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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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Editorial

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Is there a role of radiotherapy for steroid-resistant thyroid eye disease?

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Thyroid eye disease (TED), also known as Graves' orbitopathy, is the most common extrathyroidal manifestation of Graves' disease [1]. Autoimmune reactions against thyroid-stimulating hormone receptors expressed in the orbital tissues result in fibroblast proliferation and overproduction of glycosaminoglycans [2,3]. Affected patients may present with clinical manifestations including periorbital edema, lid retraction, proptosis, and diplopia. Owing to the anti-inflammatory effects and radiosensitivity of lymphocytes infiltrating the orbit, orbital radiotherapy (RT) in combination with glucocorticoids is considered an effective second-line treatment for active moderate-to-severe TED, particularly in the presence of progressive diplopia [4,5]. The efficacy of RT for TED has been debated in clinical studies [6-9], largely due to several confounding factors and the use of diverse assessment criteria [5,10].

In the recent issue of *Radiation Oncology Journal*, Park and Lee [11] evaluated the efficacy of RT in patients with steroid-resistant TED by assessing the clinical outcomes of orbital inflammation and exophthalmos. This study retrospectively analyzed 62 patients with TED who were resistant to intravenous steroid therapy and received RT. The clinical activity score (CAS) was used to evaluate the severity of inflammation, and the posterior scleral distance (PSD) was used to measure exophthalmos. The estimated marginal means of the CAS demonstrated a progressive decline from 3.309 at baseline to 2.841 after steroid treatment and then to 1.387, 0.518, and 0.187 at 1, 6, and 12 months after RT. This finding suggests that the therapeutic response after RT was sustained over 1 year. In addition, PSD also improved after RT despite initial worsening after steroid therapy. In this context, the present study is valuable, as RT may serve as an effective salvage therapy for patients with steroid-resistant disease.

Although this study demonstrated the long-term efficacy of orbital RT, extended follow-up is required to establish its safety. Although this study lacked information on diabetes, RT should be used with caution in diabetic patients to minimize the risk of retinopathy [5,12]. Another study on the long-term safety of orbital RT for Graves' ophthalmopathy reported no secondary tumors after a median follow-up of 11 years [13]. However, the authors recommend restricting orbital RT to patients older than 35 years, given the long latency of radiation-induced tumors. Park and Lee [11] included a 19-year-old patient who demonstrated sustained improvement over 7 years; however, caution is warranted regarding the potential risk of secondary malignancies.

In conclusion, RT plays a meaningful role in the management of steroid-resistant TED, providing a

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sustained therapeutic response beyond 1 year. With the advent of newer biologic agents, such as teprotumumab, rituximab, and tocilizumab, are available for the treatment of moderate-to-severe and active TED [4,5], future studies are needed to determine the optimal therapeutic approach—RT or biologic agents—for individual patients, particularly when the response to first-line treatment is inadequate and TED remains moderate to severe and active.

Conflict of Interest

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

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Original Article

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Technique and outcomes of high-dose-rate interstitial brachytherapy for lip and buccal mucosa cancer: emphasis on cosmetic results

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Purpose: High-dose-rate (HDR) brachytherapy is a promising treatment modality for organ and function preservation in lip and oral cavity cancers. This study aims to describe the technique and assess clinical outcomes of HDR interstitial brachytherapy in patients diagnosed with lip and buccal mucosa cancer treated in a comprehensive cancer center.

Materials and Methods: We conducted a retrospective analysis of six lip and four buccal mucosa cancer patients with a median age of 69 years (range, 37 to 90) and equal gender distribution, who underwent exclusive interstitial brachytherapy during the study period from May 2019 to December 2024. All procedures were performed under local anesthesia. Most patients were treated with HDR brachytherapy with a total dose of 40 Gy in 10 fractions over 5 days. Patient characteristics, treatment parameters, cosmetic and functional outcomes, and toxicity were assessed.

Results: All patients in this cohort achieved local control and remained in remission at the treatment site throughout the follow-up period. The median duration of follow-up was 29 months (range, 16 to 68). Cosmetic outcomes were rated as good in most of the patients. Any acute and late toxicities experienced were manageable; the most severe acute toxicity observed was grade 3, with late toxicity reaching grade 2.

Conclusion: Favorable tumor control, good aesthetic results with manageable toxicity, and the minimally invasive approach highlight interstitial brachytherapy as a compelling single treatment modality for eligible patients with lip and buccal mucosa cancer, particularly in older individuals with significant comorbidities.

Keywords: Brachytherapy, High-dose-rate, Lip neoplasms, Buccal mucosa neoplasms, Cosmetic outcome

Introduction

Lip and oral cancers are the 15th most common cancers worldwide, with two-thirds occurring in men [1]. Unlike other upper aerodigestive tract cancers, which are primarily caused by tobacco, sunlight exposure is a significant risk factor for lip cancers, particularly those on the lower lip, which are more common than upper lip cancers.

Due to its visible location, lip cancers are often detected early, allowing effective treatment with a single modality [2]. Early-stage

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lip cancers can be managed effectively with either radiotherapy or surgery, offering local control rates between 90% and 95% [3].

While surgery provides excellent disease control, reconstructing the lips, oral commissure, and mucosa defects post-tumor resection poses significant challenges [4]. Functionally, lips are crucial for oral competence during swallowing and play a key role in emotional and verbal communication. Aesthetically, they are a focal point of facial identity. Poor reconstructive approaches can lead to microstomia, disfigurement, loss of sensation, and issues with oral competence and natural oral angle [5]. Elderly patients face additional challenges in reconstruction due to complex medical histories, prolonged general anesthesia, issues of age-related tissue quality, and significant comorbidities like diabetes that delay wound healing [6]. External beam radiotherapy (EBRT) is another treatment modality for lip and buccal mucosa cancers. Still, it does not adequately spare adjacent normal tissues, such as the salivary glands and mandible, leading to undesirable late side effects [7].

Brachytherapy in lip and oral cavity cancers is an important alternative to surgery or conventional EBRT, aiming to preserve normal anatomy and enhance both cosmesis and functional outcomes. Moreover, the affordable cost, shorter treatment duration, and ability to provide high localized doses with rapid dose fall-off make it an excellent tool for delivering highly conformal therapy with fewer side effects than EBRT [8].

Traditionally low-dose-rate (LDR) brachytherapy was used to treat tumors in head and neck sites like lips, tongue, buccal mucosa, etc. However, it is being replaced by high-dose-rate (HDR), which gives similar local control, and functional and cosmetic outcomes [9]. Besides safety and convenience, HDR brachytherapy has added advantages like intensity modulation using varying dwell time and position. The introduction of 3-dimensional (3D) imaging modality for brachytherapy planning has refined the definition of target volume and organs at risk, enhancing overall treatment accuracy.

Despite its efficacy, the use of brachytherapy is declining in oral tumors due to the limited availability of data, insufficient dissemination of the technique, advancements in EBRT, and a lack of training and experience among healthcare professionals [10]. Given the technique's efficacy in cancer treatment, providing data on treatment outcomes and discussing the technique is crucial. This retrospective study aims to evaluate the outcomes of image-guided HDR brachytherapy as a sole treatment modality for lip and buccal cavity cancers, focusing on disease control, and organ and function preservation.

Materials and Methods

1. Patient selection

This retrospective study reviewed 10 consecutive patients with histologically confirmed squamous cell carcinoma of the lip (n = 6) or buccal mucosa (n = 4) treated with exclusive brachytherapy at our institution between May 2019 and December 2024.

Eligible patients included those with histologically confirmed early to moderately advanced squamous cell carcinoma (T1–T4 categories) who were considered suitable for brachytherapy as a sole treatment modality. Individuals with contraindications to surgery, such as advanced age, significant comorbidities, or personal unwillingness to undergo surgical intervention, were included in the study. Patients with a history of prior surgery, radiation therapy, or systemic chemotherapy in the same treatment area were excluded. All patients were assessed and approved as appropriate candidates for brachytherapy by a multidisciplinary tumor board.

Clinical staging of th T1 (n = 3), T2 (n = 6), and T4 (n = 1). Table 1 enumerates individual patients and tumor characteristics, dose fractionation, and outcome. A significant number of patients in our study had multiple health issues, including compulsive obstructive pulmonary disease, myocardial infarction, a second malignancy, and kidney transplantation. Additionally, two patients were over 90 years old, one of whom had suffered a myocardial infarction leading to poor cardiac function precluding general anesthesia.

All patients underwent comprehensive staging, including physical examination, a biopsy of the primary site, chest X-ray, and contrast-enhanced computed tomography (CT)/magnetic resonance imaging of the head and neck when necessary. An ultrasonogram of the neck was done in all cases. Positron emission tomography–CT was not done either due to early-stage disease or due to financial limitations. Baseline blood counts and biochemistry were obtained.

2. Implantation technique

All implants were performed under local anesthesia via nerve or field block. The implantation volume was defined as tumor plus a 1 cm margin of surrounding normal tissue to ensure adequate coverage. The tumor and planned needle track including entry and exit points were marked in the skin using clinical examination and imaging data (Fig. 1). Using tactile guidance, a hollow stainless steel guide needle was inserted along the predetermined entry and exit points. Flexible afterloading plastic catheters were threaded along the steel guide needle and the steel guide needle was removed. Catheters were then cut to the desired length and secured with buttons. The spacing between catheters was 8 mm to 1 cm. Most patients received single-plane implants, while one lower lip case

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Table 1. Patients and tumor characteristics, HDR dose regimens, and treatment response

Patient no.	Age (year)/ Sex	Site	Tumor stage	Tumor grade	Comorbidity	No. of catheters	BT dose/fractionation	Local control
1	52/M	UL	T1N0M0	1	Colon cancer survivor	3	40 Gy in 10 fx bid HDR	NED in 68 mo
2	37/F	LL	T1N0M0	1	None	3	40 Gy in 10 fx bid HDR	NED in 41 mo
3	61/F	LL	T2N0M0	1	Kidney transplant	3	40 Gy in 10 fx bid HDR	NED in 31 mo
4	67/F	LL	T4N0M0	1	Chronic obstructive pulmonary disease	7	42 Gy in 12 fx bid HDR	NED in 31 mo
5	71/F	LL	T2N0M0	1	None	3	40 Gy in 10 fx bid HDR	NED in 24 mo
6	90/M	BM	T1N0M0	1	None	3	40 Gy in 10 fx bid HDR	NED in 27 mo
7[a)]	90/M	BM	T2N0M0	2	Hypothyroidism	6	40 Gy in 10 fx bid HDR	NED in 20 mo
8	85/F	LL	T2N0M0	2	Myocardial infarction	3	44 Gy in 11 fx bid HDR	NED in 16 mo
9	60/M	BM	T2N0M0	1	None	4	44 Gy in 11 fx bid HDR	NED in 16 mo
10	85/M	BM	T2N0M0	1	Hypertension, diabetes mellitus, hypothyroidism, dyslipidemia	4	44 Gy in 11 fx bid HDR	NED in 64 mo

HDR, high-dose-rate; BT, brachytherapy; M, male; UL, upper lip; fx, fractions; bid, twice daily; NED, no evidence of disease; mo, months; F, female; LL, lower lip; BM, buccal mucosa.
[a)]The patient underwent salvage surgery for regional nodal recurrence.

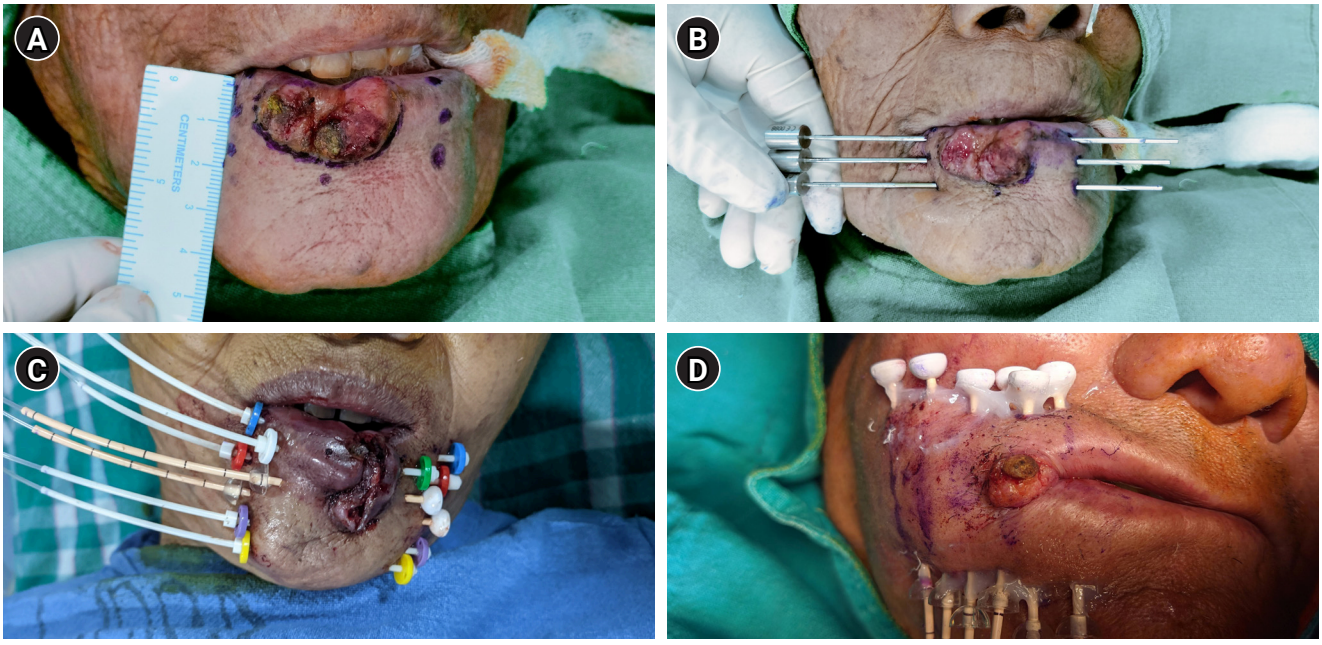

Fig. 1. Examples of interstitial catheter placement. (A) Carcinoma of the lower lip with tumor and needle entry and exit points marked in the skin. (B) Same patient after steel needles placement along the skin marks. (C) Example of double plane flexible catheter placement in T4 lower lip cancer with skin involvement. (D) Flexible catheter placement in tumor of the angle of mouth with buccal mucosa involvement.

required a two-plane implant which was performed following the Paris method.

To maintain the implant during the radiation therapy, catheters were secured in place using adhesive dressing and buttons to prevent displacement. Patients were provided with a soft or liquid diet, often using a straw to take liquid or semi-solid food, to avoid disturbing the implant and minimize irritation to the treatment area. Nutritional supplements were offered as needed to ensure adequate caloric intake.

Despite the use of rigid needles in some published studies for HDR brachytherapy, we always use plastic tubes. This preference enables CT-based planning, facilitates the contouring of clinical target volume (CTV), and allows for a 3D calculation of the isodose distribution and comfort to the patient.

3. Radiation planning and delivery

Simulation CT scans for dose specification were obtained on the second day of the implant using a 1 mm slice thickness at the implant region in a 16-slice CT Scanner (Toshiba Alexion, Otawara, Japan). Dwell positions and times were computer-optimized following Paris system rules. The aim was to cover 90% of the target volume with more than 90% of the prescription dose while minimizing the volume receiving 150% (V150) and 200% of the prescription dose (Fig. 2). The dosimetric parameters were recorded and a linear regression model was used to model the relationship between CTV and V150.

A personalized mold or spacer made from wax or thermoplastic was used, with lead shielding added during treatment to protect nearby healthy tissue, particularly the mandible and tongue.

HDR brachytherapy was delivered using an iridium-192 afterloader (Gammamed, Varian Inc., Palo Alto, CA, USA) with 40-44 Gy doses given in 4 Gy fractions twice daily over a median of 5 days (range, 5 to 6) [11]. The dose prescription was based on the CTV volume. Patients stayed in the hospital for logistical reasons throughout their HDR brachytherapy treatment. Anti-inflammatory medications, analgesics, and antibiotics were prescribed as needed. After the implant was removed, patients received post-procedure instructions and were discharged.

4. Follow-up and outcome measures

Patients were asked to visit the hospital for routine follow-up weekly for the first month, every 3 months for the first year, and every 6 months thereafter. Follow-up included clinical examinations and imaging studies including ultrasonogram and CT scan. The primary endpoint was local tumor control, defined as the absence of tumor growth at the primary site. Secondary endpoints included treatment-related toxicities and overall survival. Local recurrence was defined as tumor regrowth at the treated site, while regional recurrence referred to tumor involvement of lymph nodes in the head and neck region. Response to treatment was categorized as complete response, partial response, disease progression, or recurrence. Descriptive statistics were used to summarize patient characteristics and treatment parameters. Treatment-related toxicities were graded according to the Common Terminology Criteria for Adverse Events version 5.0.

Aesthetic and functional outcomes were assessed using standardized photography evaluated by a panel of five plastic surgeons and five ear, nose and throat surgeons with an average of 8.5 and 8 years of clinical experience, respectively. Outcomes were rated on a three-point scale: 1 (good result), 2 (moderate result), and 3 (poor result) [12].

Results

Brachytherapy was safely administered to all 10 patients without any severe pain, discomfort, or complications, such as bleeding or infection. After the treatment, all the patients achieved complete

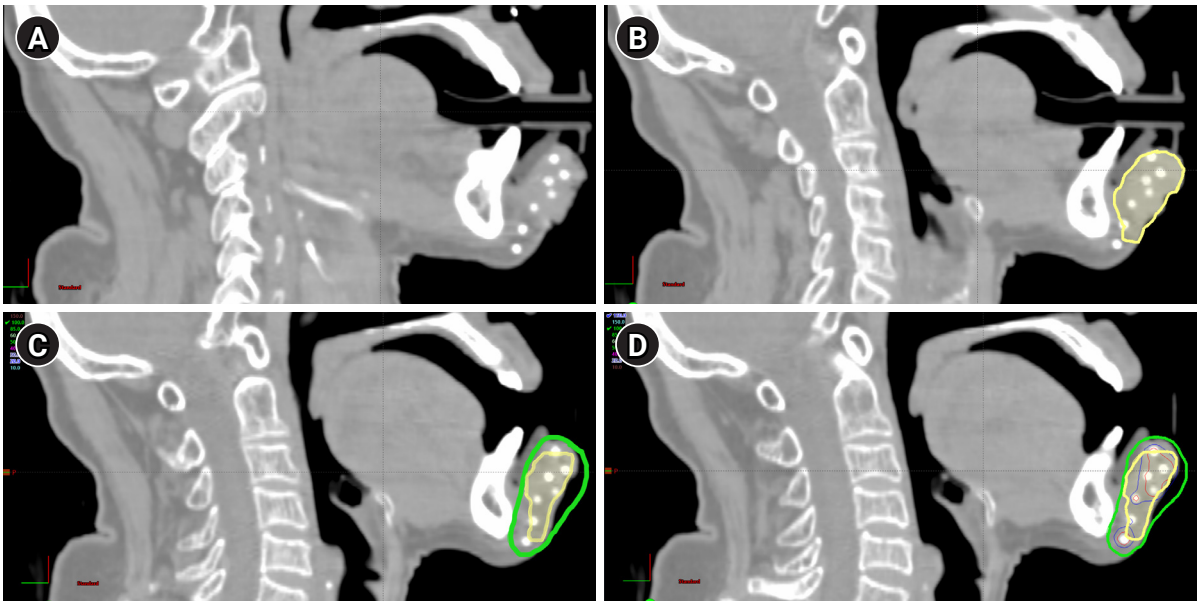

Fig. 2. Computed tomography (CT) simulation and dosimetry images. (A) Sagittal CT scan demonstrating the implant in two anatomical planes. (B) Gross tumor volume contoured in yellow. (C) 100% isodose distribution represented by the green line. (D) Higher isodose distributions shown in blue (150%) and red (200%).

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response and maintained their remission over the median follow-up period of 29 months (range, 16 to 68). All of the patients are still in follow-up.

