results

A total of 298 patients with stage I to IV NHL treated with combined modality or radiation alone were analysed. Of them, 98 patients had low-grade NHL, 16 were lost to follow-up. The records of 184 patients were analysed (Table 1). There was no significant difference in the baseline characteristics between the high and low dose groups. The median age of the study population was 50 years

https://doi.org/10.3857/roj.2023.00339

Table 1. Patient characteristics (n = 184)

	RT dose		p-value (χ^2)
	> 30 Gy (n = 114)	≤ 30 Gy (n = 70)	
Age (yr)			0.058
≤ 50	62 (54.4)	31 (44.3)	
> 50	52 (45.6)	39 (55.7)	
Median age (range)	50 (15–90)	53.5 (15–87)	0.980
Sex			0.194
Female	38 (33.3)	30 (42.9)	
Male	78 (68.4)	40 (57.1)	
ECOG performance status			0.853
0	26 (22.8)	13 (18.6)	
1	70 (61.4)	44 (62.9)	
2	15 (13.2)	10 (14.3)	
3	3 (2.6)	3 (4.3)	
Stage			0.504
I	36 (31.6)	25 (35.7)	
II	46 (40.4)	24 (34.3)	
III	12 (10.5)	8 (11.4)	
IV	20 (17.5)	13 (18.6)	
IPI score			0.967
0–1	60 (52.6)	32 (45.7)	
2–3	47 (41.2)	31 (44.3)	
4–5	7 (6.2)	7 (10)	
B symptoms			0.504
No	75 (65.8)	46 (65.7)	
Yes	39 (34.2)	24 (34.3)	
Histology			0.897
DLBCL	62 (54.4)	38 (54.3)	
High grade NHL	52 (45.6)	32 (45.7)	
Nodal involvement			0.365
Nil	31 (27.2)	12 (17.1)	
< 4	63 (55.3)	43 (61.4)	
≥ 4	20 (17.5)	15 (21.5)	
Chemotherapy			0.437
CHOP	56 (49.1)	28 (40)	
R-CHOP	42 (36.8)	34 (48.6)	
COP	7 (6.2)	2 (2.9)	
Others	3 (2.6)	1 (1.4)	
Nil	6 (5.3)	5 (7.1)	

Values are presented as number (%).
RT, radiotherapy; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CHOP, rituximab and CHOP; COP, cyclophosphamide, vincristine, and prednisone.

Table 2. Response rates between the two treatment groups

	RT dose		p-value
	> 30 Gy (n = 114)	≤ 30 Gy (n = 70)	
Initial response rate			0.265
CR	65 (57.0)	48 (68.6)	
PR	13 (11.4)	3 (4.2)	
SD	1 (0.9)	1 (1.4)	
PD	35 (30.7)	18 (25.7)	
Overall response rate			0.298
CR	68 (59.6)	48 (68.6)	
PR	16 (14.1)	6 (8.6)	
SD	0 (0)	1 (1.4)	
PD	30 (26.3)	15 (21.4)	

Values are presented as number (%).
RT, radiotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

(range, 15 to 90 years). The median dose received by patients in low-dose group was 30 Gy (range, 24 to 30 Gy) and high-dose group was 36 Gy (range, 36 to 40 Gy). There was no significant difference in the doses received by patients, either in early or advanced stage. The commonly used dose regimens were 24 Gy in 12 fractions, 30 Gy in 15 fractions, 36 Gy in 18 fractions, and 40 Gy in 20 fractions, irrespective of the disease stage. No significant correlation was observed between disease stage and the prescribed dose (p = 0.63). More than half of them (51.6%) had primary disease in head and neck subsite. Of them, 173 patients (94%) received RT as, or as part of, first-line therapy, with the remaining 6% for relapsed disease. A total of 131 patients (71.2%) had early-stage disease. Of patients having advanced disease receiving RT, 36 (67.9%) had bulky disease, 37 (69.8%) had extra lymphatic involvement, while 28 (52.8%) had PR, 7 (13.2%) SD, and 4 (7.5%) PD.

The median follow-up was 66.8 months (range, 2.8 to 228 months). The response rates after first line treatment-RT ± chemotherapy (initial response) as well as the overall response rates (response at last follow-up) are described in Table 2. There was no statistically significant difference in response rates between the two groups. At the time of analysis, 125 patients (67.9%) were alive. A total of 44 (24%) of the patients expired due to the primary disease itself, 10 (5.4%) owing to cardiovascular disease and rest 5 (2.7%) deaths were related to toxicity of chemotherapy. Of the 10 cardiovascular deaths, seven patients received adriamycin as a part of their combination chemotherapy regimen (5 CHOP and 2 R-CHOP).

The 5-year OS was 72.8% in high-dose group versus 69.9% in low-dose group and 7-year OS was 66.7% versus 65.5%, respectively (p = 0.772). The median OS of the entire study population was not reached. The overall median DFS was 158.99 months (Fig. 1). The DFS rates at 5-year were 64.7% in high-dose group versus 64.1% in low-dose group and at 7-year, it was 62.2% versus 64.1% (p = 0.871). Younger patients had better OS compared to those above 50 years irrespective of the dose delivered. The 5-year OS in the young patients was 75.8% (high dose) versus 74.2% (low dose), while in the elderly group it was 69.2% versus 66.6%. Similar, results were also noted when DFS was compared between these

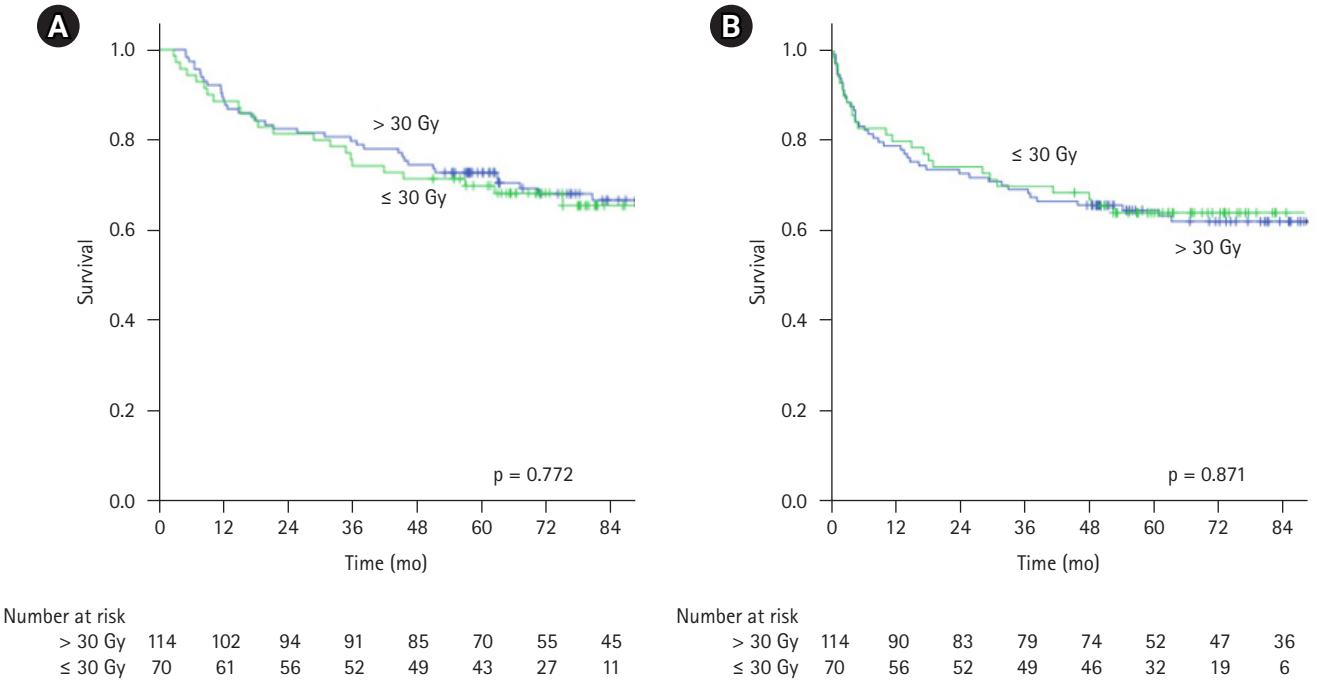

Fig. 1. (A) Overall survival and (B) disease-free survival among the two study groups.

two groups (5-year DFS: 66.1% vs. 70.8% in age ≤ 50 years, 63% vs. 58.9% in elderly; p = 0.836). Female patients receiving low dose showed better OS and DFS though not statistically significant. Patients having early-stage disease receiving low dose and those with advanced disease treated with high-dose radiation had better OS and DFS though it did not reach statistical significance (5-year OS: 65.6% vs. 42.9% in advanced stage, 75.6% vs. 81.5% in early-stage, p = 0.747; 5-year DFS: 53.1% vs. 38.1% in advanced stage, 69.3% vs. 75.3% in early-stage, p = 0.912) (Fig. 2).

Addition of rituximab was associated with significantly better OS and DFS. The 7-year OS and DFS of those receiving rituximab were 80.6% and 77.8% as compared to those without rituximab, 57.6% and 52.3% (overall, p = 0.003 and p = 0.001, respectively). This benefit of adding rituximab was evident irrespective of the radiation dose delivered (Fig. 3). Better OS and DFS were also noted with lower IPI score although no correlation was observed with radiation doses received.

In low-risk patients (IPI 0 and 1), the 5-year OS was comparable (90% vs. 90.3%), but 5-year DFS was slightly lower in the high-dose group (83.3% vs. 90.3%) (Fig. 4). In patients with IPI scores of 2 and 3, survival was slightly better in low dose group (Fig. 5), 5-year OS 59.6% versus 64.5% (p = 0.931), 5-year DFS 48.1% versus 51.6% (p = 0.57). The median OS of patients having IPI score 3, 4, and 5 was 44.6 months, 10.2 months, and 8.4 months, respectively (p = 0.001). Patients having high IPI scores (4 and 5), high RT dose had better OS and DFS (5-year OS: 14.3% vs. 0%; 5-year DFS: 14.3% vs. 0%) (Fig. 6). Patients with CR had significant better survival than those with non-CR irrespective of the dose group (Fig. 7).

Using Cox regression proportional hazards model to identify the prognostic factors affecting OS and DFS, it was observed that early-stage disease, IPI score, and addition of rituximab were the only significant factors, on univariate analysis but stage did not assume statistical significance in multivariate analysis (Table 3). No significant effect on survival or disease control was observed with reduced RT doses.

Acute radiation induced toxicities showed no statistical significance irrespective of the dose received (p = 0.82). Since about half of the patients received RT to the head and neck region, the most common acute toxicities in both groups, was oropharyngeal mucositis, 19 (16.7%) in high dose versus 9 (12.9%) in low dose, followed by dysphagia 16 (14%) versus 10 (14.3%) and dermatitis 9 (8%) versus 5 (7.1%), respectively. However, the toxicities noted were grade 1–2 only. Only two patients (1.9%) in high-dose group and one (1.6%) in low-dose group experienced grade 3 toxicity (hematological) that required treatment interruption. Other noted acute toxicities were abdominal pain (5 [4.4%] in high dose vs. 4 [5.7%]), diarrhea (6 [5.3%] vs. 4 [5.7%] in low dose), fatigue (10 [8.8%] vs. 6 [8.6%]), respectively. When late toxicities were compared, one (0.8%) patient developed second malignancy. Five pa-

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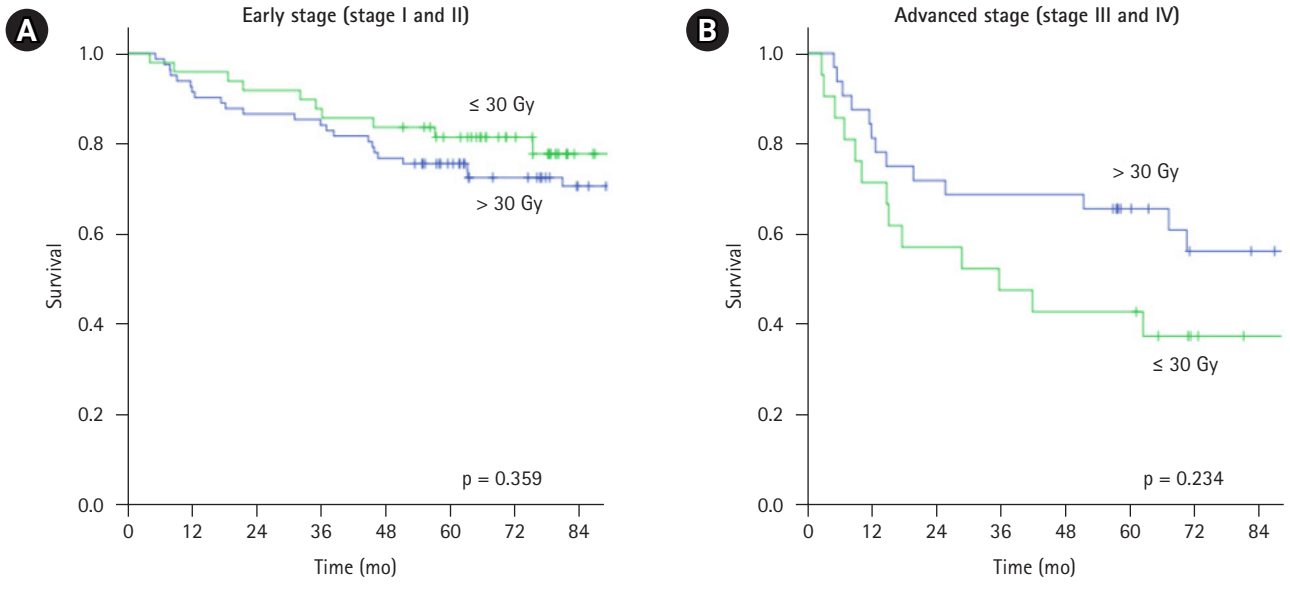


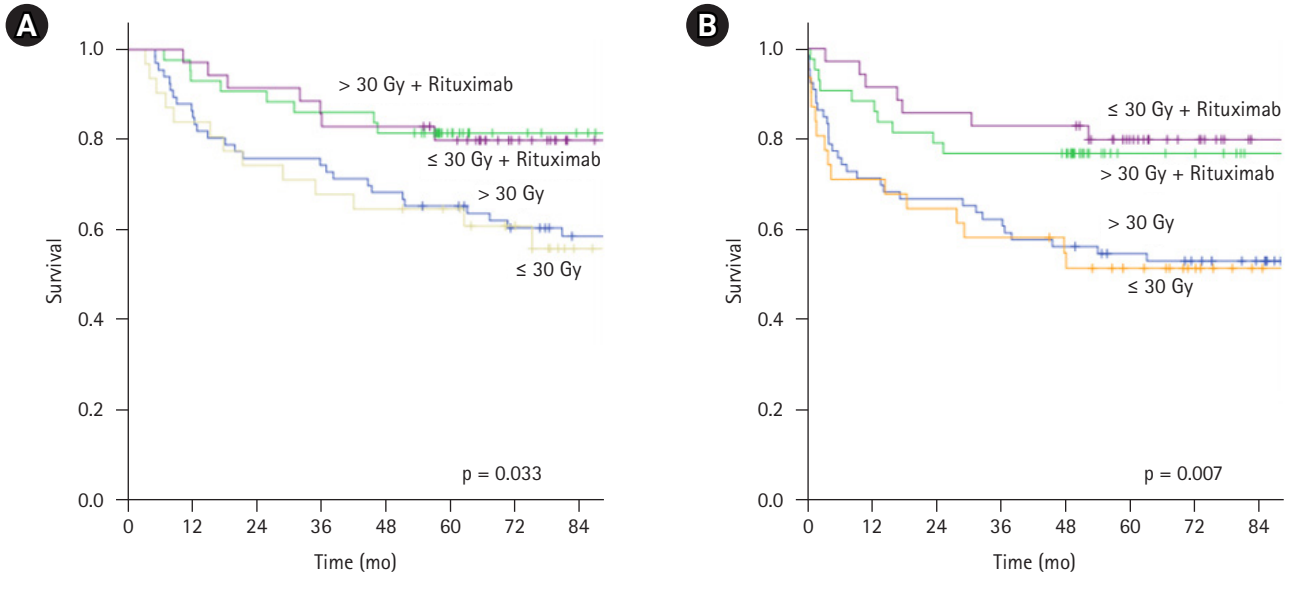
Number at risk

> 30 Gy	82	70	64	60	57	42	38	30
≤ 30 Gy	49	46	43	40	38	26	16	4

Number at risk

> 30 Gy	32	20	19	19	17	10	9	6
≤ 30 Gy	21	10	9	9	8	6	3	3

Fig. 2. Overall survival in (A) early stage and (B) advanced stage patients in two groups.



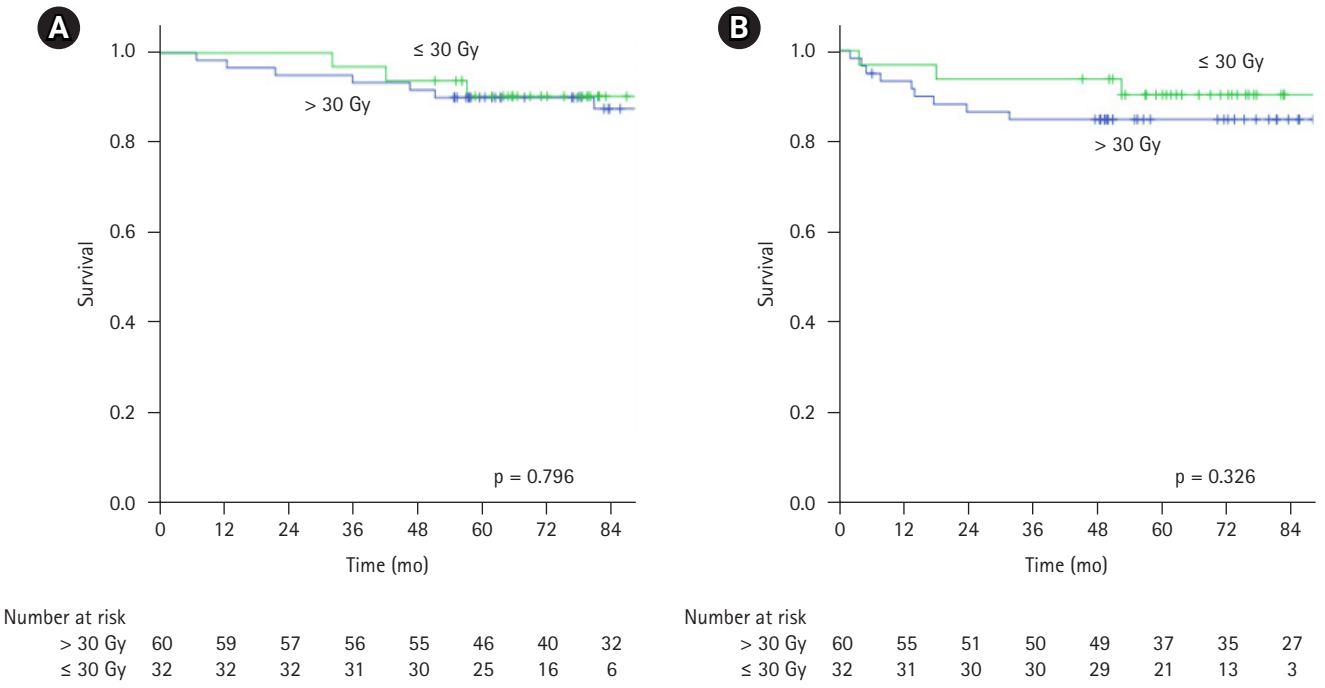
Number at risk

> 30 Gy + R	42	40	39	37	35	23	15	12
> 30 Gy	66	57	50	49	45	42	36	31
≤ 30 Gy + R	35	34	32	29	29	26	15	6
≤ 30 Gy	30	26	23	21	20	18	12	5

Number at risk

> 30 Gy + R	42	38	34	33	32	14	13	8
> 30 Gy	66	47	44	41	37	33	30	26
≤ 30 Gy + R	35	32	30	29	29	20	12	4
≤ 30 Gy	30	22	20	18	16	12	7	2

Fig. 3. Impact of rituximab on (A) overall survival and (B) disease-free survival.



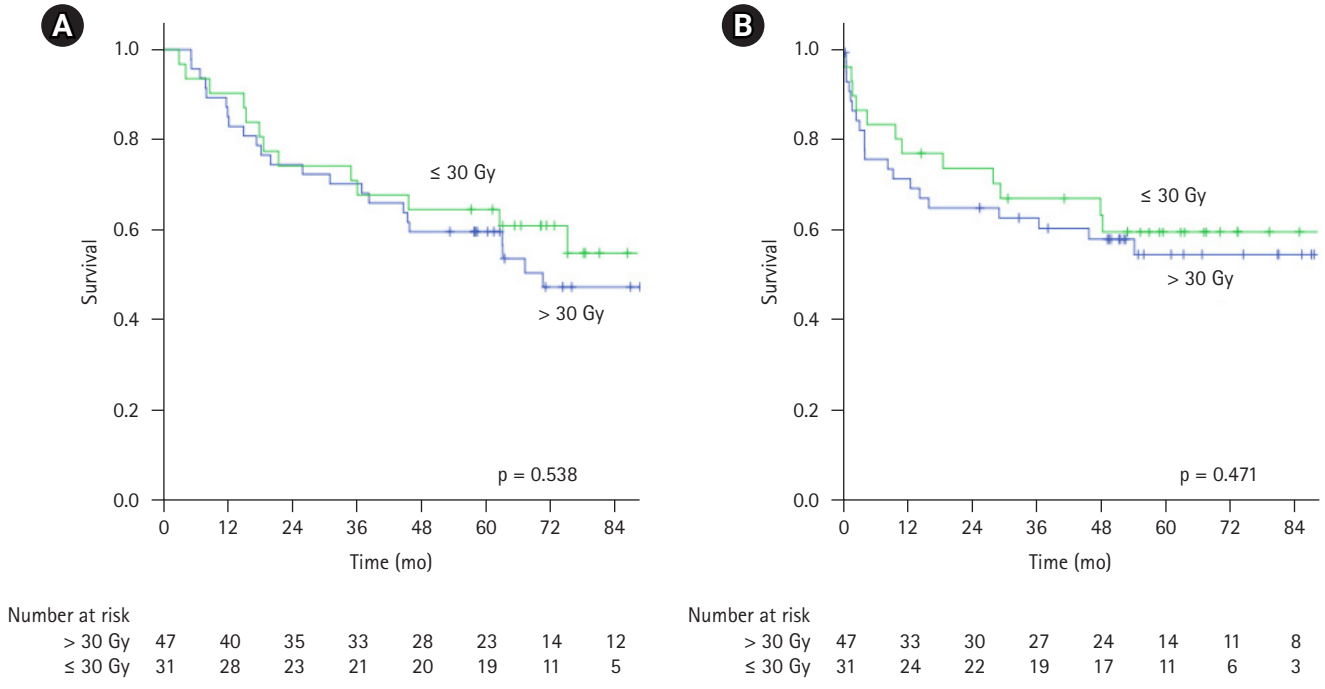
Number at risk

> 30 Gy	60	59	57	56	55	46	40	32
≤ 30 Gy	32	32	32	31	30	25	16	6

Number at risk

> 30 Gy	60	55	51	50	49	37	35	27
≤ 30 Gy	32	31	30	30	29	21	13	3

Fig. 4. (A) Overall survival and (B) disease-free survival of IPI scores 0 and 1 in two groups. IPI, International Prognostic Index.



Number at risk

> 30 Gy	47	40	35	33	28	23	14	12
≤ 30 Gy	31	28	23	21	20	19	11	5

Number at risk

> 30 Gy	47	33	30	27	24	14	11	8
≤ 30 Gy	31	24	22	19	17	11	6	3

Fig. 5. (A) Overall survival and (B) disease-free survival of IPI scores 2 and 3 in two groups. IPI, International Prognostic Index.

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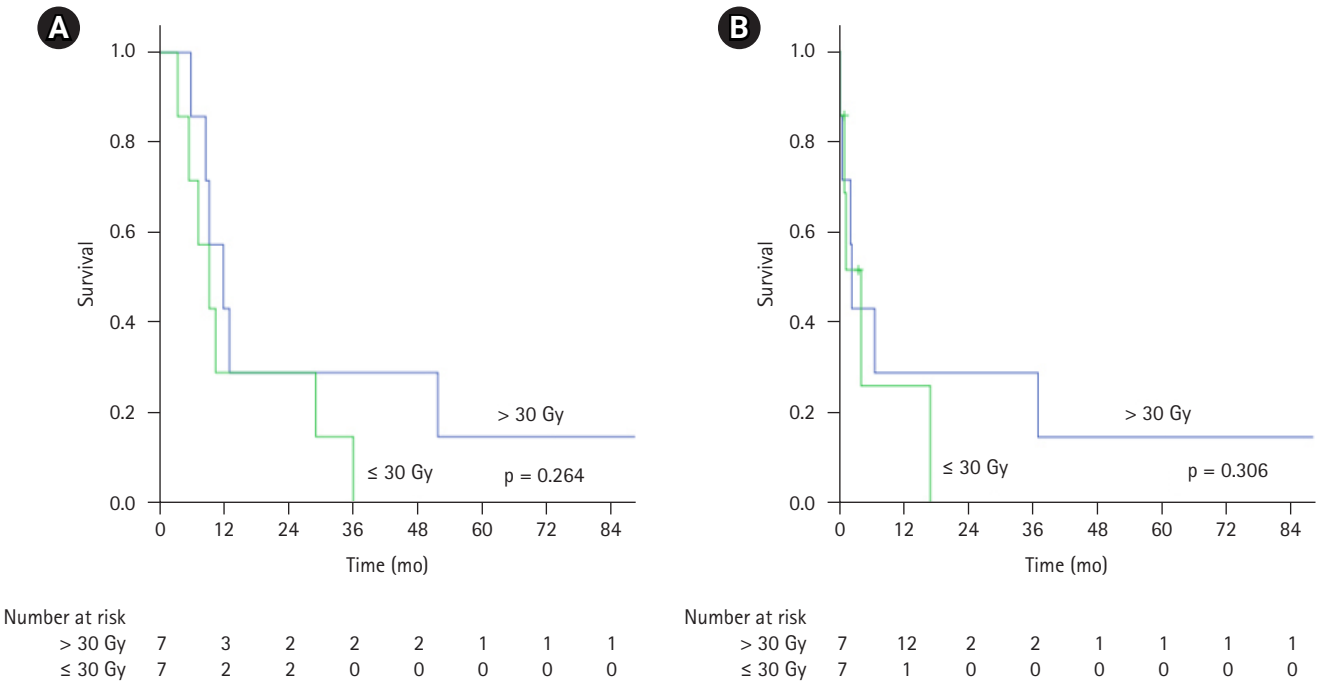

Fig. 6. (A) Overall survival and (B) disease-free survival of IPI scores 4 and 5 in two groups. IPI, International Prognostic Index.

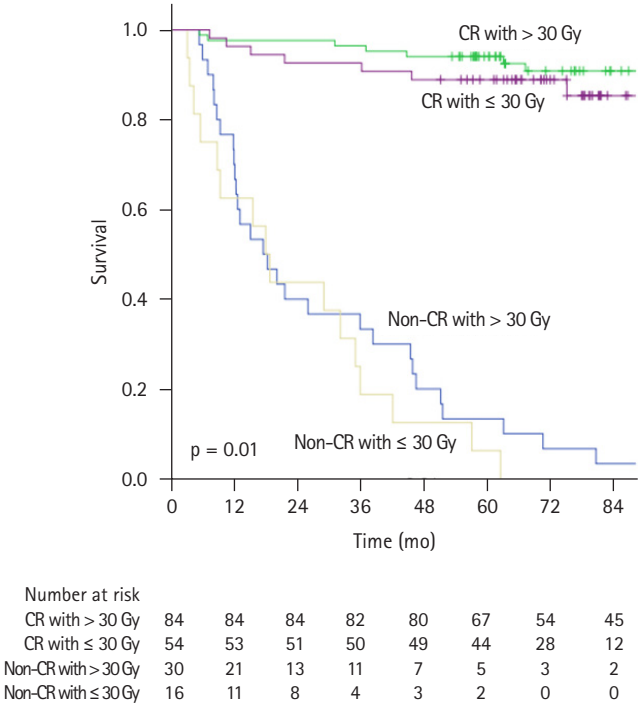

Fig. 7. Impact of treatment response and dose delivered on overall survival. CR, complete response.

tients in each arm died due to cardiovascular complications (4.4% vs 7.1%, p = 0.595). Of them, two (1.7%) in high-dose arm and none in low-dose arm have received RT to mediastinum or cardiac structures. Xerostomia (23 [20.2%] vs. 13 [18.6%]), dry eyes (20 [17.5%] vs. 14 [20%]), and cataract (19 [16.7%] vs. 10 [14.3%]) were the most common late toxicities observed.

Discussion and Conclusion

In this retrospective analysis of 184 patients with high-grade NHL, we observed that delivering RT dose ≤30 Gy does not affect survival as well as local disease control. Disease stage, IPI scores, and inclusion of rituximab in chemotherapy regimen remain the only significant factors which affected both DFS and OS. However, it may be noted that in early-stage disease, low-dose group and in advanced disease, high-dose RT group fared better both in terms of OS and DFS although not statistically significant.

NHL, being a radiosensitive tumor, has a long survival, 10-year OS of 50% [13]. This has led to more emphasis on achieving optimal treatment schedules with minimum acceptable toxicities. With the advent of modern imaging techniques as well as highly conformal RT techniques, the shift from IFRT to involved site radiotherapy and involved node radiotherapy has reduced the irradiated volumes which have led to decreased risk of late toxicities including development of secondary malignancies [14]. Apart from reducing treatment volumes, RT dose de-escalation might also have a potential long-term benefit. In high-grade NHL, the International Lymphoma Radiation Group (ILROG) recommends a dose of 30–36 Gy in PET

Table 3. Prognostic factors affecting OS and DFS

Factor	OS				DFS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age, ≤ 50 yr	0.723 (0.432–1.209)	0.216	0.837 (0.622–1.196)	0.234	0.839 (0.519–1.357)	0.475	1.645 (0.951–2.846)	0.075
Sex, female	0.853 (0.646–1.125)	0.969	0.842 (0.713–1.316)	0.839	0.917 (0.711–1.184)	0.508	1.125 (0.849–1.490)	0.412
Advanced stage	1.573 (1.216–2.035)	0.001	1.135 (0.805–1.602)	0.470	1.658 (1.270–2.164)	0.001	0.989 (0.721–1.357)	0.945
No rituximab	1.539 (1.144–2.072)	0.004	1.446 (1.066–1.962)	0.018	1.606 (1.216–2.122)	0.001	1.539 (1.152–2.055)	0.003
IPI score								
2–3	5.503 (2.727–11.105)	0.001	6.617 (2.995–14.621)	0.001	1.026 (0.738–1.426)	0.881	1.069 (0.752–1.519)	0.709
4–5	26.162 (11.237–60.912)	0.001	37.235 (11.842–117.079)	0.001	4.535 (2.950–6.970)	0.001	5.022 (2.831–8.911)	0.001
RT dose ≤ 30 Gy	0.962 (0.740–1.250)	0.773	0.965 (0.729–1.277)	0.804	1.021 (0.797–1.307)	0.871	1.059 (0.811–1.382)	0.675
Complete response	0.039 (0.021–0.073)	0.001	0.054 (0.026–0.112)	0.001	0.045 (0.025–0.079)	0.001	0.077 (0.040–0.147)	0.001

OS, overall survival; DFS, disease-free survival; IPS, International Prognostic Index; RT, radiotherapy; HR, hazard ratio; CI, confidence interval.