One patient experienced regional nodal failure. All patients achieved complete remission and 100% local control in the implanted site, exhibiting good to excellent cosmetic results. Representative photographs of tumor sites before and after treatment are shown in Fig. 3. Dosimetric parameters are presented in Table 2. In two patients, surface catheters were added to improve dose coverage (sandwich technique) [13].

Regarding dosimetry, the median number of interstitial catheters used in the treatment was 3 (range, 3 to 7). The regression analysis demonstrated a correlation between the CTV and the V150 (R^2 = 0.85, $p < 0.001$), as shown in Fig. 4.

Patients experienced some acute events during the procedure which were mild to moderate, with none beyond grade 3. The most common acute toxicities were pain, mucositis and dermatitis. For the late adverse events, the highest level of toxicity was grade 2 fibrosis in one patient. No late side effects, such as dry mouth (xerostomia), soft tissue damage, or bone necrosis, were observed in the patients (Table 3).

All patients maintained lip symmetry and projection during follow-up assessments, resulting in pleasing aesthetic outcomes. Out of the 100 individual ratings given by the panel of 10 doctors, 77 were scored as 1 (good), indicating high satisfaction with the outcomes. Twenty-two ratings were scored as 2 (moderate), and only one was scored as 3 (poor).

All patients exhibited adequate facial expressions. Clinical evaluations indicated normal mouth opening, pouting, lip control, and sensation. In cases involving lesions near the oral commissure or modiolus, oral competence was preserved without the development of a narrowing of opening (microstomia) or loss of angle of the mouth, demonstrating preservation of form and function.

Discussion and Conclusion

In the treatment of lips and perioral cancers, the objective is twofold: achieving adequate tumor control while concurrently preserv-

Fig. 3. Patient photographs before (left) and in follow-up after high-dose-rate interstitial brachytherapy (right). (A) Patient no. 1, baseline and after 61 months of the treatment. (B) Patient no. 2, baseline and after 20 months of the treatment. (C) Patient no. 4, baseline and after 23 months of the treatment. (D) Patient no. 5, baseline and after 10 months of the treatment. (E) Patient no. 7, baseline and after 4 months of the treatment. (F) Patient no. 8, baseline and after 5 months of the treatment. (G) Patient no. 9, baseline and after 3 months of the treatment. These patients have no evidence of disease with excellent cosmetic and functional outcomes over the follow-up period of 61, 34, 24, 24, 16, 10, and 10 months, respectively.

ing optimal functional and cosmetic outcomes. Specifically, it aims to maintain patency for adequate oral aperture and ensure satisfactory cosmesis.

Table 2. Dosimetric data of brachytherapy implants

	Median (range)
Dose	40 Gy (40 Gy/10–44 Gy/11 fractions)
No. of catheters	3 (3–7)
CTV (cm^3)	9.35 (4.20–33.10)
D90 (%)	94.35 (53.00–115.70)
V100 (%)	86.45 (57.30–97.00)
V150 (%)	54.60 (32.90–68.90)
V200 (%)	28.85 (11.37–44.30)
Dose nonuniformity ratio	0.64 (0.45–0.71)

CTV, clinical target volume; D90, minimum dose received by the 90% of treatment volume; Vx, volume of tissue receiving dose ≥x% of the prescription dose.

In our study, we achieved excellent local control and preserved cosmesis using HDR brachytherapy as the sole treatment for lip and buccal mucosa cancers. The acute and late adverse events observed in the patients were manageable, with most patients experiencing only low-grade toxicities at the median prescribed dose of 40 Gy in 10 fractions twice daily.

Similarly favorable outcomes of HDR interstitial brachytherapy have been reported by Guinot et al. [14] in 102 patients of lip cancer with a local control rate of 94.6%, a nodal regional control rate of 88.6%, and a disease-free survival rate of 84.6%. Likewise, in a systematic review consisting of seven studies comprising 456 patients with early-stage oral cancers, Draghini et al. [15] observed 5-year local control rates ranging from 60% to 100%, disease-free survival rates between 82% and 91%, and overall survival rates between 50% and 84%.

In brachytherapy, most of the past literature was based on LDR

Table 3. Acute and late radiation-induced toxicities in brachytherapy patients as per CTCAE criteria

	Toxicity grade (HDR brachytherapy, n = 10)						
	Acute toxicity				Late toxicity		
	0	1	2	3	0	1	2
Pain	1 (10)	6 (60)	2 (20)	1 (10)	7 (70)	3 (30)	0
Mucositis	0	2 (20)	6 (60)	2 (20)	10 (100)	0	0
Dermatitis	0	6 (60)	1 (10)	3 (30)	8 (80)	2 (20)	0
Hypo/hyperpigmentation	-	-	-	-	4 (40)	6 (60)	0
Induration/fibrosis	-	-	-	-	8 (80)	1 (10)	1 (10)

Values are presented as number (%).
CTCAE, Common Terminology Criteria for Adverse Events; HDR, high-dose-rate.

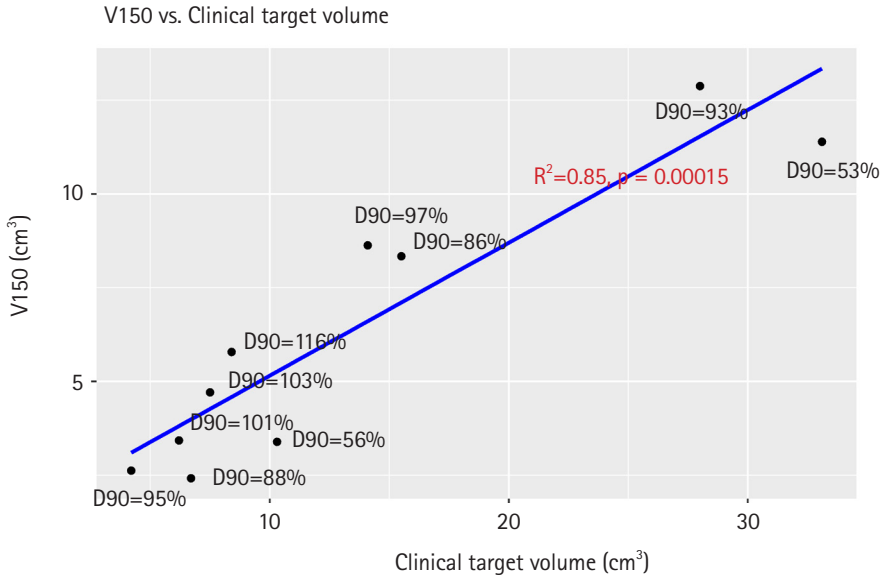

Fig. 4. Correlation between the clinical target volume and volume receiving 150% of the prescribed dose (V150).
D90, minimum dose received by the 90% of treatment volume.

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and manual afterloading techniques [16]. Initially, when HDR was introduced, there were some concerns about the radiobiological effects and toxicity of HDR [17]. However, Ghadjar et al. [18] compared the treatment outcomes of HDR and LDR brachytherapy in 103 lip cancer patients and reported a 5-year regional recurrence-free survival of 90% with no significant difference between the two modalities. Another study by Guinot et al. [19] in a series of 203 lip cancer patients reports a comparable 95% local control between HDR brachytherapy and LDR brachytherapy in lip cancer but fewer complications and no bone or soft tissue necrosis associated with HDR brachytherapy. A meta-analysis of trials devoted to HDR vs. LDR brachytherapy for oral cancer concludes that HDR brachytherapy is a comparable alternative to LDR brachytherapy in the treatment of oral cancer, and it might become a standard treatment option in oral cancers [20].

Previous literature has reported various fractionation schedules for HDR brachytherapy in oral cancers [21]. Our median total dose of 40 Gy in 10 fractions of 4 Gy each resulted in an acute biologically effective dose (α/β ratio = 10 Gy) of 56 Gy and a late biologically effective dose (α/β ratio = 3 Gy) of 93.3 Gy. Guidelines recommend a total dose of 45–54 Gy, administered in 4–4.5 Gy fractions with two fractions per day spaced at least 6 hours apart, which is slightly higher than the dose we used in our study [22].

The dose nonuniformity ratio (DNR) of 0.64 observed in our study is slightly higher than recommended in some guidelines [22]. Higher DNR values have been observed when the gross tumor volume volume and number of catheters are small or brachytherapy is performed particularly in complex areas like the head and neck without a corresponding increase in toxicity [23,24].

However, more dosimetry studies would be needed as there is no clear consensus on the acceptable value of DNR.

In the treatment of head and neck cancer, several authors have proposed the concept of "in-field" and "out-of-field" toxicity for radiation-induced toxicity [24,25]. The adverse effect occurring right in the area of treatment with the prescribed dose of radiation is referred to as in-field toxicity while unintended radiation exposure to adjacent tissues other than the primary radiation area is referred to as out-field toxicity [26]. We used a personalized spacer made from wax or thermoplastic material during simulation, which was combined with lead shielding during treatment delivery. The use of custom shielding/spacer in our approach contributed to the improved results by reducing out-field toxicity.

Studies have reported acceptable acute and late adverse events with major toxicities of acute mucositis and skin reactions in the treatment of lip and buccal mucosa cancer with HDR brachytherapy [14]. Guinot et al. [14] reported acute reactions of grade 4 hemorrhaging mucositis in 50% of patients and grade 3 confluent mucositis in 50% of patients with no severe late events. Acute and late adverse events observed in our patients were minimal and manageable. We observed hypopigmentation in the needle entry point in some patients, where a high dose had to be delivered to the skin due to disease conditions [27].

High quality-of-life (QOL) scores and high satisfaction levels have been reported among patients undergoing interstitial brachytherapy, particularly in the periorificial face region [27,28]. Likewise, our excellent cosmetic and functional outcomes as assessed by the panel of experts, serve as evidence that HDR brachytherapy confers significant aesthetic and functional benefits to the patients. However, the lack of a commonly shared grading system adds challenges in standardizing assessments across studies. A consistent and widely adopted method of assessing functional and cosmetic outcomes would ensure consistent and objective evaluation.

Whether or not to address the neck nodes in lip cancer patients is a debatable issue. Management of the neck in brachytherapy as monotherapy has varied from watchful waiting to elective nodal irradiation and/or radical neck dissection [29]. In a study of 617 patients, the lymph node involvement was 7.9% in T1 to T2 and 27.9% in T3 to T4 and in another study by Cowen et al. [30] conducted with 299 patients, it was 5.6% in T1 to T2 and 17.6% in T3 [20-31]. In our series, a 90-year-old gentleman with a T2 tumor at the angle of the mouth suffered a nodal relapse in level Ib after 7 months of brachytherapy completion. The patient subsequently underwent a modified neck dissection for right lymph node recurrence. Pathological examination revealed malignancy in 1 out of 10 lymph nodes at level 1b and was subsequently kept in follow-up. Another young patient opted for upfront prophylactic neck dissection, while the primary lip tumor was treated with brachytherapy for a better cosmetic outcome.

This combined brachytherapy to primary and neck dissection approach can be a good strategy for younger lip or buccal mucosa cancer patients. However, most of the patients are older and have comorbidities, and ultrasound surveillance of the neck may be reasonable for them [32]. Since early-stage lip cancers, especially those limited to the lip itself, have a low risk of nodal spread, observation of the neck can be considered [33]. Sentinel node biopsy is another potentially less aggressive option than surgery or radiation and can be done on the same day of the procedure [34].

Our study demonstrates that HDR brachytherapy is an effective monotherapy for oral cancers, particularly for the lip and buccal mucosa. All patients achieved good functional outcomes. Despite significant comorbidities in many patients, treatments were successful, indicating the efficacy of HDR brachytherapy for lip and buccal mucosa cancer patients with diverse underlying conditions,

especially among the elderly. Additionally, the minimally invasive nature, lack of general anesthesia requirement, curative approach, and short treatment duration of around one week make HDR brachytherapy particularly suitable for elderly patients [35].

This study encompasses several limitations including its retrospective nature, small patient number, single institute-based study, short follow-up period, and operator dependence. However, given the paucity of prior studies evaluating HDR brachytherapy for lip and buccal mucosa cancers in our region, our study adds significant additional information to the available body of knowledge on the use of HDR brachytherapy for treating these cancers

This study explores the procedure and outcomes of using HDR interstitial brachytherapy for treating lip and buccal mucosa cancers. Our approach of delivering a median dose of 40 Gy in 10 fractions of brachytherapy twice daily, has shown to be a safe and effective treatment in achieving excellent local control, cosmetic results, and function preservation. These findings underscore that interstitial brachytherapy with a dose fractionation regimen of 40-44 Gy effectively balances the need for robust local cancer control with QOL in cases of lip and buccal mucosa cancers.

Statement of Ethics

Ethical approval was obtained from the Nepal Health Research Council's ethical committee (approval no. 379/2023). Patients gave informed consent for pictures taken for publication.

Conflict of Interest

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

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Author Contributions

Conceptualization, SP, SS (Simit Sapkota), AA, JB; Methodology, AA, DY, RY, RP, SR; Data analysis and investigation, JB; Supervision, AKJ; Writing original draft, SP, JB; Reviews and editing, SS (Simit Sapkota), SS (Sunil Shrestha).

Data Availability Statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Implications of interfractional bladder volume variations in proton beam therapy for rectal cancer

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Purpose: This study evaluated interfractional bladder volume variations and the resulting dosimetric changes during short-course radiotherapy (SCRT) 5 × 5 Gy (relative biological effectiveness) in patients with locally advanced rectal cancer.

Materials and Methods: Twenty patients received either protons or photons with daily cone-beam computed tomography (CBCT). All patients received the same drinking instructions prior to the planning computed tomography (CT) and each fraction. For each patient, volumetric modulated arc therapy (VMAT) and proton beam therapy (PBT) plans were generated. The bladder was delineated on each CBCT which were registered to the planning CT in the treatment planning system. The baseline bowel bag structure was adjusted accordingly for each bladder volume. Volumetric and dosimetric data for the bladder and bowel bag were then analyzed.

Results: Baseline bladder volumes were on average 71 cm^3 larger than the average volume during treatment (95% confidence interval, 15 to 126). No significant difference was detected during treatment. Mean bladder doses decreased significantly from baseline to during treatment for both VMAT and PBT treatment plans ($p = 0.021$ and $p = 0.002$, paired two-sided t-test). Compared to baseline, the dose to the bowel bag adjusted for daily bladder volume increased by 3.8% for VMAT ($t = -2.56$, $p = 0.019$, two-tailed) and 18.7% for PBT ($t= -2.415$, $p = 0.026$, two-tailed).

Conclusion: We report consistently smaller bladder volumes during SCRT compared to baseline. This resulted in lower-than-expected mean bladder doses during the treatment course and consequently an increase in dose to bowel bag. Variations in bladder volume resulted in larger changes in delivered dose to bladder and bowel bag in PBT compared to VMAT.

Keywords: Bladder, Bladder volume, Proton beam therapy, Rectal cancer

Introduction

Proton beam therapy (PBT) has the potential to reduce side effects compared to conventional photon therapy due to the proton's physical properties with the characteristic Bragg Peak [1]. Organs distal to the intended target can potentially be spared from dose due to this effect. This contrasts with conventional photon therapy where the exit dose is unavoidable. By reducing radiation dose to the organs at risk (OAR) and normal tissue surrounding the intended target, less side effects can be expected. Dosimetric studies have repeatedly shown that PBT in many cases can reduce radiation dose to OAR [2-4]. However, clinical benefits of such dose reduction in terms of reduced side effects remain largely unclear due to lack of clinical data, especially from randomized trials. This was re-

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cently confirmed by the Particle Therapy Cooperative Group gastrointestinal subcommittee [5]. The physical properties of PBT make it susceptible to changes in the anatomy and as a result, even a small displacement of organs i.e., the bladder or bowel, may considerably affect the dose distribution. This effect is less pronounced in conventional photon therapy [1].

Variability in bladder volume represents a clinical challenge in pelvic radiotherapy. The variations in volume can subsequently affect the surrounding organs by dislocating them [6,7]. Pelvic radiotherapy studies show that a small bladder volume on many occasions predicts a higher dose than expected at planning to the intestine [8]. Furthermore, a full bladder might result in larger dose to the bladder itself [9]. As a result, the advantages of PBT may be limited due to these daily treatment uncertainties.

Several methods have been described to control the variability of the bladder during the treatment course. However, previous studies have shown a limited effect of bladder-filling instructions [10-12].

To investigate the possible clinical advantages of PBT for patients with locally advanced rectal cancer (LARC) the prospective randomized PROtons compared to photons in high-risk RECTal cancer (PRORECT) trial was initiated in 2021 (NCT04525989). The primary endpoint in PRORECT is the incidence of acute preoperative gastrointestinal toxicity associated with PBT vs photon therapy. Patients eligible for short-course radiotherapy (SCRT) are randomized between PBT or conventional photon therapy (volumetric modulated arc therapy [VMAT]). The prescribed dose for all patients is 5 Gy relative biological effectiveness (RBE)* x5 (* applies to all doses in Gy mentioned in future text) [1]. Bladder-filling instructions were included in the trial for all patients. A dosimetric analysis of the first 20 patients including detailed information on the treatment planning procedures was described previously [4].

The aim of the present study is to analyze the bladder variability and its consequences on the delivered dose using the same cohort [4]. We investigated possible differences between the pre-planned and the actual delivered dose to the bladder and bowel due to daily bladder volume variations during SCRT for LARC. In addition, we compare the difference in delivered dose between PBT and VMAT.

Materials and Methods

1. Randomized phase II trial PRORECT

From May 2021 to June 2022 20 consecutive patients (8 females and 12 males) aged 36–73 years with a mean clinical target volume of 812 cm^3 were treated in the ongoing randomized phase II trial PRORECT (NCT04525989). More information regarding the patient characteristics of this initial cohort and the methods of the PRORECT study, including detailed information on the treatment planning procedure, was described previously [4]. We report the dose parameter "mean dose" to bladder and bowel bag according to the clinical goals in the PRORECT trial, in keeping with "as low as reasonable achievable" principles. The dose constraint to bowel bag is that the volume receiving 18 Gy should be equal or less than 450 cm^3.

2. Summary of clinical procedures

PBT have been delivered at the Swedish national proton facility Skandionkliniken. The delivered dose was 25 Gy in five fractions with daily cone-beam computed tomography (CBCT) used for setup verification at each treatment fraction. A planning computed tomography (CT) was conducted and used for dose planning and dose calculations. Both a PBT and a VMAT treatment plan were generated for all 20 patients in Eclipse Treatment Planning System (version 16.01.10, Varian Medical Systems, Palo Alto, CA, USA).

To minimize bladder volume variability, all patients were subjected to the following procedure: after voiding, the patients were asked to drink 300 mL of liquid, preferably water. The CBCT was performed 45–60 minutes after this procedure. The same procedure was performed before the planning CT and before each treatment fraction. The anatomical structures of interest were reviewed online on daily CBCT-images. Daily feedback to the patient was delivered with instructions to adjust the preparations accordingly.