CR while those with PR, 36–50 Gy is recommended for both primary nodal and extra nodal subtypes [15,16]. Similar doses are also recommended by the National Comprehensive Cancer Network 2022 guidelines for consolidative RT after chemotherapy. If primary RT is given without chemoimmunotherapy, 40–55 Gy should be prescribed [17]. In a phase II trial by Kelsey et al. [18], consolidative RT to a dose of 19.5–20 Gy was delivered. At a median follow-up of 51 months, 5-year OS and progression-free survival (PFS) were 83% and 90%, respectively. However, majority (79%) was early-stage disease and only 28% had bulky disease, both of which are important prognostic factors in NHL. The OS and PFS reported is better than observed in our study population which may be due to addition of rituximab with chemotherapy and utilization of PET-CT for precise response assessment. In another prospective trial by Lowry et al. [11], the overall response rate was 90% with no significant difference in OS, PFS or progression within irradiated field with 30 Gy dose. These results are similar to our observation. The study by Lowry et al. [11] had a major drawback, patients received heterogenous chemotherapy regimens, hence it will be difficult to comment upon the efficacy of consolidative RT in such a situation. In addition, the primary end point of this study was local control instead of OS and PFS, which do not represent treatment efficacy. Based on these studies and our experience, in patients with NHL who achieve clinical or radiological CR after chemotherapy, 30 Gy may be an adequate dose.

Long survival of NHL patients makes treatment induced toxicities, both acute and late, a matter of concern. Second malignancy and cardiopulmonary toxicities have been studied extensively which may be contributed by both RT and chemotherapy (adriamycin, alkylating agents, etc.). In a retrospective analysis on the GELA cohort, the 7-year cumulative incidence of second malignancy was 2.75% [19]. Age was the only significant risk factor and chemoradiotherapy had no significant impact. However, only 4% patients received radiation as a part of their first line management while 18% received RT alone or combined with chemotherapy in refractory or relapse settings. In our study, one (0.8%) patient developed second malignancy (sarcoma) in the RT field, although, he had received combined treatment. Around 2% developed late cardiovascular complications and 0.4% pulmonary toxicities, not influenced by RT. The Surveillance, Epidemiology, and End Results analysis of NHL patients showed significantly higher chances of developing second malignancy compared to endemic rate, although the incidence rates were similar between irradiated and unirradiated patients. The only difference noted was the predominance of solid tumors (sarcoma, breast, and lung cancer) in patients treated with RT [20]. Since RT induced secondary cancers occur in the irradiated field, attempts may be made to lower dose exposure by using mod-

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ern RT techniques, e.g., deep inspiration breath hold, protons, and use of involved node RT.

Most of our knowledge regarding cardiotoxicity in long-term lymphoma survivors comes from RT delivered 20–30 years ago using mantle field and prescribed doses of ≥ 40 Gy. Today, radiation portals are significantly smaller and prescribed doses are lower with the advent of chemotherapy. Currently, doses of 20–36 Gy are typically prescribed to a more precisely defined target volume depending on the stage of the disease, type of lymphoma and response to chemotherapy [21]. In this study, we observed 5.4% deaths due to cardiovascular causes, of which only 1.1% patients have received RT to mediastinal or cardiac structures. Compared to the general population, NHL survivors are estimated to be 5.3–7.3 times more prone to develop long-term cardiovascular mortality [22]. However, reduction in treatment volume from mantle field to involved field or node RT has reduced D_{mean} of heart by 35%–72% [23,24]. A systematic review of cardiotoxicities in patients receiving mediastinal RT showed a linear dose-response relationship between D_{mean} of heart and death due to cardiac disease, especially when D_{mean} exceeds 5 Gy [25,26]. D_{mean} of ≥ 15 Gy significantly increased chances of symptomatic cardiac injury [27]. The 30-year risk of clinically significant valvular heart disease was estimated to be increased by around 1.4% in patients receiving modern mediastinal RT to a dose of 20–30 Gy [28]. Use of deep inspiratory breath hold along with either three-dimensional conformal radiotherapy, intensity-modulated radiotherapy or even proton therapy further reduces the heart dose [29-31]. With proton therapy, heart-D_{mean}, $V_{5–30}$ and heart wall-D_{mean} could be reduced by ≥ 30%, left anterior descending artery $V_{5–30}$ by 11%–28%, D_{mean} by 72% and mean dose to heart chambers by 47%–100% [32-34]. However, the ILROG recommends use of proton therapy to reduce cardiotoxicity in only two patient subsets; first, patients with mediastinal disease below the origin of the left main coronary artery and secondly in heavily pretreated patients, who are at a higher risk of radiation-related toxicity [35].

A retrospective German study reported acute and late toxicities (xerostomia, dry eyes, cataract, dysphagia, etc.) which were comparable to our report [36]. Of the 75 patients analyzed, 61% received 24–36 Gy radiation while 37% received higher doses. No significant difference in toxicities were observed here with respect to the dose delivered ($p = 0.197$).

This is a single institute retrospective analysis which included patients from the pre-rituximab era also, 41% received rituximab along with chemotherapy. Most of the patients could not afford rituximab because of financial constraints. Addition of rituximab have been shown to improve the long-term outcomes. There was no effect on the response and outcome with RT in this study.

This retrospective series suggest that RT dose reduction may be possible in high-grade NHL without compromising the tumor control, both short term and long term. Radiation dose de-escalation may be the new standard of care in future for patients receiving RT for NHL in the era of rituximab and PET scan. However, our observations need to be confirmed in a large randomised multicentric trial.

Statement of Ethics

This study protocol was reviewed and approved by Postgraduate Institute of Medical Education and Research (No. RT 12/03/23). Written informed consent was obtained from participants to participate in the study.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Author Contributions

Conceptualization, BSY. Investigation and methodology, BSY. Resources, BSY, TD. Writing of the original draft, BSY. Writing of the review and editing, TD. Formal analysis, BSY, TD. Data curation, BSY, TD.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2023;41(4):248-257
https://doi.org/10.3857/roj.2023.00248

A comparison of conventional and accelerated hypofractionated radiotherapy in definitive chemoradiation for locally advanced head and neck carcinoma: a retrospective cohort study

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Received: April 10, 2023
Revised: August 10, 2023
Accepted: August 14, 2023

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Purpose: The study evaluates accelerated hypofractionated radiotherapy (AHRT) compared to conventional fractionation radiotherapy (CFRT) in patients with locally advanced head and neck cancer (LAHNC) receiving definitive chemoradiation therapy.

Materials and Methods: The study includes a retrospective cohort analysis of 120 patients. CFRT arm (n = 65) received 2 Gy per fraction to a dose of 70 Gy over 7 weeks in a three-volume approach, whereas the AHRT arm (n = 55) received 2.2 Gy per fraction to a dose of 66 Gy in 6 weeks with a two-volume approach. The primary outcome was overall survival (OS).

Results: With a median follow-up of 18.9 months, 23 patients died in the AHRT arm, and 45 deaths in the CFRT arm. The median OS was 23.4 and 37.63 months in the CFRT and AHRT arms, respectively (hazard ratio [HR] = 0.709; 95% confidence interval [CI], 0.425–1.18; p = 0.189). The median time to loco-regional control was 33.3 months in the CFRT arm and was not reached in the patient group receiving AHRT (HR = 0.558; 95% CI, 0.30–1.03; p = 0.065). The median progression-free survival was 15.9 months in the CFRT arm and 26.9 months in the AFRT arm (HR = 0.801; 95% CI, 0.49–1.28; p = 0.357). Out of 11 acute toxic deaths, eight were in the CFRT arm.

Conclusion: The study showed a trend towards benefit in terms of locoregional control in the AHRT arm and similar OS. A longer follow-up of patients receiving AHRT is required to assess the benefit.

Keywords: Radiotherapy, Altered fractionation, Survival, Locoregional neoplasm recurrence

Introduction

Head-and-neck carcinoma (HNC) is a significant contributor to the cancer burden in India, accounting for 21.3% of cases [1]. A majority of patients (over 65%) present with locally advanced disease, for which concurrent chemoradiation (CRT) is the mainstay of treatment, providing a 5-year overall survival (OS) benefit of 6.5% compared to radiation therapy (RT) alone [2]. The standard practice of conventional fractionated RT (CFRT) involves 70 Gy delivered in 35 fractions using a three-volume approach over 7 weeks. However, our experience has shown poor locoregional control (LRC) and OS with this regimen, as well as significant grade 3–5 acute toxicities [3,4].

To improve outcomes, an alternate regimen of accelerated hypofractionated RT (AHRT) delivering 66 Gy in 30 fractions over 6 weeks has been adapted, resulting in increased LRC and OS rates

[5,6]. Using the AHRT regimen, the 2-yeare OS was 95.5% and the 2-year LRC rates were 91% without the addition of concurrent chemotherapy in early oropharyngeal carcinoma [7]. For advanced carcinomas of the oropharynx, the 3-year LRC rate was 92% and OS was 83% [8]. The reduction in the overall treatment time (OTT) by 1 week accelerated RT improves the LRC and disease-free survival [9,10]. At our institute, we switched from CFRT to AHRT with the hypothesis that it would deliver a biologically equivalent dose while reducing OTT and improving outcomes. This retrospective cohort study compares the two radiotherapy regimens (CFRT vs. AHRT) and includes measures to reduce acute toxicity like optimizing the dose to dysphagia-aspiration related-structures, weekly concurrent chemotherapy, and surveillance of sepsis.

Materials and Methods

1. Study design and setting

This retrospective cohort study was conducted at the Department of Radiation Oncology, St John's Medical College and Hospital, Bengaluru, following Institute Ethical Clearance. The study included patients with locally advanced (stage III, IVA and IVB) head-and-neck cancer (LAHNC) who had been treated with definitive CRT between January 2013 and December 2021. Patients who had previously undergone head-and-neck irradiation were excluded. Patients were evaluated in a multidisciplinary tumour board, and disease staging was done according to the American Joint Committee on Cancer (AJCC) 8th edition [11]. The cancer staging was reconstructed according to AJCC 8th edition treated prior to 2017. Pre-treatment baseline assessments included a complete blood count, renal function test, liver function test, creatinine clearance, and computed tomography (CT) scan. Data was collected from radiotherapy review charts and follow-up records, and included patient characteristics, disease characteristics, RT details, chemotherapy details, outcome details, and toxicities.

2. Treatment

All patients received definitive CRT with intensity-modulated radiotherapy (IMRT) technique and 6-MV photons after immobilization with thermoplastic masks. All patients underwent a contrast-enhanced CT simulation with 2.5-mm slice thickness from vertex to the carina. The segmentation was done on the MONACO workstation. Patient in CFRT arm, gross tumor volume (GTV), high-risk clinical target volume (CTV1), intermediate-risk CTV (CTV2), and low-risk CTV (CTV3) were defined. High-risk planning targe volume (PTV1), intermediate-risk PTV (PTV2), and low-risk PTV (PTV3) were generated with an isotropic expansion of 3–5 mm from CTV1, CTV2, and CTV3, respectively. The target volumes, i.e., PTV1, PTV2, and PTV3, were irradiated to a total dose of 70, 63, and 56 Gy in conventional fractionation, respectively. In the AFRT arm, only two volumes were defined: CTV1 and CTV3. The CTV2 was removed. An isotropic expansion of 3–5 mm from CTV is given to generate respective PTV. PTV1 and PTV2 received a dose of 66 and 54 Gy, respectively in AHRT arm. All organ-at-risk (OAR) structures were contoured, such as parotids, submandibular glands (SMGs), pharyngeal constrictors (PC), larynx, and cervical esophagus (CE). The PC was contoured from the pterygoid plates to the inferior border of the cricoid cartilage. The CE was contoured from the lower end of the PC to the lower edge of the C7 vertebral body. The dose constraints used were: spinal cord (D_{max} < 44 Gy), brainstem (D_{max} < 54 Gy), parotid (D_{mean} < 26 Gy), SMG (D_{mean} < 35 Gy), PC (D_{mean} < 45 Gy), larynx (D_{mean} < 45 Gy), and CE (D_{mean} < 45 Gy). A 7-field IMRT plan with 6-MV photons was generated using the MONACO treatment planning system [12]. Patients in the AHRT arm received 66 Gy in 30 fractions at 2.2 Gy per fraction to PTV1 and 54 Gy in 30 fractions to PTV2, 5 fractions a week over 6 weeks. Concurrent chemotherapy in the CFRT arm consisted of either weekly cisplatin chemotherapy at 40 mg/m^2 or 3 weekly cisplatin chemotherapy at 100 mg/m^2, as decided by the treating medical oncologist. All patients in the AHRT arm received concurrent weekly cisplatin chemotherapy at 40 mg/m^2 weekly. Chemotherapy was not given after completion of RT. Hydration, anti-emetics, and dose modifications were done according to the National Comprehensive Cancer Network guidelines. Active surveillance of sepsis was done for patients since June 2018.

3. Sepsis surveillance

The initial experience with 70 Gy in 35 fractions using a three-volume approach showed a high incidence of acute toxicities, leading to treatment discontinuation or death. This was attributed to a toxicity syndrome called the "mucositis-dysphagia-aspiration-sepsis" complex [13]. To address this, a more stringent review process was implemented during the course of concurrent CRT to monitor for sepsis. This involved meticulous monitoring of symptoms, vitals, and blood counts, with steps taken to prevent infection and sepsis. If it was indicative of impending development of infection and sepsis, steps were taken to prevent the same and halt progression. First chemotherapy, hypothesised to aggravate grade 3–4 toxicities was withheld. Conservative management in the form of hydration, antibiotics, and granulocyte colony stimulating factors were tried. The last resort was to withhold RT.

4. Follow-up

During CRT, all patients were reviewed at least twice a week. After completion of scheduled treatment, patients were followed up

weekly until acute reactions subsided, then monthly until 3 months, 3 monthly until 2 years, and then yearly. The response to treatment was evaluated after 8–12 weeks of completing RT with clinical, endoscopy, and/or imaging.

5. Outcome measures

The primary outcome was median OS. The secondary outcomes were LRC, progression-free survival (PFS), determination of factors affecting the OS, treatment compliance, and the incidence of acute toxicity. OS is defined from the time of diagnosis to death due to any cause. LRC was calculated from the time of diagnosis to locoregional disease recurrence or death due to any cause. PFS was calculated from the time of diagnosis to any disease event, i.e., recurrence (locoregional or distal), second primary or death due to any cause. Toxicity grading was done with the Common Terminology Criteria for Adverse Events v4.03. For assessing compliance, median radiation dose received, duration of concurrent CRT schedule, the number of patients receiving planned radiation or chemotherapy, and the adequate cumulative dose of cisplatin were compared between the two groups.

6. Statistical analysis

The study population size was based on consecutive convenience sampling. The data were analysed using STATA software version 16 (StataCorp LLC, College Station, TX, USA). All categorical data were presented using frequency and percentages, and all continuous data using mean and standard deviation or median and inter-quartile range (IQR) based on the distribution. OS, PFS, and locoregional progression-free survival (LRPFS) were analysed with Kaplan-Meier survival methods and compared using log-rank tests. Univariate and multivariate analyses were performed using Cox proportional hazard regression analysis. The difference in acute toxicities between the two arms was compared with chi-square test. A p-value was considered significant at a 5% level of significance for all comparisons.

Table 1. Patient and tumour baseline characteristics

Characteristic	CFRT (n = 65)	AHRT (n = 55)
Age (yr)	60 (25–80)	57 (19–73)
Sex		
Male	46 (70.8)	48 (87.2)
Female	19 (29.2)	7 (12.8)
ECOG performance status		
0	6 (9.2)	13 (23.6)
1	54 (83.1)	41 (74.5)
2	5 (7.7)	1 (1.9)
CCI (median)	4	4
Tobacco usage	50 (76.9)	45 (81.8)
Site		
Oral cavity	12 (18.5)	15 (27.3)
Oropharynx	23 (35.4)	14 (25.4)
Nasopharynx	2 (3.1)	6 (10.9)
Hypopharynx	13 (20.0)	4 (7.3)
Larynx	11 (16.8)	13 (23.6)
Others (PNS, CUP)	4 (6.2)	3 (5.5)
T stage		
T0	1 (1.5)	1 (1.8)
T1	1 (1.5)	1 (1.8)
T2	7 (10.8)	6 (10.9)
T3	28 (43.1)	22 (40.0)
T4	27 (41.6)	23 (41.8)
Unknown	1 (1.5)	2 (3.7)
N stage		
N0	17 (26.1)	11 (20.0)
N1	13 (20.0)	5 (9.1)
N2	30 (46.2)	24 (43.6)
N3	5 (7.7)	15 (27.3)
AJCC stage group		
II	1 (1.5)	0 (0)
III	22 (33.9)	18 (32.7)
IV	42 (64.6)	37 (67.3)
Chemotherapy type		
Weekly	41 (63.1)	55 (100)
3-weekly	24 (36.9)	0 (0)

Values are presented as median (range) or number (%).
CFRT, conventional fractionated radiation therapy; AHRT, accelerated hypofractionated radiation therapy; ECOG, Eastern Cooperative Oncology Group; CCI, Charlson Comorbidity Index; PNS, paranasal sinus; CUP, carcinoma of unknown primary; AJCC, American Joint Committee on Cancer.

Results

1. Baseline characteristics

A total of 120 patients with LAHNC were treated from January 2013 to December 2021. Of these, 65 patients received CFRT between January 2013 and May 2018, and 55 patients received AHRT from June 2018 onwards. Table 1 shows the baseline characteristics of the patients. The median age of the cohort was 59 years, and 78.3% of the patients were male. Most patients (95%) had an European Cooperative Oncology Group (ECOG) performance status of 0/1, and 79.1% of the patients had a history of tobacco usage. The oropharynx was the most commonly involved subsite (30.8%), followed by the oral cavity (22.5%). Around 85% of the patients had a T3/T4 primary lesion, 76.7% had lymph nodes involved, and 65.8% had Stage IVA/B disease. In the CFRT arm, around 63% of the patients received weekly concurrent chemotherapy, while 37% received 3-weekly chemotherapy. All patients receiving AHRT received weekly chemotherapy.

2. Treatment compliance

The median duration of RT completion was 46 days (6.6 weeks) and 40 days (5.7 weeks) in the CFRT and AHRT arms, respectively, and

https://doi.org/10.3857/roj.2023.00248

the median radiation dose received was 66 Gy for both groups. Only 84.2% of the patients received the planned dose, with acute toxicities being the main reason for not completing RT. About 40% of the patients had unplanned breaks of more than 2 days during the RT course. Twenty-six patients in CFRT arm received 3-weekly cisplatin chemotherapy. Rest of the patients in CFRT arm and all in AHRT arm received weekly cisplatin chemotherapy. Only 28.3% of the patients received the planned chemotherapy cycles. Table 2 provides additional details regarding treatment compliance.

3. Outcome

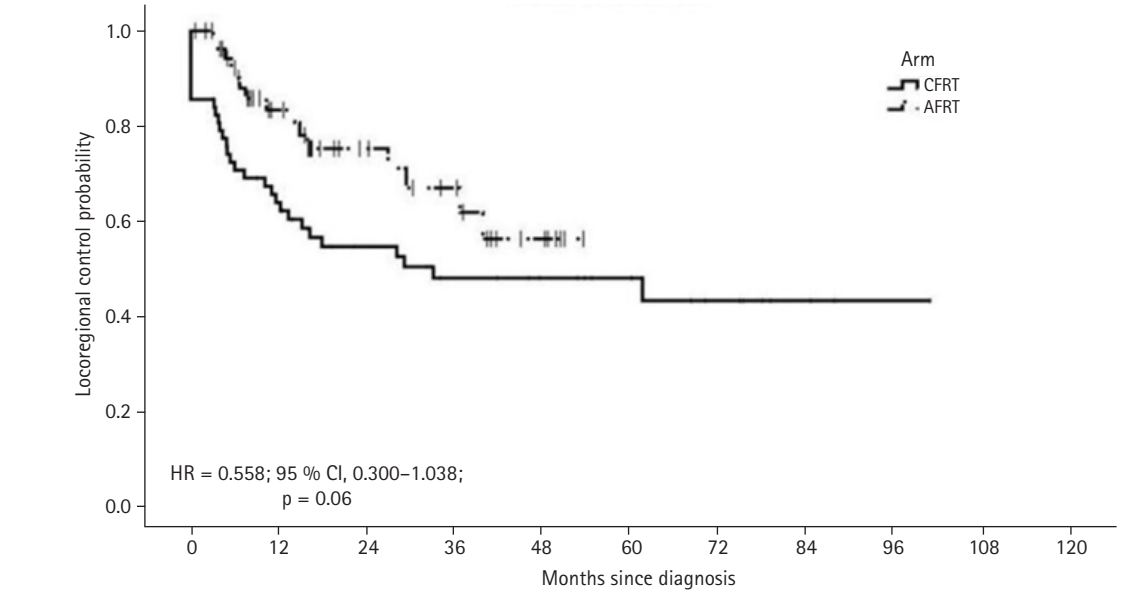
The median follow-up period for the entire cohort was 18.9 months (IQR, 8.4 to 41.7 months); with a median follow-up of 23 and 16.5 months for CFRT and AHRT arms, respectively. Complete response was achieved in 56.9% (n = 37) of CFRT and 56.4% (n = 31) of AHRT arm patients. Partial response was seen in 24.6% (n = 16) and 30.9% (n = 17) of CFRT and AHRT arms, respectively. Response status was unknown for 12 (18.5%) and 2 (12.7%) patients receiving CFRT and AHRT, respectively. A total of 42 patients had locoregional progression, with 27 in the CFRT arm and 15 in the AHRT arm. The median time to locoregional progression was 33.3 months in the CFRT arm and not reached in AHRT group (HR = 0.558; 95 % CI, 0.300–1.038; p = 0.065) (Fig. 1). The number of patients with locoregional relapse (LRR), distal metastasis, and both (LRR and distal) in the CFRT and AHRT arms were 21 and 9, 4 and 4, and 2 and 2, respectively (Supplementary Table S1). The median PFS was 15.9 months in the CFRT arm and 26.9 months in the AHRT arm (HR = 0.801; 95 % CI, 0.499–1.285; p = 0.357) (Fig. 2).

In the cohort, there were a total of 68 deaths, with 45 in the CFRT arm and 23 in the AHRT arm. The median OS was 23.4 months in the CFRT arm, while it was 37.6 months in the AHRT arm (HR = 0.709; 95% CI, 0.425–1.184; p = 0.189) (Fig. 3). Of the 45 deaths in the CFRT arm, 29 were caused by the disease, eight were due to acute toxicities related to treatment, and eight were caused by other reasons (cardiac, natural causes, one patient committed suicide). In the AHRT arm, 15 of the 23 deaths were caused by disease progression, three were due to acute toxicities, one death occurred due to the development of a second primary, and four were due to cardiac causes. The HR of death was 0.709 (95% CI, 0.425–1.184; p = 0.189) in patients receiving AHRT arm compared with CFRT arm. On Cox univariate analysis, age over 60 years and AJCC stage group IVA/B had a statistically significant negative

Table 2. Treatment compliance

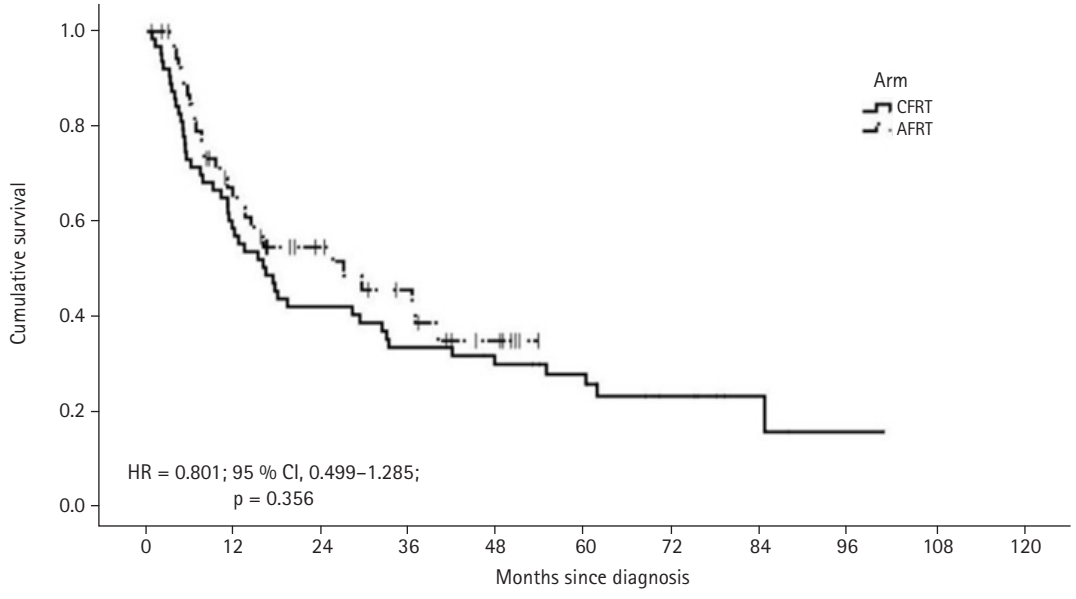
	CFRT (n = 65)	AHRT (n = 55)	p-value
RT dose received (Gy)	66 (50–70)	66 (55–66)	
Planned dose received	52 (80.0)	49 (89.1)	
Incomplete radiation	13 (20.0)	6 (10.9)	0.174
Reason for not completing RT			
Acute toxicities	11 (84.6)	3 (50.0)	
Patient refused/defaulted	2 (15.4)	3 (50.0)	
Unplanned RT break of >2 days	24 (36.9)	24 (43.6)	0.454
Reason for breaks			
Acute toxicities	20 (83.3)	21 (87.5)	
Patient refused/defaulted	1 (4.2)	0 (0)	
Unknown	3 (12.5)	3 (12.5)	
Completed chemotherapy cycles	19 (29.2)	15 (27.3)	-
Incomplete chemotherapy cycles			
1 of 3	5 (10.9)	0 (0.0)	
2 of 3	12 (26.1)	0 (0.0)	
1 of 6	2 (4.3)	0 (0.0)	
2 of 6	2 (4.3)	4 (10.0)	
3 of 6	9 (19.6)	9 (22.5)	
4 of 6	10 (21.7)	14 (35.0)	
5 of 6	6 (13.1)	13 (32.5)	
Reason for not completing chemotherapy	46 (70.8)	40 (72.7)	0.813
Acute toxicities	41 (89.1)	35 (87.5)	
Patient refused/defaulted	5 (10.9)	3 (7.5)	
Unknown	0 (0)	2 (5.0)	

Values are presented as median (range) or number (%).
CFRT, conventional fractionated radiation therapy; AHRT, accelerated hypofractionated radiation therapy; RT, radiation therapy.



Number at risk									
CFRT	65	36	26	19	16	12	7	3	1
AFRT	55	25	17	8	4	0	0	0	0

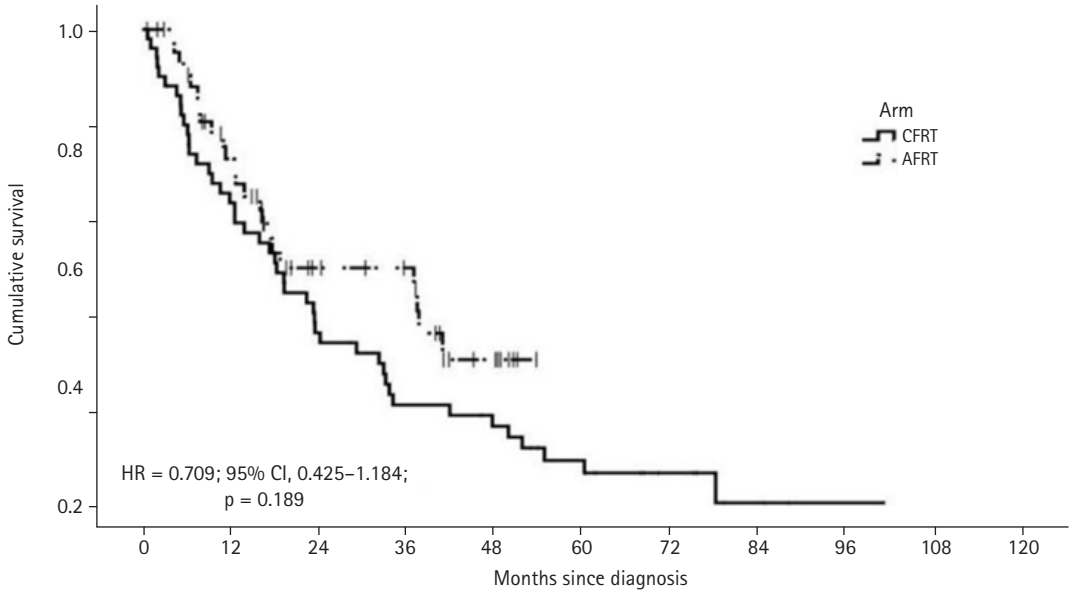
Fig. 1. Kaplan-Meier estimates of locoregional control. CFRT, conventional fractionated radiation therapy; AHRT, accelerated hypofractionated radiation therapy; HR, hazard ratio; CI, confidence interval.



Number at risk									
CFRT	65	35	25	19	16	12	7	3	1
AFRT	55	24	17	8	4	0	0	0	0

Fig. 2. Kaplan-Meier estimates of progression-free survival. CFRT, conventional fractionated radiation therapy; AHRT, accelerated hypofractionated radiation therapy; HR, hazard ratio; CI, confidence interval.

https://doi.org/10.3857/roj.2023.00248



Number at risk									
CFRT	65	42	29	21	18	12	7	3	1
AFRT	55	29	18	10	4	0	0	0	0

Fig. 3. Kaplan-Meier estimates of overall survival. CFRT, conventional fractionated radiation therapy; AHRT, accelerated hypofractionated radiation therapy; HR, hazard ratio; CI, confidence interval.

impact on OS. On Cox multivariate regression analysis, there was no significant difference in OS between the two arms based on gender, ECOG, Charlson Comorbidity Index, T stage, N stage, and AJCC stage group. Only age >60 years maintained its significant negative impact (Table 3).

4. Toxicities

Grade 3–4 acute toxicities developed in 49 (52.1%) patients in the CFRT arm as compared to 45 (47.9%) patients in the AHRT arm. The cumulative incidence of acute grade 3–5 dermatitis, mucositis, pain, dysphagia, and aspiration in the CFRT and AHRT arms were 3.1% and 14.5%, 36.9% and 56.4%, 32.3% and 70.9%, 58.5% and 29.1%, 15.4% and 3.6%, respectively (Table 4). There was a total of 11 deaths due to acute toxicity, with eight in the CFRT arm and the remaining three in the AHRT arm.