3. Daily volume and dose distribution in the bladder and bowel bag

The CBCT scans were taken approximately one minute prior to radiation delivery. All CBCT scans were uploaded to the Eclipse Treatment Planning System (Varian Medical Systems). A total of 100 CBCTs were included in this study. To minimize the interobserver uncertainties, all structures were delineated by a single oncologist with 10 years of experience in radiation oncology (JF). The bladder was manually delineated on five CBCT scans for each patient, representing the bladder volume of each treatment fraction (Fig. 1). Delineated structures were then referred to the planning CT using rigid registration relative to the bony anatomy. Daily dose distribution in each CBCT bladder volume was subsequently extracted from the original dose-volume histogram (DVH) for both PBT and VMAT treatment plans, respectively. The structure "bowel bag" was delineated on planning CT according to the Radiation Therapy Oncology Group guidelines [13]. To investigate the dosimetric impact of daily bladder volume variations on the bowel bag, the following approach was implemented: the bladder delineated in each CBCT scan was referred to the planning CT. For each daily bladder volume, the original bowel bag structure was manually adjusted, creating five daily bowel bag volumes. Daily dose distribution of bowel

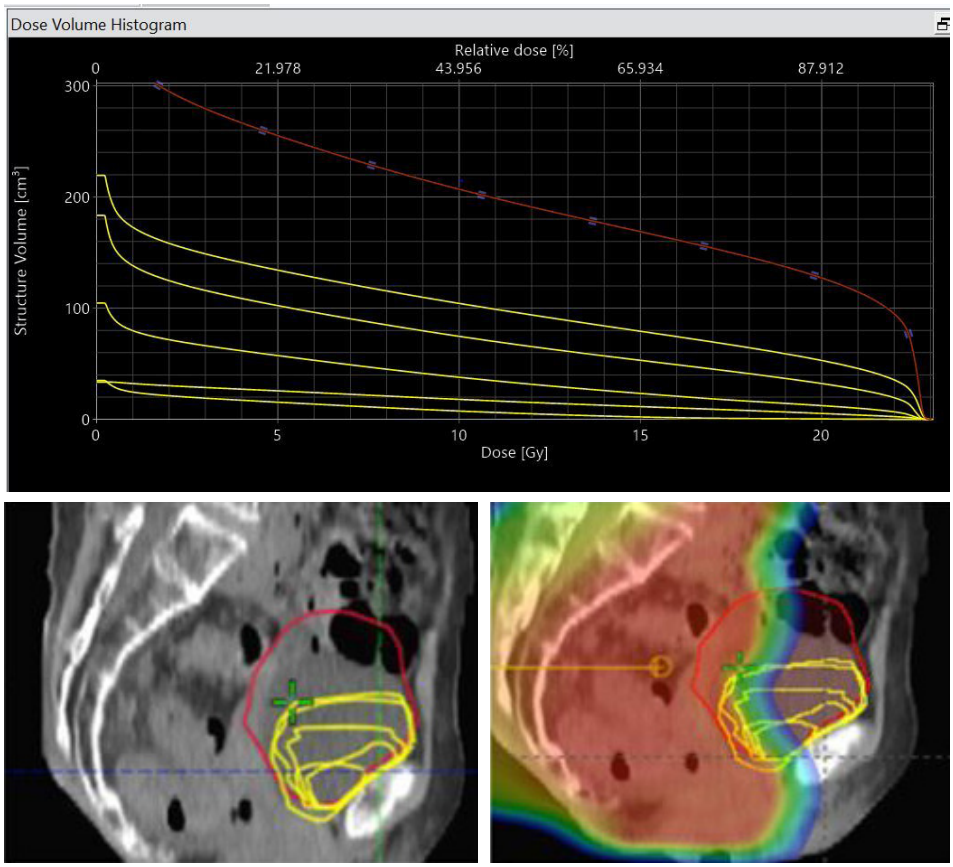

Fig. 1. The cumulative dose-volume histogram (DVH) of bladder at baseline (red) and fractions 1–5 (yellow) in proton beam therapy treatment plan (top). Structures corresponding to DVH (bottom left). Color wash dose distributions (range, 0 to 25 Gy relative biological effectiveness) (bottom right).

bag was subsequently extracted from the original DVH for both PBT and VMAT treatment plans.

4. Statistical analysis

Statistical analyses were made in SPSS version 28 (IBM Corp., Armonk, NY, USA). Two-sided t-test was used to compare average baseline and average bladder volumes and bowel bag volumes. Pearson correlation coefficient was employed to measure correlations. Intra-patient mean bladder volume variation over five treatment fractions was analyzed with one-way repeated measured analysis of variance (ANOVA). p-values of less than 0.05 were considered statistically significant.

Results

1. Bladder volume evaluation

Fig. 2 presents differences in volume between baseline volume derived from the planning CT (Vo) and average volume of the five CBCT scans (Vavg) in each patient, respectively.

In the entire cohort, bladder volumes ranged between 33.5–658.9 cm^3 with an overall baseline mean volume (Vo, standard deviation [SD]) of 274.0 ± 166.1 cm^3. The overall average bladder volume during the treatment, Vavg was 203.8 ± 91.7 cm^3. Mean Vo and mean Vavg were strongly correlated ($r = 0.71$, $p < 0.001$). The 25.7% decrease from Vo to Vavg was significant (paired two-sided t-test, $p = 0.016$). Average bladder volume at first treatment fraction was numerically largest (Fig. 3). When changes in intra-patient bladder volumes over five CBCT measurements were analyzed with one-way repeated measured ANOVA, as presented in Fig. 3, no significant time effect on mean bladder volumes measured at five different timepoints was found ($F(4, 16) = 2.7$, $p = 0.068$). Further analysis of intra-patient variations during the 5 days of treatment revealed that the largest variation in bladder volume in a single patient was 597.9 cm^3 (min 61.0–max 658.9 cm^3). Near-empty bladder (< 70 cm^3) was observed in 12 of the CBCT scans. Four patients presented with near-empty bladder once (3 female and 1 male), and another four presented it twice (1 female and 3 male) during treatment. In four out of 12 occasions (33.3%), near-empty bladders were observed on second treatment fraction, and in 11/12 near-empty bladder observations (91.7%),

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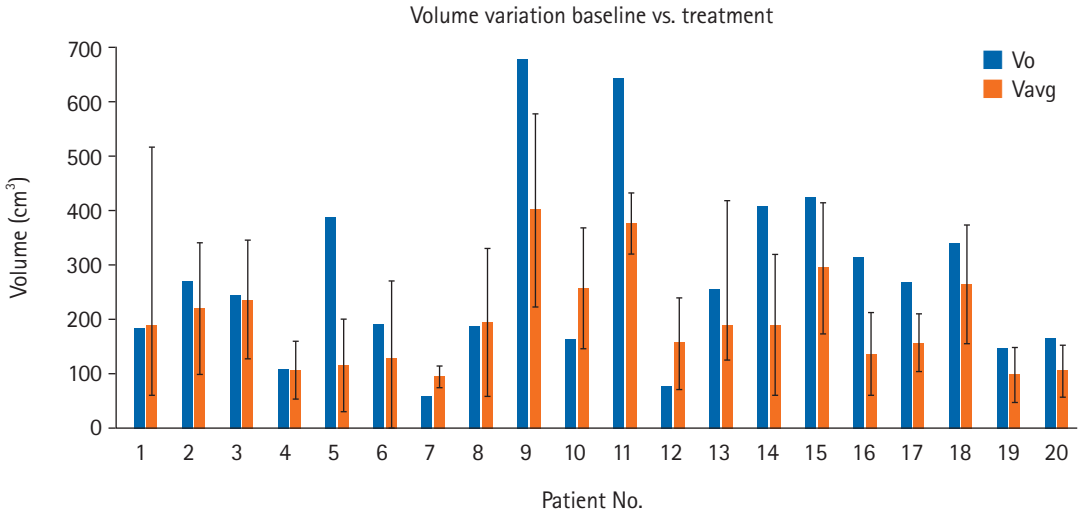


Fig. 2. Comparative baseline bladder volume (Vo, blue) and average cone-beam computed tomography bladder volumes (Vavg, orange). Error bars indicate ± standard deviation.

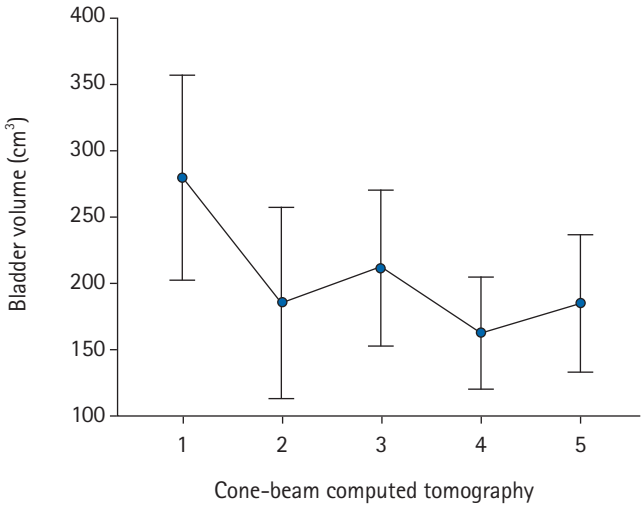


Fig. 3. Average (95% confidence interval [CI]) cone-beam computed tomography bladder volumes for each treatment fraction in 20 patients. Error bars indicate 95% CI.

bladder volume on the following treatment fraction was not near empty.

2. Bowel bag volume evaluation

For each patient, the baseline bowel bag volume (BowVo) and the average bowel-bag volume over five CBCT scans (BowAvg), was extracted. Baseline mean BowVo (SD) in the entire cohort was 966.5 ± 427.0 cm^3. The mean BowAvg (SD) in the cohort was 1,027.2 ± 404.0 cm^3. The difference in volume was significant (paired t-test, p = 0.002).

3. Dose evaluation for bladder

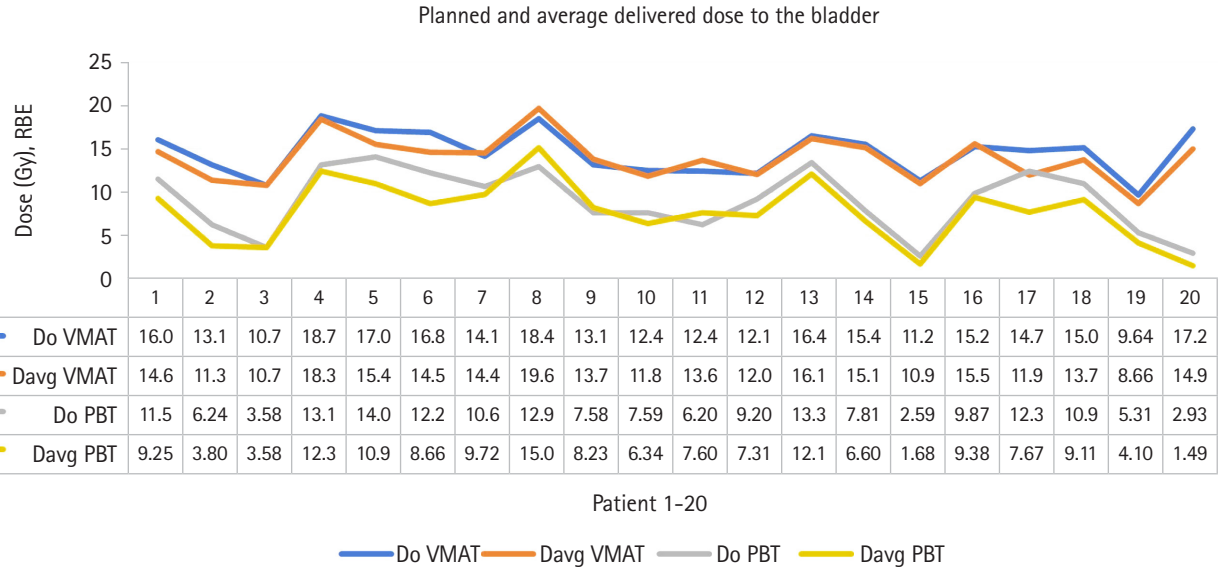
The mean absolute bladder dose at baseline (Do) was derived from the PBT and VMAT treatment plans, respectively. The average dose to the bladder during 5 treatment days (Davg) represents the average mean absolute dose derived from five daily CBCT scans registered to the planning CT as illustrated in Fig. 1. Fig 1 also illustrates the general reduction in the bladder volume included in the isodose volume as previously demonstrated [4]. The differences in dose are presented in Fig. 4.

For VMAT, the mean Do and Davg (SD) were 14.5 (± 2.6) Gy and 13.8 (± 2.6) Gy, respectively. Corresponding numbers for PBT were 9.0 (± 3.6) Gy and 7.8 (± 3.5) Gy. There was a significant difference between Do and Davg for both VMAT and PBT treatment plans (p = 0.021 and p = 0.002, respectively, paired two-sided t-test). The resulting average relative dose reduction from Do and Davg for VMAT and PBT was 4.8% and 13.3%, respectively.

In the female cohort (n = 8) the Do was 14.36 Gy for VMAT and 9.8 Gy for PBT. The corresponding numbers for males (n = 12) were 14.63 Gy and 8.47 Gy, respectively. Davg in the female cohort was 13.61 Gy for VMAT and 8.4 Gy for PBT. Corresponding numbers were 14.06 Gy and 7.32 Gy in males. No significant differences in dose to the bladder were found between sexes.

4. Bowel bag dose evaluation

The mean absolute dose to bowel bag at baseline (BowDo) was derived from the VMAT and PBT treatment plans, respectively. The mean BowDo for the entire cohort for VMAT was 10.42 Gy and for PBT the mean BowDo for the entire cohort was 4.79 Gy. The average dose to bowel bag during 5 days of treatment (BowDavg) represents the average mean dose derived from the five daily bowel



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Do VMAT	16.0	13.1	10.7	18.7	17.0	16.8	14.1	18.4	13.1	12.4	12.4	12.1	16.4	15.4	11.2	15.2	14.7	15.0	9.64	17.2
Davg VMAT	14.6	11.3	10.7	18.3	15.4	14.5	14.4	19.6	13.7	11.8	13.6	12.0	16.1	15.1	10.9	15.5	11.9	13.7	8.66	14.9
Do PBT	11.5	6.24	3.58	13.1	14.0	12.2	10.6	12.9	7.58	7.59	6.20	9.20	13.3	7.81	2.59	9.87	12.3	10.9	5.31	2.93
Davg PBT	9.25	3.80	3.58	12.3	10.9	8.66	9.72	15.0	8.23	6.34	7.60	7.31	12.1	6.60	1.68	9.38	7.67	9.11	4.10	1.49

Fig. 4. Absolute bladder dose at baseline (Do) and average dose to the bladder during 5 treatment days (Davg) for proton beam therapy (PBT) and volumetric modulated arc therapy (VMAT) plans for 20 patients. RBE, relative biological effectiveness.

bag structures adjusted for the daily bladder volume in the treatment plan. The mean BowDavg for the entire cohort was for VMAT 10.82 Gy and for PBT 5.69 Gy respectively. The increase in dose to bowel bag during treatment compared to the dose expected at planning was significant. For VMAT the 3.8% increase in dose was significant ($t = -2.56$, $p = 0.019$, two-tailed) For PBT the 18.7% increase in dose was significant ($t = -2.415$, $p = 0.026$, two-tailed).

No significant correlation was observed between mean daily bladder volume (Vavg) and mean daily dose to the bowel bag (BowDavg) across the cohort. For VMAT, Pearson's correlation coefficient yielded $r = -0.43$ with a p-value of 0.057. For PBT, the corresponding values were $r = -0.39$ and $p = 0.087$.

In the subject with numerically largest change in bladder volume during treatment (max–min range), the bladder volume varied from 658.9 cm^3 (day 1) to 61.0 cm^3 (day 2). For VMAT, the larger bladder volume on day 1 corresponded to a daily dose to bowel bag of 15.39 Gy, while the lower volume on day 2 resulted in a VMAT dose of 13.47 Gy. For PBT, the corresponding doses were 9.06 Gy (day 1) and 8.19 Gy (day 2).

Discussion and Conclusion

We report an in-depth analysis of image guided PBT in treatment for LARC, focusing on the bladder volume variability and its dosimetric consequences. The bladder volumes in our cohort were relatively stable during 5-days long radiotherapy. However, average bladder volumes were significantly smaller during the treatment course compared to baseline at treatment planning. Similar findings are described in previous studies conducted in a number of other pelvic malignancies. It is noteworthy that most of these treatments last for a minimum of 25 days. In line with our findings the bladder volume in these studies is reported to be smaller during treatment than on planning CT. However, contrary to our findings the volume throughout the treatment is most often found to be less stable and diminishing towards the end of treatment period [8,11,14,15]. It can be hypothesized that side effects such as urgency and cystitis that often begin after approximately two weeks into the treatment could be a contributing factor to the variation in bladder volumes. In the case of a 5-day long radiotherapy course the side effects largely appear after completed radiotherapy and are not expected to affect bladder volumes during the treatment. Our study indicates that the bladder volume is smaller during treatment than expected from the treatment plan, regardless of the length of treatment. The underlying causes of this finding remain uncertain. Contributing factors may encompass physiological processes such as organ displacement and treatment-induced effects, including urgency. The timing between fluid intake and imaging has been identified as a factor [16]. Compliance with drinking protocols may diminish despite mitigation strategies.

If near-empty bladder was observed, the volume was recovered the following day on nearly every occasion. This observation might be an effect of daily intervention. CBCT bladder volumes are routinely reviewed and feedback to the patient is provided. Previous studies on drinking instructions to maintain stable bladder volume and treatment plan robustness are inconclusive. Some indicate that

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verbal instructions might be sufficient [11,17] while others report that the procedures give little, or no effect [10,15]. This study indicates that instructions and feedback is a contributing factor to the rapid recovery of the bladder volume during SCRT. This makes the treatment more robust since the bladder volume can be adjusted promptly if needed and the volume of bladder can be maintained as stable as can be expected considering the natural variations in the human body. However, despite these efforts it is unclear if the instructions are clear enough for the patients to follow and if there are other contributing factors affecting participants' ability to comply with the instructions as intended, but this is not the scope for the present trial.

Reduction in bladder volume during the treatment resulted in a significant although minor lowering in mean dose to the bladder. However, the decrease in bladder dose was larger in PBT treatment plans compared to VMAT, confirming the fact that PBT is more sensitive to changes in patient anatomy [1]. As expected from the previous analysis [4], the mean dose to the bladder delivered with PBT was significantly lower than with VMAT. These results are consistent and even more pronounced when considering the daily bladder volumetric changes. The clinical implications of these observations will be analyzed in the ongoing PRORECT trial. Additionally, these results could be of value when considering other PBT treatment regimes in the pelvic area when dose to the bladder is of major concern. The observed larger reduction in delivered dose to bladder with PBT may potentially have clinical relevance in future dose-escalation and re-irradiation trials.

Another important aspect is the possible implications of bladder volume variation on dose to the bowel bag. Previous studies have shown that there is a correlation between bladder volume and size and location of the bowel [8,15]. This effect is visible in Fig. 1. When the bladder volume diminishes and dislocates inferiorly, the intestines will usually follow and subsequently move further down into the irradiated area. After adjusting the bowel bag structure for the daily bladder volume variations, we found a significantly higher dose to bowel bag during treatment than expected at treatment planning for both VMAT and PBT plans. The correlation between daily bladder volume and dose to bowel was not statistically significant, however there was a trend towards a negative correlation. The hypothesis that a smaller bladder results in a higher dose to bowel than expected is supported by our findings.

One limitation of the present study is that the quality of CBCT scans for PBT does not allow for accurate dose calculation directly on the scans since it requires detailed stopping power measurements [1]. Furthermore, the CBCT scans for PBT have a limited field of view. The rigid registration procedure assumes that the anatomy of the patient is largely unchanged, which is not always the case. Additionally, deformable registration could not be done in a reliable way for CBCT scans in the PBT planning system.

When selecting patients for PBT in the pelvic region, careful consideration of specific patient cohorts is warranted. Our findings highlight that large variations in bladder volume and substantial internal organ motion may exert a greater influence on PBT compared to VMAT.

There are several promising projects and technical advances on the horizon. One possibility for the imminent future is using information from the original CT in combination with the CBCT scans to make a synthetic CT enabling CBCT-based online adaptive radiotherapy. This workflow is reported feasible for SCRT for rectal cancer [18]. Integrating PBT and magnetic resonance imaging to enable real-time imaging is a promising solution for pelvic PBT in the more distant future [19].

To the best of our knowledge, the variability in bladder volume and its possible effect on the delivered dose to the bladder, as well as its potential impact on the dose to the bowel bag during PBT for LARC, has not been previously investigated. In this study we perform the first comparison of the planned and delivered dose to the bladder and bowel bag during PBT for LARC. Additionally, we present initial results from the first randomized trial using PBT and VMAT regarding dose variability to the bladder. Moreover, we describe the variation of bladder volume during SCRT, a period of 5 days, in contrast to longer fractionation schedules.

The bladder volumes during the treatment course were significantly smaller than expected at the time of treatment planning. In contrast, the volume remained relatively stable throughout the treatment.

The volume reduction compared to baseline translated into lower mean doses to the bladder, and a corresponding increase in mean dose to the bowel bag compared to the anticipated dose at treatment planning.