Discussion and Conclusion

The results of the study suggest a potential benefit in OS, PFS, and LRPFS with AHRT compared to CFRT, although the difference was not statistically significant. Both treatment arms had similar rates of complete response, and the median radiation dose was 66 Gy. However, less than one-third of patients received the planned cycles of chemotherapy due to acute toxicities, which were the main reason for treatment interruption. About 50% of all patients developed grade 3–4 toxicities, and 11 deaths occurred due to acute toxicities. Nevertheless, treatment-related acute toxic deaths were reduced in the AHRT arm, although not statistically significant.

AHRT appears to be a promising treatment option for early oropharyngeal carcinomas, with a 2-year locoregional failure rate of 9% and a 2-year OS of 95.5% [7]. In advanced oropharyngeal carcinomas, AHRT resulted in a 3-year LRC rate of 92% and an OS of 83% [8]. However, when compared with another regimen of 69.96 Gy/33 fractions, AHRT showed lower LRC rates of 72.6%. Nonetheless, there was no difference in the OS and disease-free survival (DFS) [14]. Another study comparing AHRT to CFRT reported a non-significant benefit of AHRT over CFRT in terms of 2-year DFS (62.1% vs. 56.3%; p = 0.640) and 2-year OS (53% vs. 44.5%; p = 0.510), with a 2-year LRF rate of 27.2% versus 33.8% in CFRT and AHRT arms, respectively [15]. These results are consistent with the present study and the original hypothesis that reducing the overall treatment time by 1 week leads to better tumour control, which may be reflected in better OS.

A two-volume approach avoiding intermediate risk volume has the potential to reduce the dose received by OARs and hence reduce the toxicities associated with it. The dosimetry comparison of two- and three-volume approach in head-and-neck treatment plans showed similar intermediate-risk CTV coverage and similar

Table 3. Factors affecting overall survival

Parameter	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (yr)						
< 60 (reference)						
> 60	1.707	1.056–2.760	0.029*	1.772	1.055–2.942	0.028*
Sex						
Female (reference)						
Male	0.646	0.372–1.120	0.120	0.709	0.383–1.311	0.257
ECOG performance status						
0 (reference)						
1	1.873	0.854–4.108	0.265	1.537	0.665–3.440	0.320
2	3.724	1.085–12.774	0.037	3.422	0.914–12.583	0.070
No tobacco (reference)						
Usage	1.253	0.683–2.299	0.422	-	-	
Tumour site						
Larynx (reference)						
Oral cavity	1.818	0.808–4.064	0.151	1.481	0.643–3.412	0.376
Oropharynx	1.462	0.607–3.531	0.398	1.129	0.488–2.573	0.760
Hypopharynx	1.625	0.627–3.892	0.219	1.369	0.569–3.294	0.479
T stage						
1 (reference)						
2	0.229	0.045–1.158	0.075	-	-	
3	0.305	0.071–1.303	0.109	-	-	
4	0.545	0.129–2.298	0.409	-	-	
N stage						
0 (reference)						
1	1.107	0.501–2.445	0.802	-	-	
2	1.124	0.598–2.115	0.717	-	-	
3	1.389	0.640–3.016	0.406	-	-	
Stage						
III (reference)						
IV	1.801	1.064–3.050	0.029*	1.556	0.862–2.810	0.138

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.
*p < 0.05. On Cox univariate analysis, age >60 years and AJCC stage group IVA/B had a statistically significant negative impact on OS. Only age >60 years maintained a significant negative impact on overall survival on multivariate Cox regression analysis.

Table 4. Acute toxicity profile

Grade 3–5 toxicities	CFRT (n = 65)	AHRT (n = 55)	p-value
Dermatitis	2 (3.1)	8 (14.5)	0.024
Mucositis	24 (36.9)	31 (56.4)	0.033
Pain	21 (32.3)	39 (70.9)	< 0.001
Dysphagia	38 (58.5)	16 (29.1)	0.001
Aspiration	10 (15.4)	2 (3.6)	0.033
Acute toxic deaths	8 (12.3)	3 (5.4)	0.195

The cumulative incidence of dermatitis, mucositis, pain, and dysphagia was higher in the AHRT arm, while the incidence of aspiration and acute toxic deaths was increased in the CFRT arm.
CFRT, conventional fractionated radiation therapy; AHRT, accelerated hypofractionated radiation therapy.

$V_{95\%}$ in both two- and three-volume plans for the same case (although two volumes delivered slightly lower dose). The two-volume approach however was more likely to have cold spots at the periphery of the intermediate-risk region [16]. In another study considering human papillomavirus positive oropharyngeal carcinoma who received definitive radiotherapy, a retrospective delineation of intermediate-risk PTV was done after documented LRR. No potential patients were found whose recurrences could have been prevented by giving an intermediate-risk dose. So, emitting the same and following a two-volume approach may be acceptable [17].

Sepsis is a life-threatening complication that can occur in cancer patients undergoing chemotherapy and RT. The risk of sepsis is particularly high in patients with HNC due to the immunosuppressive effects of treatment and the potential for treatment-related mucositis and infections. To reduce the incidence and severity of sepsis in HNC patients undergoing CRT, surveillance protocols have been proposed. These protocols involve close monitoring of patients for signs and symptoms of infection, such as fever, chills, and

https://doi.org/10.3857/roj.2023.00248

difficulty swallowing, and prompt initiation of appropriate antibiotic therapy when necessary. A literature review and consensus statement by Mirabile et al. [18] suggested that sepsis surveillance during CRT for HNC may result in a reduction in treatment-related acute toxic deaths. In the present study, active sepsis surveillance during CRT for HNC patients was found to be beneficial in reducing treatment-related acute toxic deaths in the AHRT arm, although not statistically significant. This was reflected in a higher percentage of patients completing RT as planned, although with a higher number of breaks during RT in the AHRT arm due to acute toxicities. The cumulative incidence of acute dermatitis, mucositis, pain, and dysphagia was more in AHRT arm, but incidence of aspiration and acute toxic deaths were increased in CFRT arm. This may be due to retrospective nature of the study, and better monitoring and toxicity recoding in AHRT arm done for sepsis surveillance.

Despite the promising findings of this study, there are few limitations that must be considered. First, the study is retrospective in nature, which means that it is subject to the biases and limitations inherent in such studies. Additionally, the two treatment arms were tested at different time points, with median follow-up of AHRT arm lesser than the CFRT arm. This could have introduced confounding variables that were not accounted for in the analysis. Additionally, the study had a relatively small sample size, with 120 patients included in the analysis. The decrease in toxic deaths by surveillance of sepsis is still a hypothesis and has to proven in a prospective study, after clearly defining the surveillance parameters. Also, 3-weekly concurrent cisplatin was received by 40% (n = 26) patients in CFRT arm and none in AFRT arm. This might be one of the reasons for more toxic deaths in CFRT arm. Another limitation is the subjective grading of acute toxicities, which could have introduced variability in the data. Furthermore, the study had a relatively short follow-up period, which may not have been long enough to fully evaluate the benefits of AHRT over CFRT. Longer follow-up is needed to assess the true benefits of AHRT in terms of OS, PFS, and LRC. Moreover, the study population was limited to patients with LAHNC stage III or IV, with unresectable disease and history of tobacco usage. This limits the generalizability of the findings to other patient populations. Furthermore, the study did not include patients with comorbidities, which are common in the older adult population. Finally, the study did not evaluate the impact of AHRT on patient quality of life, which is an important consideration in cancer treatment.

The strength of the study lies in its real-world setting, where patients encountered in the clinical setting are similar to those in the study. Patients with locally advanced head and neck cancer, stage III or IV, with unresectable disease and history of tobacco usage were included in the study, which is representative of the patient population that typically presents to radiation oncology clinics in India. Another strength of the study is the comparison of AHRT and CFRT, which are both commonly used treatment approaches, and the results provide valuable insight into the potential benefits and limitations of these approaches. The study also used rigorous statistical analysis to compare the outcomes between the two treatment arms, which add to the strength of the study. The use of a two-volume approach for RT and sepsis surveillance during CRT course is another strength of the study, as it resulted in reduced treatment-related acute toxic deaths in the AHRT arm.

Overall, the study provides valuable information on the potential benefits and limitations of AHRT and CFRT in the treatment of locally advanced HNC. The study's real-world setting and rigorous statistical analysis add to the strength of the study, while the use of a two-volume approach for RT and sepsis surveillance during CRT course reduces treatment-related acute toxic deaths. The study provides valuable insights into the potential benefits and limitations of different treatment approaches for HNC and adds to the body of literature on the use of AHRT in this patient population. The findings of the study could be useful for radiation oncologists and clinicians involved in the treatment of LAHNC, providing an insight into the efficacy and safety of AHRT, and the potential benefits of the two-volume approach for RT and sepsis surveillance during CRT course. Further studies with larger and more diverse patient populations are needed to confirm the findings and address the limitations of this study.

In conclusion, the present study suggests a potential benefit of AHRT compared to CFRT in terms of LRC in patients with LAHNC receiving CRT. However, the difference was not statistically significant. The PFS and OS were similar in both the arms. AHRT appears to be a promising treatment option for patients with LAHNC fit for CRT. A longer follow-up of patients receiving AHRT is required to assess the benefit.

Statement of Ethics

The study was approved by the Institutional Ethics Committee of St. Johns Medical College with IEC reference No. 198/2022. Being a retrospective analysis, permission for waiver of consent was obtained.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgements

The authors thank all the staff of department of Radiation Oncology, Medical Oncology, Surgical oncology, Pain & Palliative, and ENT at St John's Medical College and Hospital.

Funding

None.

Author Contributions

Conceptualization, Muzumder S, Tripathy A. Investigation and methodology, Tripathy A, Muzumder S, Srikantia N, Udayashankar AH. Writing of the original draft, Tripathy A, Muzumder S. Writing of the review and editing, Srikantia N, Vashishta GD, Udayashankar AH, John Sebastian MG. Validation, Tripathy A, Muzumder S, Srikantia N, Udayashankar AH. Formal analysis, Raj JM, Tripathy A. Data curation, Tripathy A, Babu A, Muzumder S, John Sebastian MG, Udayashankar AH, Vashishta GD. Visualization, Tripathy A, Muzumder S, John Sebastian MG.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2023.00248.

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ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2023;41(4):258-266
https://doi.org/10.3857/roj.2023.00563

CyberKnife-based stereotactic radiosurgery or fractionated stereotactic radiotherapy in older patients with brain metastases from non-small cell lung cancer

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Received: July 4, 2023
Revised: August 24, 2023
Accepted: August 25, 2023

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Purpose: We analyzed clinical results of CyberKnife (CK)-based stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT) in older patients (age ≥65 years) affected by brain metastases (BM) from non-small cell lung cancer (NSCLC).

Materials and Methods: Forty-three older patients with 92 BM were treated with CK-based SRS/FSRT at our institution between 2009 and 2019. The end-point was overall survival (OS). Univariate and multivariate analyses were performed to identify the prognostic factors influencing OS. The in-field local control (IFLC) within the SRS/FSRT field was also assessed.

Results: During a median follow-up period of 18 months, the median OS was 32 months. NSCLC-specific graded prognostic assessment (GPA) ($p = 0.027$) was an independent significant factor affecting OS in the multivariate analysis. The median IFLC period was 31 months, and the total BM volume ($p = 0.025$) appeared to be a significant feature of IFLC. No adverse events >grade 2 were reported after SRS/FSRT.

Conclusion: CK-based SRS/FSRT is a safe and efficient option for older patients with BM arising from NSCLC, showing good OS without severe side effects. GPA, which was consisted in age, performance status, extra-cerebral metastasis, and number of BM, seemed to be predictive factors for OS.

Keywords: Brain metastases, Non-small cell lung carcinoma, Stereotactic radiosurgery, Radiotherapy

Introduction

Brain metastases (BMs) are the most common intracranial neoplasms and a significant cause of mortality in adults. In fact, up to 40% of patients affected by cancer will develop BM during their oncological history [1]. Recently, BM has frequently been diagnosed in long-term cancer survivors because of improved systemic therapies and early detection of BM by active surveillance using magnetic resonance imaging (MRI). The incidence of BM has shown a five-fold increase over the past few decades and is likely to continue to increase due to improvements in anti-cancer therapies [2]. It has been postulated that, in future, most new cancer diagnoses will be reported in the older population. Consequently, clinicians have been encountering a larger number of aging patients with BMs. Particularly, the incidence of BM derived from non-small cell lung cancer (NSCLC) is the highest, at approximately 20% [3].

The management of BM includes medical management, surgical resection, whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), and fractionated stereotactic radiotherapy (FSRT). When the number of BMs are limited, local treatments, such as surgical treatment, SRS, and FSRT can be used rather than WBRT. SRS and FSRT are effective treatments for patients with up to 10 BM, in terms of decreasing neurotoxicity, as the concept of oligometastases has emerged in BM [4-6].

Management of older patients with BMs remains a difficult issue, as it comprises an inhomogeneous population with diverse comorbidities and different physical statuses [7-9]. Age has been used as an important prognosticator in the recursive partitioning analysis (RPA) for classifying patients with BMs, as proposed by the Radiation Therapy Oncology Group, where patients ≥ 65 years old were classified as an intermediate risk group with RPA class II [7]. SRS and FSRT have increasingly been used for older patients with BMs, mainly because of the reduction in cognitive decline and the requirement of only a few treatment days [10-13].

To our knowledge, few studies have reported the efficacy of SRS in older patients with BMs using CyberKnife-based SRS or FSRT (CK-SRS/FSRT). Here, we analyzed the clinical results of CK-SRS/FSRT in an older cohort (≥ 65 years old, RPA class II) affected by BMs arising from NSCLC.

Materials and Methods

1. Study design

This retrospective study was approved by the Institutional Review Board of Inha University Hospital (No. 2022-09-006). Our institution administered CK-SRS/FSRT to patients with BM with a life expectancy of ≥ 3 months, ≤ 10 number of BM, and a diameter of BM ≤ 3 cm. CK-SRS/FSRT was administered on patients with BM not requiring decompressive surgery and those with Karnofsky performance status (KPS) scores ≥ 60. Those with leptomeningeal seeding were excluded.

For this study, we identified patients with BMs arising from NSCLC who were treated with upfront CK-SRS/FSRT between 2009 and 2019. After that, we extracted RPA class II patients who were aged ≥ 65 years and had a KPS ≥ 70 at the time of CK-SRS/FSRT. We scored patients with BM based on a diagnosis-specific graded prognostic assessment (GPA) index related to NSCLC [9].

2. CyberKnife treatment

All patients received SRS/FSRT using a CyberKnife (Accuray Inc., Sunnyvale, CA, USA) equipped with a 6-MV linear accelerator mounted on a computer-controlled robotic arm with submillimeter accuracy. During CK-SRS/FSRT, each patient was placed in the supine position and fitted with a thermoplastic mask for immobilization. Computed tomography (CT) images of 1-mm slice thickness were fused with contrast-enhanced magnetic resonance images, Clinical target volume (CTV) was defined as the enhanced lesion observed on contrast-enhanced MRI. The planning target volume (PTV) was generated by adding a 2-mm margin to the CTV. The organs-at-risk (OARs), including the eyes, lenses, optic nerves, optic chiasm, brainstem, and spinal cord, were contoured. Plans were generated using a multiple inverse treatment-planning algorithm.

The total dose of CK-SRS/FSRT, with a range of 15–32 Gy given in 1–3 fractions, was prescribed to D90 (the radiation dose received by 90% of the PTV) based on BM size and proximity to OARs. To compensate for various dose-fractionation schedule, radiation doses were calculated as a biological effective dose (BED) based on the linear-quadratic equation with an alpha/beta ratio of 10. Target displacements caused by patient movement during treatment were automatically corrected. Stereoscopic X-ray images acquired during treatment were co-registered with a set of digitally reconstructed radiographs (DRRs) from dose-planning CT. The displacement vector was calculated by matching pairs of stereoscopic live images with the DRR.

3. Outcomes

In this study, the primary endpoint was overall survival (OS) following CK-SRS/FSRT, and the secondary endpoints were in-field local control (IFLC) within the CK-SRS/FSRT CTV and CK-SRS/FSRT-related toxicities. Additionally, we evaluated local tumor response within 6 months after CK-SRS/FSRT using the response assessment in neuro-oncology (RANO) criteria [14]. IFLC was defined as complete remission, partial remission, or stable disease, and progressive disease was categorized as in-field local failure.

4. Statistical analysis

OS and IFLC were analyzed using the Kaplan–Meier method. Univariate analysis was performed using log-rank tests to identify prognostic factors related to OS or IFLC. To assess the risk factors associated with OS or IFLC, multivariate Cox regression analyses were performed. IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) was used, and a $p < 0.05$ was defined as significant.

Results

1. Patient and treatment characteristics

Forty-three patients (92 BMs) were identified; their characteristics are listed in Table 1. The median patient age was 70 years (range, 65 to 89 years). Overall, 27 were males (63%). Of the 43 patients, 37 patients (86%) had ≤ 3 lesions. Thirty-two patients (74%) were diagnosed with adenocarcinoma. The median total BM volume per person was 1.70 cm^3 (range, 0.07 to 81.84 cm^3). With respect to diagnostic-specific GPA index scoring criteria based on lung cancer [9], three patients (7%) had a GPA of 0.5, 34 patients (79%) had a GPA of 1.0–2.5, and six patients (14%) had a GPA of 3. Seventeen patients (40%) had extracranial disease present at the time of CK-SRS/FSRT.

Table 1. Patient characteristics (n = 43)

Characteristic	Value
Age at CK-SRS/FSRT (yr)	70 (65–89)
65–70	25 (58.1)
> 70	18 (41.9)
Sex	
Male	27 (62.8)
Female	16 (37.2)
KPS	
70–80	19 (44.2)
90–100	24 (55.8)
Number of metastatic brain lesions	
1–3	37 (86.0)
> 3	6 (14.0)
Volume of metastatic brain lesions (mL)	1.70 (0.08-81.84)
≤ 3	26 (60.5)
> 3	17 (39.5)
Pathology	
Adenocarcinoma	32 (74.4)
Squamous cell carcinoma	8 (18.6)
Others	3 (7.0)
NSCLC specific GPA index	
0.5	3 (7.0)
1.0–2.5	34 (79.0)
3	6 (14.0)
Extracranial metastases at CK-SRS/FSRT	
No	26 (60.5)
Yes	17 (39.5)

Values are presented as median (range) or number (%).
CK, CyberKnife; SRS, stereotactic radiosurgery; FSRT, fractionated stereotactic radiotherapy; NSCLC, non-small cell lung cancer; GPA, graded prognostic assessment.

Among the 92 BM lesions, 78 lesions (85%) were treated with CK-SRS and 14 (15%) were treated with CK-FSRT. The median prescribed dose was 22 Gy per fraction. The median BED was 81.6 Gy. The details of CK-SRS/FSRT for the 92 BM are summarized in Table 2.

2. Outcomes and factors affecting outcomes

Within a median follow-up time of 18 months (range, 2 to 104 months), OS at 12 and 24 months was 78.3% and 57.6%, respectively (Fig. 1A). The median OS period was 32 months (95% confidence interval [CI], 17–46 months). In univariate analysis, GPA ($p < 0.001$, Fig 1B) and total metastatic tumor volume ($p = 0.014$, Fig 1C) were risk factors that significantly affected OS (Table 3). The number of BMs showed a borderline significance associated with OS ($p = 0.095$). Multivariate Cox regression analysis identified the GPA score as a powerful prognostic factor ($p = 0.027$) (Table 3).

Within 6 months after CK-SRS/FSRT, according to the RANO criteria for BM, complete remission was observed in 34.9% of patients (14/43), partial remission in 41.9% (18/43), and stable disease in 16.3% (7/43). Progressive disease was found in 3% of patients (3/43). IFLC within 6 months of CK-SRS/FSRT was observed in 40 of 43 patients (93.0%).

Table 2. Characteristics of CyberKnife-based SRS/FSRT (n = 92)

Variable	n (%)
Number of BMs	92 (100)
Treatment type	
SRS	78 (84.8)
FSRT	14 (15.2)
SRS/FSRT prescription dose (BED)	
24 Gy in 1 fx (81.6)	44 (47.8)
22 Gy in 1 fx (70.4)	5 (5.4)
20 Gy in 1 fx (60.0)	20 (21.7)
18 Gy in 1 fx (50.4)	9 (9.8)
32 Gy in 2 fx (83.2)	1 (1.1)
26 Gy in 2 fx (59.8)	9 (9.8)
24 Gy in 3 fx (43.2)	2 (2.2)
21 Gy in 3 fx (35.7)	2 (2.2)

SRS, stereotactic radiosurgery; FSRT, fractionated stereotactic radiotherapy; BM, brain metastasis; BED, biological effective dose based on the linear-quadratic equation with an alpha/beta ratio of 10.

The overall IFLC at 12 months and 24 months was 84.5% and 58.4%, respectively (Fig. 2A). Additionally, the median IFLC period was 31 months (95% CI, 12–50 months). Three clinical factors, including GPA ($p < 0.001$, Fig. 2B), total metastatic tumor volume ($p < 0.001$, Fig. 2C), and BED ($p = 0.021$, Fig. 2D) were found to be significant factors determining the IFLC period in the univariate analysis (Table 4). Subsequently, in the multivariate analysis, IFLC differed according to the total tumor volume ($p = 0.025$) (Table 4).

No acute or late adverse events higher than grade 2 were reported after CK-SRS/FSRT or during the follow-up.

Discussion and Conclusion

For cancer patients with a limited number of BMs, SRS/FSRT has increasingly been used in the initial management because this approach achieves excellent local control while avoiding the detrimental neurocognitive decline associated with WBRT. In particular, two randomized studies have shown no significant difference in OS or preservation of neurological function in patients with 1–4 BMs who received WBRT with SRS, or SRS alone [5,6,15]. Since then, in keeping with the increase in the number of older cancer patients, several reports have explored the benefits in terms of OS in cohorts focusing on geriatric patients with BMs, although most physicians have historically considered cancer patients aged > 65 years with BM as unfavorable candidates for active treatment, including surgery or SRS/FSRT. These studies have reported a median OS time of 7–15 months and a 1-year IFLC rate of 80%–99%, proving that SRS administration is a reasonable treatment for older patients

https://doi.org/10.3857/roj.2023.00563

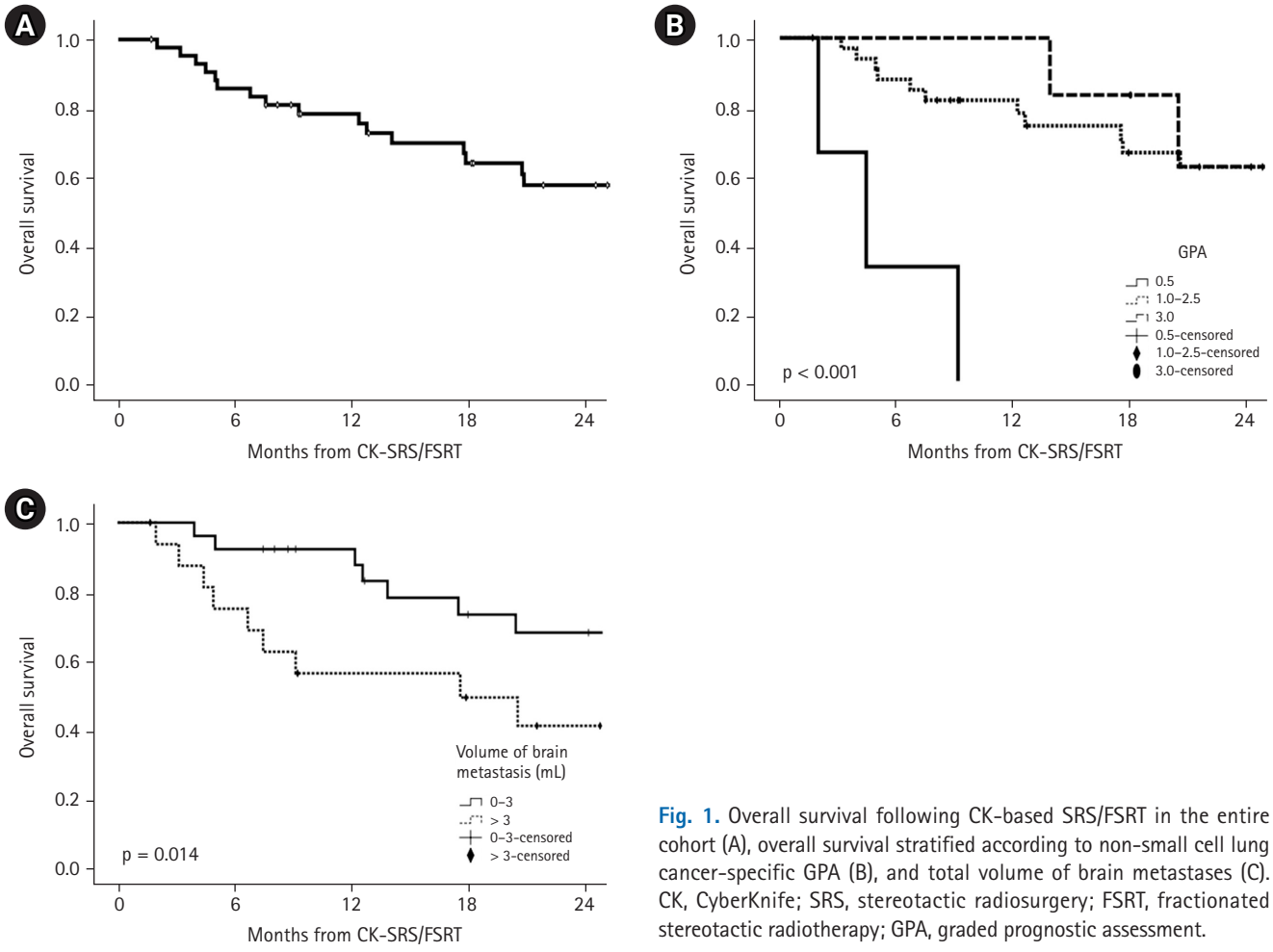

Fig. 1. Overall survival following CK-based SRS/FSRT in the entire cohort (A), overall survival stratified according to non-small cell lung cancer-specific GPA (B), and total volume of brain metastases (C). CK, CyberKnife; SRS, stereotactic radiosurgery; FSRT, fractionated stereotactic radiotherapy; GPA, graded prognostic assessment.

Table 3. Prognostic factors related to overall survival

Characteristic	Univariate			Multivariate	
	1-yr OS	2-yr OS	p-value	HR (95% CI)	p-value
Age (yr)					
65–70	75.8	66.9	0.298	-	
> 70	82.4	37.6		-	
GPA score					
0.5	0	0	< 0.001	Ref	0.027
1.0–2.5	57.2	62.4		0.131 (0.030–0.579)	0.007
3	83.3	62.5		0.127 (0.017–0.972)	0.047
Primary controlled					
Controlled	85.7	20.2	0.892	-	
No controlled	75.0	51.1		-	
Volume of brain metastasis (mL)					
≤ 3	73.3	46.7	0.014	Ref	0.119
> 3	56.3	13.7		2.280 (0.808–6.434)	
BED (Gy)					
< 81.6	78.8	42.2	0.465	-	
≥ 81.6	78.1	62.6		-	

GPA, graded prognostic assessment; BED, biological effective dose based on the linear-quadratic equation with an alpha/beta ratio of 10; HR, hazard ration; CI, confidence interval.

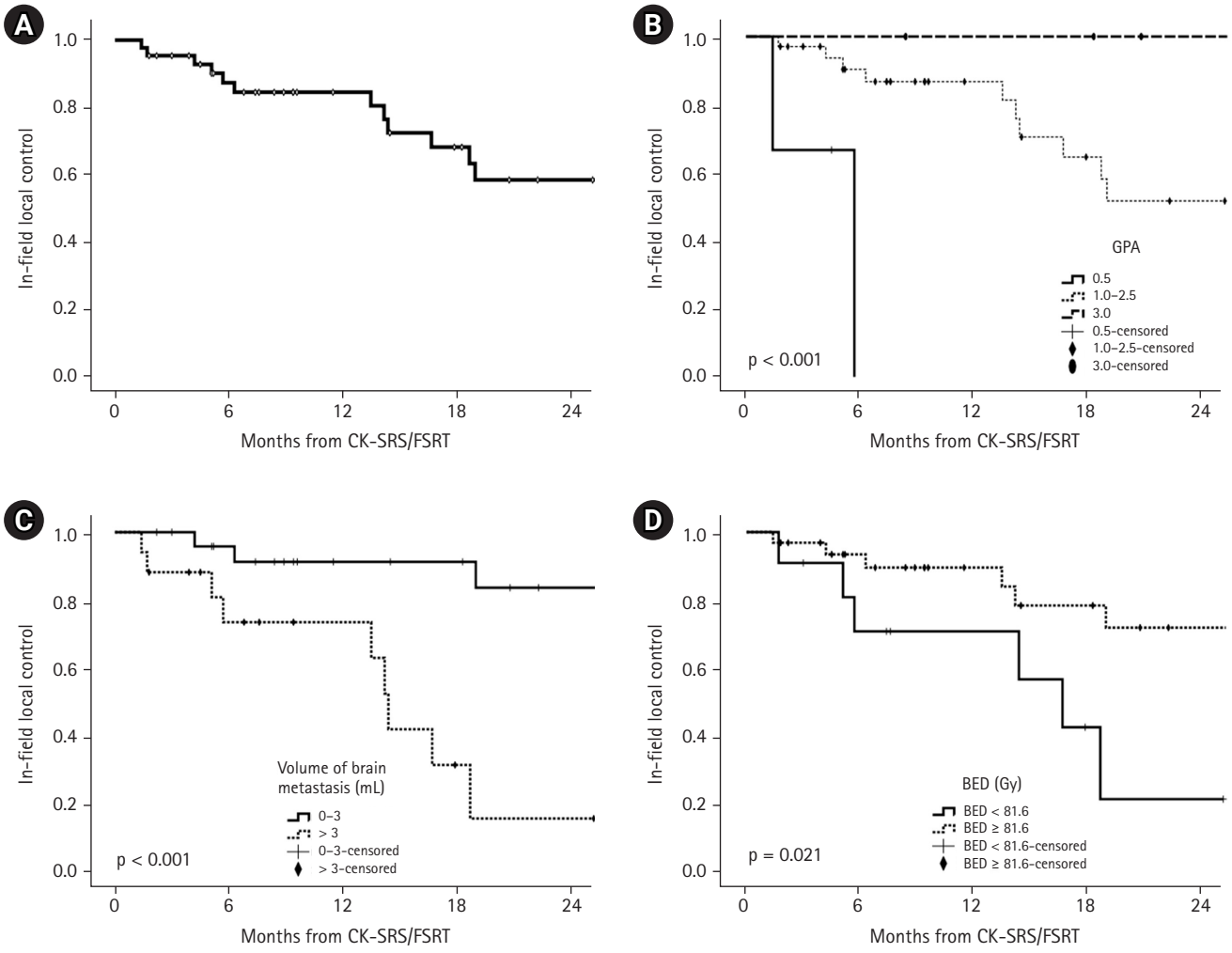

Fig. 2. In-field local control of brain metastasis treated with CK-based SRS/FSRT in the entire cohort (A), in-field local control stratified according to non-small cell lung cancer-specific GPA (B), total volume of brain metastases (C), and BED (D). CK, CyberKnife; SRS, stereotactic radiosurgery; FSRT, fractionated stereotactic radiotherapy; GPA, graded prognostic assessment; BED, biological effective dose based on the linear-quadratic equation with an alpha/beta ratio of 10.

with BM [10-13,16-19] (Table 5).

In line with these studies, our retrospective study showed the efficacy of upfront CK-SRS/FSRT in older patients with BM derived from NSCLC. In the present cohort, the OS and local control rate at 12 months after CK-SRS/FSRT were 78.3% and 84.5%, respectively. In addition, all patients in our study completed the planned CK-SRS/FSRT regimen without moderate or severe acute toxicity. NSCLC-specific GPA was demonstrated to be a strong prognosticator of OS, and the total BM volume was found to be a powerful factor in IFLC after adjusting for other confounding factors. In a previous study, patients aged >65 years with RPA class II had a median OS of 5 months [7]. Additionally, the GPA index showed an OS of 10 months in older patients affected by NSCLC [8,9]. When compared to these results, our study found a median OS of 32 months in ≥65-year-old patients with BM from NSCLC. This difference in survival time may be due to the good performance status (KPS ≥70), ≤10 BMs, with diameters ≤3 cm, and a short follow-up period.

Age, which is a common component of RPA and GPA [7-9], has been defined as an important prognostic factor in most patients with metastatic brain tumors. In many studies in which the proportion of older patients was low, outcomes were worse in older than in younger patients. However, some trials suggested that age should not be a criterion for excluding SRS in patients with BM [16,19]. Noel et al. [16] analyzed the outcomes of LINAC-based SRS for BMs in patients aged ≥65 years, by showing that the median OS was 8 months, which is comparable to that in the younger population. In addition, Higuchi et al. [19], in the prospective study

 https://doi.org/10.3857/roj.2023.00563

Table 4. Prognostic factors related to in-field local control

Characteristic	Univariate			Multivariate	
	1-yr IFLC	2-yr IFLC	p-value	HR (95% CI)	p-value
Age (yr)					
65–70	82.7	61.1	0.999	-	
> 70	87.2	46.5		-	
GPA score					
0.5	0	0	< 0.001	Reference	0.134
1.0–2.5	86.8	51.7		0.163 (0.025–1.041)	0.055
3	100	100		0.083 (0.005–1.485)	0.091
Primary controlled					
Controlled	82.5	51.6	0.976	-	
No controlled	85.2	60.9		-	
Volume of brain metastasis (mL)					
≤ 3	91.3	83.7	< 0.001	Reference	0.025
> 3	73.5	15.8		8.546 (1.314–55.568)	
BED (Gy)					
< 81.6	70.7	21.2	0.021	Reference	0.576
≥ 81.6	89.5	71.8		1.538 (0.340–6.954)	

GPA, graded prognostic assessment; BED, biological effective dose based on the linear-quadratic equation with an alpha/beta ratio of 10; HR, hazard ration; CI, confidence interval.

Table 5. Publications on SRS or FSRT for elderly patients with brain metastases

Study, year	Number of patients	Primary type	RT modality	Treatment modalities (no.)	Outcomes
Noel et al. [16], 2005	117 (≥ 65 yr)	lung (45%), GI (14%), kidney (12%), melanoma (10%)	LINAC (100%)	SRS (79); SRS+WBRT (38)	Mean OS time: 8.0 mo OS rate at 1 yr: 31%
Kim et al. [11], 2008	44 (≥ 75 yr)	lung (39%), others (61%)	LINAC (21%), GK (79%)	SRS (25); SRS+WBRT (19)	Median OS time: 7.3 mo
Minniti et al. [10], 2013	102 (≥ 70 yr)	lung(57%), breast (17%), melanoma (7%)	LINAC (100%)	SRS (102)	Median OS time: 13.2 mo OS rate at 1 yr/2 yr: 63%/28%
Yomo et al. [17], 2016	106 (≥ 80 yr)	lung (70%), GI (15%), melanoma (3%)	GK (100%)	SRS (106)	Median OS time: 7.1 mo
Chen et al. [18], 2017	119 (≥ 70 yr)	lung (85%), kidney (2%), melanoma (2%)		SRS (37); upfront WBRT (82)	Median OS time: 14.4 mo (SRS), 4.3 mo (WBRT)
Higuchi et al. [19], 2019	693 (≥ 65 yr), (JLGK0901-Elderly)	lung (80%), GI (7%), breast (7%)	GK (100%)	SRS (693)	Median OS time: 10.3 mo OS rate at 1 yr: 45%
Gregucci et al. [12], 2019	40 (≥ 65 yr)	lung (57%), breast (18%), melanoma (7%)	LINAC (100%)	SRS (693)	Median OS time: 9 mo OS rate at 1 yr: 39%
Yamamoto et al. [13], 2020	2,915 (≥ 65 yr): NSCLC (1,552 of 65–74 yr; 889 of ≥ 75 yr), SCLC (343 of 65–74 yr; 131 of ≥ 75 yr)	lung (100%): NSCLC (84%), SCLC (16%)	GK (100%)	SRS (2915)	NSCLC Median OS time: 9.7 mo (65–74 yr), 7.8 mo (≥ 75 yr) SCLC Median OS time: 7.3 mo (65–74 yr), 6.9 mo (≥ 75 yr)
Present study	43 (≥ 65 yr)	lung (100%)	CK (100%)	SRS/FSRT (43)	Median OS time: 32 mo OS rate at 1 yr/2 yr: 78%/58%

RT, radiotherapy; GI, gastrointestinal; LINAC, linear accelerator; GK, Gamma Knife; CK, CyberKnife; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy; FSRT, fractionated stereotactic radiotherapy; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; OS, overall survival.

(JLGK0901-Elderly), reported that the median survival time following Gamma Knife SRS was 10 months in older patients (aged ≥ 65 years), although the OS time was shorter than that in those younger than 65 years. The authors concluded that SRS is a favorable treatment option for older patients with BMs.

Korea's population is aging at an unprecedented rate [20]. The proportion of the population aged ≥ 65 years increased from 7% in 1999 to 11.8% in 2012 and is expected to increase to 20.8% by 2026, becoming a super-aged society. Population aging is a medical crisis related to high medical costs for individuals and long-term care costs for families and society [21]. Therefore, this study is valuable in this context, given that it is necessary to continue to consider optimal management for older patients, including those with BMs, to reduce the degree of medical crisis.

We found that the IFLC rate at 12 months was 84.5%, with a median IFLC period of 31 months. In the multivariate analysis related to IFLC, the total metastatic tumor volume was defined as a prognostic factor significantly associated with IFLC. Several studies have explored the efficacy of SRS as primary treatment for BMs, reporting a 12-month IFLC rate of 80%–90%, with low IFLC observed in patients with larger lesions or volumes [17,22,23]. Vogelbaum et al. [22] reported a 12-month IFLC rate of 45% for lesions > 2 cm as compared with 85% for lesions < 2 cm. Chang et al. [23] reported a 12-month

IFLC rate of 86% in tumors ≤ 1 cm in size and 56% in tumors > 1 cm in BM treated with single-fraction SRS. In addition, Yomo et al. [17] defined a cumulative tumor volume (> 2 mL) as the only predictor of a higher IFLC rate. Similar results were observed in our study, showing 73% and 53% of 12-month IFLC for cases with total BM volume of ≤ 3 mL versus > 3 mL, respectively.

All patients completed the planned CK-SRS/FSRT without moderate or severe acute toxicity. Regarding CK-based therapy [24], CK is known as a dedicated SRS/FSRT device consisting of a compact and lightweight linear accelerator mounted on a robotic arm capable of movement with 6 degrees of freedom, allowing submillimeter targeting and unobstructed access to the entire body. Moreover, the device uses an image-guided control loop with target tracking that can be adjusted according to the patient's movement. According to these characteristics, in our study, CK-SRS/FSRT allowed the maintenance of the present quality of life by preventing neurological symptom deterioration or neurological catastrophe.

In recent decades, the circumstances surrounding cancers, including BM, have changed. As systemic therapies have become more efficacious in metastatic disease, the patterns of disease progression have changed with improvements in OS. Among them, oligometastatic BM is an emerging phenomenon, with limited or multiple BMs occurring while extra-cranial disease often remains under control. Yamamoto et al. [25] demonstrated that SRS might be a suitable approach for patients with up to 10 BMs, considering that it has fewer side effects than WBRT, by showing that the median OS in patients with 5–10 BMs was 10.8 months, similar to that of a cohort with 2–4 BMs. Yamamoto et al. [26] also performed a case-matched analysis comparing patients with 2–9 BMs and ≥ 10 BMs, who were treated with SRS. The median OS or SRS-related complications did not differ between the cohorts. The authors suggested that even patients with ≥ 10 BMs could be suitable for SRS. In the new era with changing natural cancer history, establishing the proper approach for intracranial metastatic disease remains crucial [27-29]. Improving the preservation of a patient's quality of life and improving or maintaining tumor control are central dogmas in oncology research. Our study of CK-SRS/FSRT for BM with a focus on older patients represents an effort to achieve this trend and goal by de-escalating treatment volumes [29,30].

This study had several limitations. A significant issue is the patient selection bias inherent to retrospective studies. Our current study included older patients with a limited number of patients with BM who were able to tolerate the treatment. Given the retrospective nature of this study, we could not compare the potential role of SRS/FSRT with that of WBRT. Additionally, although the patient cohort had low heterogeneity overall as their BMs all arose from NSCLC, the relatively small number of patients and short-term follow-up period may have limited the statistical power of the analyses, leading to incomplete conclusions.

In conclusion, we investigated the efficacy of CK-SRS/FSRT for BMs in a cohort of older patients (≥ 65 years of age) and suggested that CK-SRS/FSRT may be an effective treatment individuals of advanced age who have BMs. In particular, among these geriatric patients, those with a high GPA and low total BM tumor volume were considered favorable candidates for active BM treatment, such as SRS/FSRT, as these treatments contribute to longer survival and high local control, without severe side effects.

Statement of Ethics

This retrospective study was reviewed and approved by the Institutional Review Board of Inha University Hospital (No. 2022-09-006).

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

https://doi.org/10.3857/roj.2023.00563

Funding

This work was supported by the Inha University Hospital Research Grant.

Author Contributions

Conceptualization, Lee J. Investigation and methodology, Lee J. Resources, Lee J, Kim HJ, Kim WC. Supervision, Kim HJ, Kim WC. Writing of the original draft, Lee J. Writing of the review and editing, Lee J, Kim HJ, Kim WC. Formal analysis, Lee J. Data curation, Lee J. All the authors have proofread the final version.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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 https://doi.org/10.3857/roj.2023.00563

ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2023;41(4):267-273
https://doi.org/10.3857/roj.2023.00528

Different approaches to target volume definition and boost delivery in surgery de-escalation clinical trial in breast cancer patients with pathological complete response

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Received: June 22, 2023
Revised: September 6, 2023
Accepted: September 12, 2023

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Purpose: We evaluate various approaches to target volume definition and boost delivery in patients with complete response to neoadjuvant systemic therapy (NST) who were treated by radiotherapy without a surgery.

Materials and Methods: A pathological complete response (pCR) was diagnosed in 21 of 27 patients included in "surgery de-escalation" prospective observation study. Clips were placed in the primary tumor volume (PrTV) before NST and during the vacuum aspiration biopsy. Twenty patients with pCR underwent the whole breast irradiation and a boost to the PrTV. High-dose rate brachytherapy (HDRB) was the basic technique for boost delivery. Finally, we identified the value of fused images (computed tomography [CT] before NST with simulation CT), clips and their combination for an accurate boost delivery.

Results: A complete overlap between PrTV on pre-treatment CT with the localization of the clips on simulation CT was mentioned in 10, partial mismatch in three patients. In 12 of these 13 women, HDRB was successfully used for the boost delivery. In five cases we mentioned a marked discrepancy between the PrTV on fused images and the topography of the clips. In other two women we did not find clips on simulation CT. The fused images in five of these seven patients showed anatomical landmarks (scar, fibrosis) used for identification of the gross tumor volume. In all 20 women with pCR (average follow-up of 16.6 months), there were no locoregional recurrences.

Conclusion: Combination of the clips with fusion of pre-NST and simulation CTs is important for an accurate boost delivery.

Keywords: Breast cancer, Neo-adjuvant therapy, De-escalation, Boost, Brachytherapy

Introduction

In patients with triple negative and epidermal growth factor receptor 2-positive (HER2+) breast cancer (BC), modern neoadjuvant systemic treatment (NST) is associated with 60%–80% of pathological complete response (pCR) and improved prognosis [1-3]. It seems that eradication of viable tumor cells advocates for a less aggressive locoregional treatment strategy in these exceptional responders to systemic therapy. Some preliminary data indicate that modern methods of functional imaging are accurate in predicting pCR [4]. On the other hand, markers-guided vacuum-assisted biopy (VAB) is proposed as the option of "de-escalated" minimal invasion surgery permitting pathomorphological evaluation of tumor response to NST [5]. In 2019, we started a single center prospective

observation study of surgery de-escalation in BC patients with pCR to NST. The combination of instrumental diagnostic procedures with VAB is used in protocoling to identify patients with complete response to systemic therapy. Taking into account that in some studies [6,7] the false negative rate of VAB in pCR diagnosis reaches 15%–25%, we consider that radiotherapy with an obligatory boost to the primary lesion is an important component of our protocol. After launching this study, we recognized several different scenarios that influenced the strategy of boost delivery: in some cases, brachytherapy was substituted for external-beam boost, in others gross tumor volume (GTV) was expanded, or "surrogate markers" (fibrosis) were used for implantation and GTV identification.

The aim of this study was to analyze different approaches to target volume definition and boost delivery in complete responders: clips-based strategy, fusion of primary computed tomography (CT) images with simulation CT and combinations of both methods.

Materials and Methods

The single center prospective observation study "Refusal of surgical treatment in patients with pCR after NST of triple negative or HER2-positive BC" was initiated in 2019. The primary endpoint of the study is a 3-year ipsilateral local recurrence rate. The secondary endpoint is a 5-year overall and a relapse-free survival. The protocol was approved by the Institute's Ethics Committee of N.N. Petrov National Cancer Center (No. 1/107, dated 15.08.2019). A written voluntary informed consent was obtained from all patients. Details of this protocol are presented on ClinicalTrials.gov (NCT04293796). Briefly, the inclusion criteria were as follows: women with early (T1-2 N0-1 M0) triple negative or HER2+ BC with lesions not more than 3 cm who received NST according to the protocol. Patients with multicentric disease and women who did not receive the full program of NST and/or indicated radiotherapy, were excluded from the study. All 27 women registered in the study in March 2023 were included in this preliminary analysis. Patients' characteristics are presented in Table 1. All women included in the trial underwent standard staging with mammography, breast and regional lymph nodes ultrasound with obligatory aspiration biopsy of suspicious lymph nodes. As single photon emission computed tomography-CT (SPECT-CT) with ^{99m}Tc-metoxiisobutilisonitril was characterized by high accuracy in diagnosing local extent and lymph node involvement by BC [8], these examinations were used as obligatory for primary staging. Taking into account that in our practice the supine position with the hand behind the head is standard for SPECT-CT examinations of the breasts, it was possible to use CT component of SPECT-CT data for further fusion with simulation CT. Another important component of the study was obligatory clipping of the primary lesion and suspicious/confirmed metastatic lymph nodes before the starting NST.

Details of NST are presented in Table 1. Two–four weeks after the end of neoadjuvant program, all patients underwent mammography, ultrasound, and molecular breast imaging. Subsequent surgical restaging consisted of sentinel lymph node biopsy combined with the excision of clipped suspicious/confirmed metastatic lymph nodes (targeted biopsy) and simultaneous ultrasound-guided VAB with pathomorphologic verification of tumor response to NST. During VAB the primary tumor area was again marked by at least three clips. In patients with residual disease determined as non-complete response in primary tumor and/or axillary lymph nodes, standard surgical treatment with/without adjuvant radiotherapy was initiated according to national guidelines. In women with pCR adjuvant radiotherapy was used as the only adjuvant loco-regional treatment. The whole-breast irradiation (WBI) was performed through tangential fields using the "field-in-field" technique. Initial 15 patients received WBI as 25 fractions of 2 Gy, the rest six patients as 16 fractions of 2.7 Gy. Boost to the primary tumor volume was considered as an obligatory component of adjuvant radiotherapy. As high-dose rate brachytherapy (HDRB) is assumed as a preferred technique for boost delivery, it was performed

Table 1. Baseline patient, tumor, and treatment characteristics

Characteristic	Value
Age (yr)	48.9 (35–68)
Maximum tumor diameter before treatment (mm)	20.1 (7–35)
Tumor grade	
2	13 (48.1)
3	14 (51.9)
Molecular subtype	
HER2+	15 (55.6)
Triple negative	12 (44.4)
Clinical stage (TNM)	
T1N0M0	7 (25.9)
T1N1M0	1 (3.7)
T2N0M0	13 (48.2)
T2N1M0	6 (22.2)
Systemic treatment	
AC+T	2 (7.4)
AC+TC	10 (37)
DCHP	2 (7.4)
AC+DHP	13 (48.2)

Values are presented as median (range) or number (%).
HER2+, epidermal growth factor receptor 2 positive; AC+T, doxorubicin and cyclophosphamide followed by paclitaxel; AC+TC, doxorubicin and cyclophosphamide followed by paclitaxel and carboplatin; DCHP, docetaxel, carboplatin, trastuzumab, and pertuzumab; AC+DHP, doxorubicin and cyclophosphamide followed by docetaxel, trastuzumab, and pertuzumab.

https://doi.org/10.3857/roj.2023.00528

within 1 week after WBI. Interstitial plastic or steel needles (catheters) were placed using intravenous sedation and anaesthesia. Implantations were performed under CT control following the Paris system geometric recommendation.

Planning boost delivery was performed in accordance with the general principles: GTV, the volume of the tumor that was determined before NST; and clinical target volume (CTV), 10–20 mm area around GTV with an increased risk of subclinical invasion of the tumor. Fortunately, in case of "non-surgical" BC treatment, the shape and volume of the breast were similar before the treatment and at the moment of boost delivery. In accordance with the standard technique of postoperative boost delivery, we proposed that clips placed after VAB could be used as the "cornerstones" for delineation of GTV. The Groupe Européen de Curiethérapie–European Society for Radiotherapy and Oncology (GEC-ESTRO) guidelines recommend using images of the primary lesion obtained before the surgery as an additional tool for GTV and CTV contouring [9]. In the presented study, we fused CT component of primary staging SPECT-CT in the supine position with simulation CT in the supine position with hand above the head performed just before the image-guided HDRB or during simulation for external-beam radiotherapy boost. Taking into account possible differences in the position of the arms and bones, the manual 3-dimensional fusion procedure was primarily based on the contours of the breast and localisation of the sub-mammary fold. Another important point for the fusion was the localisation of the nipple. Sternum and ribs were considered as additional but not obligatory fusion points. After the fusion, we determined the correspondence between the position of the clips and primary tumor volume. If the markers accurately corresponded the primary tumor volume, we considered those cases as complete overlap of the volumes; when markers were partly inside and partly outside the primary tumor volume with the distance to primary tumor contour below 2 cm, we determined those cases as a partial mismatch. All other cases were evaluated as marked discrepancy.

Treatment planning was performed on Oncetra Brachy (Elekta, Stockholm, Sweden) planning system by the automatic and graphical dose optimization. HDRB boost dose was delivered as 7 fractions of 2 Gy in/within 4 days or 3 fractions of 4 Gy in/within 3 days. The minimal interval between fractions was 6 hours, maximal 20 hours. External-beam radiotherapy was considered as an alternative "boost" technique in women who refused HDRB or when it was considered suboptimal, for example, when the tumor was localized close to the skin.

Results

From February 2020 to March 2023, 27 consecutive patients (mean age, 48.9 years; range, 35 to 68 years) were included in the study: 24 women obtained clinical complete response (cCR) and 21 of them obtained pCR to the NST (Table 2). The follow-up period ranged from 9 to 26 months (average of 16.6 months). During the follow-up, there were no cases of local and/or regional failure.

After the WBI, 20 of 21 women with pCR finished the treatment according to the protocol and received boost to the primary tumor volume: in 18 cases by HDRB and in the remaining 2 with external-beam radiotherapy. One woman was irradiated in the regional hospital and was excluded from the study. In the remaining 20 patients, pretreatment SPECT-CT (CT component) was fused with simulation CT (in the cases of HDRB before needle insertion).

Data analysis following the fusion demonstrates a complete overlap of primary tumor volumes on SPECT-CT images with the localization of the clips on simulation CT (Fig. 1A, 1B) in 10 of 20 evaluated patients. We mentioned that even after very gentle needle insertion, dramatic changes in breast shape occurred in most of the cases, and accurate fusion of pre-treatment SPECT-CT with post-implantation planning CT was very difficult or impossible (Fig. 2). For this reason, in post-implantation planning CT, we used clips as the guide for GTV contouring. In one woman of that group, we performed the electron boost because the primary tumor volume on fused images and clips was located close to the skin.

A partial mismatch of the tumor volume on staging SPECT-CT with the position of the clips on simulation CT was mentioned in three cases (Fig. 3). In these patients, final planning GTV (GTV_{fin})

Table 2. Outcome data in patients included in the study

Characteristic	n (%)
Clinical response after NST	
Partial (cPR)	3 (11.1)
Complete (cCR)	24 (88.9)
Pathologic response after NST	
HER2+	
Partial (pPR)	4 (26.7)
Complete (pCR)	11 (73.3)
Triple negative	
Partial (pPR)	2 (16.6)
Complete (pCR)	10 (83.4)
Lymph node status according to sentinel lymph node biopsy	
N+	1 (3.7)
N0	26 (96.3)
Locoregional recurrence	
No	26 (96.3)
Yes	1[a] (3.7)

NST, neoadjuvant systemic treatment; HER2+, epidermal growth factor receptor 2 positive.
[a]Local recurrence (tumor bed) after breast-conserving surgery, whole-breast irradiation, and boost to the tumor bed (patient with residual tumor after NST; pPR).

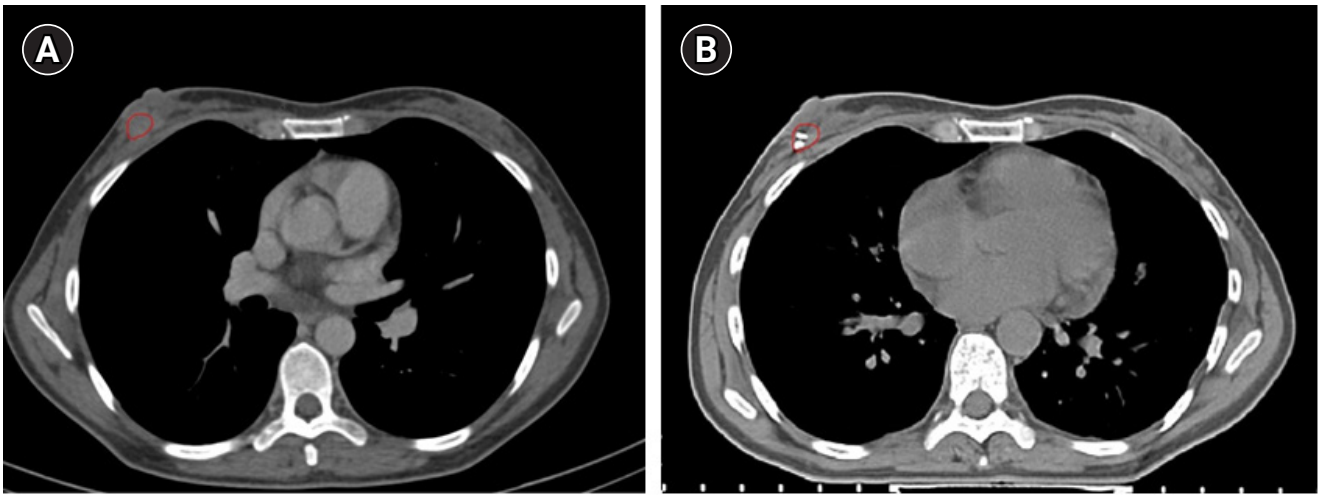

Fig. 1. Complete overlap of primary tumor volume and clips placed during vacuum aspirated biopsy. (A) CT image from staging SPECT-CT with ^{99m}Tc-methoxyisobutylisonitrile. Primary tumor volume clearly identified and contoured with the red line. (B) Fusion of the staging CT with simulation CT performed before needle insertion. Primary tumor volume contoured with the red line, clips perfectly correspond to the primary tumor volume. CT, computed tomography; SPECT, single photon emission computed tomography.

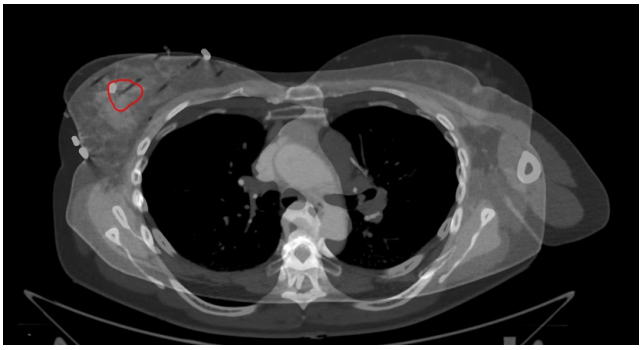

Fig. 2. Prominent differences in the breast shape and volume on the computed tomography images obtained before and after the implantation of the needles for brachytherapy.

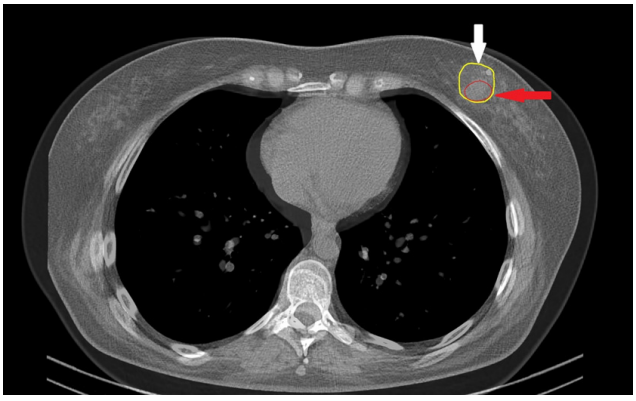

Fig. 3. Fused images of CT performed before starting treatment (from staging SPECT-CT) and simulation CT before boost delivery. Example of partial mismatch between the tumor contours on staging CT (red) with the position of the clips on simulation CT (white arrow). Final GTV (yellow) created as the sum of the GTV delineated after fusion (red) and expansion of this volume to cover clips placed during vacuum aspirated biopsy. CT, computed tomography; SPECT, single photon emission computed tomography; GTV, gross tumor volume.

was created as the sum of the GTV_{fus} obtained after the fusion of pre-treatment SPECT-CT with planning CT and GTV_{clips} contoured according to the localization of the clips. From our experience both volumes can be used on planning CT after the needle insertion, so it is the reason for choosing HDRB as the preferred method of boost delivery in these patients too.

The third situation is characterised by a marked discrepancy in the localization of primary lesion in fused images and topography of the clips placed after VAB (Fig. 4). This scenario was mentioned in five observations. The migration of the clips can be considered the most probable explanation of these discrepancies; in addition, technical defects during the clip placement can cause these inaccuracies. Optimal technique of boost delivery and GTV delineation was chosen according to the following algorithm: in those three cases when it was possible (after fusion of SPECT-CT with pre-implantation CT) to identify anatomical landmarks for subsequent brachytherapy planning (the scar and fibrosis in the area of the primary lesion (Fig. 5), HDRB can be considered as an acceptable method for boost delivery. In these cases, the identified anatomical landmarks were used on post-implantation CT for contouring of the GTV. On the contrary, when we failed to find anatomical landmarks for identification of the GTV after the needle insertion in one woman, she was considered for external-beam boost with GTV_{fin}

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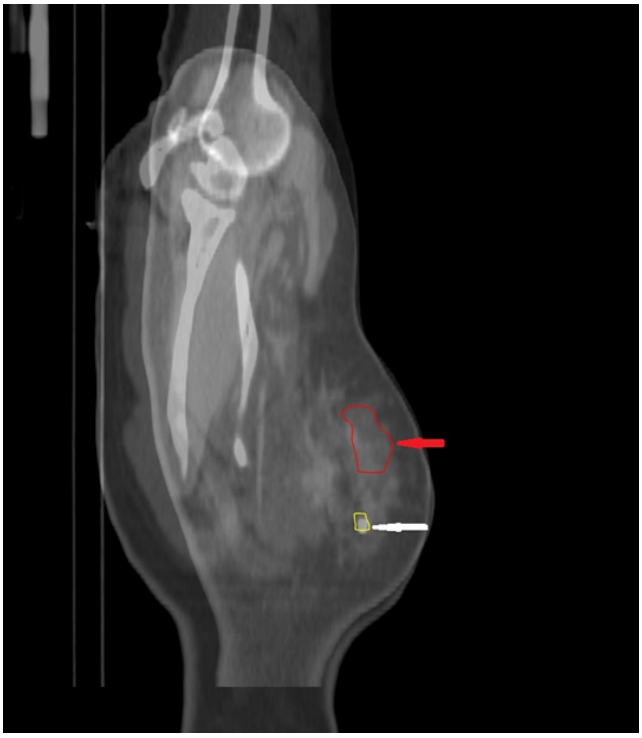

Fig. 4. Fused images of CT performed before starting treatment (from staging SPECT-CT) and simulation CT. Major mismatch between primary tumor volume (red) and localization of the clips (white arrow). In this case, boost to the primary tumor area was performed by external-beam radiotherapy, gross tumor volume contoured on fused images according to the localization of the primary lesion on SPECT-CT. CT, computed tomography; SPECT, single photon emission computed tomography.

identical to GTV_{fus} (Fig. 5).

In one observation the differences in the topography of GTV_{clips} and GTV_{fus} were pronounced (without overlap of the volumes) and unclear. In that case, we used external-beam radiotherapy as the preferable technique for boost delivery and delineated boost GTV_{fin} as the sum of GTV_{fus} and GTV_{clips}

In the remaining two women we failed to find the clips but both patients had extensive focal fibrotic areas localised directly in the area of primary tumor volume in the fused images. In both cases, we performed "fibrosis-guided" HDRB boost.