The analysis of daily volumetric variations in the bladder and the implications for dose delivery substantiates the sustained reduction in dose to OAR observed in PBT compared to VMAT, consistent with previous research findings. Additionally, variations in bladder volume during the treatment course resulted in larger changes in dose to the OARs in PBT compared to VMAT.

Statement of Ethics

The PRORECT-trial has received approval from the Swedish Ethical Review Authority (Dnr 2020–02192). All patients gave written consent before any study procedures were performed.

Conflict of Interest

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

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Author Contributions

Conceptualization, JF, KS, AV; Data curation, BS, AV; Formal analysis, AV; Investigation, JF; Methodology, JF; Project administration, AV; Resources, JF, BS, AV; Supervision, KS, AV; Visualization, JF; Writing - original draft, JF; Writing - review, and editing: BS, KS, AV.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author, JF.

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Prognostic factors and risk stratification for survival in oligometastatic colorectal cancer treated with stereotactic body radiotherapy

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Purpose: This study aimed to evaluate treatment outcomes with associated prognostic factors, and to guide treatment strategies in colorectal cancer patients with oligometastatic disease (OMD) treated with stereotactic body radiotherapy (SBRT).

Materials and Methods: This retrospective study included 74 colorectal cancer patients who received SBRT for 113 lesions (88 lung, 19 liver, and 6 lymph node). Each OMD was considered a separate case for patients repeatedly diagnosed with OMD. The log-rank test and Cox proportional hazards model were used to assess prognostic factors for progression-free survival (PFS).

Results: A total of 84 cases were analyzed. The median follow-up period was 32.2 months (range, 8.2 to 89.3 months). The 2-year PFS, widespread failure-free survival (WSFFS), and overall survival (OS) rates were 35.1%, 67.4%, and 80.8%, respectively. In the multivariable analysis, oligometastatic status (repeat/induced vs. de novo; hazard ratio [HR], 2.66; 95% confidence interval [CI], 1.40 to 5.04; p = 0.003) and planning target volume (PTV) volume (≥17.6 vs. <17.6 cm^3; HR, 1.99; 95% CI, 1.09 to 3.62; p = 0.025) were significant prognostic factors for PFS. Cases with two risk factors for PFS demonstrated significantly worse OS and WSFFS ($p < 0.05$), whereas those with one risk factor did not show a significant difference compared to cases with no risk factors.

Conclusion: SBRT for oligometastatic colorectal cancer showed favorable clinical outcomes. Oligometastatic status and PTV volume were significantly associated with PFS. Risk stratification based on the number of poor prognostic factors of PFS may help guide treatment strategies for colorectal cancer patients with OMD.

Keywords: Colorectal neoplasms, Neoplasm metastasis, Radiosurgery, Progression-free survival

Introduction

In 2020, colorectal cancer accounted for 10% of all newly diagnosed cancer cases globally, making it the third most diagnosed cancer worldwide [1]. Although 50%–70% of colorectal cancer patients undergo curative surgery, more than one-third of patients

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experience relapse or death [2-4]. Among patients with recurrence, approximately 75%–80% develop distant metastases, primarily in the liver, lungs, and peritoneum [4-6]. Oligometastasis, an intermediate stage between localized disease and widespread metastasis, has gained attention in treatment strategies [7]. Surgical resection of oligometastatic lesions has shown survival benefits in various cancers, including colorectal cancer [8-12]. However, for many patients, local therapies, such as radiofrequency ablation and stereotactic body radiotherapy (SBRT), are often preferred over surgery to avoid surgery-related morbidity [12,13]. Despite the promising results of SBRT, the outcomes for colorectal oligometastasis are generally less favorable compared to those observed in other primary cancers [12-16]. Given this challenge, further research is needed to improve the management of oligometastatic lesions in colorectal cancer. Moreover, due to limited and heterogeneous data and complex treatment considerations for these patients, understanding the effectiveness of SBRT and the factors influencing its outcomes is crucial. This study aimed to evaluate treatment outcomes and identify prognostic factors for survival in colorectal cancer patients with oligometastatic lesions treated with SBRT to optimize treatment strategies.

Materials and Methods

1. Study design and patient selection

This retrospective study analyzed patients with oligometastatic colorectal cancer who underwent SBRT for oligometastatic lesions at Kyungpook National University Chilgok Hospital between 2016 and 2022. A total of 141 treatment sessions involving 171 metastatic lesions were initially reviewed among 128 patients. Oligometastatic disease (OMD) was defined as the presence of five or fewer metastatic lesions, all amenable to local therapies, with the primary tumor under control. For patients repeatedly diagnosed with OMD, each OMD was considered as a separate case. After excluding patients who did not receive SBRT for all active oligometastatic lesions, those who had brain metastasis at the diagnosis of OMD, those who underwent both SBRT and other local therapies at the diagnosis of OMD, those with a biologically effective dose (BED) of <72 Gy_{10}, and those with follow-up durations shorter than 6 months after SBRT, 84 cases involving 113 metastatic sites (88 lung, 19 liver, and 6 for lymph node) in 74 patients were included in the analysis. Computed tomography (CT) was the routine imaging modality, while magnetic resonance imaging (MRI) was typically performed when liver metastases were suspected. Positron emission tomography–computed tomography (PET-CT) was performed at the physician's discretion. The Institutional Review Board approved this study, and the requirement for informed consent was waived owing to the retrospective nature of the study.

2. Radiotherapy

All patients underwent CT simulation in the supine position immobilized with Body Pro-Lok (CIVCO Inc., Coralville, IA, USA), with a slice thickness of 3 mm. For moving tumors, 4-dimensional (4D)-CT was performed to account for respiratory motion. The gross tumor volume (GTV) was contoured based on visible tumors, and the internal gross tumor volume (iGTV) was defined as the combination from each set of 4D-CT scans. A 5-mm margin in all directions was typically added to the iGTV to define the planning target volume (PTV). SBRT plans were generated with dynamic conformal arcs, static conformal beams, or intensity-modulated beams. The algorithms used to calculate dose distributions included the pencil beam algorithm, X-ray voxel Monte Carlo, the analytical anisotropic algorithm, and Acuros XB. The prescription dose was set to achieve at least 95% PTV coverage. Cone-beam CT was used for image guidance before each treatment. SBRT was performed using the VERO system (Mitsubishi Heavy Industries Ltd., Japan; BrainLab AG, Feldkirchen, Germany), VitalBeam (Varian Medical Systems, Palo Alto, CA, USA), and RapidArc (Varian Medical Systems). The BED was calculated using the following formula: $BED = nd(1 + d/[\alpha/\beta])$, where n represents the number of fractions, d is the dose per fraction, and an α/β ratio of 10 was applied.

3. Follow-up

The post-SBRT follow-up consisted of blood tests, clinical evaluations, and imaging studies, including chest CT, abdominopelvic CT, and chest X-ray. Subsequent imaging intervals were tailored to individual patient needs, ranging from 2 to 6 months. At each follow-up visit, a thorough clinical assessment was conducted, including physical examinations and symptom evaluations. Additional diagnostic modalities, such as MRI and PET-CT, were performed as needed based on clinical indications or when specific patient factors warranted further investigation.

4. Study endpoint

Local failure was defined as the progression of the treated lesion within the PTV. Widespread failure was defined as the occurrence of six or more newly developed or recurrent metastatic lesions after the completion of SBRT.

The primary endpoint of this study was progression-free survival (PFS), defined as the period from the initiation of SBRT for oligometastasis to the first documented recurrence of any type. Additionally, prognostic factors influencing PFS were evaluated. Secondary endpoints included widespread failure-free survival (WSFFS), defined as the period from SBRT initiation to the develop-

ment of widespread failure, and overall survival (OS), defined as the period from SBRT initiation to death from any cause, with their associated prognostic factors. For cases with multiple lesions treated using SBRT simultaneously or sequentially, the earliest start date of all SBRT treatments was used for the calculation.

Treatment-related toxicity was also assessed using the Common Terminology Criteria for Adverse Events version 5.0. Acute toxicity was defined as adverse events that occurred within the first 3 months following radiotherapy, while late toxicity was defined as events occurring beyond the 3-month post-treatment period.

5. Statistical analysis

Categorical variables are presented as frequencies (%) and were compared using Pearson's chi-squared test or Fisher's exact test. Survival outcomes were analyzed using the Kaplan-Meier method, with survival curves compared through the log-rank test to identify statistically significant differences between groups. Variables with a p-value <0.10 in the univariable Cox proportional hazards regression models were used to identify prognostic factors with multivariable Cox proportional hazards regression models with backward elimination. All statistical analyses were conducted with R Statistics version 4.4.2 (The R Foundation for Statistical Computing, Vienna, Austria). A p-value <0.05 was considered statistically significant.

Results

1. Characteristics of cases

This study included 84 cases with a median age of 71 years (range, 49 to 91). Of these 84 cases, 55 (65.5%) were male. Primary tumor sites were the colon in 39 cases (46.4%) and the rectum in 45 cases (53.6%). Most cases were stage III (41.7%) or IV (33.3%) at the time of the diagnosis. All tumors were adenocarcinoma. Fifty-eight cases (69.0%) had a single oligometastatic lesion. The lung was the most common metastatic site (73.8%), followed by the liver (20.2%). All patients were free of active disease, except for the lesion(s) treated with SBRT. The median SBRT dose for each lesion was 50 Gy (range, 36 to 60) delivered in a median number of 4 fractions (range, 3 to 10), with a median BED of 112.5 Gy_{10} (range, 72.0 to 180.0). The most common dose-fractionation regimens were 52 Gy in 4 fractions (BED 119.6 Gy_{10}; 27 lesions, 23.9%), followed by 48 Gy in 4 fractions (BED 105.6 Gy_{10}; 23 lesions, 20.4%), and 50 Gy in 4 fractions (BED 112.5 Gy_{10}; 17 lesions, 15.0%). Detailed information on the patient, tumor, and treatment characteristics is summarized in Table 1 and Supplementary Table S1.

2. Survival outcomes and prognostic factors

The median follow-up duration was 32.2 months (range, 8.2 to 89.3 months). The 2-year PFS, WSFFS, and OS rates were 35.1%, 67.4%, and 80.8%, respectively (Fig. 1). Local failure was observed in 18 cases (21.4%).

Table 1. Characteristics of 84 cases

Characteristic	Value
Age (year)	71 (49–91)
≤ 70	40 (47.6)
> 70	44 (52.4)
Sex	
Male	55 (65.5)
Female	29 (34.5)
Primary cancer site	
Colon	39 (46.4)
Rectum	45 (53.6)
Initial stage	
I	4 (4.8)
II	17 (20.2)
III	35 (41.7)
IV	28 (33.3)
Histology	
Adenocarcinoma	84 (100)
Differentiation	
Well/moderate	74 (88.1)
Poor/mucinous	10 (11.9)
Oligometastatic status	
De novo	33 (39.3)
Repeat	41 (48.8)
Induced	10 (11.9)
No. of lesions	
1	58 (69.0)
2	23 (27.4)
3	3 (3.6)
Multiplicity	
Single	58 (69.0)
Multiple	26 (31.0)
Oligometastatic site	
Lung	62 (73.8)
Liver	17 (20.2)
Lymph node	4 (4.8)
Lung and lymph node	1 (1.2)
Planning target volume (cm^3)	17.6 (2.9–134.8)
< 17.6	42 (50.0)
≥ 17.6	42 (50.0)
Biologically effective dose (Gy_{10})	112.5 (72.0–180.0)
< 112.5 Gy_{10}	31 (36.9)
≥ 112.5 Gy_{10}	53 (63.1)

Values are presented as median (range) or number (%).

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The results of univariable analyses for PFS, WSFFS, and OS are summarized in Supplementary Table S2, where five variables with a p-value < 0.10 were identified: age (> 70 vs. ≤ 70 years), sex (female vs. male), oligometastatic status (repeat/induced vs. de novo), metastatic site (lung-confined vs. others), and PTV volume (≥ 17.6 vs. < 17.6 cm^3).

In multivariable analysis of PFS, oligometastatic status (hazard ratio [HR], 2.66; 95% confidence interval [CI], 1.40 to 5.04; p = 0.003) and PTV volume (HR, 1.99; 95% CI, 1.09 to 3.62; p = 0.025) were identified as significant prognostic factors (Table 2). When cases were categorized based on the number of adverse prognostic factors for PFS (repeat/induced oligometastasis, and larger PTV volume), having one (HR, 3.15; 95% CI, 1.11 to 8.98; p = 0.031) or two (HR, 5.14; 95% CI, 1.72 to 15.34; p = 0.003) adverse prognostic factors was significant adverse factors for PFS, compared to those with no adverse prognostic factors, in multivariable analysis adjusting for age, sex, metastatic site, and number of risk factors (Supplementary Table S3). Corresponding results for OS and WSFFS are shown in Table 2 and Supplementary Table S3.

For the purpose of risk stratification for OS and WSFFS, the number of risk factors (0 vs. 1 vs. 2) was used in the multivariable analyses. In addition, local failure was included as a covariate in the models for OS and WSFFS, as it was a significant factor in the univariable analyses (HR, 2.97; 95% CI, 1.55 to 5.68; p = 0.001 for OS and HR, 2.41; 95% CI, 1.17 to 4.98; p = 0.017 for WSFFS).

In the multivariable analysis that included age, sex, metastatic site, number of risk factors and local failure as covariates, older age (HR, 2.74; 95% CI, 1.32 to 5.72; p = 0.007), local failure (HR, 2.54; 95% CI, 1.27 to 5.09; p = 0.008), and having two adverse prognostic factors for PFS (HR, 3.39, 95% CI, 1.07 to 10.77; p = 0.039) were identified as poor prognostic factors for OS (Table 3). For WSFFS, female sex (HR, 2.04; 95% CI, 1.01 to 4.14; p = 0.047) and having two adverse prognostic factors for PFS (HR, 4.72; 95% CI, 1.04 to 21.39; p = 0.044) were identified as poor prognostic factors (Table 3). Survival curves for PFS, WSFFS, and OS stratified by the number of adverse prognostic factors for PFS are presented in Fig. 2.

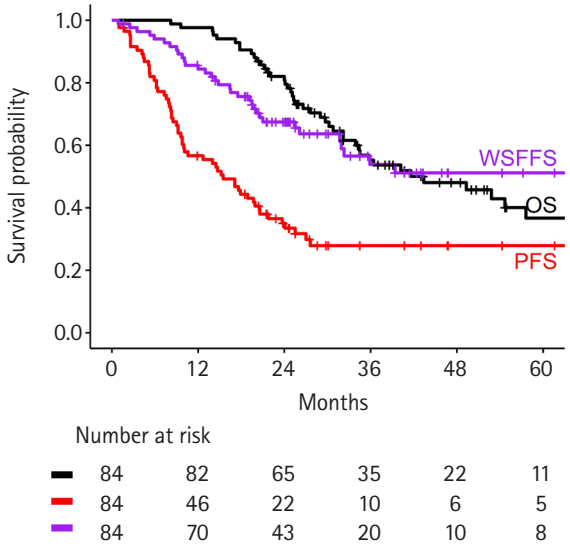

Fig. 1. Survival curves for the 84 cases. OS, overall survival; PFS, progression-free survival; WSFFS, widespread failure-free survival.

3. Toxicities

Acute toxicity was observed in 10 out of 84 cases (11.9%), primarily presenting as fatigue and nausea, with no grade 3 or higher acute toxicities reported. Late toxicity occurred in 11 out of 84 cases (13.1%), with 10 cases classified as grade 1 or 2. One patient developed grade 3 late cardiac toxicity. No grade 4 or life-threatening late toxicities were observed.

Discussion and Conclusion

This study found that oligometastatic status and PTV volume were significantly associated with PFS after SBRT for OMD in colorectal cancer patients. The number of poor prognostic factors (repeat/induced OMD and larger PTV volume) was also associated with OS and WSFFS, suggesting a potential for stratifying patients to deter-

Table 2. Multivariable analyses of prognostic factors, adjusted for age, sex, oligometastatic status, metastatic site, and PTV volume

Variable	PFS		OS		WSFFS	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (> 70 vs. ≤ 70 years)	1.62 (0.90–2.94)	0.109	1.78 (0.93–3.42)	0.084	-	-
Sex (female vs. male)	-	-	2.22 (1.19–4.11)	0.012	2.24 (1.13–4.45)	0.022
Oligometastatic status (repeat/induced vs. de novo)	2.66 (1.40–5.04)	0.003	-	-	1.75 (0.82–3.71)	0.147
Metastatic site (lung-confined vs. others)	0.60 (0.33–1.11)	0.102	-	-	-	-
PTV volume (≥ 17.6 vs. < 17.6 cm^3)	1.99 (1.09–3.62)	0.025	2.91 (1.52–5.57)	0.001	2.76 (1.33–5.74)	0.007

PTV, planning target volume; PFS, progression-free survival; OS, overall survival; WSFFS, widespread failure-free survival; HR, hazard ratio; CI, confidence interval.

Table 3. Multivariable analyses of prognostic factors for OS and WSFFS, adjusted for age, sex, metastatic site, local failure, and number of risk factors

Variable[a]	OS		WSFFS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (> 70 vs. ≤ 70 years)	2.74 (1.32–5.72)	0.007	-	-
Sex (femlae vs. male)	1.82 (0.97–3.41)	0.062	2.04 (1.01–4.14)	0.047
Local failure (present vs. absent)	2.54 (1.27–5.09)	0.008	1.79 (0.84–3.83)	0.134
No. of risk factors[b] (1 vs. 0)	1.45 (0.48–4.32)	0.510	2.30 (0.52–10.17)	0.274
No. of risk factors[b] (2 vs. 0)	3.39 (1.07–10.77)	0.039	4.72 (1.04–21.39)	0.044

OS, overall survival; WSFFS, widespread failure-free survival; HR, hazard ratio; CI, confidence interval; PTV, planning target volume.
[a]Metastatic site is not shown, as it was eliminated during the backward elimination process.
[b]Risk factors included repeat/induced oligometastatic disease and larger PTV volume (>17.5 cm^3).

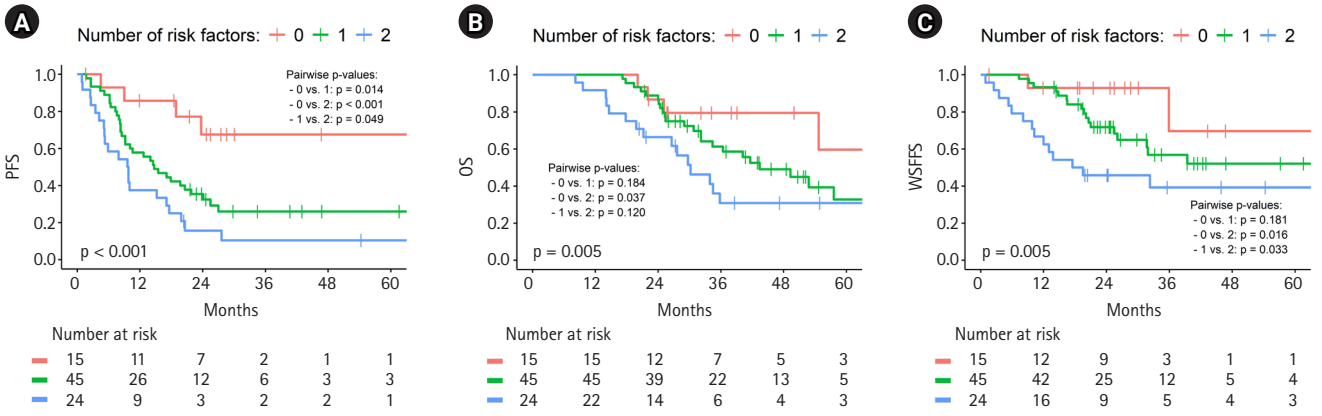

Fig. 2. Survival curves based on the number of adverse prognostic factors: repeat/induced oligometastasis and larger planning target volume. (A) Progression-free survival (PFS). (B) Overall survival (OS). (C) Widespread failure-free survival (WSFFS). p-values are from multivariable analyses including age, sex, metastatic site, and the number of adverse prognostic factors as covariates.

mine optimal treatment strategies.