Discussion and Conclusion

In the presented study group, modern NST demonstrated high (77.8%) rate of pCR comparable with the data of some other studies [1-3]. This indicates that many recent patients with triple negative and Her2+ BC can be good candidates for the surgery de-escalation. On the other hand, our recent unpublished research of 97 patients with residual BC after NST treated with a standard surgery with postoperative irradiation indicates that 5-year rates of locoregional relapses were even higher than distant failure: 20% versus 19% in triple-negative, and 8% versus 6% in HER2+ BC. This leads us to the following: the adjuvant radiotherapy with obligatory boost to the primary tumor volume must be considered as an important part of protocols with surgery de-escalation. The choice of HDRB as the basic method of boost delivery has several reasons. From one point of view, dosimetric studies demonstrate that brachytherapy boost compared to external-beam techniques is

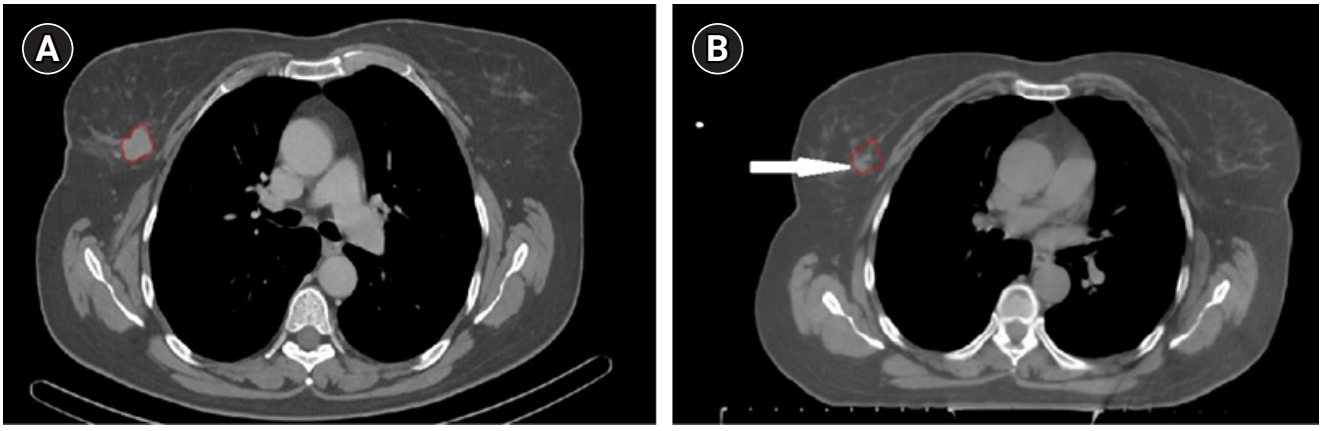

Fig. 5. Focal fibrosis that helps identifying primary tumor volume. (A) CT image from staging SPECT-CT with ^{99m}Tc-methoxyisobutylisonitrile. Primary tumor volume clearly identified and contoured with the red line. (B) Fusion of the staging CT with simulation CT performed before needle insertion. On fused images, focal fibrosis (white arrow) perfectly corresponds to the localization of the primary tumor volume (red contour). This anatomical landmark guided needle insertion was used for contouring gross tumor volume for boost delivery. CT, computed tomography; SPECT, single photon emission computed tomography.

characterized by significantly lower doses to the organs-at-risk [10]; first of all, by significant reduction (2–10 times) of the ipsilateral breast irradiated volume [11]. In addition, it is well known that HDRB technique is characterized by the measurable inhomogeneity of dose distribution. According to GEC-ESTRO recommendation, in patients with BC HDRB the boost non-uniformity index must be kept below 0.35 in order to preserve good cosmetic results [9]. This means that up to one-third of boosting tumor volume would receive 150% and more of the prescribed dose and probably because of this feature the brachytherapy boost is associated with the highest local control [12,13]. In particular, Poortmans et al. [12] in the largest prospective multicenter randomized boost study reported only 2.3% recurrence rate after brachytherapy boost and non-significant but substantial increase in local recurrence rate after electron or photon boosts (4.7% and 4.0%, respectively). Of special value for our decision was the study of Guinot et al. [13] stating that 248 BC patients with close or positive resection margins demonstrated that even in this unfavorable clinical situation HDRB can successfully substitute re-resection with free margins: 86.9%–96.2% 10-year local tumor control can be reached with 3 × 4.4 Gy HDRB boost.

Placement of the clips is a simple and perfectly validated tool for accurate identification of the primary tumor volume used for boost delivery. Unfortunately, VAB performed for a pathologic verification of tumor response took away those clips together with the tumor sample. As was shown in our study, the secondary clipping of the VAB area can successfully navigate the delivery of the boost to the primary tumor volume in many (65%) but not in all cases. In some patients (35%) the displacement of the clips can be corrected by anatomical landmarks of the primary tumor volume. In most difficult situations when clip displacement is associated with the absence of anatomical landmarks of primary tumor, the best solution for boost delivery seems to be external-beam radiotherapy with the use of fused images for GTV contouring. The diversity of clinical situations indicates that the "verification" fusion of the primary CT with the simulation CT is a very useful tool for identification of the optimal strategy for boost delivery.

Now it is possible to mention that the strategy of surgery de-escalation is only making its first steps: from the early publications [14-16] to the recent reports [5,17] the opportunities of nonsurgical treatment of BC were discussed with cautions. Mature results of few ongoing studies would be probably able to change this situation.

From our point of view, the attempts for eliminating VAB can be a very interesting and promising opportunity for further development of this strategy that would convert minimal invasive treatment to non-invasive protocols. A low diagnostic accuracy of modern diagnostic modalities (positron emission tomography-CT, magnetic resonance imaging, ultrasound, mammography) in predicting pCR is considered the main obstacle on the way to refuse invasive diagnostic procedures such as VAB [18]. On the other hand, it was already demonstrated that scintimammography performed in the middle of NST could identify (with moderate sensitivity but very high specificity patients (94%) who could reach pCR after the end of NST [19]. It seems that in these patients, VAB particularly can be safely omitted, and women can be treated with a "no surgery" approach. Even if we assume that the risk to overestimate the response to NST in these cases is slightly higher than after VAB, the adjuvant radiotherapy with local boost would probably be able to control this misdiagnosed "pCR."

In conclusion, we would like to propose several recommendations for the radiotherapy part of surgery de-escalation protocols.

Similarities in the shape and volume of the breast along the whole treatment time in patients included in the protocol of BC treatment with surgical de-escalation permit an effective utilization of pre-NST CT and simulation CT fusion before the boost delivery. Fusion enables visualization of the primary tumor volume and verification of correct/incorrect localization of clips that mark the primary tumor volume.

Brachytherapy boost can be performed in women with correct clip placement and in cases when primary tumor volume can be correctly determined with the help of anatomical landmarks. In the remaining patients, boost delivery with external-beam radiotherapy seems more accurate and effective.

Statement of Ethics

The study was approved by the Institute's Ethics Committee (No. 1/107, dated 15.08.2019). A written voluntary informed consent was obtained from all patients.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Author Contributions

Conceptualization, Novikov SN, Krivorotko P, Kanaev S. Investigation and methodology, Novikov SN, Krivorotko P, Bryantseva Z,

Akulova I, Krzhivitskiy P. Data curation, Emelyanov A, Krzhivitskiy P, V, Ponomareva O. Writing of the original draft, Novikov SN, Bryantseva Z, Emelyanov A, Kanaev S. Writing of the review and editing, Novikov SN, Krivorotko P, Bryantseva Z, Akulova I, Emelyanov A, Mortada V, Ponomareva O, Krzhivitskiy P, Kanaev S.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2023;41(4):274-282
https://doi.org/10.3857/roj.2023.00773

Pulmonary function and toxicities of proton versus photon for limited-stage small cell lung cancer

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Received: September 1, 2023
Revised: September 26, 2023
Accepted: October 10, 2023

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Purpose: We aimed to compare the oncological outcomes and toxicities of definitive proton beam therapy (PBT) and photon beam therapy in patients with limited-stage small cell lung cancer (LS-SCLC).

Materials and Methods: We retrospectively reviewed 262 patients with newly diagnosed LS-SCLC who underwent definitive PBT (n = 20; proton group) or photon beam therapy (n = 242; photon group) with concurrent chemotherapy between January 2016 and February 2021 and compared overall survival (OS), progression-free survival (PFS), dose-volume parameters, and toxicities between the groups.

Results: The median follow-up duration was 24.5 months (range, 3.7 to 78.7). Baseline lung function was significantly worse and clinical target volume (CTV) was larger in the proton group (CTV: 296.6 vs. 215.3 mL; p = 0.080). The mean lung V_{10} was 37.7% ± 16.8% and 51.6% ± 24.5% in the proton and photon groups, respectively (p = 0.002). Two-year OS and PFS rates were 57.2% and 35.7% in the proton group and 65.3% and 40.8% in the photon group, respectively (p = 0.542 and 0.748, respectively). Grade ≥2 radiation pneumonitis and esophagitis occurred in 5 (25.0%) and 7 (35.0%) PBT-treated patients and 66 (27.3%) and 40 (16.5%) photon beam therapy-treated patients, respectively (p = 0.826 and 0.062, respectively).

Conclusion: Although the proton group had poorer lung function and a larger CTV than that in the photon group, both groups exhibited comparable treatment outcomes and radiation-related toxicities in LS-SCLC. PBT may be a valuable therapeutic modality in patients with poor pulmonary function or extensive disease burden owing to its lung-sparing ability.

Keywords: Small cell lung cancer, Proton beam therapy, Radiation therapy

Introduction

Assessing pulmonary function is essential before determining whether thoracic surgery or definitive radiation therapy (RT) is necessary [1]. Poor baseline lung function is often considered a contraindication to definitive RT for lung cancer [1]. Radiation pneumonitis is one of the most important dose-limiting factors of RT in patients with thoracic cancer [1]. It is the most frequent toxicity following concurrent chemoradiotherapy (CCRT), with decreased respiratory function and reduced quality of life [2-5]. Worse pulmonary function at treatment may adversely affect lung complications or survival outcomes following definitive RT [6-8].

Proton beam therapy (PBT) can reduce radiation exposure to neighboring normal tissues due to its "Bragg peak" property [9]. The ability of PBT to reduce doses to these normal organs-at-risk (OARs) has been demonstrated in locally advanced non-small cell

lung cancer, and dosimetric advancements have been reported in comparison with photon beam therapy [10-12]. The dosimetric benefits of PBT can result in reduced toxicity and even improved survival rates [13]. As CCRT is the mainstay of treatment for limited-stage small cell lung cancer (LS-SCLC), it can increase the risk of esophagitis and pulmonary toxicity, in part because of the anatomic proximity of the large target volume and centrally located disease to critical OARs [14,15]. However, evidence on the efficacy and safety of PBT compared to photon beam therapy in patients with LS-SCLC is scarce. Herein, we conducted a study to determine whether PBT is effective despite poor lung function compared to photon beam therapy in patients with LS-SCLC.

Materials and Methods

1. Study design and patients

This retrospective study was conducted at a single tertiary institution. The eligibility criteria were as follows: histologically diagnosed SCLC, no history of prior therapy for the targeted lesion, and underwent RT between January 2016 and February 2021.

After obtaining approval from the Institutional Review Board of Samsung Medical Center (No. 2022-10-108-001), we identified 511 patients who underwent RT for SCLC between January 2016 and February 2021. A total of 249 patients were excluded because of combined histology (n = 27); extensive stage (n = 12); treatment of salvage, adjuvant, or palliative therapy (n = 188); or RT alone (n = 8); and incomplete treatment (n = 14). Ultimately, we retrospectively reviewed the medical records of 262 patients; 20 patients had undergone PBT (proton group), while 242 had received photon beam therapy (photon group). A consort diagram is shown in Fig. 1. The requirement for informed consent was waived due to the retrospective nature of this study.

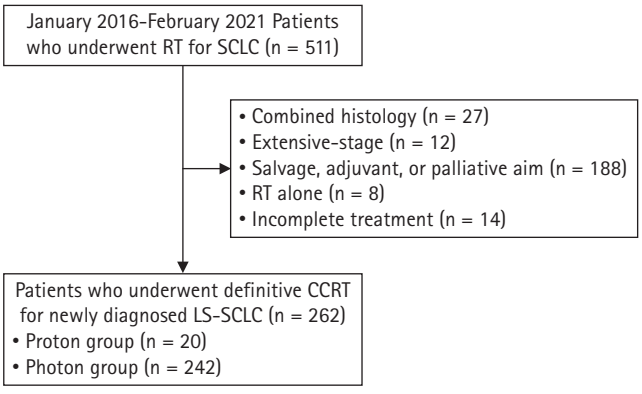

Fig. 1. Consort diagram. RT, radiation therapy; SCLC, small cell lung cancer; CCRT, concurrent chemoradiotherapy; LS, limited-stage.

2. Treatment plan

Most chemotherapy regimens were comprised of etoposide and cisplatin administered via intravenous infusion. Based on our previous findings, CCRT was mostly initiated on the third cycle (n = 223, 85.1%), followed by the first cycle of chemotherapy [16]. Consolidative durvalumab was administered every 3 weeks when prescribed [17].

Prior to RT, each patient underwent a four-dimensional simulation computed tomography (CT). Based on all available clinical information, the gross tumor volume (GTV) was delineated on CT images from 10 breathing phases, covering all phases of the breathing cycle. The internal target volume (ITV) was generated from the GTV of each CT image. The clinical target volume (CTV) was defined by expanding up to a 0.5–0.7 cm margin from the ITV and was modified according to the adjacent organs. In cases where RT was administered after two cycles of chemotherapy, the CTV was modified to reflect primary tumor shrinkage, considering the post-chemotherapy chest CT images [16]. However, despite the significant response, the initially involved lymph node stations were included within the CTV [16]. An additional margin of 5 mm was applied to the CTV to generate the planning target volume. For the prescribed dose, a biologically effective dose was calculated using the standard linear-quadratic model with an α/β of 10 Gy for SCLC, a commonly used value. A median total dose of 52.5 Gy (range, 52.5 to 61.6) was prescribed, with a fractional dose of 2.1 Gy (range, 2.0 to 2.2), as reported previously [16]. The criteria for selecting PBT at our institution are poor pulmonary function at baseline or underlying pulmonary diseases, such as pulmonary fibrosis or chronic obstructive pulmonary disease. The relative biological effectiveness (RBE) of PBT was considered a fixed value of 1.1.

Prophylactic cranial irradiation (PCI) was administered to patients who achieved a complete or very good partial response after CCRT [16]. The main dose scheme for PCI was 25 Gy in 10 fractions.

3. Endpoints and statistical analysis

The primary endpoints were to compare patients' characteristics, including pulmonary function and toxicities, between the two groups. The secondary endpoints were overall survival (OS) and progression-free survival (PFS). The duration of OS was calculated from the start date of chemotherapy to the date of death or last follow-up. Likewise, PFS duration was calculated from the start date of chemotherapy to the date of progression or the last follow-up. Dosimetric parameters for the target volume or normal organs were analyzed using dose-volume histograms. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (version 5.0).

Differences in continuous variables between the two groups were analyzed using Student t-test or the Mann-Whitney U test.

Chi-squared or Fisher exact test was used to evaluate differences in categorical variables between the two groups. OS and PFS were estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariate analyses of OS and PFS were performed using Cox regression analysis. The RT modality and factors ($p < 0.2$ in the univariate analysis) were further assessed using multivariate analysis. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS Statistics (version 27.0; IBM Inc., Armonk, NY, USA).

Results

1. Patients' characteristics

Table 1 describes the patients' baseline characteristics according to the RT modality. Approximately 75% of the patients in the photon group underwent intensity-modulated RT. The proton group comprised more patients aged ≥ 65 years than in the photon group (70.0% vs. 49.2%, respectively). Regarding baseline lung function, PBT-treated patients had worse values in terms of forced expiratory

Table 1. Baseline characteristics according to radiation modality

Characteristic	Proton (n = 20)	Photon (n = 242)	p-value
Age (yr)			0.073
< 65	6 (30.0)	123 (50.8)	
≥ 65	14 (70.0)	119 (49.2)	
Sex			0.272
Female	4 (20.0)	27 (11.2)	
Male	16 (80.0)	215 (88.8)	
ECOG performance status			0.745
0	2 (10.0)	17 (7.0)	
1	18 (90.0)	221 (91.3)	
2–3	0 (0)	4 (1.7)	
Smoking history			0.398
Yes	17 (85.0)	222 (91.7)	
No	3 (15.0)	20 (8.3)	
Elevated LDH[a]			0.503
Yes	10 (50.0)	96 (39.7)	
No	9 (45.0)	116 (47.9)	
Unknown	1 (5.0)	30 (12.4)	
FEV1 (% of predicted)			0.012
< 50	4 (20.0)	7 (2.9)	
≥ 50	16 (80.0)	226 (93.4)	
Unknown	0 (0)	9 (3.7)	
DLCO (% of predicted)			0.011
< 60	9 (45.0)	39 (16.1)	
≥ 60	11 (55.0)	190 (78.5)	
Unknown	0 (0.0)	13 (5.4)	
TTF-1			0.517
Positive	16 (80.0)	165 (68.2)	
Negative	3 (15.0)	40 (16.5)	
Unknown	1 (5.0)	37 (15.3)	
Stage[b]			1.000
I, II	2 (10.0)	32 (13.2)	
III	18 (90.0)	210 (86.8)	
Durvalumab			0.383
Yes	2 (10.0)	48 (19.8)	
No	18 (90.0)	194 (80.2)	
PCI			0.378
Yes	5 (25.0)	84 (34.7)	
No	15 (75.0)	158 (65.3)	

Values are presented as number (%).
ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; FEV1, forced expiratory volume in one second; DLCO, diffusing capacity for carbon monoxide; TTF1, thyroid transcription factor-1; PCI, prophylactic cranial irradiation.
[a]Values higher than the reference range (135–225 U/L).
[b]Stage according to the American Joint Committee on Cancer 8th edition.

https://doi.org/10.3857/roj.2023.00773

volume in one second, i.e., <50% of the predicted value (20.0 vs. 2.9; p = 0.012), and diffusing capacity for carbon monoxide (DLCO), i.e., < 60% of the predicted value (45.0 vs. 16.1; p = 0.011), than in patients who received photon beam therapy. There was no difference in the use of consolidative durvalumab between the two groups (19.8% vs. 10.0%; p = 0.383).

2. Dosimetric parameters

The proton group had a larger mean CTV than the photon group (296.6 vs. 215.3 mL; p = 0.080). The dosimetric parameters are shown in Fig. 2. The mean lung V_{10} was 37.7% ± 16.8% and 51.6% ± 24.5% in the proton and photon groups, respectively (p = 0.002). The mean lung dose in the proton group was numerically lower than that in the photon group, but it was not statistically different (857.3 vs. 983.1 cGy; p = 0.343). Furthermore, the proton group had a significantly lower mean heart dose than that in the photon group (651.5 vs. 938.4 cGy; p = 0.004). Additionally, we found that the mean esophagus V_{45} was 12.6% ± 18.7% and 10.9% ± 14.1% in the proton and photon groups, respectively (p = 0.697).

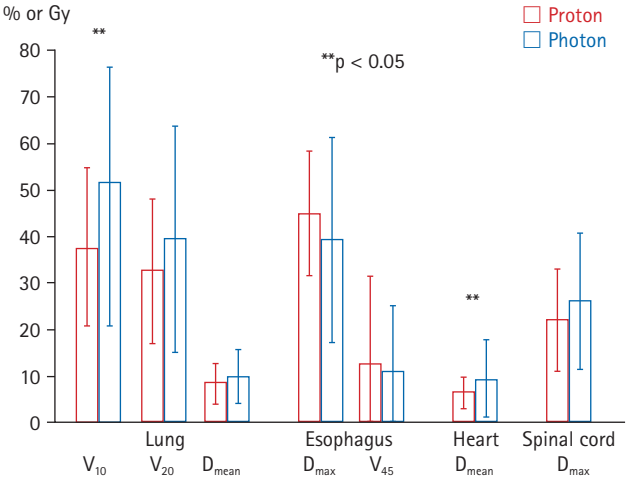

Fig. 2. Comparison of dosimetric parameters of lung and other organs at risk between the proton group (red color) and photon group (blue color). Data are presented as the mean with standard deviation. V_x, volume receiving x% of the prescription dose; D_{mean}, mean dose; D_{max}, maximum dose.

3. Clinical outcomes

Considering the total cohort, the median follow-up was 24.5 months (range, 3.7 to 78.7); 21.9 and 24.6 months in the proton and photon groups, respectively. Fig. 3 shows a comparison of OS and PFS between the two groups. The 2-year OS and PFS rates were 57.2% and 35.7%, respectively, in the proton group and 65.3% and 40.8%, respectively, in the photon group (p = 0.542 and 0.748, respectively); however, there were no statistically significant differences between the two groups.

Table 2 shows the univariate and multivariate models of OS. Univariate analysis revealed no statistically significant differences between RT modalities (p = 0.514). Multivariate analysis revealed that RT modality was not associated with OS (hazard ratio [HR] = 1.885; 95% confidence interval [CI], 0.878–4.050; p = 0.104), although DLCO, stage, PCI, and durvalumab were significant prognostic factors for OS.

Additionally, Table 3 shows the univariate and multivariate analyses of PFS. According to the Cox regression analysis, RT modality was not associated with PFS (HR = 1.064; 95% CI, 0.580–1.950; p = 0.841). Stage and PCI were demonstrated as significant prognostic factors for PFS.

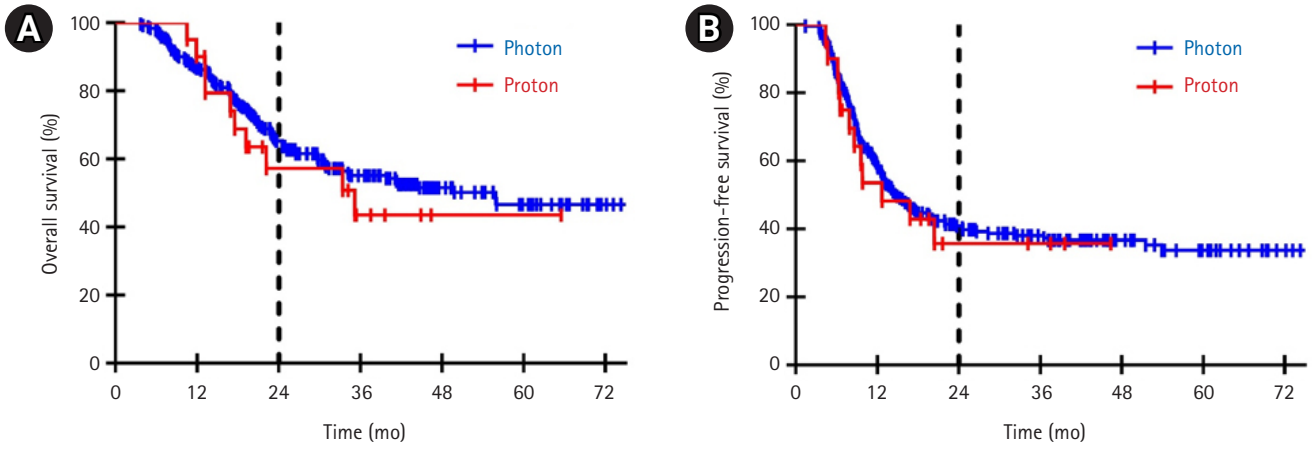

Fig. 3. (A) Overall survival and (B) progression-free survival between the proton group (red line) and photon group (blue line).

Table 2. Prognostic factors for overall survival (OS) in univariate and multivariate analyses

Variable	n	Univariate analysis		Multivariate analysis	
		2-year OS (%)	p-value	HR (95% CI)	p-value
RT modality			0.514		0.104
Proton	20	57.2		1	
Photon	242	65.3		1.885 (0.878–4.050)	
Age (yr)			0.042		0.247
< 65	129	70.8		1	
≥ 65	133	58.6		1.305 (0.831–2.049)	
Sex			0.812		
Female	31	70.4		-	
Male	231	63.9		-	
Smoking history			0.302		
Yes	239	63.4		-	
No	23	79.9		-	
FEV1 (% predicted)			0.645		
< 50	11	72.7		-	
≥ 50	242	64.4		-	
DLCO (% predicted)			0.018		0.020
< 60	48	51.7		1.739 (1.091–2.771)	
≥ 60	201	67.7		1	
TTF-1			0.616		
Negative	43	64.4		-	
Positive	181	64.9		-	
CTV (mL)			0.003		0.054
< 300	204	68.1		1	
≥ 300	58	52.3		1.586 (0.993–2.534)	
Stage[a]			0.009		0.038
I, II	34	83.4		1	
III	228	61.9		2.209 (1.046–4.664)	
Elevated LDH[b]			0.125		0.234
Yes	106	59.3		1.275 (0.855–1.901)	
No	125	65.9		1	
PCI			< 0.001		0.005
Yes	89	83.0		1	
No	173	54.9		2.083 (1.245–3.483)	
Durvalumab			0.002		0.008
Yes	50	78.5		1	
No	212	61.4		2.902 (1.329–6.337)	
SER (day)			0.128		0.296
< 90	204	67.7		1	
≥ 90	58	54.7		1.273 (0.810–2.000)	

RT, radiation therapy; FEV1, forced expiratory volume in one second; DLCO, diffusing capacity for carbon monoxide; TTF1, thyroid transcription factor-1; CTV, clinical target volume; LDH, lactate dehydrogenase; PCI, prophylactic cranial irradiation; SER, time between the start of chemotherapy and the end of radiation therapy; HR, hazard ratio; CI, confidence interval.
[a]Stage according to the American Joint Committee on Cancer 8th edition.
[b]Values higher than the reference range (135–225 U/L).

4. Safety

Table 4 summarizes the treatment-related complications according to the RT modality. Grade ≥ 2 radiation pneumonitis was observed in five (25.0%) PBT-treated patients, and 66 (27.3%) patients who received photon beam therapy (p = 0.826). Furthermore, the proton group had a higher incidence of grade ≥ 2 radiation esophagitis than the photon group (35.0% vs. 16.5%; p = 0.062). Additionally, the rate of grade 2 or higher radiation dermatitis was not different between the two groups (5.0% vs. 1.2%; p = 0.274). None of the patients in either group experienced grade ≥ 4 toxicities.

Discussion and Conclusion

This study compared the clinical efficacy and safety of PBT and

https://doi.org/10.3857/roj.2023.00773

Table 3. Prognostic factors for progression-free survival (PFS) in univariate and multivariate analyses

Variable	n	Univariate analysis		Multivariate analysis	
		2-year PFS (%)	p-value	HR (95% CI)	p-value
RT modality			0.748		0.841
Proton	20	35.7		1	
Photon	242	40.8		1.064 (0.580–1.950)	
Age (yr)			0.034		0.555
< 65	129	46.5		1	
≥ 65	133	34.4		1.120 (0.769–1.630)	
Sex			0.903		
Female	31	42.6		-	
Male	231	40.2		-	
Smoking history			0.845		
Yes	239	40.1		-	
No	23	45.1		-	
FEV1 (% predicted)			0.282		
< 50	11	54.5		-	
≥ 50	242	39.3		-	
DLCO (% predicted)			0.481		
< 60	48	32.1		-	
≥ 60	201	41.4		-	
TTF-1			0.758		
Negative	43	49.6		-	
Positive	181	38.8		-	
CTV (mL)			0.082		0.200
< 300	204	42.4		1	
≥ 300	58	33.8		1.290 (0.874–1.905)	
Stage[a]			0.007		0.011
I, II	34	55.7		1	
III	228	38.1		2.020 (1.174–3.474)	
Elevated LDH[b]			0.219		
Yes	106	38.2		-	
No	125	39.1		-	
PCI			0.003		0.022
Yes	89	51.1		0.618 (0.409–0.934)	
No	173	34.8		1	
Durvalumab			0.150		0.394
Yes	50	47.7		0.830 (0.541–1.274)	
No	212	38.7		1	
SER (day)			0.986		
< 90	204	40.6		-	
≥ 90	58	39.8		-	

RT, radiation therapy; FEV1, forced expiratory volume in one second; DLCO, diffusing capacity for carbon monoxide; TTF1, thyroid transcription factor-1; CTV, clinical target volume; LDH, lactate dehydrogenase; PCI, prophylactic cranial irradiation; SER, time between the start of chemotherapy and the end of radiation therapy; HR, hazard ratio; CI, confidence interval.
[a]Stage according to the American Joint Committee on Cancer 8th edition.
[b]Values higher than the reference range (135–225 U/L).

photon beam therapy in patients with LS-SCLC. Although PBT-treated patients had relatively worse lung function and a larger target volume than those who received photon beam therapy, the oncological outcomes and treatment-related toxicities did not significantly differ between the two groups.

In this study, neither OS nor PFS differed significantly between the two groups (p = 0.542 and 0.748, respectively). Specifically, the proton and photon groups demonstrated 5-year OS rates of 43.6% and 46.6%, respectively, which are consistent with previously reported rates [16,18]. The addition of thoracic RT has been shown to improve the survival of patients with LS-SCLC [18-20]. Previous meta-analyses that included more than 2,000 patients revealed that thoracic radiation for LS-SCLC could yield a 5% to 7% improvement in the 2-year OS compared to that in chemotherapy

Table 4. Treatment-related toxicities according to radiation modality

Toxicities	Proton (n = 20)	Photon (n = 242)	p-value
Radiation pneumonitis			0.826
Grade 0–1	15 (75.0)	176 (72.7)	
Grade 2–3	5 (25.0)	66 (27.3)	
Radiation esophagitis			0.062
Grade 0–1	13 (65.0)	202 (83.5)	
Grade 2–3	7 (35.0)	40 (16.5)	
Radiation dermatitis			0.274
Grade 0–1	19 (95.0)	239 (98.8)	
Grade 2–3	1 (5.0)	3 (1.2)	

Values are presented as number (%).

alone [19,20]. Furthermore, a more recent series has reported a 5-year OS rate exceeding 30%, approaching the outcomes of locally advanced NSCLC at a similar stage [18].

Although the rate of grade ≥2 esophagitis was higher in the proton group (35.0% vs. 16.5%; p = 0.062), PBT showed similar toxicity profiles compared to that in photon beam therapy. The higher rate of grade ≥2 esophagitis in the proton group might be caused by the higher dose to the esophagus as shown in the maximum dose of the esophagus and the results of esophagus V_{45}. We also analyzed the shortest distances between CTV and esophagus in the total cohort. As a result, we identified that the mean distance was 4.7 ± 13.6 mm and 6.1 ± 11.7 mm in the proton and photon groups, respectively (p = 0.661). This anatomical relationship might have affected the results of esophagitis. PBT has been increasingly used as a definitive treatment for patients with LS-SCLC [14,21]. Colaco et al. [21] reported the results of six patients who received PBT with cisplatin/etoposide chemotherapy. Except for one patient, all patients received concurrent treatment, and only one received daily RT (60–66 Gy [RBE]). None of the patients experienced grade ≥3 toxicities. The largest prospective observational study involving 30 patients was recently reported [14]. All the patients received platinum and etoposide concurrently with PBT. Twelve patients received twice-daily PBT (45 Gy [RBE]), and the remainder underwent daily treatment (59.4–66.6 Gy [RBE]). Dosimetric analyses revealed substantially lower heart dose parameters with PBT, along with reductions in lung V5 and mean lung doses (not V_{20}). Grade 3 toxicities were limited to one case of anorexia (daily treatment) and one case each of pneumonitis and pericardial effusion (twice-daily treatment). We consistently observed that PBT-treated patients had substantially lower lung V_{10} and mean heart dose values than in patients who received photon beam therapy. The findings of our study and those reported previously suggest that PBT may be tolerated and appropriate for limiting normal tissue toxicity, such as in normal lung tissues, because of its unique depth-dose curve with a Bragg peak [22,23]. Furthermore, given that patients with LS-SCLC can develop locoregional recurrence after the initial CCRT, PBT may allow safe re-irradiation [24].