In the current study, 2-year PFS, WSFFS, and OS rates were 35.1%, 67.4%, and 80.7%, respectively, which are consistent with previously reported findings. In previous studies, SBRT for various sites of oligometastatic colorectal cancer has been reported to achieve 2-year PFS rates ranging from 26.4% to 31.6% [17,18]. Widespread progression rates following SBRT for oligometastatic colorectal cancer have been reported to be around 35% at 2 years [18]. Colorectal patients with various oligometastatic sites treated with SBRT exhibit 2-year OS rates ranging from 76.1% to 79% [17,18].

Our study found that repeat/induced OMD and larger PTV volume (≥ 17.6 cm^3) were associated with worse PFS outcomes (Table 2). Various prognostic factors for PFS after SBRT for oligometastatic colorectal cancer have been reported; some align with our findings, while others report different factors. Lee et al. [19] identified that oligoprogression (vs. oligometastasis), multiple lung lesions (vs. single), the presence of extrapulmonary metastatic lesions at presentation, and M1 disease at initial diagnosis were significantly associated with worse PFS after SBRT for pulmonary metastases from colorectal cancer. Agolli et al. [20] reported that metachronous OMD (vs. synchronous OMD) and complete response (vs. partial response/stable disease vs. disease progression) were positive prognostic factors for PFS in pulmonary oligometastatic colorectal cancer treated with SBRT. In the study by Sheikh et al. [18], PTV volume (> 17.5 vs. ≤ 17.5 cm^3) was the sole prognostic factor for PFS after SBRT to multiple-site OMD. However, due to differences in patient cohorts and the prognostic factors considered across studies, further research is required to validate prognostic factors for PFS in oligometastatic colorectal cancer treated with SBRT.

Several studies identified prognostic factors for OS, including PTV or GTV volume, metastatic sites, SBRT dose, lines of previous systemic therapy, oligoprogression, etc. [17-19,21-24]. In the current study, older age (> 70 years), the presence of local failure, and having two risk factors for PFS (both repeat/induced OMD and larger PTV volume) were significant adverse prognostic factors for OS after SBRT (Table 3). Widespread failure after local therapy for OMD is important, as it indicates systemic disease progression re-

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quiring systemic therapies [12,18]. Sheikh et al. [18] reported that a larger PTV volume (> 17.5 cm^3) and prior systemic therapy were associated with worse WSFFS after SBRT for oligometastatic colorectal cancer. In the current study, female sex and having two risk factors for PFS were significantly associated with worse WSFFS (Table 3).

These identified prognostic factors for OS and WSFFS may have important clinical implications in treatment decision-making. Patients with two risk factors for PFS may benefit from initiating or modifying chemotherapy in addition to SBRT, as they demonstrated significantly worse OS and WSFFS compared to those with no risk factors (Table 3). SBRT alone may be sufficient for patients with zero or one risk factor, allowing them to potentially defer chemotherapy or continue their current chemotherapeutic regimen. Although the BED of prescribed doses was not a significant factor for survival outcomes in this study, dose escalation may offer benefits in terms of local control and OS when applying SBRT to OMD. Consistent with our findings, local control has been reported to be correlated with better OS [22,25]. Several studies have demonstrated that a higher SBRT dose is associated with improved local control in oligometastatic colorectal cancer, which is known to have a lower local control rate after SBRT compared to other primary cancers [18,19,23,26-28]. Although local failure was not a statistically significant factor for WSFFS, its impact on widespread failure warrants further investigation, as widespread failure tended to occur more frequently in patients with local failure (11/18, 61.1% vs. 22/66, 33.3%; p = 0.062).

The limitations of our study include its single-institution, retrospective design, small patient cohort, and heterogeneity in prior disease status (e.g., oligometastatic vs. polymetastatic) and in prior treatments, including variations in primary tumor management, chemotherapeutic regimens, the number and cycles of chemotherapy, and local therapies for previously treated OMD. All of these factors may restrict the generalizability of our findings. Therefore, larger, multicenter prospective studies that take into account heterogeneity not captured in the current study are needed to identify more generalizable prognostic factors.

In conclusion, SBRT demonstrated favorable and safe clinical outcomes, supporting its role as an effective treatment option for oligometastatic colorectal cancer. Oligometastatic status and PTV volume were significantly associated with PFS. Additionally, risk stratification based on the number of poor prognostic factors contributed to a better understanding of survival outcomes, underscoring the necessity of a personalized approach to patient management. Further research is necessary to validate these findings and refine patient stratification for SBRT in colorectal cancer patients with OMD.

Statement of Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki and received approval from the Institutional Review Board of Kyungpook National University Chilgok Hospital (No. 2024-10-020). Written informed consent was waived by the Institutional Review Board due to the retrospective nature of the study.

Conflict of Interest

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

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None.

Author Contributions

Conceptualization, MKK, BKB; Investigation and methodology, MKK, HK; Resources, MKK, GSC, JGK, JSP, SYP, HJK, JHB, BWK, ANS; Supervision, GSC, JGK; Writing of the original draft, HK, BKB; Writing of the review and editing, MKK, BKB; Formal analysis, HK, MKK; All the authors have proofread the final version.

Data Availability Statement

The data supporting the conclusions of this study can be obtained from the corresponding author upon a reasonable request.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2025.00066.

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Analysis of radiotherapy in patients with intermediate- and high-risk meningiomas

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Purpose: This study aimed to investigate treatment outcomes in patients with intermediate- and high-risk meningioma who underwent radiotherapy (RT) and identify prognostic factors for progression-free survival (PFS). In addition, failure patterns after RT were analyzed.

Materials and Methods: We retrospectively reviewed 61 patients with intermediate- and high-risk meningiomas, categorized according to the NRG Oncology/Radiation Therapy Oncology Group 0539 trial, who underwent surgery followed by adjuvant or salvage RT.

Results: We included 12 and 49 patients with intermediate- and high-risk meningiomas, respectively. A total of 26 cases of tumor progression and 17 deaths after RT were identified. The 5-year PFS and overall survival of the entire cohort were 55.8% and 74.2%; intermediate-risk group, 80.2% and 100%; high-risk group, 48.7% and 67.1%, respectively. The World Health Organization (WHO) grade 3 (hazard ratio [HR], 16.7; 95% confidence interval [CI], 3.0 to 92.3; p = 0.001) and recurrent tumor (HR, 41.2; 95% CI, 3.6 to 473.6; p = 0.003) were identified as adverse prognostic factors for PFS in high-risk patients. Among the 15 patients who had recurrence after conventional fractionated radiotherapy (CFRT), 13 experienced local failure (LF) and two experienced distant failure.

Conclusion: RT with adjuvant or salvage intent showed favorable treatment outcomes in patients with intermediate- to high-risk meningioma. WHO grade 3 histology and recurrent tumors were identified as adverse prognostic factors for PFS in high-risk patients. LF was the dominant failure pattern after CFRT, accounting for 86.7% of all recurrences. These findings underscore the need for further studies on dose-escalated RT to enhance local control in patients with these adverse features.

Keywords: Meningioma, Radiotherapy, Treatment failure, Prognosis

Introduction

Meningiomas are the most common primary brain tumors, accounting for 36.1% of all central nervous system neoplasms [1]. Radiotherapy (RT) has been the mainstay of treatment, along with surgery [2,3]. Current guidelines from the European Association of Neuro-Oncology and National Comprehensive Cancer Network recommend postoperative RT for patients with World Health Organization (WHO) grade 2 meningioma following subtotal resection, and for patients with WHO grade 3 meningioma, as a therapeutic modality to reduce recurrence and improve survival [2,3]. A consensus has not been reached regarding the benefit of postoperative RT for patients with WHO grade 2 meningioma who have undergone complete resection [4-6]. Recently, two phase II prospective trials reported favorable progression-free survival (PFS) and overall survival (OS) outcomes following the introduction of postoperative RT in patients with meningioma [7,8]. The NRG Oncology/Radiation Therapy Oncology Group (RTOG) 0539 trial reported favorable outcomes with postoperative RT, showing improvements compared to historical data in patients with intermediate- and high-risk menin-

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gioma [7,9]. In this trial, the "intermediate-risk" meningioma was defined as recurrent WHO grade 1 or newly diagnosed WHO grade 2 following gross total resection. "High-risk meningioma" included WHO grade 2 with subtotal resection, recurrent WHO grade 2, and all WHO grade 3 cases. The European Organisation for Research and Treatment of Cancer (EORTC) 22042-26042 trial introduced high-dose postoperative RT (60 Gy) in patients with WHO grade 2 after complete resection and reported superior PFS compared to previous historical data [8]. Both the NRG Oncology/RTOG 0539 and EORTC 22042-26042 trials demonstrated the potential benefits of postoperative RT in improving recurrence and survival outcomes in patients with WHO grade 2-3 meningioma and recurrent grade 1 meningioma. However, despite these findings, patients with high-risk meningioma continue to show relatively poor PFS after postoperative RT. Ongoing studies are investigating dose-escalation RT strategies to improve these outcomes [10,11]. In this study, we aimed to investigate the treatment outcomes of RT in patients with intermediate- and high-risk meningioma, as defined by the NRG Oncology/RTOG 0539 trial, in a real-world clinical setting. In addition, we sought to identify the prognostic factors for PFS and analyze recurrence patterns following RT to assist clinicians identify patients who may benefit from more intensive RT.

Materials and Methods

1. Patient selection

We retrospectively reviewed patients with intracranial meningiomas who underwent surgery followed by RT at two tertiary institutions between January 2000 and May 2024. Eligible patients were aged 18 years or older, had an Eastern Cooperative Oncology Group performance status of 0–2, and were diagnosed with intracranial meningioma through surgical resection. All patients included in this study underwent surgical resection at the time of initial diagnosis, and their grade was assessed according to the 2007 WHO classification [12]. Through a retrospective review of patients with meningioma who underwent surgery followed by RT at two institutions, 61 patients with intermediate- and high-risk meningioma, as defined by the NRG Oncology/RTOG 0539 trial, were ultimately included in this study [7,9]. Intermediate-risk meningioma" was defined as recurrent WHO grade 1 or newly diagnosed WHO grade 2 meningioma following gross total resection. "High-risk meningioma" was defined as WHO grade 2 meningioma with subtotal resection, recurrent WHO grade 2, and all WHO grade 3 meningioma. Patients who had newly diagnosed WHO grade I meningioma, did not complete the planned RT, or lacked available follow-up radiologic imaging were excluded from the study. The extent of surgical resection was evaluated using Simpson's classification, based on a review of the operative records [13]. Simpson grades I-III were considered gross total resection, while Simpson grades IV–V were categorized as subtotal resection. Recurrent meningioma was defined as the condition in which salvage treatment was conducted owing to the occurrence of a new enhancing lesion or a radiographic increase in the remnant tumor on contrast-enhanced T1-weighted brain magnetic resonance imaging (MRI).

2. Treatment delivery

All patients underwent surgical resection at the time of initial meningioma diagnosis. RT was delivered either as adjuvant treatment or as salvage treatment after tumor recurrence. RT was administered as either conventionally fractionated radiotherapy (CFRT), or stereotactic radiosurgery (SRS). During the RT simulation, patients were immobilized with either an individualized thermoplastic mask or a stereotactic frame, and contrast-enhanced computed tomography (CT) with 1.25–2.5 mm slice thickness was conducted. Contrast-enhanced T1-weighted MRI images obtained prior to RT simulation were fused with simulation CT scans for treatment planning. The gross tumor volume (GTV) included the enhancing lesion, thickened meninges, and/or surgical cavity. For grade 1 meningioma, a 0–3 mm isotropic margin was added to define the clinical target volume (CTV), while a 5–10 mm margin was added for grade 2–3 meningioma, respecting anatomic boundaries. The planning target volume was defined with a 3–5 mm margin from the CTV to account for geometric uncertainties and setup error. For SRS, the RT dose was prescribed to the GTV without a margin. SRS was implemented as a salvage treatment for recurrent tumors <2 cm in size and a single mass, and as an adjuvant therapy when there was a limited volume of residual tumor after surgery. In principle, SRS was applied to grade 1–2 meningiomas, with limited use for grade 3 meningiomas. CFRT was administered in 1.8–2.2 Gy single doses over 27–31 fractions. CFRT was delivered using three-dimensional conformal radiotherapy or intensity-modulated radiation therapy (IMRT). SRS was delivered at a median dose of 18 Gy (range, 12 to 22 Gy) using either the CyberKnife (Accuray Inc., Sunnyvale, CA, USA) or Novalis Tx system linear accelerator (Varian, Palo Alto, CA, USA) at the two institutions.

3. Follow-up and failure pattern analysis

Patients were monitored weekly during RT through clinical evaluation and complete blood count testing. Three months after completing RT, contrast-enhanced brain MRI was performed to evaluate post-treatment tumor response. Subsequently, patients with grade 1 meningioma underwent annual follow-up with enhanced MRI, while those with grade 2–3 meningioma were followed every 6 months for 5 years. Tumor progression was defined as the occur-

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rence of a newly developed enhancing mass or any radiographic increase in the residual tumor compared to prior contrast-enhanced brain MRI, as confirmed by a neuroradiologist. In cases of tumor progression following RT, brain MRI scans at the time of progression and RT plans were comparatively analyzed to identify pattern of failure. T1-weighted contrast-enhanced brain MRI and RT plans were uploaded and fused using MIM software 7.0.8 (MIM Software Inc., Cleveland, OH, USA), and the recurrent mass was contoured by a radiation oncologist. Local failure (LF) was defined as any recurrence occurring within a 1 cm isotropic margin of the prescription volume. Any failure occurring outside this margin was classified as distant failure (DF). An example of the analysis of the failure pattern is shown in Fig. 1.

4. Statistical analysis

The primary and secondary endpoints of this study were PFS and OS, respectively. PFS and OS defined as the time between the initiation of RT to the date of tumor progression and to the date of death or last follow-up, respectively. The actuarial survival rate was estimated using the Kaplan-Meier method. The log-rank test was performed to analyze the significance of the prognostic factors for recurrence. Multivariate analysis was performed using the Cox proportional hazards model, including factors with a $p \leq 0.05$ on a log-rank test or those deemed clinically significant [5]. Areas under the curve (AUC) were calculated to estimate the prognostic efficacy of the continuous variable on progression using a receiver operating characteristic curve. The optimal cut-off values of continuous variable for progression were determined using Youden's index. Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using the R software version 4.4.3 (R Development Core Team, Vienna, Austria).

Results

1. Patient and treatment characteristics

Data from 61 patients with histologically confirmed meningiomas who underwent RT were retrospectively investigated. The median follow-up duration was 47.2 months (range, 3.1 to 202.4). The median patient age was 61 years (range, 20 to 78), with a female predominance (39 patients, 63.9%). Twelve patients had intermedi-

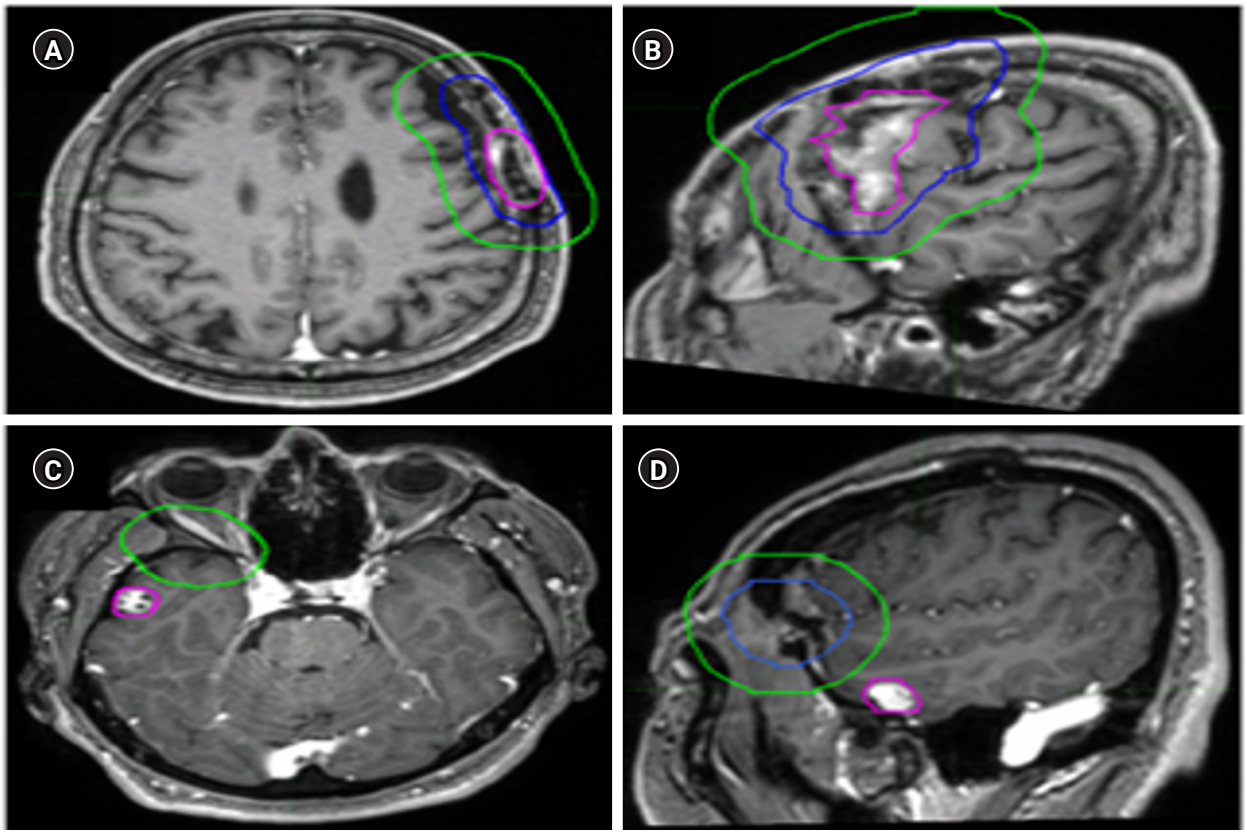

Fig. 1. Illustrations of failure pattern analysis. Local failure pattern on axial (A) and sagittal (B) images of T1-weighted brain magnetic resonance imaging (MRI) at tumor recurrence. Distant failure pattern in the axial (C) and sagittal (D) image of T1-weighted brain MRI. The planning target volume is outlined in blue, and a 1 cm isotropic expansion of the planning target volume is delineated in green. The recurrent tumor is delineated in magenta.

ate-risk meningioma, and 49 patients had high-risk meningioma. WHO grade 2 tumors were the most common (47 patients, 77.0%), followed by grade 3 (9 patients, 14.8%) and grade 1 (5 patients, 8.2%). Meningiomas located at the skull base were observed in 37 patients (60.7%). Patient's characteristics are summarized in Table 1. RT was delivered at initial diagnosis in 24 patients and at recurrence in 37 patients. For recurrent tumors, the median duration from the date of initial diagnosis to the date of occurrence of recurrence before RT was 27.9 months (range, 2.7 to 138.5). Among 37 patients with recurrent tumors, 15 underwent salvage surgery followed by adjuvant RT, while 22 received salvage RT alone. In the surgery immediately before RT, 31 patients (50.8%) underwent Simpson grade 1–3, and 30 underwent Simpson grade 4–5 resections. RT was delivered as adjuvant treatment in 39 patients and as salvage treatment in 22. CFRT was delivered using IMRT in 40 cases, while four received 3-dimensional conformal radiation therapy. CFRT was administered at a median dose of 55 Gy (range, 50.4 to 60) over 27–31 fractions. SRS was delivered at a median dose of 18 Gy (range 12 to 22). Treatment characteristics are detailed in Table 2.

Table 1. Patient characteristics

Characteristic	Value (n = 61)
Age (year)	61 (20–78)
Sex	
Male	22 (36.1)
Female	39 (63.9)
ECOG performance status	
0–1	49 (80.3)
2–3	12 (19.7)
WHO grade	
1	5 (8.2)
2	47 (77.0)
3	9 (14.8)
Risk group	
Intermediate	12 (19.7)
High	49 (80.3)
Tumor location	
Skull base	37 (60.7)
Non-skull base	24 (39.3)
Tumor size (cm)	
< 5	37 (60.7)
≥ 5	22 (36.0)
Unknown	2 (3.3)
Brain invasion	
Yes	19 (31.1)
No	40 (65.6)
Unknown	2 (3.3)
Bone invasion	
Yes	5 (8.2)
No	54 (88.5)
Unknown	2 (3.3)
Peritumoral edema	
Yes	34 (55.7)
No	25 (41.0)
Unknown	2 (3.3)
Ki-67 index (%)	
Median, 11% (range, < 1 to 40)	54 (88.5)
Unknown	7 (11.5)
Tumor status at introduction of radiotherapy	
Initial diagnosed	24 (39.3)
Recurrent	37 (60.7)

Values are presented as median (range) or number (%).
ECOG, Eastern Cooperative Oncology group; WHO, World Health Organization.

2. Treatment outcomes and prognostic factors

At the time of analysis, 26 cases of tumor progression were identified: four in the intermediate-risk group and 22 in the high-risk group. Seventeen patients had died, including one in the intermediate-risk group and 16 in the high-risk group. The median PFS of the entire cohort was 103.8 months. The 3- and 5-year PFS rates were 72.9% and 55.8%, respectively. Median OS was not reached, with 3- and 5-year OS rates of 86.0% and 74.2%, respectively. For the intermediate-risk group, the 3-and 5-year PFS rates were 91.7% and 80.2%, and OS rates were 100% at both time points. Conversely, the high-risk group showed 3- and 5-year PFS rates of 67.6% and 48.7%, and OS rates of 82.2% and 67.1%, respectively. The high-risk group demonstrated a trend toward lower PFS ($p = 0.074$) and significantly lower OS ($p = 0.009$) compared to the intermediate-risk group (Fig. 2).

Owing to the small number of intermediate-risk patients (n = 12), the prognostic factor analysis was limited to the high-risk group to identify significant prognostic factors within the risk group. The cut-off value of the Ki-67 index for progression in the high-risk group was 6.8% (AUC, 0.609). In the univariate analysis of the high-risk group, WHO grade 3 tumors showed a distinctly lower PFS than WHO grade 2 tumors, but the difference was not statistically significant (5-year PFS, 25% vs. 53.6%; $p = 0.256$) (Fig. 3). The high Ki-67 group (> 6.8%) showed a trend toward a lower PFS than the low Ki-67 group (5-year PFS, 41.2% vs. 78.7%; $p = 0.050$). Patients who received RT at recurrence had significantly lower PFS compared to those treated at initial diagnosis (5-year PFS, 36.3% vs. 92.9%; $p = 0.002$) (Fig. 3). No statistically significant differences in PFS were observed between CFRT and SRS (5-year PFS, 52.3% vs. 39.2%; $p = 0.562$). The results of the univariate analysis for PFS in high-risk group are summarized in Table 3.

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Table 2. Treatment characteristics

Characteristic	Value (n = 61)
Simpson grade of surgical resection[a]	
Grade 1–3	31 (50.8)
Grade 4–5	30 (49.2)
Aim of radiotherapy	
Adjuvant	39 (63.9)
Salvage	22 (36.1)
Radiotherapy technique	
IMRT	40 (65.6)
3D-CRT	4 (6.5)
SRS	17 (27.9)
Radiotherapy type	
CFRT	44 (72.1)
PTV (cm^3)	63.8 (3.7–398.2)
Dose (Gy)	55 (50.4–60)
50.4 Gy/28 fractions	1 (1.6)
52.7 Gy/27 fractions	1 (1.6)
54 Gy/30 fractions	16 (26.2)
55 Gy/25 fractions	6 (9.8)
55.8 Gy/31 fractions	7 (11.5)
60 Gy/30 fractions	13 (21.3)
SRS	17 (27.9)
PTV (cm^3)	2.5 (0.6–14.6)
Dose (Gy)	18 (12–22)
Salvage treatment for recurrent tumor	37
Operation + adjuvant radiotherapy	15 (24.6)
Salvage radiotherapy alone	22 (36.1)

Values are presented as number (%) or median (range).
IMRT, intensity-modulated radiation therapy; 3D-CRT, three-dimensional conformal radiotherapy; SRS, stereotactic radiosurgery; CFRT, conventional fractionated radiotherapy; PTV, planning target volume.
[a]In cases of recurrent tumors, the Simpson grade was determined according to the most recent surgery conducted before radiotherapy.

Table 3. Univariate analysis for PFS in high-risk group

Factor	No. (n = 49)	3-year PFS (%)	5-year PFS (%)	p-value
Age (year)				
< 50	14	65.8	26.3	0.294
≥ 50	35	68.5	54.1	
Sex				
Male	22	66.9	37.6	0.502
Female	27	68.2	61.4	
ECOG performance status				
0–1	38	64.9	42.2	0.419
2	11	77.1	77.1	
WHO grade				
2	40	71.7	53.6	0.256
3	9	50.0	25.0	
Tumor location				
Skull base	28	68.4	48.5	0.832
Non-skull base	21	64.8	48.6	
Tumor size (cm)				
< 5	30	64.6	57.4	0.784
≥ 5	18	76.7	38.4	
Peritumoral edema				
Yes	28	71.6	49.1	0.629
No	20	66.0	52.8	
Brain invasion				
Yes	24	67.2	42.7	0.815
No	24	71.5	56.9	
Bone invasion				
Yes	5	100	-	0.652
No	43	67.2	49.9	
Ki-67 index (%)				
< 6.8	15	78.7	78.7	0.050
> 6.8	30	66.0	41.2	
Simpson grade				
Grade 1–3	23	69.3	60.6	0.347
Grade 4–5	26	65.3	37.3	
Tumor status				
Initial	17	92.9	92.9	0.002[a]
Recurrent	32	57.6	36.3	
RT type				
CFRT	36	68.4	52.3	0.562
SRS	13	52.3	39.2	

PFS, progression-free survival; ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization; RT, radiotherapy; CFRT, conventional fractionated radiotherapy; SRS, stereotactic radiosurgery
[a]Statistically significant.

Multivariate analysis in high-risk group identified WHO grade 3 (hazard ratio [HR], 16.7; 95% confidence interval [CI], 3.0 to 92.3; p = 0.001) and recurrent tumor status (HR, 41.2; 95% CI, 3.6 to 473.6; p = 0.003) as significant adverse prognostic factors for PFS (Table 4).

3. Pattern of failure

Tumor progression was confirmed in 26 patients based on follow-up brain MRI after RT at the time of analysis. Among the 26 patients with recurrence, 10 received RT with SRS and 16 were treated with CFRT. In the SRS group, the number of patients eligible for failure pattern analysis was limited (3 of 10 patients) because of problems with the CyberKnife plan restoration; therefore, the analysis was performed only in the CFRT group. Failure pattern analysis was finally performed in 15 of the 16 patients who experienced recurrence after CFRT treatment. LF and DF occurred in 13 (of 15 cases, 86.7%) and 2 (of 15 cases, 13.3%) patients, respectively. Failure patterns were further analyzed according to the WHO

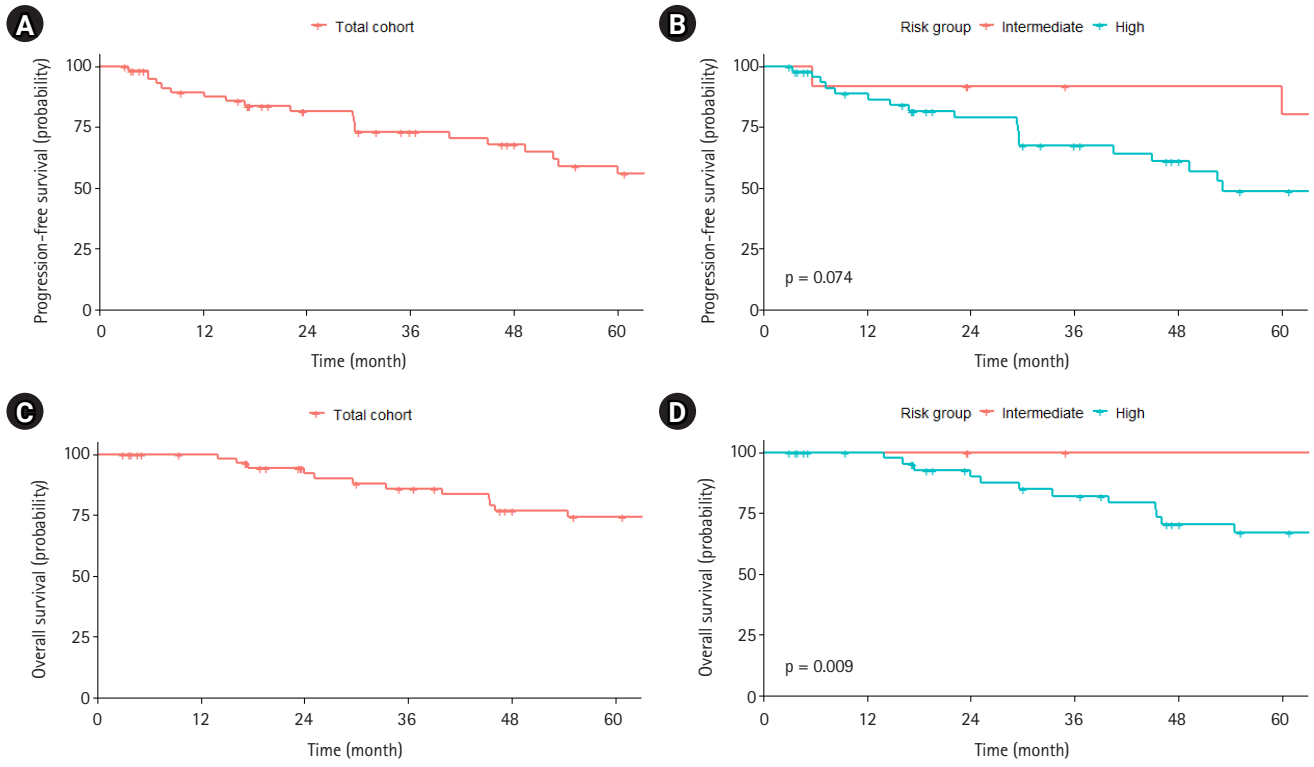

Fig. 2. Kaplan-Meier curves for progression-free survival and overall survival for the entire cohort and by risk group. (A) Progression-free survival of the entire cohort. (B) Progression-free survival according to risk group. (C) Overall survival of the entire cohort. (D) Overall survival according to risk group.

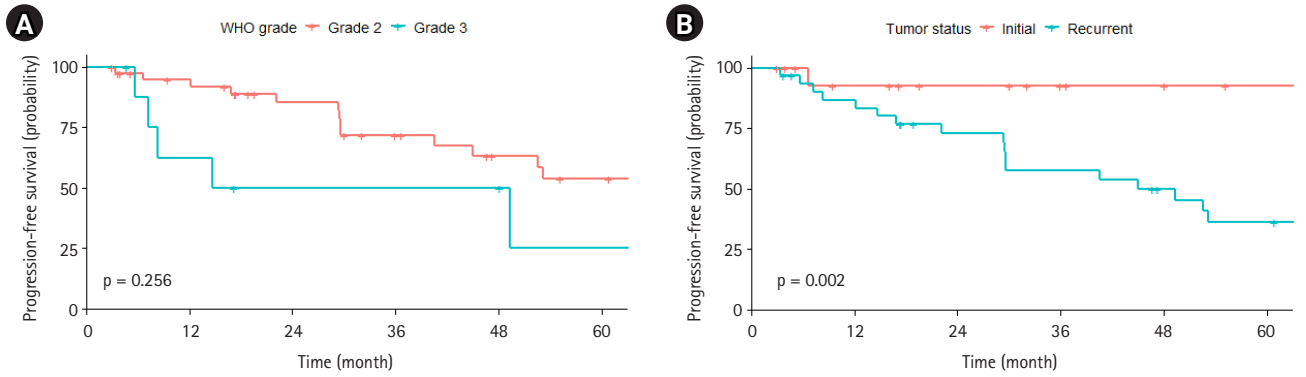

Fig. 3. Kaplan-Meier curve for progression-free survival of high-risk patients stratified by World Health Organization (WHO) grade (A) and tumor status at introduction of radiotherapy (B).

grade (2/3), risk group (high-risk), and tumor status (initial/recurrent). In the WHO grade 3 group (n = 4), all initial recurrences were LF. In the high-risk group (n = 15), LF was the predominant pattern (86.7%), with two cases of DF. Among patients with recurrent tumors, LF was observed in 12 of 14 cases (85.7%) and DF was observed in two cases (14.3%). The recurrence patterns according to the subgroups are summarized in Table 5.

Discussion and Conclusion

This study investigated the PFS and OS of patients with intermediate- and high-risk meningiomas, as defined by the NRG Oncology/RTOG 0539 criteria. In our study, the 3-year PFS and OS for the intermediate-risk group were 91.7% and 100%, respectively, while for the high-risk group, these were 67.6% and 82.2%. These findings are consistent with the results reported in the NRG Oncology/

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RTOG 0539 and EORTC 22042-26042 trials, where 3-year PFS ranged from 88.7% to 93.8% and 3-year OS ranged from 96% to 98.2% in the intermediate-risk patients [7,8]. For high-risk meningioma, prior studies have reported 3-year PFS and OS ranging from 58.8% to 66.1% and 78.6% to 80.6%, respectively [9,14].

In our study, WHO grade 3 and recurrent tumors were identified as significant adverse prognostic factors for PFS in high-risk group. This aligns with the findings by Wang et al. [5], who reported that both WHO grade 3 and recurrent status were associated with poorer PFS among patients undergoing either adjuvant or salvage RT. WHO grade has been reported to be one of the most significant predictors of recurrence of meningioma [15,16]. Although WHO grade 3 accounts for only 1-3% of all meningiomas, it is characterized by aggressive malignant features and poor survival outcomes, with a 5-year PFS and OS of 37% and 65%–66% after treatment [17,18].

Recurrent meningiomas are also associated with worse outcomes compared to newly diagnosed cases [9,19]. Previous literature has reported that 6.3% to 41.4% of recurrent meningiomas undergo transformation to a higher WHO grade [20-22]. A subgroup analysis from the NRG Oncology/RTOG 0539 trial demonstrated that patients with recurrent WHO grade 2 meningioma had worse outcomes than those with newly diagnosed WHO grade 3 disease [9]. Talacchi et al. [19] observed that the recurrence-free interval becomes shorter with each recurrence and that marginal failure and DF become more frequent during the clinical course of recurrent atypical meningioma.

In this study, LF was the dominant failure pattern among the 15 patients who received CFRT. All patients evaluable for failure pattern analysis belonged to the high-risk group, and LF was the dominant pattern, accounting for 86.7% of the total failures. This is consistent with the results of previous studies that analyzed the recurrence pattern after RT in high-risk patients, in which LF ranged from 85.2% to 87.5% of the total recurrences [9,22]. In our study, all initial recurrences occurred as LF in the WHO grade 3 group. A study by Kuhn et al. [23], which analyzed recurrence patterns after SRS, reported that multifocal disease and high-grade histology (WHO grades 2 and 3) were associated with higher local recurrence. Owing to the rarity of the disease, studies analyzing recurrence patterns in patients exclusively with WHO grade 3 meningioma are scarce. In our study, WHO grade 3 was identified as an adverse prognostic factor for PFS, and LF was the principal failure pattern in these groups. In the recurrent tumor group, LF was the dominant pattern, while DF accounted for 14.3% of total recurrences. Talacchi et al. [19] reported that marginal and distant recurrences increased over the clinical course of patients with recurrent atypical meningiomas who underwent RT. The recurrence patterns and distinct clinical behaviors of recurrent meningiomas should be further clarified in future studies.

In this study, LF was identified as the predominant pattern of recurrence in patients with high-risk meningioma following RT in consistent with previous studies [9,22]. This finding suggests that dose-escalated RT may be a potential strategy to improve local control in these patients. Several previous studies have reported that dose-escalated RT (equivalent dose in 2 Gy fractions, 64 to 70

Table 4. Multivariate analysis for progression-free survival in high-risk group

Factor	Progression-free survival	
	HR (95% CI)	p-value
WHO grade (grade 2/3)	16.7 (3.0–92.3)	0.001[a]
Tumor status (initial/recurrent)	41.2 (3.6–473.6)	0.003[a]
Ki-67 index (%) (< 6.8/> 6.8)	2.3 (0.7–7.7)	0.197

HR, hazard ratio; CI, confidence interval; WHO, World Health Organization.
[a]Statistically significant.

Table 5. Analysis of failure patterns in the conventional fractionated radiotherapy group based on the WHO grade, risk group, and tumor status

Group	No. of patients[a]	Progression (available, total n = 15)	
		Local failure (n = 13)	Distant failure (n = 2)
WHO grade			
Grade 1–2	11	9/11 (81.8)	2/11 (18.2)
Grade 3	4	4/4 (100)	0 (0)
Risk group			
High	15	13/15 (86.7)	2/15 (13.3)
Tumor status			
Initial	1	1/1 (100)	0 (0)
Progression/Recurrent	14	12/14 (85.7)	2/14 (14.3)

Values are presented as number (%).
WHO, World Health Organization.
[a]Number of patients in each group for whom failure pattern analysis was available.

Table 6. Previous studies of dose-escalation RT for meningiomas

Studies	No.	Patients	RT	Dose	Outcome
Zeng et al. (2024) [10]	118	Grade 2–3 meningioma	CFRT	> 66 Gy vs. < 66 Gy (EQD2, α/β = 10)	3- and 5-year PFS, 78.9% and 64.6% vs. 57.2% and 40.8% (p = 0.03)
Deng et al. (2024) (MARCIE trial) [24]	33	Grade 2 with STR	CFRT-carbon boost	50 Gy/25 fxs followed by 18 Gy (RBE) in 6 fxs	3-year PFS and LC: 80.3% and 86.7%
Pontoriero et al. (2023) [25]	16	Grade 2 with STR or recurrent grade 2	CFRT-HFRT boost	46 Gy/23 fxs followed by boost RT (15 Gy/3 fxs)	3-year PFS, STR group, 100% recurrent tumor, 55.5%
Kim et al. (2023) [26]	158	Newly diagnosed grade 2 meningioma	CFRT	> 57.42 Gy vs. ≤ 57.42 Gy (EQD2, α/β = 4)	5-year PFS, 87.4% vs. 72.0% (p = 0.049)
Sethi et al. (2015) [27]	101	Grade 1–3 meningioma	SRS	Grade 1: 10–18 Gy, Grade 2: 12–16 Gy, Grade 3: 15–20 Gy	LC, 1 Gy dose escalation, 42% relative reduction in local recurrence

RT, radiotherapy; CFRT, conventional fractionated radiotherapy; EQD2, equivalent dose in 2 Gy fractions; α/β, alpha/beta ratio; PFS, progression-free survival; STR, subtotal resection; fxs, fractions; RBE, relative biologic effectiveness; LC, local control; HFRT, hypofractionated radiotherapy; SRS, stereotactic radiotherapy.

Gy) improves PFS in high-risk patients with meningioma, including those with grade 2–3 meningioma, those who underwent subtotal resection, and those with recurrent tumors (Table 6). In our study, no patients in the CFRT group underwent dose-escalated RT exceeding 60 Gy; therefore, a meaningful RT dose analysis could not be performed. Because this study had limitations in analyzing the RT dose owing to the characteristics of the cohort, the benefit of dose-escalated RT, and the optimal RT dose in patients with adverse features such as recurrent tumor or WHO grade 3 should be clarified in future studies involving a larger number of patients.

This study has several limitations. First, this study included a relatively small number of patients and failure pattern analysis was performed only in patients who underwent CFRT. Second, as this was a retrospective study involving two institutions, variations in treatment policies may have influenced the outcomes. In addition, owing to the long duration of the study, some heterogeneity may be inherent in the diagnostic and treatment methods used for patients with meningioma. Third, this study included patients who received RT with SRS or CFRT, which may have affected treatment outcomes. These points could be sources of bias in observational studies, and caution should be exercised when interpreting the results of this study. Fourth, owing to data limitations, the analysis of molecular factors known to affect the clinical behavior and prognosis of meningiomas was not performed. Despite these limitations, this study clarified the treatment outcomes of RT in intermediate- and high-risk meningiomas and identified prognostic factors for PFS in high-risk patients. The recurrence pattern after CFRT identified in this study may be supported when considering intensified RT in some patients with meningiomas.