Based on clinical trial data, the preferred first-line systemic treatment for extensive-stage SCLC involves durvalumab in combination with etoposide and cisplatin (or carboplatin), followed by maintenance durvalumab [25-27]. However, there is limited evidence supporting the use of immunotherapy in patients with LS-SCLC. A recent phase II study demonstrated the promising clinical efficacy of consolidative durvalumab in combination with CCRT for LS-SCLC [17]. With a median follow-up duration of 26.6 months, the 2-year OS rate was 67.8%. These findings suggest that durvalumab with CCRT may be clinically relevant, affording improved survival outcomes compared to the historical control treatment in patients with LS-SCLC. In this study, durvalumab was identified as a significant prognostic factor for OS in the multivariate analysis. Furthermore, it has been reported that proton or carbon ion may stimulate the immune system to a greater degree than photons [28,29].

Intracranial metastases have been found to occur in more than 50% of patients with SCLC. According to randomized studies, PCI can effectively decrease the incidence of brain metastases; however, most individual studies lack sufficient power to demonstrate a meaningful survival benefit [30]. However, a meta-analysis of available randomized trials reported a 5.4% increase in the 3-year OS of PCI-treated patients, from 15.3% in the control group to 20.7% in the PCI group [31]. The observed advantages were similar between the patients with LS and those with extensive-stage SCLC. Similarly, in this study, we identified PCI as a significant prognostic factor for OS. Accordingly, PCI can be recommended for patients with LS-SCLC. In contrast, shared decision-making is recommended for patients aged ≥70 years with a risk of neurocognitive impairment [17,32].

This study has several limitations. First, the potential for selection bias due to the retrospective nature of the study cannot be excluded. Second, the clinical outcomes may have been distorted due to the insufficient sample size and single-center design. Finally, the oncological outcomes may have been overestimated because of the short follow-up period. Despite these limitations, to the best of our knowledge, this study is the first to compare proton and photon therapies as curative RT modalities in patients with newly diagnosed LS-SCLC; hence, it is highly relevant.

In conclusion, despite poor pulmonary function and large target coverage, the PBT group did not differ from the photon group in radiation pneumonitis. Moreover, none of the patients experienced grade ≥4 toxicities. Thus, our findings suggest that PBT could be a feasible definitive treatment option, especially for patients with a

https://doi.org/10.3857/roj.2023.00773

high risk of pulmonary toxicity or who are expected to undergo extensive irradiation volume. Further large-scale studies, including prospective randomized controlled trials with long-term follow-ups, are required to validate our results.

Statement of Ethics

This study was approved by the Institutional Review Board of Samsung Medical Center (No. 2022-10-108-001). The study was performed in accordance with the Declaration of Helsinki.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Author Contributions

Conceptualization, Noh JM. Investigation and methodology, Seo SH, Noh JM. Project administration, all authors. Supervision, Noh JM. Writing of the original draft, Seo SH. Writing of the review and editing, Noh JM. Software, Seo SH, Noh JM. Validation, Seo SH, Noh JM. Formal analysis, Seo SH, Noh JM. Data curation, Seo SH, Noh JM. Visualization, Seo SH, Noh JM. All the authors have proofread the final version.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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 https://doi.org/10.3857/roj.2023.00773

ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2023;41(4):283-291
https://doi.org/10.3857/roj.2023.00787

Target movement according to cervical lymph node level in head and neck cancer and its clinical significance

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Received: September 8, 2023
Revised: October 12, 2023
Accepted: October 25, 2023

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Purpose: To evaluate set-up error for head and neck cancer (HNC) patients according to each neck lymph node (LN) level. And clinical factors affecting set-up error were analyzed.
Materials and Methods: Reference points (RP1, RP2, RP3, and RP4) representing neck LN levels I to IV were designated. These RP were contoured on simulation computed tomography (CT) and cone-beam CT of 89 HNC patients with the same standard. After image registration was performed, movement of each RP was measured. Univariable logistic regression analyses were performed to analyze clinical factors related to measured movements.
Results: The mean value of deviation of all axes was 1.6 mm, 1.3 mm, 1.8 mm, and 1.5 mm for RP1, RP2, RP3, and RP4, respectively. Deviation was over 3 mm in 24 patients. Movement of more than 3 mm was observed only in RP1 and RP3. In RP1, it was related to bite block use. Movement exceeding 3 mm was most frequently observed in RP3. Primary tumor and metastatic LN volume change were clinical factors related to the RP3 movement.
Conclusion: Planning target volume margin of 4 mm for neck LN level I, 3 mm for neck LN level II, 5 mm for neck LN level III, and 3 mm for neck LN level IV was required to include all movements of each LN level. In patients using bite block, changes in primary tumor volume, and metastatic LN volume were related to significant movement.

Keywords: Head and neck neoplasms, Planning target volume, Neck lymph nodes

Introduction

Head and neck cancer (HNC) is the seventh most common cancer worldwide. Its incidence is increasing, showing more than 660,000 new cases each year [1]. Radiotherapy (RT) is one of the main treatment options for HNC [2]. Intensity-modulated RT (IMRT) is widely used in HNC to improve oncologic outcomes, reduce RT-related toxicities, and even enable re-irradiation [3]. IMRT is a highly sophisticated RT technique that can deliver a high radiation dose to the target volume while minimizing radiation exposure to nearby organ-at-risk. Paradoxically, the excessive sophistication of this technique makes it more sensitive to errors, which can lead to an inaccurate treatment. Set-up error is among the most significant errors. It is defined as any deviation of the target position during treatment compared to the reference position in the planning computed tomography (CT) scan [4]. Therefore, the use of various image-guided RT (IGRT) techniques and the application of an appropriate planning target volume (PTV) margin are essential for an

accurate IMRT.

The PTV is a geometric volume defined to secure the dose delivery to the clinical target volume (CTV) by reflecting set-up and mechanical uncertainties [5]. The HNC CTV is often large from the skull base to the clavicle, including the regional lymphatic chain. If the target is large, the set-up error of the center and the edge of the target might be different. Nevertheless, contouring guidelines related to HNC do not recommend the PTV margin with detailed distinction [6]. The aim of this study was to prove the necessity of subdividing the PTV margin in HNC. Target deviation between planning CT and cone-beam CT (CBCT) was recorded for each neck lymph node (LN) level and clinical factors affecting its deviation were analyzed.

Materials and Methods

1. Patient selection and data collection

Patients who underwent curative-intent IMRT for locally advanced HNC from January 2017 to December 2021 at Gyeongsang National University Changwon Hospital were selected for this retrospective analysis. Locally advanced stage was defined as clinical stage III to IVB based on the 8th edition of the American Joint Committee on Cancer [7] except that nasopharyngeal cancer was defined as a locally advanced stage from stage II to stage IVA. Among those with HNC, patients whose primary tumor site was skin, eye, orbit, ear, lip, thyroid, or unknown primary were excluded. Patients with a history of surgery or RT that could cause structural changes in the head and neck or who could not obtain sufficient images to measure target movement due to failure to complete planned RT were excluded from the analysis. This study was approved by the Institutional Review Board of Gyeongsang National University Changwon Hospital (No. 2023-04-005).

Medical records and treatment records (ARIA record and verification system; Varian Medical Systems, Palo Alto, CA, USA) were reviewed. Age, sex, primary tumor location, stage group, contralateral LN metastasis, PTV volume, primary tumor volume change, metastatic LN volume change, body weight change, number of CBCT scans, bite block, and chemotherapy were recorded. The primary tumor location was categorized into three parts: nose, mouth, and neck. The nose part consisted of the nasopharynx (NPX), nasal cavity, and paranasal sinus. The mouth part consisted of the oral cavity, oropharynx, and salivary gland. The neck part consisted of the hypopharynx and larynx. Primary tumor and metastatic LN volume changes were defined as changes between planning CT and re-simulation CT. Body weight change was defined as the difference between the weight measured at the time of diagnosis of HNC and the weight measured within 1 month after RT.

2. Simulation, treatment planning, and set-up procedures

All patients were immobilized by Type-S Head & Neck, Shoulder Thermoplastic mask (CIVCO, Kalona, IA, USA). Bite block (Sejong Medical, Paju, Korea) was additionally used in the nose and mouth parts of patients. After immobilization, CT simulation with a 3-mm slice thickness was performed using a Brilliance CT Big Bore (Philips Medical Systems, Amsterdam, Netherlands). Scanned CT images were imported into an Eclipse treatment planning system Version 13.7 (Varian Medical Systems). A radiation oncologist delineated the target and normal structure. IMRT was performed using a Varian TrueBeam 2.0 (Varian Medical Systems) with a prescribed total dose of 6,000–7,200 cGy in 25–35 fractions.

All patients received the conventional laser set-up procedure using set-up fiducial lines marked on the immobilization mask. After that, CBCT images were periodically obtained once a week for image guidance set-up procedure. Image registration was performed with an automatic algorithm applying a region-of-interest containing the PTV and, if necessary, re-positioned by six-dimensional CBCT guidance. Final set-up corrections were confirmed by a radiation oncologist and manually adjusted when necessary, focusing more on the primary tumor site. Quality assurance procedures for CBCT images and geometrical accuracy analysis were performed monthly to ensure accuracy. During the set-up process, if an error was over 5 mm in any axis, the simulation CT was re-scanned and re-planned. Except for this reason, re-simulation CT was planned after 4,400–5,000 cGy irradiation due to tumor shrinkage or patient weight loss.

3. Measurement of deviation of neck LN level and statistical analysis

Neck LNs were divided into 10 levels based on anatomical configuration and drainage patterns [8]. Among head and neck structures, seven reference points (RP) representing each neck LN level were determined based on the first cervical vertebra, mandible, hyoid bone, manubrium, and sternocleidomastoid muscle, which were clearly distinguished in CBCT (Table 1, Fig. 1). Seven RP were named level I (RP1), and left and right level II (RP2), III (RP3), and IV (RP4), respectively. These RP were consistently drawn on simulation CT and CBCT images. Simulation CT and each CBCT performed image registration using an automatic algorithm, focusing on the PTV and primary tumor site on the same basis as in the treatment. The magnitude of deviation of each RP was recorded with three translational axes—anterior-posterior (AP), left-to-right (LR), and superior-to-inferior (SI). The overall radial movement was computed as $\sqrt{\delta_{AP}{}^2+\delta_{LR}{}^2+\delta_{SI}{}^2}$, with δ_x representing a magnitude of movement along the x-axis. All measurements were calculated as mean and standard deviation (SD). For statistical analysis, it is beneficial to trans-

https://doi.org/10.3857/roj.2023.00787

Table 1. Seven reference points of neck lymph node

Level	Name	Definition
I	RP1	The most antero-inferior point of the mandible midline
II	RP2 (Lt./Rt.)	The most lateral point of the transverse processes of C1
III	RP3 (Lt./Rt.)	The most posterior point of the SCM in the CT slice (2 cm below from inferior border of the hyoid bone)
IV	RP4 (Lt./Rt.)	The most posterior point of the SCM in the CT slice (2 cm above from superior border of the manubrium)

RP, reference point; C1, first cervical vertebra; SCM, sternocleidomastoid muscle; CT, computed tomography; Lt., left; Rt., right.

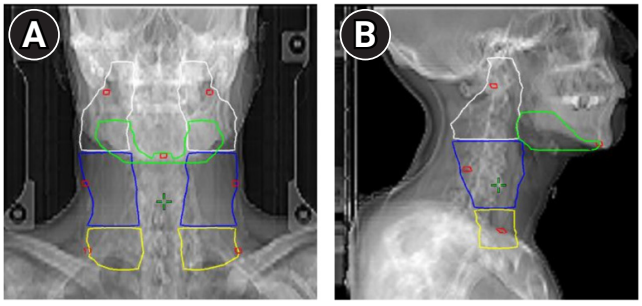

Fig. 1. Seven reference points representing each neck lymph node (LN) level: (A) anterior-posterior view and (B) lateral view. Reference points are shown in red; neck LN level I, green; neck LN level II, white; neck LN level III, blue; and neck LN level IV, yellow.

form these series of RP movements into a single representative value. The formula of van Herk could be the first theoretical background for this transformation [9]. In this formula, the optimal margin was determined to be $2.5\Sigma+0.7\sigma$, with Σ and σ representing the average value and SD of motion series, respectively. This relationship indicated that the fluctuated motion around the baseline had 0.7/2.5 times less impact on dosimetric change than the average baseline shift. Based on this rationale, the effective magnitude of deviation (D_{eff}) was defined by adding weighted fluctuated RP movement into the average shift and expressed as $\Sigma+(0.7/(2.5))\ \sigma$. Unless otherwise specified, the magnitude value for deviation written throughout this paper was D_{eff}. Univariable logistic regression analyses were conducted to identify factors affecting deviation. All analyses in this study were performed using SPSS software version 21.0 (IBM, Armonk, NY, USA). A p-value <0.05 was considered statistically significant.

Results

1. Patient characteristics

A total of 89 patients were included in this study. Patient characteristics are summarized in Table 2. Seventy-two patients (80.9%) were male. The median age of all patients at the time of RT was 65 years (range, 33 to 93 years). Numbers of patients with primary tumor location being the nose part, mouth part, and neck part were 16 (18.0%), 33 (37.1%), and 40 (44.9%), respectively. Regarding the stage group, except for NPX, numbers of patients with stage III, IVA, and IVB were 20 (25.6%), 46 (51.7%), and 12 (13.4%), respectively. All patients had LN metastasis and 29 (32.6%) had contralateral LN metastasis. Concurrent chemotherapy was administered to 76 patients (85.4%). Twenty-four patients (27%) used a bite block for immobilization. The CBCT was scanned 606 times, averaging 6.8 times per patient. The median value of the initial PTV volume was 429.3 cm^3 (range, 175.8 to 658.8 cm^3). Median values of changes in primary tumor volume, metastatic LN volume, and body weight were 19.5% (range, 0% to 76.0%), 29.0% (range, 0% to 87.7%), and 6.0 kg (range, 3.0 to 13.0 kg), respectively.

Table 2. Patient characteristics (n=89)

Characteristic	Value
Age (yr)	65 (33–93)
Sex	
Male	72 (80.9)
Female	17 (19.1)
Primary tumor location	
Nose part	16 (18.0)
Mouth part	33 (37.1)
Neck part	40 (44.9)
Stage group[a]	
III	20 (25.6)
IVA	46 (51.7)
IVB	12 (13.4)
Contralateral LN metastasis	
Yes	29 (32.6)
No	60 (67.4)
Concurrent chemotherapy	
Yes	76 (85.4)
No	13 (14.6)
Bite block	
Yes	24 (27.0)
No	65 (73.0)
PTV volume (cm^3)	429.3 (175.8–658.8)
Primary tumor volume change (%)	19.5 (0–76.0)
Metastatic LN volume change (%)	29.0 (0–87.7)
Body weight change (kg)	6.0 (3.0–13.0)

Values are presented as median (range) or number (%).
LN, lymph node; PTV, planning target volume.
[a]Stage group excluding nasopharyngeal cancer patients.

2. Magnitude of deviation of each reference point

Seven RP represented neck LN levels I, II, III, and IV. A total of 606 CBCT images were compared with simulation CT images. Because the difference between the left and right deviation of each RP was slight, the left and right values were integrated and divided into only RP1, RP2, RP3, and RP4 in the presentation and analysis of the results. Deviation of each RP was recorded in three translational axes and the overall radial movement was calculated. Table 3 and Figs. 2–5 show the effective magnitude of deviation of each RP. Movement values of all translational axes did not exceed 5 mm. For RP1, the magnitude of deviation exceeded 3 mm in the AP direction in 5 patients (5.6%) and the SI direction in 5 patients (5.6%). RP3 deviations exceeded 3 mm in the LR direction in 1 patient (1.1%) and the SI direction in 21 patients (23.6%). Deviation of more than 3 mm in one or more axial directions was observed in 24 patients (27.0%) regardless of the RP. Regarding radial movement, more than 5 mm was observed in 1 patient (1.1%) in RP1 and 3 patients (3.4%) in RP3. Radial movement of more than 3 mm was observed in 28 patients (31.5%) in RP1, 1 patient (1.1%) in RP2, 50 patients (56.2%) in RP3, and 27 patients (30.3%) in RP4.

Table 3. Magnitude of deviation of each reference point (unit: mm)

	Mean	Range	AP	LR	SI	RA
RP1	1.6	0.7–3.9	1.7 ± 0.7	1.3 ± 0.2	1.7 ± 0.7	2.9 ± 0.8
RP2	1.3	0.6–2.8	1.3 ± 0.2	1.3 ± 0.2	1.3 ± 0.3	2.3 ± 0.3
RP3	1.8	0.6–4.6	1.3 ± 0.2	1.8 ± 0.6	2.2 ± 1.0	3.3 ± 0.9
RP4	1.5	0.7–4.6	1.7 ± 0.5	1.6 ± 0.5	1.3 ± 0.3	2.8 ± 0.6

Values are presented as mean ± standard deviation.
RP, reference point; AP, anterior-posterior; LR, left-right; SI, superior-inferior; RA, radial.

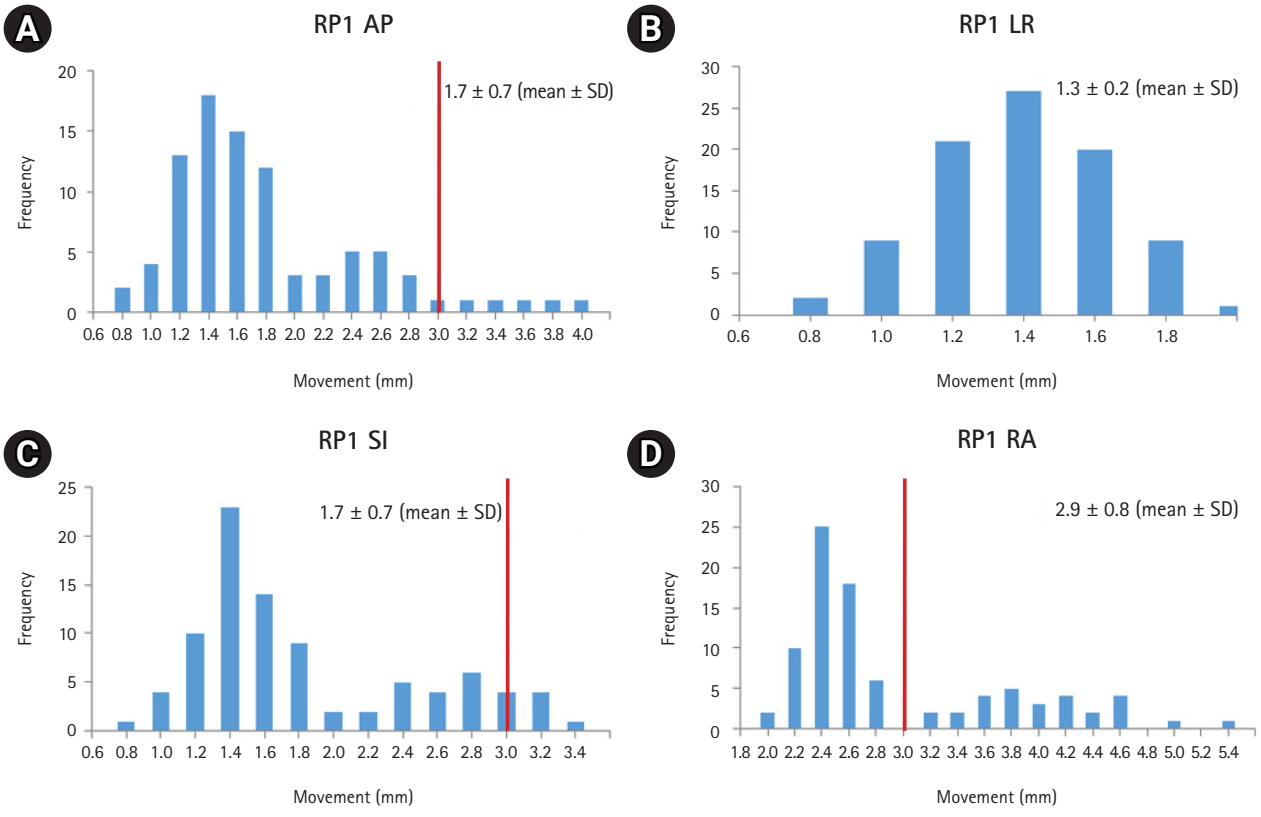

Fig. 2. Population histogram for movement of the reference point corresponding to neck lymph node level I along three translational axes: (A) AP, (B) LR, (C) SI directions, and (D) overall RA magnitude. The red line indicates the point where the movement exceeds 3 mm. AP, anterior-posterior; LR, left-right; SI, superior-inferior; RA, radial, SD, standard deviation.

https://doi.org/10.3857/roj.2023.00787

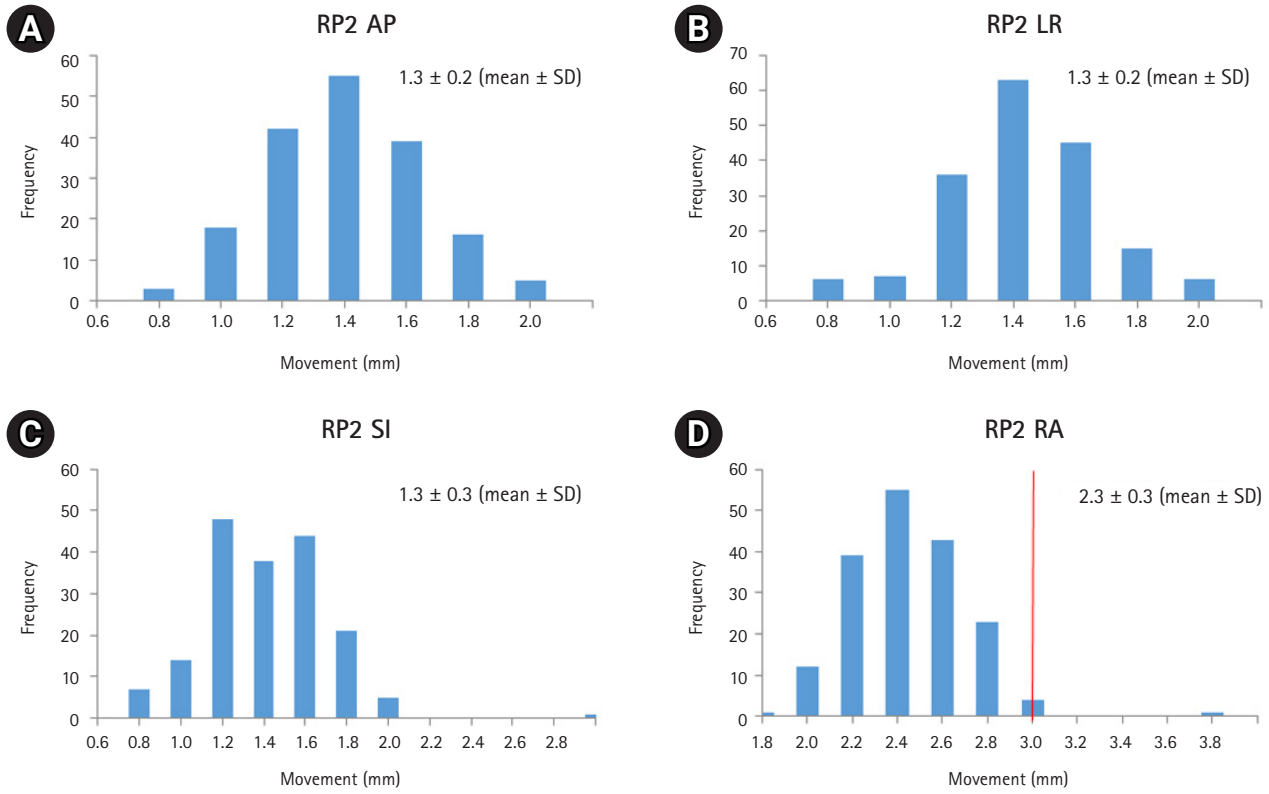

Fig. 3. Population histogram for movement of the reference point corresponding to neck lymph node level II along three translational axes: (A) AP, (B) LR, (C) SI directions, and (D) overall RA magnitude. The red line indicates the point where the movement exceeds 3 mm. AP, anterior-posterior; LR, left-right; SI, superior-inferior; RA, radial, SD, standard deviation.

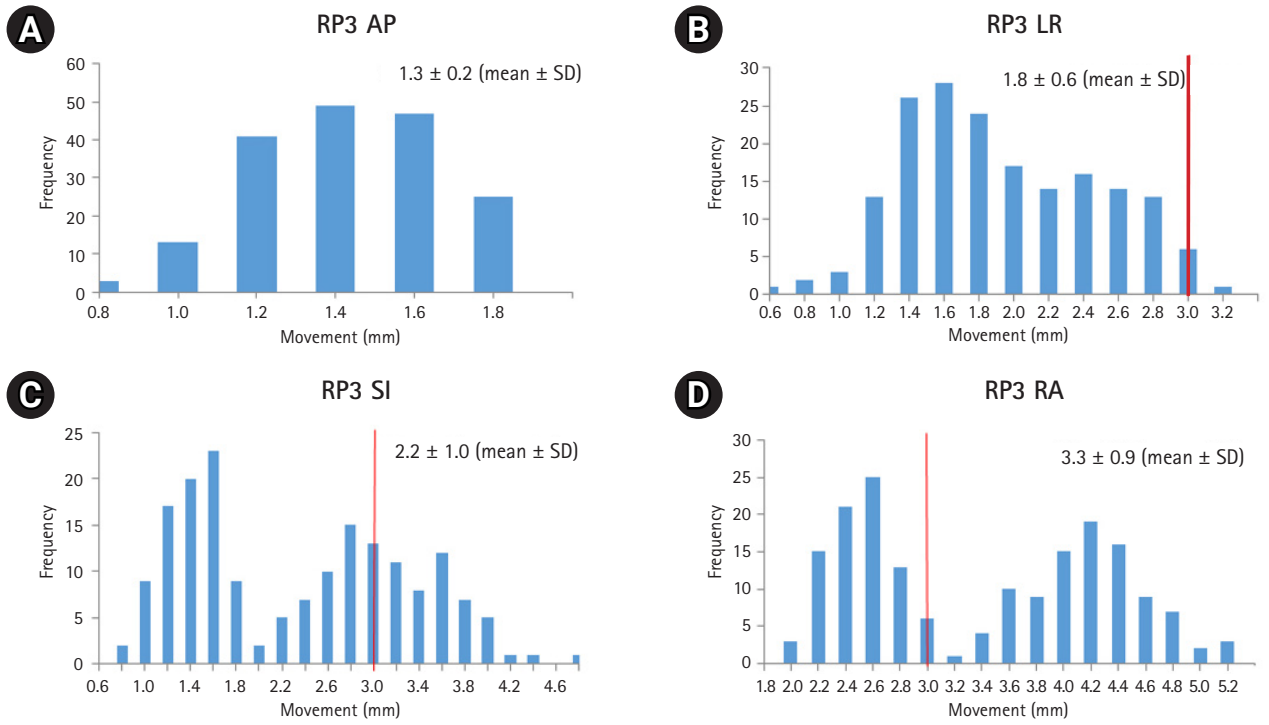

Fig. 4. Population histogram for movement of the reference point corresponding to neck lymph node level III along three translational axes: (A) AP, (B) LR, (C) SI directions, and (D) overall RA magnitude. The red line indicates the point where the movement exceeds 3 mm. AP, anterior-posterior; LR, left-right; SI, superior-inferior; RA, radial, SD, standard deviation.

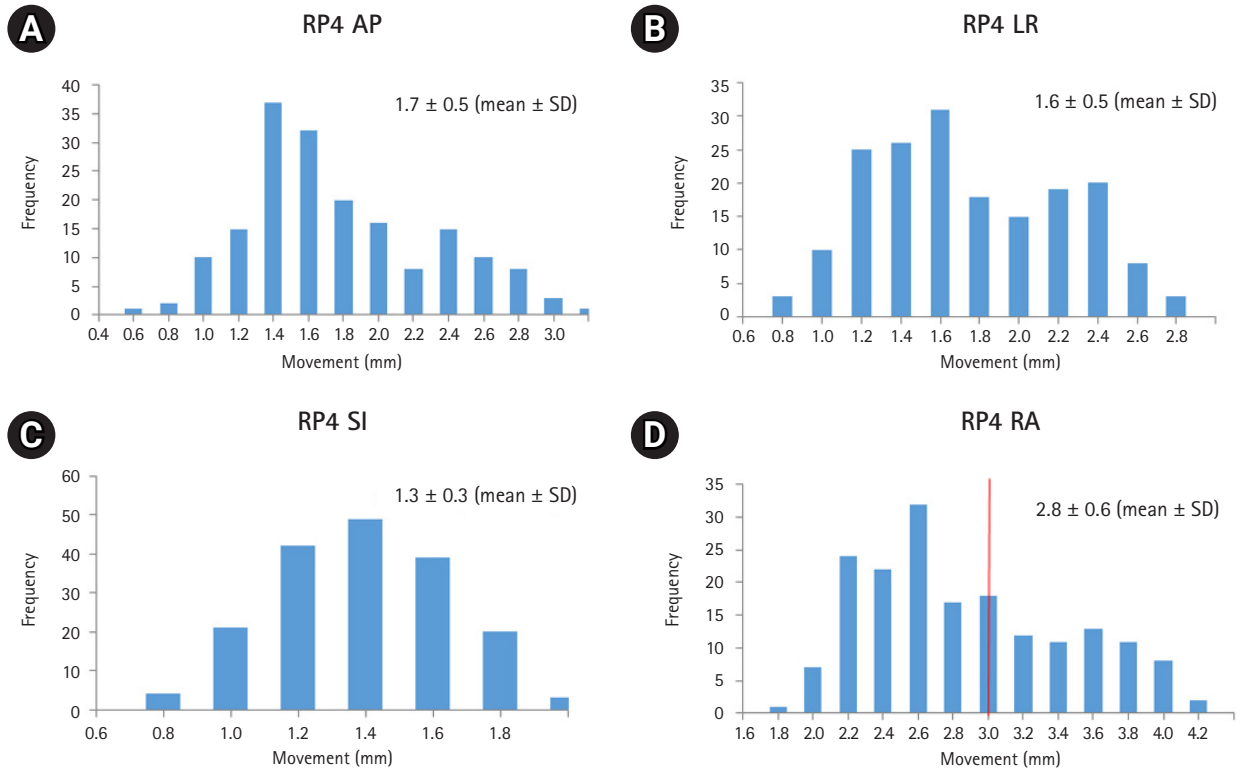

Fig. 5. Population histogram for movement of the reference point corresponding to neck lymph node level IV along three translational axes: (A) AP, (B) LR, (C) SI directions, and (D) overall RA magnitude. The red line indicates the point where the movement exceeds 3 mm. AP, anterior-posterior; LR, left-right; SI, superior-inferior; RA, radial, SD, standard deviation.

3. Factors affecting deviations

A case in which the overall radial movement of each RP was more than 3 mm was defined as an event and related clinical factors were statistically analyzed. RP2, which had a relatively small movement and an event that occurred in only one patient, was excluded from the analysis. Results are summarized in Table 4. Events in RP1 occurred in all patients (100%) who used a bite block. Another factor associated with events in RP1 was primary tumor location ($p = 0.002$). Significantly fewer RP1 events occurred when the primary tumor location was the neck part. Events in RP3 occurred in all patients (100%) with sufficiently metastatic LN volume change. In addition, statistically significant differences were shown in primary tumor volume change ($p = 0.001$). RP4 events occurred significantly more in patients with large body weight changes ($p = 0.046$).