In conclusion, RT with adjuvant or salvage intent showed favorable treatment outcomes in patients with intermediate-to high-risk meningiomas. WHO grade 3 histology and recurrent tumor status were identified as adverse prognostic factors for PFS in high-risk meningiomas. In addition, LF was the predominant recurrence pattern following CFRT, accounting for 86.7% of all recurrences. These findings underscore the need for further studies on dose-escalated RT to enhance local control in patients with these adverse features.

Statement of Ethics

This study was approved by the institutional review board of the Catholic Medical Center Ethics Committee (IRB No. XC25RIDI0024). The need for informed consent was waived owing to the retrospective nature of the study.

Conflict of Interest

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

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None.

Author Contributions

Conceptualization, SJL; Data curation, JK; Formal analysis, JK, SJL; Investigation, JK, methodology: JK, JHS, SJL; Visualization, JK; Writing of the original draft, JK; Writing of the review and editing, SJL, JHS.

Data Availability Statement

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

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Feasibility study of dose de-escalation in postoperative intensity-modulated radiation therapy for locally advanced thymoma

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Purpose: This study aimed to investigate retrospectively the feasibility of reducing the standard postoperative radiation therapy (PORT) dose of 45–50 Gy for locally invasive thymoma to shorten treatment duration and minimize side effects, while preserving disease-specific survival (DSS) and progression-free survival (PFS).

Materials and Methods: Between January 2016 and June 2022, 150 locally advanced thymoma patients underwent surgery followed by intensity-modulated radiation therapy, with a median follow-up of 40.8 months; the standard regimen was 45–50 Gy in 25 fractions (median biological effective dose [BED] 60 Gy), compared to a de-escalation regimen of 30–35 Gy in 10 fractions (median BED 47.25 Gy), with PFS as the primary endpoint, and overall survival (OS), DSS, and toxicity as secondary endpoints.

Results: No significant differences were found between standard and de-escalation groups in 3-year PFS ($p = 0.406$), with both groups achieving 100% 3-year DSS; two deaths in the de-escalation group were due to double primary cancers. All locoregional recurrences occurred outside the radiation field. Factors including age, initial tumor size, myasthenia gravis, and pathological type showed no correlation with PFS or OS. No grade II toxicities occurred in the de-escalation group, whereas the standard group had three cases of grade II toxicity, specifically radiation pneumonitis.

Conclusion: Radiation dose de-escalation in locally advanced thymoma patients undergoing PORT showed comparable survival outcomes with reduced toxicity and shorter treatment duration, but requires longer follow-up to confirm efficacy and safety.

Keywords: Thymoma, Adjuvant radiotherapy, Radiation dose hypofractionation, Dose-response relationship

Introduction

Thymomas are rare tumors which originated from thymic epithelial cells (TEC). While thymoma is one of the most common tumors of the anterior mediastinum neoplasm, the etiology of thymoma has not been confirmed yet [1]. The most widely used prognostic factors for thymoma are Masaoka stage and histologic types. Given the limited predictive value of the TNM stating system for individuals with thymoma, the classification relies on the Masaoka stage, which assessed the extent of tumor invasion into adjacent fatty tissue or organs. Histological subtypes of thymoma are categorized based on their morphological appearance and the ratio of lymphocytes to TEC [2,3]. Histological types A, AB, and B1 are considered to carry a lower risk, whereas types B2 and B3 are associated with

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a higher risk. Consequently, the approach to treating thymoma varies according to these Masaoka stages and histological classifications. Complete surgical removal stands as the foremost treatment approach for thymoma, with the extent of resection being a critical prognostic indicator for both progression-free survival (PFS) and disease-specific survival (DSS) [4-6]. Given the high sensitivity of thymoma to radiation, radiation therapy (RT) is utilized in several therapeutic contexts, including as postoperative treatment [7], as a definitive solution for thymomas that cannot be surgically removed, and as preoperative (neoadjuvant) therapy. RT aimed at palliation is also a viable option for thymomas deemed inoperable.

However, RT can cause several side effects. Mou et al. [8] have shown that although postoperative radiation therapy (PORT) following surgery enhanced both overall survival (OS) and cancer-specific survival than surgery alone group, PORT can also increase the risk of developing secondary cancers. Additionally, Adams et al. [9] have documented various side effects following mediastinal RT, including coronary artery disease, pericarditis, lung fibrosis, and valvular disease. These side effects were even progressed after finishing RT and the severity were dependent on radiation doses [9,10]. Ratosa et al. [11] have revealed a direct correlation between the average dose of radiation absorbed by the heart (heart-D_{mean}) and the occurrence of coronary heart disease, and the incidence of death due to radiation-related cardiac disease was especially high when heart-D_{mean} exceeds 5 Gy. Okubo et al. [12] reported a case of mycotic pseudoaneurysm of the brachiocephalic artery developed long after the administration of 50 Gy to the mediastinal region, which was administered after surgical removal of an invasive thymoma.

The increase in various side effects from mediastinal irradiation, which correlate with the radiation dose, suggests that dose de-escalation could be feasible way to reduce complications while shortening treatment duration, provided that it does not diminish the efficacy of the therapy. This research explored the possibility of lowering radiation doses and shortening the number of radiation fractions to lessen side effects, all while preserving rates of PFS, OS, and DSS.

Materials and Methods

1. Patients and treatment

In this retrospective study, we examined the data of patients from the Yonsei Cancer Center diagnosed with locally advanced thymoma who underwent RT following surgery from January 2016 to June 2022. A total of 152 patients were initially considered, all of whom received intensity-modulated radiation therapy. In all patients, the thymomas were completely resected (R0). The conventional RT regimen delivered 45–50 Gy across 25 fractions (with a median biological effective dose [BED] of 60 Gy), whereas the dose de-escalation RT cohort received 30–35 Gy over 10 fractions (with a median BED of 47.25 Gy). Two patients who underwent chemotherapy were excluded, leaving 150 patients for analysis. We collected clinical information at initial diagnosis and at the time of recurrence, including variables such as age, gender, Masaoka stage, histologic type, size of the initial tumor, presence of a secondary primary cancer, and existence of myasthenia gravis from the electronic medical records. Additionally, data on the location of thymoma recurrence, the interval to recurrence, survival time, cause of death, and types of salvage treatments for recurrence were also gathered. To compare the biological effective RT doses between the two groups, we calculated the BED using on alpha/beta ratio of 10.

Treatment results were assessed through chest computed tomography scans 1 month after the completion of PORT, followed by routine scans every 6–12 months throughout the follow-up period. Infield recurrence was classified as a recurrence within the planning target volume (PTV), outfield recurrence as an intrathoracic recurrence outside the PTV receiving 95% to 100% of the prescribed dose, and distant metastasis as recurrences occurring outside the thoracic region. The grading of adverse events (AEs) after RT was done according to the Common Terminology Criteria for Adverse Events version 4.0.

2. Statistical analysis

Statistical analyses were performed using SPSS software version 29.0 (IBM Corp., Armonk, NY, USA). The time from completion of RT to the first observed progression of thymoma defined PFS. OS was the time from the end of RT until the death of the patients, whole DSS measured the time from the conclusion of PORT to death specifically due to thymoma. The Kaplan-Meier method was employed to compute PFS, OS, and DSS, with the log-rank test assessing any significant differences between the two groups. Univariate Cox regression analysis was performed to identify significant prognostic factors, with p-values less than 0.05 considered statistically significant. In cases where no deaths occurred within certain patient groups, the Cox model yielded excessively wide confidence intervals. To mitigate this issue, Firth's bias correction method was applied.

Results

1. Patient characteristics

This study identified 152 patients with locally invasive thymoma from January 2016 to June 2022. Two patients who underwent chemotherapy both before and after surgery were omitted from

the study. Consequently, 150 patients were included in the analysis. These patients were divided into two groups based on the radiation dose they received: the standard dose group, which received 45–50 Gy over 25 fractions in 5 weeks, and the de-escalation group, which received 30–35 Gy over 10 fractions in 2 weeks (Fig. 1).

Table 1 outlines the overall demographics of the entire study cohort. Within this cohort, the de-escalation group comprised 28 male patients (62.2%), while the standard group included 53 male patients (50.5%), showing no significant gender distribution difference between the two groups (p = 0.126). Every patient underwent PORT. Among entire population, 50 patients were diagnosed at Masaoka stage IIA (33.3%), 90 at IIB (62.7%), and six at stage III (4.0%), with no notable variance in distribution between the de-escalation and standard groups (p = 0.509). The World Health Organization histologic types of AB and B2 were predominant, and this trend consistent across both treatment groups, with no significant disparity observed between them (p = 0.741). In the study,

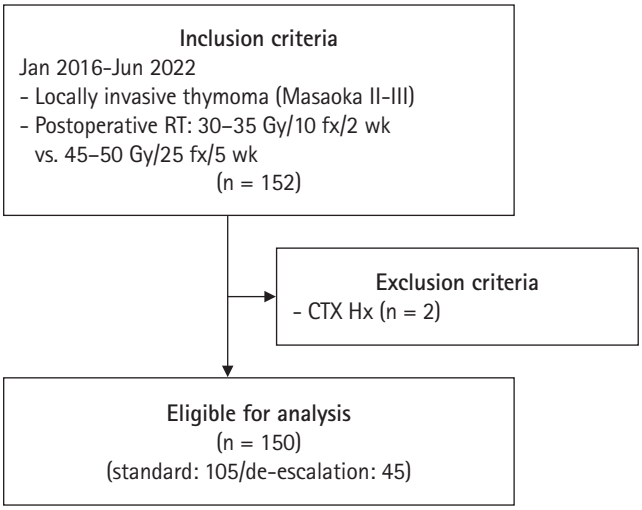

Fig. 1. Flowchart for the selection scheme of the study population. RT, radiation therapy; fx, fraction; wk, week; CTx Hx, chemotherapy history.

Table 1. Baseline characteristics of patients with locally invasive thymoma

	Total (n = 150)	De-escalation (n = 45)	Standard dose (n = 105)	p-value
Sex				0.213
Male	81 (54.0)	28 (62.2)	53 (50.5)	
Female	69 (46.0)	17 (37.8)	52 (49.5)	
Age (year)				0.936
20–29	4 (2.7)	1 (2.2)	3 (2.9)	
30–39	18 (12.0)	5 (11.1)	13 (12.4)	
40–49	27 (18.0)	9 (20.0)	18 (17.1)	
50–59	46 (30.6)	16 (35.6)	30 (28.6)	
60–69	36 (24.0)	9 (20.0)	27 (25.7)	
Over 70	19 (12.7)	5 (11.1)	14 (13.3)	
Masaoka stage				0.526
IIA	50 (33.3)	13 (28.9)	37 (35.2)	
IIB	94 (62.7)	31 (68.9)	63 (60.0)	
IIIA	6 (4.0)	1 (2.2)	5 (4.8)	
Histology type				0.744
A	10 (6.7)	3 (6.7)	7 (6.7)	
AB	54 (36.0)	15 (33.3)	39 (37.1)	
B1	17 (11.3)	7 (15.6)	10 (9.5)	
B2	50 (33.3)	16 (35.5)	34 (32.4)	
B3	19 (12.7)	4 (8.9)	15 (14.3)	
Tumor size (cm)				0.489
0–4.9	88 (58.7)	26 (57.8)	62 (59.0)	
5–9.9	59 (39.3)	19 (42.2)	40 (38.1)	
≥ 10	3 (2.0)	0 (0)	3 (2.9)	
Double primary				> 0.999
Yes	19 (12.7)	6 (13.3)	13 (12.4)	
No	131 (87.3)	39 (86.7)	92 (87.6)	

Values are presented as number (%).

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most tumors ranged in size from 0 to 4.9 cm, with merely three individuals throughout the entire group showing tumors greater than 10cm. The distribution was uniform across both treatment groups (p = 0.319). Furthermore, 12 patients were diagnosed with a secondary primary caner, each of which was completely treated with no signs of the disease left. The comparison showed no significant variance in the incidence of secondary primary cancers between the groups receiving dose de-escalation and those on the standard dose (p = 0.593).

2. OS and PFS

Median follow-up period was 40.8 months in this study. The 3-year OS rates were significantly different between de-escalation group and standard dose group (89.7% vs. 100%, p = 0.004) (Supplementary Fig. S1). Although two patients died in de-escalation group, they were dead because of secondary cancers; One patient succumbed to lung cancer, the other to stomach cancer, both of which were pathologically confirmed as secondary primary cancer following their initial diagnosis of locally invasive thymoma and subsequent surgery and RT. The 3-year DSS was identical in both groups (100% vs. 100%), indicating no significant difference in survival related to the disease itself. The 3-year PFS rates were similarly indistinguishable between the two groups (p = 0.406) (Fig. 2). Regarding recurrence patterns, all recurrences were observed in the standard dose group, with no instances of infield recurrence reported in this study (Supplementary Fig. S2).

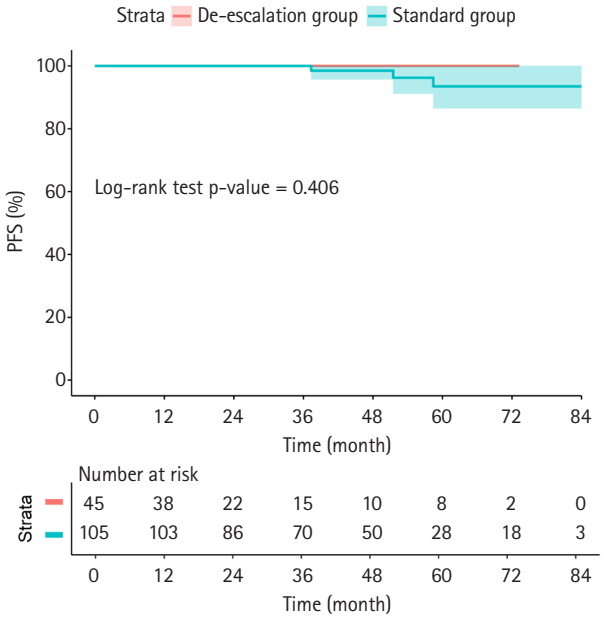

Fig. 2. Kaplan-Meier curves of progression-free survival (PFS) in de-escalation group versus standard dose group. Three-year PFS was 100% and 100% respectively (p = 0.406).

Three patients experienced distant metastases, all of whom underwent additional salvage pleurectomy to manage disease progression, including one patient undergoing third pleurectomy, another second, and a third also undergoing third pleurectomy. Following the repeated pleurectomies, these patients were still alive at the study's follow-up endpoint. There were no instances of salvage RT being used to manage disease progression or recurrence. Moreover, no instances of outfield recurrences were recorded in any patient throughout the study up to the final follow-up point.

Univariate analysis revealed that factors such as age, sex, the occurrence of a second primary cancer, the size of the tumor, the presence of myasthenia gravis, and the Masaoka stage did not significantly impact OS and PFS. Given the lack of significant predictors for OS and PFS identified in this study, a multivariate analysis was not conducted (Table 2).

3. Toxicity

Among total 45 patients in de-escalation group, just one manifested a grade 1 toxicity, presenting as slight chest pain, with none experiencing AEs beyond grade 2. Those in the standard dose population encountered higher level of toxicities. Within the 105 patients in this group, three suffered from grade 1 toxicities (one instance of chest pain and two of dyspnea on exertion), and another three displayed grade 2 (comprising one case of tachycardia and two of radiation-induced pneumonitis). The study did not report any toxicities exceeding grade 3. Despite these findings, the difference in the frequency of AEs across the two cohorts was not statistically significant. When analyzing the severity of all toxicities, the p-value for the comparison between the groups stood at 0.676, and was specifically 0.517 for grade 2 toxicities, as outlined in Supplementary Table S1.

Discussion and Conclusion

Previous research has shown that patients with locally advanced thymoma benefit from PORT [13-15]. The recommended adjuvant RT dose ranges from 45 to 50 Gy (1.8–2.0 Gy per daily fraction) for clear or close surgical margins, is largely based on retrospective analyses and empirical observations rather than phase I/II dose-finding studies [15-17] Our institutional experience with this 45–50 Gy regimen has historically shown low recurrence rates. However, considering the continuous debate regarding the clinical utility of PORT, particularly for Masaoka stage II thymoma, and the well-documented risk of dose-dependent AEs such as coronary artery disease, pericarditis, lung fibrosis, and valvular disease [8-12], the rationale for the de-escalated dose regimen was explored. This

Table 2. Prognostic factors for overall survival and progression-free survival (univariate analysis)

Variable	Overall survival		Progression-free survival	
	p-value	3-Year (%)	p-value	3-Year (%)
Sex				
Male (reference)	-	96.0	-	100
Female	0.257[a]	100	0.096[a]	100
Age (year)				
≥ 60 (reference)	-	97.1	-	100
< 60	0.763	98.5	0.343[a]	100
Double primary cancer				
No (reference)	-	100	-	100
Yes	0.006[a]	85.1	0.350	100
Tumor size (cm)				
< 5 (reference)	-	98.4	-	100
≥ 5	0.873	97.5	0.118	100
Myasthenia gravis				
No (reference)	-	98.4	-	100
Yes	0.508	96.8	0.762	100
Masaoka stage				
IIA (reference)	-	97.5	-	100
IIB	0.704[a]	98.0	0.718	100
IIIA	N/E	100	0.186	100

N/E, not evaluable.
[a]Firth's bias correction.

approach aimed to mitigate potential long-term toxicities and shorten treatment duration without compromising efficacy, referencing the outcomes of studies where PORT might be omitted entirely. The de-escalation protocol was implemented based on the treating physician's clinical judgment, balancing the known benefits of PORT with the potential to reduce treatment burden and side effects in a disease with often indolent behavior.

In this study, we compared OS, DSS, and PFS between two groups: a de-escalation group, which received 30–35 Gy over 10 fractions in 2 weeks, and a standard treatment group, which received 45–50 Gy over 25 fractions in 5 weeks. With a median follow-up of 40.8 months, there were no significant differences in PFS and DSS between the groups. Although there was a notable difference in OS, this was attributed to the occurrence of second primary cancers.

Upon examining potential prognostic variables, we found that none of the factors considered—age, sex, presence of myasthenia gravis and double primary cancer, tumor size, and Masaoka stage—had an impact on OS and PFS. Regarding local control, there were no infield recurrences in either group, defined as a relapse within the PTV volume. This indicates that the de-escalation group did not compromise progression rates compared to the standard group. Therefore, the dose de-escalation strategy is a viable method that does not impair survival or progression rates. However, while tumor size was not a significant factor in PFS, three patients in the standard group with tumors measuring 5 to 10 cm in diameter experienced distant metastases. This discrepancy might be due to the small sample size, suggesting that with a larger population, tumor size could become a more meaningful factor in predicting prognosis.

The study observed no toxicity greater than grade 3, and particularly in the de-escalation group, only grade 1 toxicity was noted. Since the de-escalation group experienced no more than grade 2 toxicity, dose de-escalation might be safer than the standard radiation dose.

It is crucial to address the ongoing debate regarding the necessity of PORT for Masaoka stage II thymoma, which is classified as a T1 tumor in the TNM staging system. While some studies suggest that PORT may be omitted in this stage, our findings, coupled with evidence from the International Thymic Malignancies Interest Group retrospective database by Rimner et al. [15], indicate that PORT is associated with a significant OS benefit even in completely resected stage II thymoma. Given that the majority (96%) of our cohort comprised patients with stage II disease, reducing the PORT dose, even if PORT might be omitted in some cases, could still be beneficial by mitigating toxicity while potentially retaining the survival advantages observed. Although the number of stage III pa-

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tients in our cohort was small, dose de-escalation did not appear to compromise recurrence or survival outcomes. A future study with a larger patient population will be necessary to draw more definitive conclusions, and we acknowledge that this is a limitation inherent to the retrospective design of our analysis.