Discussion and Conclusion

It is important to set an appropriate PTV margin because if the PTV margin is too large or too small, unnecessary radiation exposure increases or a sufficient dose is not irradiated to the CTV. Strbac et al. [10] have obtained 632 electronic portal images from 35 HNC patients undergoing RT and found that a PTV margin of at least 6 mm is necessary for CTV to receive a sufficient prescribed dose. Mesko et al. [11] have performed stereotactic ablative RT on 79 patients with recurrent and/or previously irradiated HNC and measured set-up errors according to the treatment site (skull base, neck/parotid, and mucosal). In their study, patients were immobilized at a relatively high level of quality using a cushion, thermoplastic mask, and bite block, and set-up error correction was performed using both ExacTrac X-ray (BrainLAB AG, Munich, Germany) and CBCT. They found that the appropriate PTV margin differed depending on the treatment site, 1.5–2 mm for the skull base and 2–2.5 mm for the neck and mucosal area. Based on these previous studies, the PTV margin can be different even if the same head and neck area is treated depending on the institution policy, immobilized device, and IGRT system. Even the margin can differ depending on treatment site. In the present study, patient was immobilized using a thermoplastic mask and bite block. The set-up error was corrected by taking CBCT after laser line set-up. Movements of RP averaged 1.6 mm (range, 0.4 to 4.6 mm). No one had movement over 5 mm. In 24 patients (27.0%), the movement was over 3 mm.

https://doi.org/10.3857/roj.2023.00787

Table 4. Factors affecting the radial movement of each reference point by over 3 mm (unit: %)

Variable	RP1	RP3	RP4
Primary tumor location			
Nose part	68.8 (0.002)	81.3	50.0
Mouth part	48.5	72.7	39.4
Neck part	2.5	32.5	30.0
Bite block			
Yes	100	83.3	37.2
No	6.2	46.2	37.0
Primary tumor volume change			
< 19.5%	25.6	31.1 (0.001)	33.3
≥ 19.5%	27.7	81.8	40.9
Metastatic LN volume change			
< 29.0%	31.7	15.2	32.6
≥ 29.0%	31.9	100	41.9
Body weight change			
< 6 kg	30.4	58.7	30.8 (0.046)
≥ 6 kg	32.6	53.5	54.2

RP, reference point; LN, lymph node.
p-values are given in parentheses.

Movement of more than 3 mm in any axes was observed only in RP1 and RP3.

Neck LN level I refers to the area combined with submental and submandibular space. Since it is a LN area attached to the inner side of the mandible, movement of the mandible can cause movement of neck LN level I. Therefore, oral fixation has been an essential issue for accurate RT. Various oral devices have been widely used. A bite block, one of the oral fixation devices, can be used to restrict movement of oral tongue or to reduce radiation exposure to adjacent normal tissues such as the salivary gland, mandible, upper gingiva, and hard plate [12]. However, applying bite blocks can have limited reproducibility due to certain medical conditions such as trismus, pain from mucositis, severe gag reflex, and discomfort from holding a bite block, resulting in unexpected target movement [13]. This study observed a statistically significant radial movement of RP1 exceeding 3 mm in patients who used a bite block or whose primary tumor location was the nose or mouth part where the bite block was mainly used. However, because bite block was used in most patients whose primary tumor location was in the nose or mouth part, each factor has the limitation of being a confounding variable for the movement of RP1. Nevertheless, RP1 movement over 3 mm was evident in the AP and SI directions, not the LR. Through this, it can be inferred that the movement of neck LN level I is due to the difference in oral opening caused by variation in bite block application. These results suggest that considering an additional PTV margin for neck LN level I is appropriate when applying a bite block with ongoing development of patient-specific intra-oral devices.

Neck LN level II refers to the upper third of the jugular chain area. It extends from the skull base to the inferior border of the hyoid bone. Several studies have shown that neck LN level II, closer to the base of the skull, has the slightest movement [11,14]. These studies suggest that this area is relatively close to the central axis. Thus, small movements are less amplified and better aligned by the inherently rigid cranial bones with less internal organ movement. Likewise, RP2 had a minor movement in this study compared to other RP, with an average of 1.3 mm in all axes. Only 1.1% had an overall radial movement exceeding 3 mm, suggesting that neck LN level II was fixed the most stably.

Neck LN level III refers to the middle internal jugular chain area between the hyoid superiorly and a horizontal plane defined by the inferior border of the cricoid cartilage. In this study, the movement of the RP exceeding 3 mm was measured the most in RP3 and the movement in the SI direction was particularly prominent. The reason might be due to movement of the hyoid bone, the standard for neck LN level contouring. It is already well known that the hyoid bone moves during a normal swallowing process [15,16]. Radiological and surgical classification of the neck LN level is beneficial in making treatment decisions, comparing treatment results, and communicating with medical staff [17]. However, in the field of RT where fractional treatment is commonly performed, using a moving structure like a hyoid bone as a criterion for distinguishing neck LN levels is likely to impede reproducibility. Thus, it might be necessary to make another neck LN level classification. Factors influencing the radial movement of RP3 were volume change of the primary tumor and metastatic LN. It might be difficult to predict the degree of change in the target volume before treatment. However, if the target has radiosensitive histology, it is necessary to closely observe volume change and perform immediate adaptive RT.

Neck LN level IV refers to the lower third of the jugular chain area. It extends from the inferior border of the cricoid cartilage to the clavicle. This study observed no movement beyond 3 mm in RP4 on any axis. In radial movements that integrated all axes, movements greater than 3 mm were observed, which were correlated with changes in patient's body weight. HNC patients often experience significant weight loss due to inadequate nutrient intake. It is known that such weight loss not only affects the patient's survival, but also leads to inaccurate radiation dose distribution [18]. In patients who are expected to lose weight, it is necessary to appropriately add the PTV margin of neck LN level IV or perform rapid adaptive RT through close monitoring.

The limitation of this study was that the designated RP could not accurately represent each neck LN level. Because it was necessary to define RP that could be clearly distinguished even at the low

resolution of CBCT, bone or large muscle became the standard. Because these structures are relatively fixed, movement at each LN level due to clinical factors may have been underestimated. Moreover, set-up errors might vary depending on simulation, immobilization, set-up alignment, image registration, and IGRT system for each hospital policy. Therefore, it is difficult to recommend a PTV margin with an exact value for each neck LN level. Nevertheless, this study is clinically significant because it shows that set-up error differs according to neck LN level and reports clinical factors that could affect the set-up error.

In this study, PTV margins of 4 mm for neck LN level I, 3 mm for neck LN level II, 5 mm for neck LN level III, and 3 mm for neck LN level IV were required to include all movements of each LN level that occurred. Neck LN level II had a minor movement. Neck LN level IV increased the movement according to the patient's weight change. However, no movement exceeding 3 mm was observed. In neck LN level I, movements exceeding 3 mm in AP and SI directions were observed in some patients related to bite block use. Movement exceeding 3 mm was most frequently observed in neck LN level III. Primary tumor and metastatic LN volume change were relevant clinical factors. However, since most neck LN level III movements were biased toward the SI direction, the leading cause might be vertical movement of the hyoid bone during swallowing. Therefore, in patients using bite block, an additional PTV margin for neck LN level I should be considered. If changes in primary tumor volume, metastatic LN volume, and body weight are prominent, rapid adaptive RT is needed. In addition, if a highly mobile structure such as the hyoid bone is used as a standard for classifying the level of neck LN, the range may continue to change during RT, so it is necessary that a new standard for classifying the level of neck LN.

Statement of Ethics

This study was a retrospective and informed consent was waived by the Institutional Review Board of Gyeongsang National University Changwon Hospital (No. 2023-04-005), and this study was performed by relevant guidelines and regulations.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Author Contributions

Conception and design of the study: Choi HS, Jeong BK, and Kang KM. Acquisition of data: Jeong H, Ha IB, and Choi B. Analysis and interpretation of the data: Choi HS, and Kang KM. Writing and revision of the manuscript: Choi HS, and Kang KM. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ROJ Radiation Oncology Journal

Case Report

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2023;41(4):292-296
https://doi.org/10.3857/roj.2023.00577

A case of cetuximab-induced radiation recall skin dermatitis and review of the literature

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Received: July 5, 2023
Revised: July 21, 2023
Accepted: July 24, 2023

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Radiation recall presents as an acute inflammatory reaction triggered by systemic therapy, usually chemotherapy, and is typically limited to an area that was previously irradiated. Radiation recall reactions are generally self-limiting and most commonly occur in the skin. Many systemic agents have been described to elicit a radiation recall reaction, but the exact pathogenesis is largely unknown. Here, we describe the first reported case of radiation recall dermatitis following cetuximab. While cetuximab is associated with other skin reactions, oncologists should not exclude radiation recall dermatitis as a potential complication of cetuximab infusion in patients with prior radiation, and special attention should be paid to the pattern of skin changes both in terms of location and chronology.

Keywords: Radiodermatitis, Radiotherapy, Cetuximab

Introduction

Radiation recall is a rare and poorly understood delayed reaction that occurs in an area of previous radiation exposure in response to the use of systemic anticancer (chemo-, immuno-, or targeted therapies) agents. It most commonly manifests as skin dermatitis (two-thirds of cases) but has also been reported in the lungs or along mucosal surfaces (gastritis, cystitis, or colitis) [1]. Radiation recall dermatitis was first described in 1959 as an inflammatory skin reaction in a previously irradiated area after actinomycin D infusion [2]. The etiology of radiation recall is not well understood. Radiation recall is mostly associated with the use of conventional cytotoxins, such as doxorubicin, gemcitabine, capecitabine, and taxanes [1], but the association of radiation recall dermatitis with cetuximab has not been described before. In this paper, we describe a case of radiation recall dermatitis induced by cetuximab.

Case Report

A 53-year-old man presented in July 2020 with a 2-month history of dysuria, perineal pain, and weak urinary stream. His symptoms did not improve with ciprofloxacin. Cystoscopy found an occlusive mass in the bulbar urethra and biopsy showed invasive moderately differentiated squamous cell carcinoma. Positron emission tomography/computed tomography (PET/CT) showed uptake in a well-delineated lesion in the bulbar urethra as well as a concerning left inguinal lymph node.

The patient received four cycles of paclitaxel, ifosfamide, and

cisplatin followed by bulbar urethral resection, left inguinal lymph node dissection, and perineal urethrostomy in April 2021. Pathology showed poorly differentiated invasive squamous cell carcinoma invading the corpus spongiosum and cavernosum with positive margins and five of seven lymph nodes were positive. Pathology also showed extra-nodal extension and the tumor was epidermal growth factor receptor (EGFR)-positive and human papillomavirus-negative. He then completed radiotherapy with concurrent fluorouracil/mitomycin in August 2021. He received 45 Gy in 25 fractions to the elective pelvis and right groin, 50.4 Gy in 28 fractions to the left groin, 59.4 Gy in 33 fractions to the suspected area of extranodal extension in the left groin, and 64.8 Gy in 36 fractions to the area of positive margin in the bulbar urethra (Fig. 1). During his radiation course, he developed grade 3 dermatitis with moist desquamation on the scrotum, the base of the penis, and the left groin, which was treated conservatively until resolution. On first follow-up imaging, a chest CT showed a right middle lobe nodule that was biopsied, revealing metastatic squamous cell carcinoma.

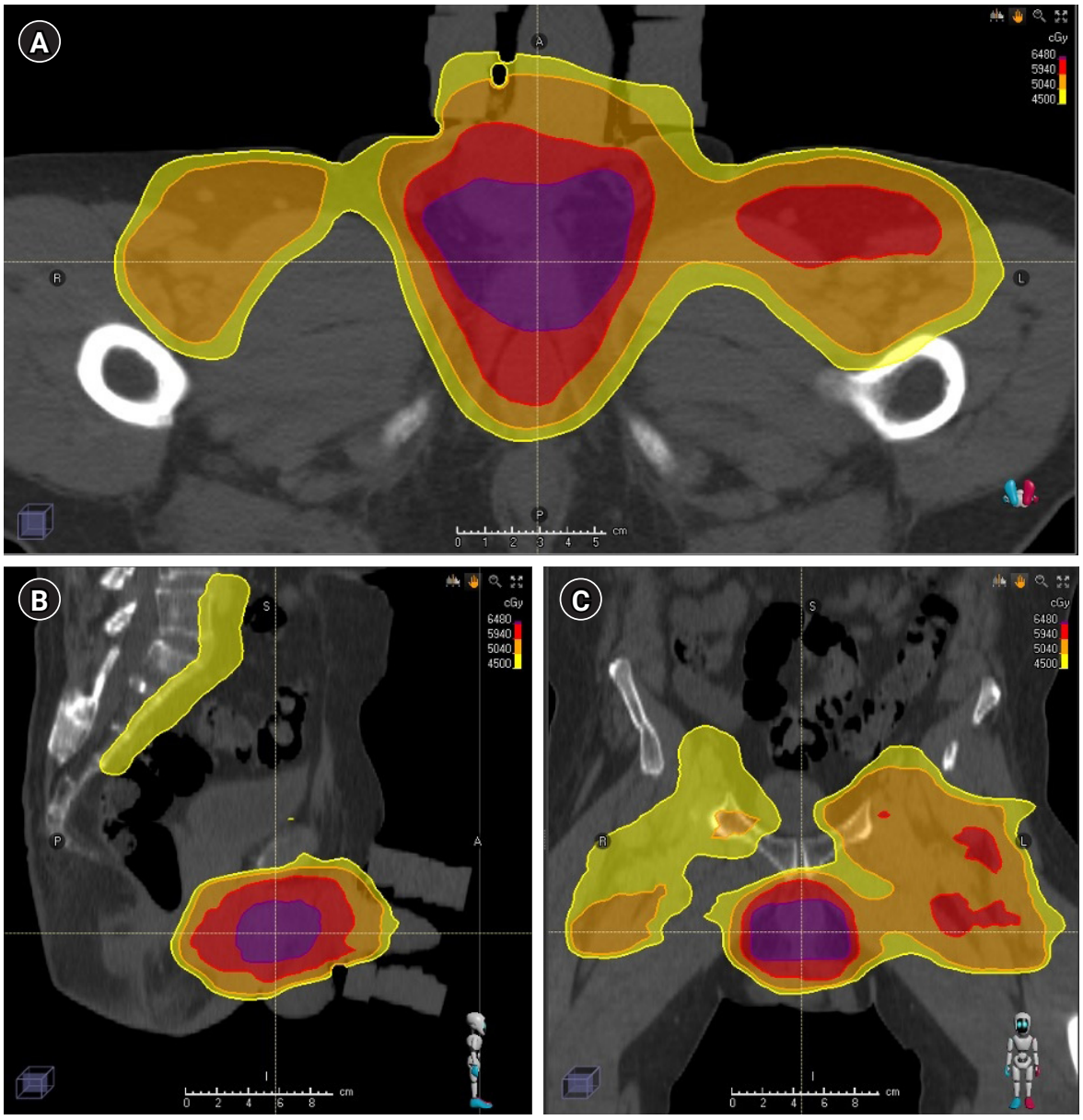

Fig. 1. Treatment plan. Representative (A) axial, (B) sagittal, and (C) coronal views of the delivered plan. The prescription dose of 45 Gy (yellow) in 25 fractions to the elective pelvis and right groin, 50.4 Gy (orange) in 28 fractions to the left groin, 59.4 Gy (red) in 33 fractions to the suspected area of ENE in the left groin, and 64.8 Gy (purple) in 36 fractions to the area of positive margin in the bulbar urethra. ENE, extranodal extension.

He was started on pembrolizumab in November 2021. While on pembrolizumab, he received 30 Gy in 10 fractions to a growing penile lesion in January 2022 and stereotactic body radiation to two enlarging lesions in the left lower lobe of the lung and a right groin nodule in May 2022.

In June 2022, imaging showed recurrent periurethral mass and in July 2022, he was started on weekly cetuximab. In August 2022, he noted an acneiform rash associated with cetuximab on his face and chest for which he was seen by a dermatologist and prescribed topical clindamycin that was subsequently switched to topical BenzaClin (Fig. 2). On cycle 7 of cetuximab, he reported significant scrotal and groin erythema and moist desquamation (Fig. 3). These skin findings were morphologically distinct from the acneiform rash on his face and chest and were similar to the skin toxicity he experienced during his course of radiation 1 year prior. Radiation recall was suspected, and the skin was managed conservatively. The patient returned for a skin check 3 days later with decreased erythema and improving moist to dry desquamation. The dermatitis completely resolved within 2 weeks and cetuximab was resumed without delay.

The informed consent was waived.

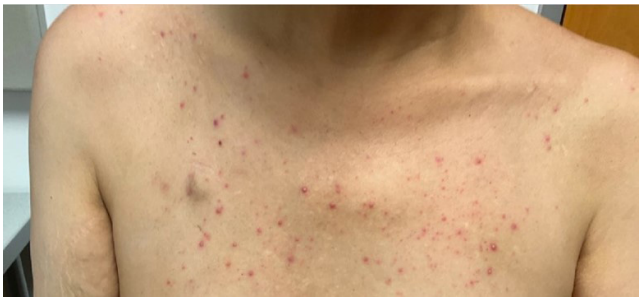

Fig. 2. Generalized cetuximab-associated skin rash. The patient experienced a papulo-pustular eruption during cetuximab infusions distinct from the skin toxicity seen in the groin.

Discussion

To our knowledge, this is the first reported case of radiation recall dermatitis with cetuximab. The true incidence of radiation recall is unknown likely due to the fact that several factors influence the development of radiation recall including systemic agent selection and dose, radiation dose and location, and the time between the end of radiation and administration of systemic therapy. Radiation recall reactions have historically been reported with conventional cytotoxic agents such as doxorubicin [3], actinomycin-D [2], bleomycin [4], capecitabine [5], paclitaxel [6], and dactinomycin [3]. It has also been reported with tamoxifen [7], trastuzumab with vinorelbine [8], pemetrexed [9], gefitinib [10], and bevacizumab with gemcitabine [11]. More recently, cases of radiation recall associated with other targeted and immunotherapeutic agents have been also reported [1].

While many systemic or topical agents have been associated with radiation recall, the exact relationship between radiation dose and recall is not clear with some reports suggesting low-dose threshold of around 18 Gy [12] and others suggesting higher threshold dose (40 Gy) [4]. It is likely that the systemic or topical agents also play a role in determining the radiation threshold dose. Timing and schedule of systemic therapy may also play a role. Some series have reported a radiation recall reaction after the first dose of a systemic therapy following radiation [13], while other reported instances of radiation recall only until the second infusion [12], raising the question of a requisite "threshold dose" to cause

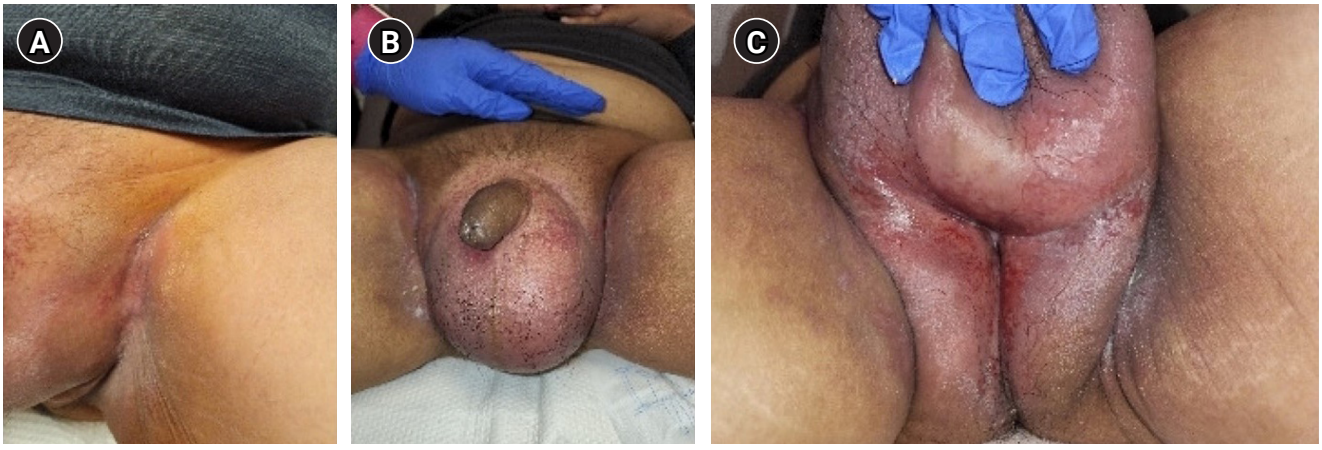

Fig. 3. Radiation recall skin reaction during cetuximab treatment. (A) Desquamation and erythema in left inguinal skin fold. (B) Scrotal swelling and erythema. (C) Wet desquamation and erythema of posterior scrotum and perineum.

https://doi.org/10.3857/roj.2023.00577

the radiation recall reaction. Analysis of the MammoSite breast brachytherapy registry trial was done to evaluate the frequency of radiation recall reactions and the impact of timing between radiation and systemic therapy. The majority of patients in this cohort (75%) received doxorubicin-based chemotherapy [14]. The rate of radiation recall reactions in patients who received chemotherapy within 3 weeks after the completion of radiation was 18% (9/50 patients) compared to 7.4% (6/81 patients) in patients who started adjuvant chemotherapy more than 3 weeks after completion of radiation [14]. This trend was not statistically significant ($p = 0.09$).

Several hypotheses have been posed related to the pathogenesis of radiation recall reactions, but they lack supportive evidence. One hypothesis is that radiation alters vascularization in normal tissue due to endothelial cell damage and capillary proliferation which may affect the pharmacokinetics of drug delivery leading to the recall phenomenon [7]. Others have suggested that stem cells in a previously irradiated area have DNA damage or altered biology, including increased proliferation, which could lead to increased sensitivity when exposed to subsequent chemotherapy [15]. These hypotheses are based on some of the early work characterizing the effect of radiation on epithelial stem cells leading to late effects of radiation by Hellman and Botnick [16] and the proposed biological changes in stem cell populations after radiation by Seymour et al. [17]. Given the fact that a rechallenge after a radiation recall reaction does not always redemonstrate the phenomenon and the fact that cytotoxic and non-cytotoxic drugs have been shown to produce the radiation recall reaction, further work into the mechanism and pathogenesis of radiation recall is needed [15].

Cetuximab is a chimeric monoclonal antibody that binds to and inhibits EGFR. To our knowledge, radiation recall dermatitis after cetuximab has not been described before. Cetuximab-induced radiation recall mucositis has been reported in one patient in a case series analyzing targeted agents [18]. The patient had head and neck cancer that was treated with radiation over 20 years prior to the administration of cetuximab and developed mucositis 7 weeks after cetuximab infusion. Interestingly, our patient also developed a dermatitis reaction on week 7 of cetuximab. In a different report, a 70-year-old male with squamous cell carcinoma of the tonsil was treated with radical neck dissection, adjuvant radiation, and weekly cetuximab, with grade 3 skin toxicity during radiation. One year later, he was found to have metastasis and was treated with carboplatin and gemcitabine. Skin ulceration developed in the area of prior skin reaction in the radiation fields [19]. While the report attributes this radiation recall reaction to the initial cetuximab treatment, it is more likely that this skin reaction is related to gemcitabine. Unlike cetuximab, reports of radiation recall dermatitis have been described with the use of erlotinib, an EGFR inhibitor [20].

The most recent version of the US National Cancer Institute Common Terminology Criteria for Adverse Events (v.5, 2017) lists "radiation recall reaction (dermatologic)" as a distinct entity defined as "a finding of acute skin inflammatory reaction caused by drugs, especially chemotherapeutic agents, for weeks or months following radiotherapy. The inflammatory reaction is confined to the previously irradiated skin and the symptoms disappear after the removal of the pharmaceutical agent," and is classified in five grades as below: (1) grade 1, faint erythema or dry desquamation; (2) grade 2, moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema; (3) grade 3, moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion; (4) grade 4, life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site, skin graft indicated; and (5) grade 5, death.

Treatment of radiation recall dermatitis is usually supportive with wound management and cessation of the suspected drug needed in high-grade cases. Therefore, the identification of the inducing agent is crucial. Cetuximab however is associated with other skin reactions, such as most commonly papulopustular acneiform dermatitis, xerosis or dry/flaky skin, or pruritis. In this case, the patient experienced two morphologically distinct skin reactions, both more classic cetuximab-associated acneiform dermatitis on the chest and radiation recall dermatitis localized to the groin with distinct morphology as shown in Figs. 2 and 3. Oncologists should not exclude radiation recall dermatitis as a potential complication of cetuximab infusion in patients with prior radiation, and special attention should be paid to the pattern of skin changes both in terms of location (localized to a prior radiation field or more diffuse or unrelated to prior radiation field), morphology of the skin changes, and chronology.

Statement of Ethics

This study was conducted and approved by University of California, San Francisco Institutional Review Board (No. 20-31257).

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Author Contributions

Conceptualization, Sabol RA, Patel AM, Sabbagh A, Wilson C, Yuen F, Lindenfeld P, Aggarwal R, Breyer B, Mohamad O. Investigation and Methodology, Sabol RA, Patel AM, Sabbagh A, Wilson C, Yuen F, Lindenfeld P, Aggarwal R, Breyer B, Mohamad O. Writing of the original draft, Sabol RA, Patel AM, Sabbagh A, Mohamad O. Writing of review and editing, Sabol RA, Patel AM, Sabbagh A, Wilson C, Yuen F, Lindenfeld P, Aggarwal R, Breyer B, Mohamad O. All authors have proofread the final version

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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 https://doi.org/10.3857/roj.2023.00577

ROJ Radiation Oncology Journal

Case Report

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2023;41(4):297-300
https://doi.org/10.3857/roj.2023.00500

Synchronous radiation-induced enterovesical and enterocervical fistulas in carcinoma of the uterine cervix

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Received: June 6, 2023
Revised: September 2, 2023
Accepted: September 12, 2023

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Radiation-induced fistulas (RIF) are uncommon therapeutic complications of radiotherapy in patients treated for carcinoma of the uterine cervix. Synchronous occurrence of enterocervical and enterovesical fistulas secondary to radiation is extremely rare and previously unreported in the literature. We report a case of synchronous enterovesical and enterocervical fistulas in a patient with carcinoma of the cervix treated using chemotherapy and radiation along with a brief overview of etiopathogenesis of RIF.

Keywords: Enterovesical fistula, Enterocervical fistula, Radiation-induced, Carcinoma cervix, Ultrasound, Computed tomography

Introduction

Radiation-induced fistulas (RIF) are rare, late complications of pelvic irradiation that may occur in cervical cancer patients treated with radiotherapy for locally advanced disease. Vagina, urinary bladder and rectum are the most frequent organs to be involved in radiation induced fistulous communications. Among them, the commonest RIF are the vesicovaginal fistulas with a reported incidence of 1%–8%, followed by enterovaginal, ureterovaginal, and enterovesical fistulas [1-3]. Small bowel involvement in radiation induced fistulas is uncommon and fistulous communications between small bowel and urinary bladder (enterovesical fistulas), and small bowel and cervix (enterocervical fistulas) are extremely rare. We searched PubMed/MEDLINE databases for previous case reports or series, using the keywords "enterovesical fistula and enterocervical fistula". We could find only a single report of spontaneous enterocervical and enterovesical fistulas published in German language in 1954 [4]. We report a case of synchronous enterovesical and enterocervical fistulas in a patient with carcinoma of the uterine cervix treated using chemotherapy and radiation along with a brief overview of etiopathogenesis of RIF.

Case Report

A 50-year-old woman diagnosed as carcinoma of the uterine cervix, stage IIB was treated with chemotherapy and radiation. Patient underwent external-beam extended-field radiation therapy using conventional four-field box technique (anteroposterior-posteroanterior, right lateral-left lateral). Intracavitary brachytherapy was not given in this patient. Patient received a total radiation dose of 50 Gy in the form of 25 fractions over 5 weeks (5 fractions per week) at the rate of 2 Gy/fraction/day. Concurrent chemotherapy with

cisplatin 40 mg/m^2 once weekly for 5 weeks was also given. No other abnormalities were noted in the history and patient was asymptomatic after the treatment. A year after chemoradiation therapy, patient developed feculent discharge per urethra and was referred to our institute, a tertiary care cancer center, for further management. Clinical examination and vital signs were normal. On vaginal and rectal examination, induration at cervix was noted. Ultrasound of abdomen and pelvis revealed multiple air foci in a partially distended urinary bladder with a communication between the bladder and ileal loop suggestive of enterovesical fistula (Fig. 1). Computed tomography (CT) of abdomen with oral contrast revealed an ileal loop between the urinary bladder and uterus with passage of contrast into the urinary bladder anteriorly and cervix posteriorly, demonstrating synchronous enterovesical and enterocervical fistulas (Fig. 2). Patient underwent surgery, and intraoperative findings showed interposition of distal ileal loop between the urinary bladder and uterus with adhesion of distal ileal loop to urinary bladder, at about 10 cm proximal to ileocecal junction. Ileal loop was pale, non-compliant and the bowel wall was communicating with both urinary bladder and cervix confirming the diagnosis of synchronous enterovesical and enterocervical fistulas. Laparoscopic

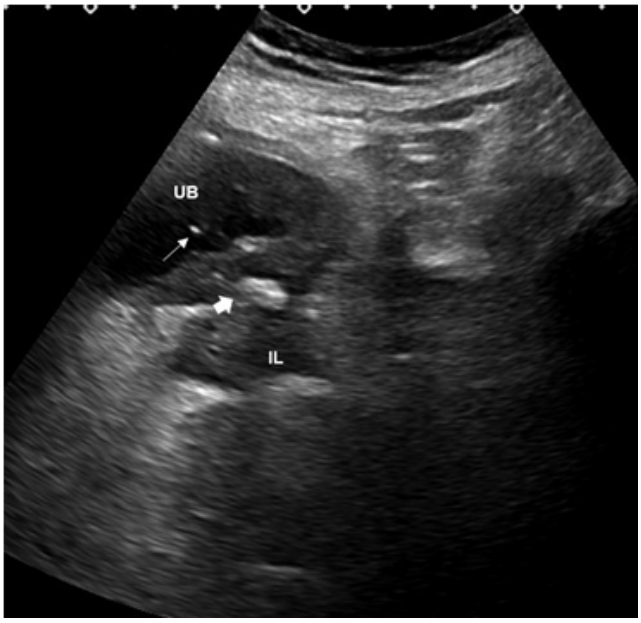

Fig. 1. Transabdominal ultrasound image reveals partially distended urinary bladder (UB) communicating with hypoechoic ileal loop (IL) through an irregular track of hyper-echoic air (thick arrow) suggestive of enterovesical fistula. Presence of air in the UB, seen as hyperechoic foci (thin arrow) is an indirect sign of vesical fistula.

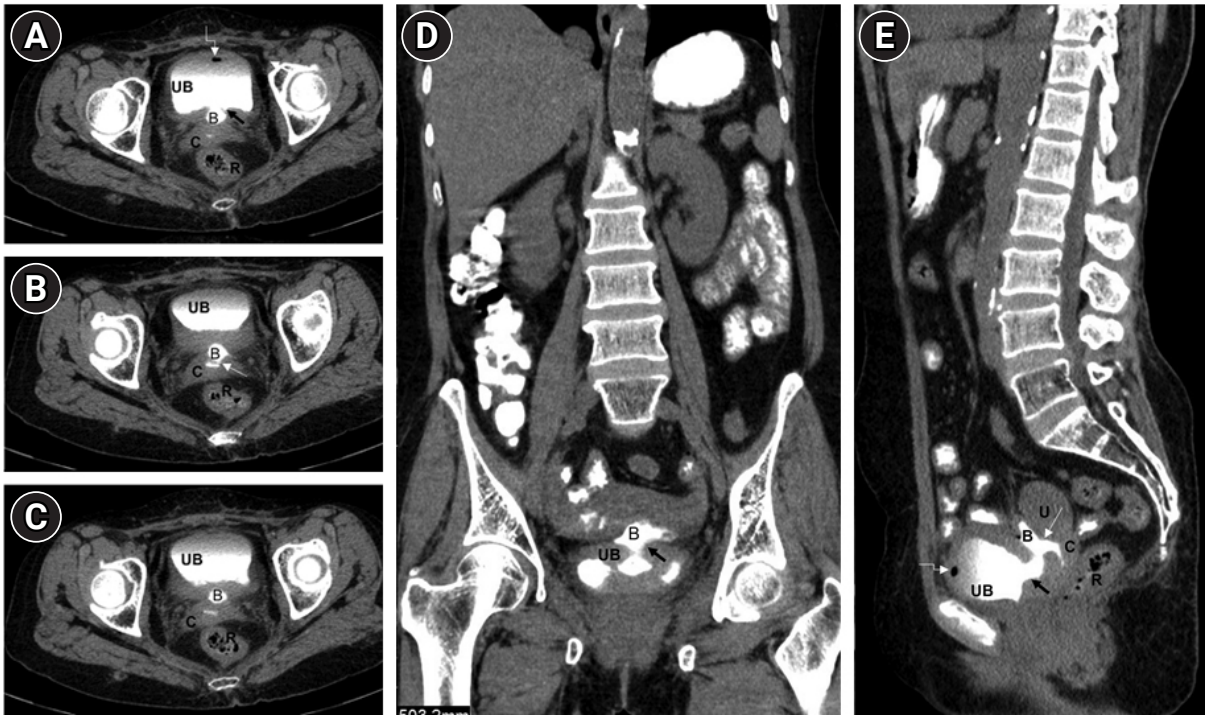

Fig. 2. (A–E) Axial and reconstructed coronal and sagittal computed tomography images of abdomen and pelvis with oral contrast show enterovesical fistula (thick black arrow) between the ileal loop (B) and urinary bladder (UB), and enterocervical fistula (thin white arrow) between the ileal loop (B) and cervix (C). Oral contrast is seen in the bowel loops in the abdomen, bladder, cervix, and the ileal loop (B) interposed between the UB and uterus (U). Air focus seen in the bladder (white elbow arrows) is an indirect sign of vesical fistula. Normal rectum (R) is seen posteriorly in the images.

https://doi.org/10.3857/roj.2023.00500

diversion ileostomy was performed and the patient recovered. Histopathology of bowel wall did not reveal any malignant cells. Microscopic examination revealed features of chronic radiation damage that included vascular changes, atypical fibroblasts and eosinophilic infiltrates, crypt distortion due to fibrosis of the lamina propria, along with fibrosis of the submucosa, muscularis propria and subserosa of bowel wall.

Discussion

RIF are uncommon and late therapeutic complications of malignancies and are associated with several predisposing factors. Systemic conditions causing microvascular ischemia such as diabetes, atherosclerosis, hypertension, and smoking are also linked to the acceleration of fistulation process [5]. The epithelial lined gastrointestinal and genitourinary organs are sensitive to radiation and are highly susceptible to radiation injury. Though small bowel is more radiosensitive than the large bowel, occurrence of fistulas is rare in small bowel due to its mobility in peritoneum. In cases of small bowel involvement, the terminal ileum, due to its relative fixity, is the most common segment to develop fistulous communications. Radiation injury to the bowel is dose dependent, hence increased incidence of fistulas is seen with higher doses of radiation and large field of irradiation. Timing of radiation is also important, as postoperative radiation is more lethal than preoperative radiation [5]. Simultaneous chemoradiation therapy, though is the standard nonsurgical treatment for cervical cancer, concurrent chemotherapy increases the early and late toxic effects of radiation including fistula formation [5-7].

Prior abdominopelvic surgeries causing adhesions between the bowel loops and adjacent organs in the pelvis can lead to inadvertent inclusion of bowel loops in the radiation field, predisposing to fistula formation [5]. Increased incidence of fistulas is also seen in patients with history of hysterectomy due to the absence of uterus that acts a protective barrier between the pelvic organs. Hence, most of the cervical cancer treatment protocols, except for stage II cancers with high-risk features, include either only radiotherapy or hysterectomy but not both [3].

The underlying etiopathogenesis of RIF is progressive chronic ischemia occurring due to endarteritis obliterans resulting in necrosis and fibrosis with loss of tissue planes leading to the development of fistulas [1,6]. Radiation-induced damage to the microvasculature of pelvic and abdominal organs initially present with acute symptoms of cystitis, enteritis, and proctitis and further progress to chronic complications like formation of strictures, abscesses, and fistulas [2,8]. Post-radiation fistulas occur late in the course of disease due to chronic toxic effects of radiation. The mean duration of occurrence is 2–3 years after radiotherapy, though cases have been reported from 6 months to 20 years after radiotherapy [9].

Post-radiation fistulas associated with cervical malignancy are usually multiple, large, and complex. Spontaneous closure is unlikely in these cases, and they invariably need surgical intervention. Bowel loops adjacent to the segment involved in the fistula formation may appear normal on gross examination. Radiation-induced damage to the intestinal microvasculature is difficult to appreciate clinically, there by presenting a challenge in assessing the viability of the tissues adjacent to fistula and in delineating the extent of radiation injury. RIF are often refractory to treatment and the failure rate of surgical repair is high due to the presence of nonviable ischemic tissue leading to anastomotic dehiscence and leaks [3,10].

Accurate diagnosis and appropriate management are the key to quality life in cervical cancer patients with radiation induced fistulas. Radiological imaging with ultrasound, CT, and magnetic resonance image (MRI) plays a crucial role in suspecting and confirming the diagnosis of fistulas. On ultrasound, the presence of a hyperechoic tract within a hypoechoic neoplastic mass described as "air contrast sign" and "ring down" artifacts are useful in detecting fistulas [11]. In suspected cases of RIF, CT with oral/rectal contrast is the imaging modality of choice as it excellently depicts the fistulous tracts, presence of malignant mass, air and/or contrast in inappropriate location [7,12]. MR imaging with its superior soft-tissue resolution may be useful in demonstrating the nonviable ischemic tissue and contrast-enhanced MRI using intravenous gadolinium can differentiate radiation-induced fibrosis which does not enhance from residual/recurrent malignancy [6].

The etiopathogenesis of the unusual enteric fistulas in the present case could be attributed to multiple factors such as adhesion of bowel loop to the urinary bladder, applying extended field radiation using conventional four-field technique that included the bowel loop within the radiation field and administering concomitant chemotherapy. Targeted radiotherapy utilizing intracavitary brachytherapy or intensity-modulated radiation therapy, prior imaging to rule out anatomical variations and appropriate contouring of radiation field are few measures useful in reducing the radiation damage to target organs and adjacent structures, thereby reducing the occurrence of fistulas.

In patients treated for cervical malignancies, fistulous communications can develop between adjacent organs in the pelvis due to either radiation injury or recurrence of malignancy. Hence, in cervical cancer patients with a past history of radiation, detection of a fistula warrants comprehensive clinical and radiological evaluation including biopsy, for appropriate management, as nearly one-third of the patients develop recurrence, typically within 18 months of therapy [2,13].

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Funding

None.

Author Contributions

Conceptualization, Mandava A; Investigation and methodology, Raju K; Formal analysis, Mandava A, Koppula V, Kandati M; Data curation, Mandava A, Koppula V, Kandati M; Writing of the original draft, Mandava A; Writing of the review and editing, Mandava A, Koppula V, Kandati M, Raju K.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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 https://doi.org/10.3857/roj.2023.00500

Instructions for Authors

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For the research and publication ethics policies not stated on this site, Good Publication Practice Guidelines for Medical Journals or Guidelines on Good Publication can be applied.

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1) Authorship

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Authors should have obtained written informed consent from all participants prior to inclusion in the study, and copies of written informed consent should be kept for studies on human subjects. For clinical studies of human subjects, a certificate, agreement, or approval by the Institutional Review Board (IRB) of the author's institution is required. If necessary, the editor or reviewers may request copies of these documents to resolve questions about IRB approval and study conduct.

The statement should be included in the Materials and Methods sec-

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- The manuscript should be written in 11-point font with double-line spacing on A4-sized (21.0×29.7 cm) paper with 25 mm margins on the top, bottom, right and left.
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3) Text

Text should be arranged in the following order: Introduction, Materials and Methods, Results, Discussion, and Conclusion.

Initiative	Type of study	Source
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STARD	Studies of diagnostic accuracy	http://www.stard-statement.org
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Introduction section should contain 1) the background and rationale of the study and 2) the objective of the study. The former part should state background information and references that inform the reader as to why the study was performed. Please avoid an extensive review of the literature. The final paragraph of the introduction should clearly state the hypothesis and the objective of the study.

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Present the results in logical sequence in the text, along with tables and figures. Do not repeat data that are already covered in the tables and/or figures; summarize only important observations. Do not illustrate minor details if their message is adequately conveyed by simple descriptive text. Make sure to give results for all items evaluated as mentioned in Materials and Methods section. State the statistical significance of the results.

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Journal articles:

1. Yu JI, Park HC, Choi DH, et al. Prospective phase II trial of regional hyperthermia and whole liver irradiation for numerous chemorefractory liver metastases from colorectal cancer. Radiat Oncol J 2016;34:34-44.
2. Childs SK, Kozak KR, Friedmann AM, et al. Proton radiotherapy for parameningeal rhabdomyosarcoma: clinical outcomes and late effects. Int J Radiat Oncol Biol Phys. 2011 Mar 4 [Epub]. http://dx.doi.org/10.1016/j.ijrobp.2010.11.048.

Book:

3. Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG. Abeloff's clinical oncology. 4th ed. Philadelphia, PA: Churchill Livingstone; 2008.
4. Jain RK, Kozak KR. Molecular pathophysiology of tumors. In: Halperin EC, Perez CA, Brady LW, editors. Perez and Brady's principles and practice of radiation oncology. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008. p. 126-41.

Conference paper:

5. Medin PM, Foster RD, von der Kogel, Sayre J, Solberg TD. Spinal cord tolerance to reirradiation with radiosurgery: a swine model. In: 52th ASTRO Annual Meeting; 2010 Oct 31 - Nov 11; San Diego, CA, USA. Farifax, VA: ASTRO; 2010.

Online sources:

6. American Cancer Society. Cancer facts & figures [Internet]. Atlanta, GA: American Cancer Society; c2011 [cited 2011 Feb 20]. Available from: http://www.cancer.org/Research/CancerFactsFigures/index.
7. National Cancer Information Center. Cancer incidence [Internet]. Goyang (KR): National Cancer Information Center; c2011 [cited 2011 Oct 20]. Available from: http://www.cancer.go.kr/cms/statics.

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Authors should have obtained written informed consent from all participants prior to inclusion in the study, and copies of written informed consent should be kept for studies on human subjects. For clinical studies of human subjects, a certificate, agreement, or approval by the Institutional Review Board (IRB) of the author's institution is required. If necessary, the editor or reviewers may request copies of these documents to resolve questions about IRB approval and study conduct.

The statement should be included in the Materials and Methods section after the IRB approval. Identifying details of the participants should not be published in written descriptions and photographs. In cases where identifying details are essential for scientific purposes, the participant should have given written informed consent for the identifying information to be published, and it should be stated separately.

Waiver of the informed consent can only be granted by the appropriate IRB and/or national research ethics committee in compliance with the current laws of the country in which the study was performed, and this should be separately stated. It should be noted that manuscripts that do not contain statements on IRB approval and patient informed consent can be returned to the authors before the review process.

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All studies involving animals must state that the guidelines for the use and care of laboratory animals of the authors' institution, or any national law, were followed.

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For clarification on result accuracy and reproducibility of the results, raw data or analysis data will be deposited to a public repository after acceptance of the manuscript. Therefore, submission of the raw data or analysis data is mandatory. If the data is already a public one, its URL site or sources should be disclosed. If data cannot be publicized, it can be negotiated with the editor. If there are any inquiries on depositing data or waiver of data sharing, authors should contact the editorial office.

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This journal follows the data sharing policy described in "Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors" (https://doi.org/10.3346/jkms.2017.32.7.1051). As of July 1, 2018, manuscripts submitted to ICMJE journals that report the results of interventional clinical trials must contain a data sharing statement as described below. Clinical trials that begin enrolling participants on or after January 1, 2019, must include a data sharing plan in the trial's registration. The ICMJE's policy regarding trial registration is explained at http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. If the data sharing plan changes after registration, this should be reflected in the statement submitted and published with the manuscript and updated in the registry record. All the authors of research articles that deal with interventional clinical trials must submit data sharing plan. Based on the degree of sharing plan, authors should deposit their data after deidentification and report the DOI of the data and the registered site.

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The Research Ethics Committee of the Korean Society for Radiation Oncology covers ethical issues involved with research and publication. This committee is composed of one chairperson and the members of the committee. The director of the ethics committee acts as the chairperson of this committee. The members of the Research Ethics Committee include the vice president, the auditor, the directors of general affairs, research, and publication committees, and two directors without a portfolio of the society become ex officio. The members of this committee serve for a term of two years, and they may be reappointed.

If presented with convincing evidence of dual publication, fragmentation, plagiarism, fabrication, or theft of intellectual property in journals, the committee meeting will be held immediately for investigation. If evidence becomes available that the regulation has been breached, publication of the corresponding manuscript is immediately canceled and all authors, including the corresponding author, are banned from any publication in the ROJ published for the next three years. The investigation results of the committee meeting must be notified for immediate disciplinary measures and reported to the board of directors. Other issues that are not specified in this regulation abide by the decisions made by board members of the society, which conform with the Ethics Code of Science Technology set forth by the Korean Federation of Science Technology Societies.

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A preprint can be defined as a version of a scholarly paper that precedes formal peer review and publication in a peer-reviewed scholarly journal. ROJ allows authors to submit the preprint to the journal. It is not treated as duplicate submission or duplicate publication. ROJ recommends authors to disclose it with DOI in the letter to the editor during the submission process. Otherwise, it may be screened from the plagiarism check program — Similarity Check (Crosscheck). Preprint submission will be processed through the same peer-review process as a usual submission. If the preprint is accepted for publication, authors are recommended to update the information at the preprint with a link to the published article in ROJ, including DOI at ROJ. It is strongly recommended that authors cite the article in ROJ instead of the preprint at their next submission to journals.

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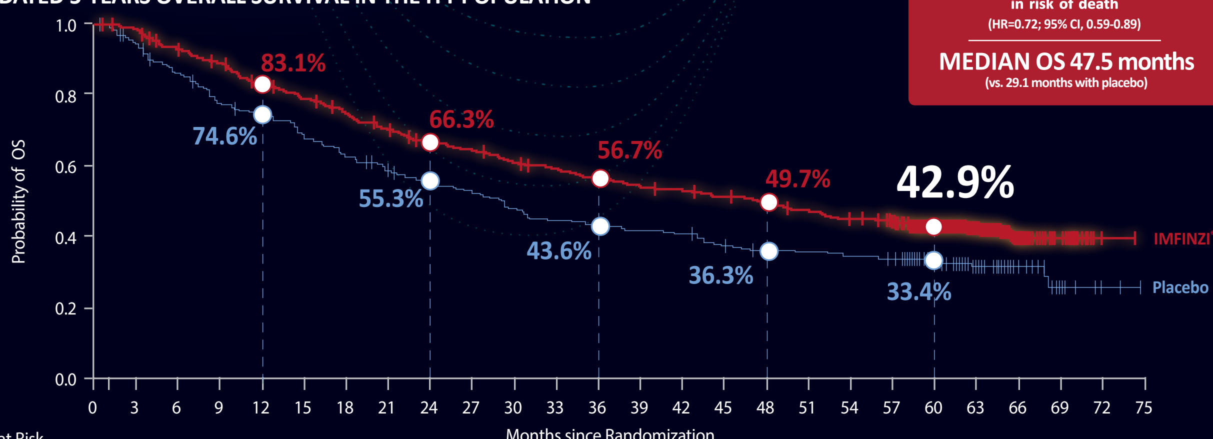

No. at Risk

Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

임핀지(durvalumab) 보험 적용 적응증[3,4]

PD-L1 발현 양성(발현 비율 ≥ 1%)이면서 백금 기반 동시적 항암화학 방사선요법 2주기 이상 투여 후 질병진행이 없는 안정병변 이상의 절제 불가능한 국소 진행성(stage III) 비소세포폐암 환자로 cCRT 치료 종료 이후 42일 내에 투여하는 경우 ※ 이전 PD-1 inhibitor 등 면역관문억제제 치료를 받지 않은 경우에 한함

- 급여 인정 기간 최대 12개월
- cCRT 치료 종료(마지막 방사선 요법 기준) 이후 42일 이내 투여할 경우
- 유도화학요법과 동시적 항암화학방사선요법의 항암요법 종류가 동일할 경우
- 방사선 요법은 54 Gy 이상, 항암화학요법은 weekly regimen 기준 4주기 이상 또는 3주기 regimen 기준 2주기 이상 투여할 경우

STUDY DESIGN The PACIFIC study design, eligibility criteria and assessments have been fully described previously. Eligible patients had histologically and/or cytologically documented Stage III, unresectable NSCLC, with a WHO performance score of 0 or 1. Patients had to have received at least two cycles of platinum-based chemotherapy concurrently with definitive radiation therapy without progression, and the last radiation dose was 1-42 days before randomization. Tumor tissue collection was not a prerequisite for inclusion in PACIFIC and enrollment was notrestricted to any threshold levels for PD-L1 expression. Patients were randomized 2:1 to durvalumab 10 mg/kg intravenously or placebo every two weeks for up to 12 months or until confirmed disease progression, initiation of alternative cancer therapy, unacceptable toxicity, or consent withdrawal. Randomization was stratified by age of the patient (<65 years vs ≥65 years), sex, and smoking history (current or former vs never smoked). The primary end points were progression free survival (as assessed by blinded independent central review) and overall survival.

NSCLC, nonsmall-cell lung cancer; cCRT, concurrent chemoradiation therapy; OS, overall survival; ITT, intent-to-treat; HR, hazard ratio; CI, confidence interval; PD-L1, programmed cell death-ligand 1; PD-1, programmed cell death protein-1.

Reference **1.** Botticella A, et al. Durvalumab for stage III non-small-cell lung cancer patients: clinical evidence and real-world experience. Ther Adv Respir Dis. 2019 Jan-Dec;13:1753466619885530; **2.** Spigel DR, et al. Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. J Clin Oncol. 2022 Feb 2. doi: 10.1200/JCO.21.01308; **3.** 건강보험심사평가원 공고 제2020-81호(시행일: 2020년 4월 1일); **4.** 건강보험심사평가원. 암질환 사용약제 및 요법: FAQ - 'Durvalumab (품명: 임핀지주)' 급여기준(공고) 관련 질의 응답[Accessed 20 Feb 2022]. Available from: https://www.hira.or.kr/bbsDummy.do?pgmid=HIRAA030023080000&brdScnBltNo=4&brdBltNo=45645&pageIndex=1

PRESCRIBING INFORMATION

임핀지주 (더발루맙) [효능•효과] 국소 진행성 비소세포폐암: 백금 기반 동시적 항암화학방사선요법 이후 질병이 진행되지 않은 절제불가능한 국소 진행성 비소세포폐암 환자의 치료 소세포폐암: 확장병기 소세포폐암 환자의 1차 치료로서 에토포시드 및 카보플라틴 또는 시스플라틴과의 병용 요법 [용법•용량] 이 약은 1시간에 걸쳐 정맥 점적 주입한다. 국소 진행성 비소세포폐암: 권장 용량은 이 약 10mg/kg을 2주 간격으로 투여하는 것이며, 질환이 진행되거나 허용 불가능한 독성 발생 전까지 투여한다. 소세포폐암: 권장 용량은 이 약 1500 mg을 화학요법과 병용하여 3주 간격으로 4주기 동안 투여한 뒤, 이 약 1500 mg 단독요법을 4주 간격으로 투여하는 것이며, 질환이 진행되거나 허용 불가능한 독성 발생 전까지 투여한다. 체중 30 kg 이하의 환자는 체중에 따라 이 약 20 mg/kg을 화학요법과 병용하여 3주 간격으로 4주기 동안 투여한 뒤, 이 약 20 mg/kg을 단독요법으로서 4주 간격으로 체중이 30 kg을 초과할 때까지 투여한다. 이 약을 화학요법과 병용할 때에는 에토포시드 및 카보플라틴 또는 시스플라틴의 허가된 용법•용량 정보를 참조한다. 화학요법과 같은 날 투여하는 경우 이 약을 먼저 투여한다. 용법조절: 이 약의 용량 증가나 감소는 권장되지 않는다. 일반적으로 중증(3등급) 면역 매개 이상사례의 경우 이약의 투여를 보류한다. 생명을 위협하는 (4등급) 면역 매개 이상사례와, 전신 면역 억제 치료가 필요하거나 코르티코스테로이드 시작 12주 이내에 프레드니손 또는 등가량 하루 10 mg 이하로 감량할 수 없는 중증 (3등급) 면역 매개 이상사례의 경우 이 약의 투여를 중단한다. 면역 매개 이상사례가 다음 표에 요약되어 있다. [이 약의 용법 조절 및 관리 권장 사항]

이상사례	중증도 (CTCAE v4.03[a])	용법 조절	코르티코스테로이드 요법 및 그 외[b]
면역 매개 폐염증/간질성 폐질환	2등급	투여 보류[c]	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	3 또는 4등급	투여 중단	
면역 매개 간염	2등급이고, 알라닌 아미노전이효소 (ALT) 또는 아스파르트산 아미노전이효소 (AST)가 정상상한치의 3~5배를 초과하거나 총 빌리루빈이 정상상한치의 1.5~3배를 초과	투여 보류[c]	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	3등급이고, ALT 또는 AST가 정상상한치의 5배 초과, 8배 이하 또는 총 빌리루빈이 정상상한치의 3배 초과, 5배 이하		
	3등급이고, ALT 또는 AST가 정상상한치의 8배를 초과 또는 총 빌리루빈이 정상상한치의 5배를 초과	투여 중단	
	다른 요인은 없으며, ALT 또는 AST가 정상상한치의 3배를 초과하고 총 빌리루빈이 정상상한치의 2배를 초과하는 경우		
면역 매개 대장염 또는 설사	2 또는 3등급	투여 보류[c]	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	4등급	투여 중단	
면역 매개 내분비병: 갑상선 기능 항진증, 갑상선염	2~4등급	임상적으로 안정할 때까지 투여 보류	대증적 관리
면역 매개 내분비병: 갑상선 기능 저하증:	2~4등급	변경하지 않음	임상 지시대로 갑상선 호르몬 대체 개시
면역 매개 내분비병: 부신 기능 부전, 뇌하수체염/뇌하수체 저하증	2~4등급	임상적으로 안정할 때까지 투여 보류	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량 및 임상 지시대로 호르몬 대체 개시
면역 매개 내분비병: 제1형 당뇨병	2~4등급	변경하지 않음	임상 지시대로 인슐린 치료 개시
면역 매개 신장염	2등급이고, 혈청 크레아티닌이 정상상한치 또는 기저치의 1.5~3배를 초과	투여 보류[c]	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	3등급이고 혈청 크레아티닌이 기저치의 3배를 초과 또는 정상상한치의 3~6배를 초과하거나, 4등급이고 혈청 크레아티닌이 정상상한치의 6배를 초과	투여 중단	
면역 매개 발진 또는 피부염 (유사 천포창 포함)	2등급으로 1주일 초과 또는 3등급	투여 보류[c]	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	4등급	투여 중단	
면역 매개 심근염	2~4등급	투여 중단	2~4 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량[d]
면역 매개 근육염/다발근육염	2 또는 3등급	투여 보류[c,e]	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	4등급	투여 중단	
주입 관련 반응	1 또는 2등급	주입을 중단하거나 느리게 주입	후속 주입 반응의 예방을 위해 사전 약물 치료를 고려할 수 있음
	3 또는 4등급	투여 중단	-
중증 근육 무력증	2등급	투여 보류[c]	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	3 또는 4등급, 또는 호흡 부전이나 자율 신경 실조증의 징후가 있는 모든 등급	투여 중단	
기타 면역 매개 이상사례[f]	3등급	투여 보류[c]	1~2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	4등급	투여 중단	

[a] 이상사례 표준 용어기준 (Common Terminology Criteria for Adverse Events; CTCAE), 버전 4.03 [b] 1등급 이하로 개선되면, 코르티코스테로이드의 감량을 시작하여 최소 1개월 간 지속하여야 한다. 악화되거나 개선이 없다면, 코르티코스테로이드의 용량 증가 및/또는 다른 전신 면역 억제제 사용을 고려한다. [c] 투여 보류 후, 1등급 이하로 개선되고 코르티코스테로이드 용량이 일일 10mg 프레드니손 또는 등가량 이하로 감소되었을 경우, 12주 이내에서 이 약의 투여를 다시 시작할 수 있다. 3등급 이상사례 재발의 경우 이 약을 중단한다. [d] 코르티코스테로이드 투여에도 불구하고 2~3일 이내에 개선이 없다면, 신속히 추가적인 면역억제 치료를 시작한다. 회복(0등급)되면, 코르티코스테로이드의 감량을 시작하고 최소 1개월 간 지속한다. [e] 이상사례가 30일 이내에 1등급 이하로 회복되지 않거나 호흡기 기능부전의 징후가 있는 경우에는 이 약 투여를 중단한다. [f] 면역 혈소판 감소증, 뇌염 포함 의심되는 면역 매개 이상사례에 대해, 병인 확인 또는 대체 병인을 배제하기 위한 적절한 평가가 수행되어야 한다. 비-면역 매개 이상사례에 대해, 2등급과 3등급 이상사례의 경우 1등급 이하가 될 때까지 이 약의 투여를 보류한다. 4등급 이상사례의 경우 이 약 투여를 중단한다 (예외적으로 4등급 실험실 검사수치 이상의 경우, 수반된 임상 징후 및 임상적 판단에 근거하여 투여 중단을 결정한다). 이 약은 경등도 간장애 환자에서는 용량 조절이 권장되지 않으며, 중등도 또는 중증 간장애 환자에서는 연구되지 않았다. 투여방법 투여 전 이 의약품의 희석에 대한 지시 사항은 사용상의 주의사항, '13. 취급상의 주의사항'을 참고한다. 멸균된 저 단백질 결합 0.2 또는 0.22 마이크로미터 인라인 필터(in-line filter)를 포함하는 정맥 주사 라인을 통해 1시간에 걸쳐 주사액을 정맥 내 투여한다. 같은 주입 라인으로 다른 약물을 동시 투여하지 않는다. 사용하고 남은 약물이나 물품은 관련 규정에 따라 폐기되어야 한다. [사용상의 주의사항] 1.다음 환자에는 투여하지 말 것 이 약의 주성분 또는 첨가제에 과민증 병력이 있는 환자. 2.다음 환자에는 신중히 투여할 것 자가면역질환 또는 자가면역질환 병력이 있는 환자 3.약물이상반응 1) 임상시험에서 보고된 이상사례 이상사례는 MedDRA의 기관계 분류에 따라 기재되었다. 각 기관계 분류에서, 이상사례는 빈도가 높은 순으로 표기되었다. 각 빈도 군에서, 이상사례는 중증도가 높은 순으로 표기되었다. 또한, 각 이상사례의 해당 빈도 분류는 CIOMS III 협의에 따르며 다음과 같이 정의된다: 매우 흔하게 (≥1/10); 흔하게 (≥1/100 ~ <1/10); 흔하지 않게 (≥1/1,000 ~ <1/100); 드물게 (≥1/10,000 ~ <1/1,000); 매우 드물게 (<1/10,000); 빈도 불명, 즉 이용 가능한 자료로부터 추정될 수 없음. 국소 진행성 비소세포폐암 - PACIFIC 연구 PACIFIC 연구 (475명)에서 국소 진행성 절제 불가능한 비소세포폐암 환자로 이 연구 시작 전 1~42일 내에 2주기 이상의 항암화학방사선요법을 완료한 환자들을 대상으로 이 약(10 mg/kg)의 안전성이 평가되었다. 이 환자 집단에서 가장 흔한 이상사례는 기침 (40.2%, 위약군 30.3%), 상부 호흡기 감염 (26.1%, 위약군 11.5%) 및 발진 (21.7%, 위약군 12.0%)이었다. 3 또는 4등급 이상사례의 발생률은 이 약 투여군에서 12.8%, 위약군에서 9.8%이었다. 가장 흔한 3 또는 4등급 이상사례는 폐렴 (6.5%, 위약군 5.6%)이었다. 이 약 투여군의 8.2% 및 위약군의 5.6%에서 이상사례로 인해 투약을 중단하였다. 이 약의 투약 중단으로 이어진 가장 흔한 이상사례는 폐염증 (4.8%)이었다. 중대한 이상사례는 이 약 투여군 12.8% 및 위약군 11.1%의 환자에서 발생하였다. 가장 흔한 중대한 약물이상반응은 2% 이상의 환자에서 보고된 폐염증과 폐렴이었다. 치명적인 폐염증과 치명적인 폐렴은 이 약 투여군과 위약군 간에 유사하게 1% 미만의 환자에서 보고되었다. 확장 병기 소세포폐암 - CASPIAN 연구 CASPIAN 연구에서 이전에 치료받지 않은 확장 병기 소세포폐암 환자에게 이 약과 에토포시드 및 카보플라틴 또는 시스플라틴을 병용투여 했을 때의 안전성이 평가되었다 (265명). 이 약과 화학요법을 병용 시의 안전성 프로파일은 이 약 단독요법 및 화학요법의 알려진 프로파일과 일관되게 나타났다. 이 임상연구에서 보고되지 않았더라도, 이 약 또는 화학요법 단독으로 발생한다고 알려진 이상사례는 병용요법 중에도 발생할 수 있다. [저장방법] 밀봉용기, 2-8℃에서 차광하여 보관 [포장단위] 2.4 mL × 1 바이알 / 박스, 10 mL × 1 바이알 / 박스 ※ 만약 구입시 사용기한이 경과되었거나 변질, 변패 또는 오손된 제품인 경우에는 구입처를 통하여 교환하여 드리며, 공정거래위원회 고시 "소비자분쟁해결기준" 에 의거 소비자의 정당한 피해는 보상하여 드립니다. 의약품 부작용 발생 시 한국의약품안전관리원에 피해구제를 신청하실 수 있습니다. 문헌개정연월일: 2022년 03월 04일 수입(수입자): 한국아스트라제네카 서울시 강남구 영동대로517 아셈타워 21층, 전화 02-2188-0800 *보다 자세한 사항은 제품설명서 전문을 참고하시기 바랍니다. aIFZ20220310

KR-10524 | Exp.2024-02 (Prep.2022-02)

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