After all, we would conclude that de-escalated dose hypofractionated PORT shows the same treatment effect as standard dose treatment, while reducing radiation toxicity and shortening the treatment period for patients with locally advanced thymoma.

However, there are several limitations in this study. First, the population size might be insufficient. As mentioned earlier, distant metastasis only occurred when the tumor size exceeded 5 cm. Therefore, if the sample size were larger, the results of the univariate analysis might differ, as other studies have shown that the Masaoka stage is a predictive factor for OS and PFS in thymoma patients [13,14]. Second, the follow-up duration should have been longer than in this research. We could only obtain 3-year OS, DSS, and PFS, as the median follow-up period was 40.8 months, showing no difference in DSS and PFS. With a longer duration, we might have been able to obtain 5-year and 10-year OS, DSS, and PFS, potentially altering the study results. Lastly, to thoroughly assess the feasibility of dose de-escalation in patients with thymic tumors, further studies are needed to include a broader range of thymic cancer patients. Since we only investigated the practicability of dose de-escalation in locally advanced thymoma patients, we could not determine whether this strategy applies to all patients with malignant thymic tumors. Therefore, further studies with larger populations, longer follow-ups, and including all Masaoka stages are needed to verify the feasibility of dose de-escalation in thymic tumor patients. Specifically, the results of this retrospective study highlight the critical need for future prospective randomized controlled trials to definitively establish the optimal and appropriate radiation dose for PORT in thymoma, moving beyond empirical selections.

Statement of Ethics

The protocol of this study was approved by the Yonsei University College of Medicine, Severance Hospital, Institutional Review Board (4-2024-0278). Written informed consent was not required, which is decided by the Yonsei University College of Medicine, Severance Hospital, Institutional Review Board committee.

Conflict of Interest

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

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None.

Author Contributions

Conceptualization, YJH, CGL; Data curation, YJH, HC, JL, SHM; Investigation, YJH, HC, JL, SHM; Statistical analysis, YJH; Validation, EHK; Project administration, CGL; Supervision, CGL; Writing of the original draft, YJH; Writing of the review and editing, EHK.

Data Availability Statement

The data supporting this study's findings are not publicly available as they contain information that could potentially compromise participant privacy but are available from the corresponding author.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2025.00255.

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Radiotherapy omission in low-risk, early-stage breast cancer: a single-center, real-world comparative analysis

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Purpose: This study aimed to compare treatment outcomes between patients who received adjuvant radiotherapy (RT) and those who did not, in a cohort of patients with low-risk, early-stage breast cancer.

Materials and Methods: Postmenopausal women with pT1N0/Nx, grade 1–2, hormone receptor-positive, human epidermal growth factor 2–negative, and Ki-67 ≤ 20% breast cancer who underwent breast-conserving surgery and adjuvant endocrine therapy between 2010 and 2020 were included. The decision on RT omission was based on physician assessment and patient preference. The primary outcome was cumulative incidence of disease recurrence. Secondary outcomes included locoregional recurrence, overall survival, and breast cancer-specific survival.

Results: Of the 742 patients, 707 received adjuvant RT (postoperative radiation therapy [PORT] group) and 35 did not (RT omission group). Baseline characteristics were generally similar; however, the RT omission group was older (median age, 76 years; range, 68 to 85 years) than the PORT group (median age, 62 years; range, 55 to 87 years). After a median follow-up of 60 months in the PORT group and 52 months in the RT omission group, the 5-year cumulative incidence of disease recurrence was 1.28% and 0%, respectively (Gray's test, p = 0.305). Locoregional recurrence occurred in seven patients (1.0%) in the PORT group, whereas no locoregional recurrences were observed in the RT omission group. The results remained consistent after propensity score matching.

Conclusion: Low-risk, early-stage breast cancer patients exhibited comparable disease recurrence and survival rates regardless of the RT status. Our study underscores the necessity for further investigation into RT omission in carefully selected patients.

Keywords: Breast neoplasm, Low-risk, Early-stage, Adjuvant radiation therapy, Omission

Introduction

Breast cancer is the most prevalent malignancy among Korean women. Its incidence has been steadily rising since 2000, and in 2021, the number of newly diagnosed cases exceeded 30,000. Notably, 44.4% of patients presented with stage I disease at diagnosis, and hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative tumors constituted 69.1% of the newly diagnosed cases [1].

Following the National Surgical Adjuvant Breast and Bowel Project B-06 trial, radiotherapy (RT) after breast-conserving surgery (BCS) has been established as a standard treatment for early breast cancer, significantly improving local control and survival rates [2]. However, subsequent evidence suggested that certain subgroups may derive limited benefit from RT [3-8]. Given the proven efficacy of adjuvant endocrine therapy in reducing recurrence risk [3,9] along with concerns regarding the side effects of irradiation, studies have explored the feasibility of RT omission, and two large ran-

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domized trials have validated RT omission in carefully selected breast cancer patients [10-13]. Consequently, several guidelines [14-16] acknowledge the possibility of omitting RT in specific cases: (1) women aged ≥ 70 years with clinical node-negative, T1, HR-positive/HER2-negative tumors; and (2) women aged ≥ 65 years with pathological node-negative, T ≤ 3 cm, HR-positive/HER2-negative tumors treated with BCS and a minimum of 5 years of adjuvant endocrine therapy. Despite these recommendations, real-world data supporting this approach in Korean patients remain limited.

Therefore, we conducted a retrospective analysis to compare treatment outcomes for low-risk, early-stage breast cancer between patients who received postoperative RT and those who did not at a single institution in Korea.

Materials and Methods

1. Study design

We retrospectively reviewed the medical records of patients with low-risk, early-stage breast cancer who underwent BCS at Asan Medical Center between 2010 and 2020. This study was approved by the Institutional Review Board of Asan Medical Center (approval no. 2024-0974) and informed consent was waived due to the retrospective nature of the study.

2. Patients

Low-risk, early-stage breast cancer was defined as occurring in postmenopausal women with a pathologic subtype of ductal, mucinous, or tubular carcinoma; cT1N0M0 and pT1N0/NxM0 according to the tumor-node-metastasis classification system [17]; histological and nuclear grades of 1–2; no lymphovascular invasion; HR-positive/HER2-negative; a Ki-67 proliferation index of ≤20%; and who were receiving adjuvant endocrine treatment. Patients were excluded if they had received neoadjuvant or adjuvant chemotherapy.

3. Treatment methods

BCS was conducted in accordance with institutional protocols with the extent of axillary surgery tailored to the characteristics of the tumor. Preoperative magnetic resonance imaging (MRI) of the breast was performed to facilitate precise treatment planning. Surgical margins were recorded, with the resection margin defined as the shortest among the six measured directions (four lateral, superficial, and deep) and a positive margin defined as "ink on tumor." The decision to omit RT was based on the physician's assessment of the patient's age, performance status, and existing comorbidities, as well as patient preference. For those who received postoperative RT, treatment commenced 4 to 8 weeks following BCS. All patients underwent computed tomography (CT) simulation and three-dimensional treatment planning, and the RT field and method were individualized at the physician's discretion, taking into account the surgical record, prior history of chest irradiation, and patient-specific comorbidities. Target volumes were delineated in accordance with guidelines set forth by the Radiation Therapy Oncology Group [18] and European Society for Radiotherapy and Oncology [19]. The tumor bed volume was localized using preoperative imaging studies, surgical clips, and postoperative pathology reports. Irradiation of the whole breast was performed using a pair of oppositional tangential fields and field-in-field techniques or through intensity-modulated RT. Dose constraints for normal organs adhered to the recommendations of Quantitative Analyses of Normal Tissue Effects in the Clinic [20]. Adjuvant endocrine therapy included both tamoxifen and aromatase inhibitors, and was prescribed at the physician's discretion.

4. Evaluation, outcomes, and statistical analysis

All patients underwent regular follow-up every 6 months for 2 years and annually thereafter. Mammography was performed annually and breast ultrasound and/or MRI were permitted when further examination was deemed necessary. When metastasis was suspected, additional imaging studies such as chest and/or abdominal CT scans, bone scans, or positron emission tomography–CT were permitted.

The primary outcome was cumulative incidence of disease recurrence. Secondary outcomes included locoregional recurrence, overall survival (OS), and breast cancer-specific survival (BCSS). Local recurrence was defined as recurrence in the ipsilateral breast; regional recurrence as any recurrence in the ipsilateral axilla, internal mammary, infraclavicular, or supraclavicular nodes; and locoregional recurrence as either local or regional recurrence. Disease recurrence was defined as either locoregional recurrence or distant metastasis. Cumulative incidence analyses used the date of BCS as the time origin. OS and BCSS were defined as the time from BCS to death from any cause and breast cancer-specific death, respectively. Patients who did not experience an event were censored at their last known follow-up.

Cumulative incidence functions for disease recurrence were estimated accounting for death as a competing risk and compared between groups using Gray's test. To identify variables associated with disease recurrence, univariate Fine-Gray subdistribution hazard models were used. For categorical variables with no events observed in one or more groups, Gray's test was employed as a non-parametric alternative. Survival outcomes were analyzed using the Kaplan-Meier method and compared with the log-rank test.

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Propensity score matching was conducted using a 1:3 nearest-neighbor approach with a caliper width set at 0.5 standard deviations of the logit. Matching covariates included patient age, histologic subtype, and type of adjuvant endocrine therapy. A two-sided p-value < 0.05 was considered significant. All statistical analyses were conducted using R software, version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria; http://cran.r-project.org and web-r.org).

Results

Between January 2010 and December 2020, a total of 24,582 patients underwent breast cancer surgery at Asan Medical Center. Among them, 13,967 patients who underwent BCS without neoadjuvant chemotherapy were identified. Of these, 7,134 patients were diagnosed with stage I A disease, and 1,144 patients met the study's definition of low-risk, early-stage breast cancer. After excluding patients with missing RT data and those with less than 6 months of follow-up, a final cohort of 742 patients was included in the analysis. Among them, 707 patients received postoperative RT (PORT group), while 35 patients did not receive adjuvant RT (RT omission group) (Fig. 1). The majority of patients (98.4%) had unilateral breast cancer, and most patients (98.2%) underwent sentinel lymph node biopsy without axillary dissection. The median tumor size was 1.1 cm (range, 0.1 to 2.0), with ductal carcinoma being the most common histologic subtype. Baseline characteristics were generally similar between the two groups; however, patients in the RT omission group were older (median, 76 years; range, 68 to 85) than those in the PORT group (median, 62 years; range, 55 to 87). Additionally, ductal carcinoma was less common in the RT omission group (80.0%) than in the PORT group (92.8%) (Table 1).

In the PORT group, the majority of patients (98.6%) received whole breast irradiation (WBI), while 10 patients underwent partial breast irradiation (PBI) to the tumor bed. Three patients (0.5%) received elective nodal irradiation at a dose of 45 Gy in 25 fractions, which encompassed the supraclavicular fossa and axillary apex. For those receiving WBI, a total dose of 41.6–50.4 Gy (median, 50.0 Gy) was administered in 16–28 fractions (median, 25). Tumor bed boost was delivered at a dose of 9–16 Gy (median, 10 Gy) in 3–8 fractions (median, 4) for patients with negative surgical margins, while those with positive surgical margins received a higher dose of either 12.5 Gy in 5 fractions or 15.0 Gy in 6 fractions. Among patients who underwent PBI, 70.0% received a total of 38 Gy in 10 fractions (Table 2). In the RT omission group, most patients did not receive treatment due to advanced age (68.6%) or comorbidities (14.3%), and six patients declined to undergo RT.

Median follow-up was 60.0 months (interquartile range [IQR], 43.0 to 86.0) in the PORT group and 52.0 months (IQR, 28.0 to 64.0) in the RT omission group (p = 0.003). Disease recurrence occurred in 10 patients (1.4%) in the PORT group and one patient (2.9%) in the RT omission group, corresponding to 5-year cumulative incidence rates of 1.28% (95% confidence interval, 0.32% to 2.24%) and 0%, respectively. This difference was not statistically significant (Gray's test, p = 0.305) (Fig. 2A). No variable demonstrated a statistically significant association with the cumulative incidence of disease recurrence in univariate analysis, and multivariate analysis was not performed due to the limited number of recurrence events (Table 3).

Regarding locoregional recurrence, two (0.3%) and five (0.7%) patients in the PORT group experienced local and regional recur-

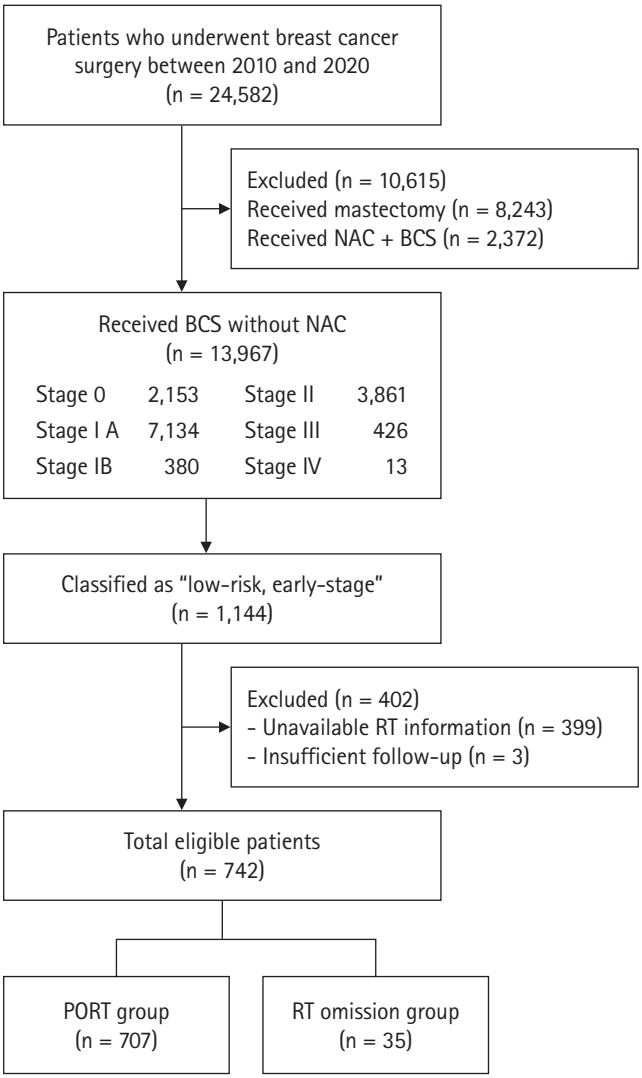

Fig. 1. Flow diagram of the study patients. BCS, breast-conserving surgery; NAC, neoadjuvant chemotherapy; RT, radiotherapy; PORT, postoperative radiation therapy.

Table 1. Characteristics of the PORT and RT omission groups

Variable	Total (n = 742)	PORT (n = 707)	RT omission (n = 35)	p-value
Age (year)	62 (55–87)	62 (55–87)	76 (68–85)	< 0.001
Location				0.850
Left	358 (48.3)	342 (48.4)	16 (45.7)	
Right	372 (50.1)	353 (49.9)	19 (54.3)	
Both	12 (1.6)	12 (1.7)	0 (0)	
Extent of axillary surgery				0.122
None	7 (0.9)	6 (0.8)	1 (2.9)	
SNB	729 (98.2)	696 (98.5)	33 (94.2)	
ALND	2 (0.3)	2 (0.3)	0 (0)	
SNB + ALND	4 (0.6)	3 (0.4)	1 (2.9)	
Tumor size (cm)	1.1 (0.1–2.0)	1.1 (0.1–2.0)	1.1 (0.2–2.0)	0.247
Histologic grade				0.490
1	108 (14.6)	101 (14.3)	7 (20.0)	
2	634 (85.4)	606 (85.7)	28 (80.0)	
Nuclear grade				0.769
1	73 (9.8)	69 (9.8)	4 (11.4)	
2	669 (90.2)	638 (90.2)	31 (88.6)	
Histology				0.008
Ductal carcinoma	684 (92.2)	656 (92.8)	28 (80.0)	
Mucinous carcinoma	34 (4.6)	28 (4.0)	6 (17.1)	
Tubular carcinoma	24 (3.2)	23 (3.2)	1 (2.9)	
EIC				0.340
Negative	516 (71.5)[a]	488 (71.0)[a]	28 (80.0)	
Positive	206 (28.5)	199 (29.0)	7 (20.0)	
Resection margin				0.176
Negative	688 (93.7)	656 (93.8)	32 (91.4)	
Positive	46 (6.3)[b]	43 (6.2)[b]	3 (8.6)	
Adjuvant endocrine therapy				< 0.001
Aromatase inhibitor	583 (78.6)	567 (80.2)	16 (45.7)	
Tamoxifen	159 (21.4)	140 (19.8)	19 (54.3)	

Values are presented as number (%) or median (range).
PORT, postoperative radiation therapy; RT, radiotherapy; SNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; EIC, extensive intraductal component.
[a]Data were not available for 20 patients.
[b]Data were not available for 8 patients.

rences, respectively. No locoregional recurrence was observed in the RT omission group. Among those with local recurrence, one patient underwent salvage mastectomy and remained disease-free, while the other did not receive further treatment due to terminal illness. Among the five patients with regional recurrence, two underwent salvage axillary dissection, one received axillary dissection followed by RT to the supraclavicular and axillary lymph nodes, one received RT alone, and one did not receive further treatment due to pre-existing comorbidities.

For survival outcomes, 18 patients (2.5%) in the PORT group and three patients (8.6%) in the RT omission group died. Breast cancer-specific death occurred in four patients (0.6%) in the PORT group and none in the RT omission group. While the 5-year OS rates differed significantly between the two groups (98.5% vs. 92.7%, p = 0.007), the difference in BCSS was not statistically significant (99.8% vs. 100%, p = 0.737) (Fig. 2B, 2C).

Propensity score matching was conducted to minimize selection bias and potential confounding effects, yielding 70 matched patients in the PORT group and 32 in the RT omission group. After matching, baseline characteristics were generally well balanced – most covariates showed standardized mean differences of ≤ 0.2, and the largest remaining imbalances observed in patient age and histologic subtype were small and clinically negligible (Table 4). Median follow-up remained longer in the PORT group than in the

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Table 2. Treatment profiles of the PORT group

Variable	PORT (n = 707)
RT field	
Whole breast only	1 (0.1)
Whole breast + tumor bed	693 (98.0)
Whole breast + SCL/axilla + tumor bed	3 (0.5)
Partial breast irradiation	10 (1.4)
Dose per fraction, whole breast (Gy)	
1.8	49 (7.0)
2.0	326 (46.8)
2.2	1 (0.1)
2.6	321 (46.1)
Dose per fraction, tumor bed boost (Gy)	
1.8	3 (0.5)
2.0	94 (13.5)
2.5	598 (85.9)
3.5	1 (0.1)
Dose per fraction, partial breast irradiation (Gy)	
2.0	1 (10.0)
3.5	2 (20.0)
3.8	7 (70.0)
RT method	
3D-CRT	698 (98.7)
IMRT	9 (1.3)

Values are presented as number (%).
PORT, postoperative radiation therapy; RT, radiotherapy; SCL, supraclavicular lymph node; 3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy.

RT omission group (63.5 months [IQR, 44.3 to 83.5] vs. 43.0 months [IQR, 27.3 to 68.3]; p = 0.006). Disease recurrence occurred in only one patient in each cohort, at 66 months in the PORT group and 100 months in the RT omission group. No locoregional recurrence was observed in both groups. A competing-risk analysis showed no significant difference in the cumulative incidence of disease recurrence between groups (Gray's test, p = 0.468) (Fig. 3A), and no significant differences were observed in OS or BCSS between the two groups after matching (p = 0.502 and p = 0.617, respectively) (Fig. 3B, 3C).

Discussion and Conclusion

Our study demonstrated two principal findings. First, there was no statistically significant difference in overall disease recurrence between the groups. Second, locoregional recurrence rates were low across both cohorts, with no instances of locoregional recurrence observed among the 35 patients in the RT omission group.

Although the long-term follow-up results of the Cancer and Leukemia Group B 9343 trial demonstrated no survival benefit from

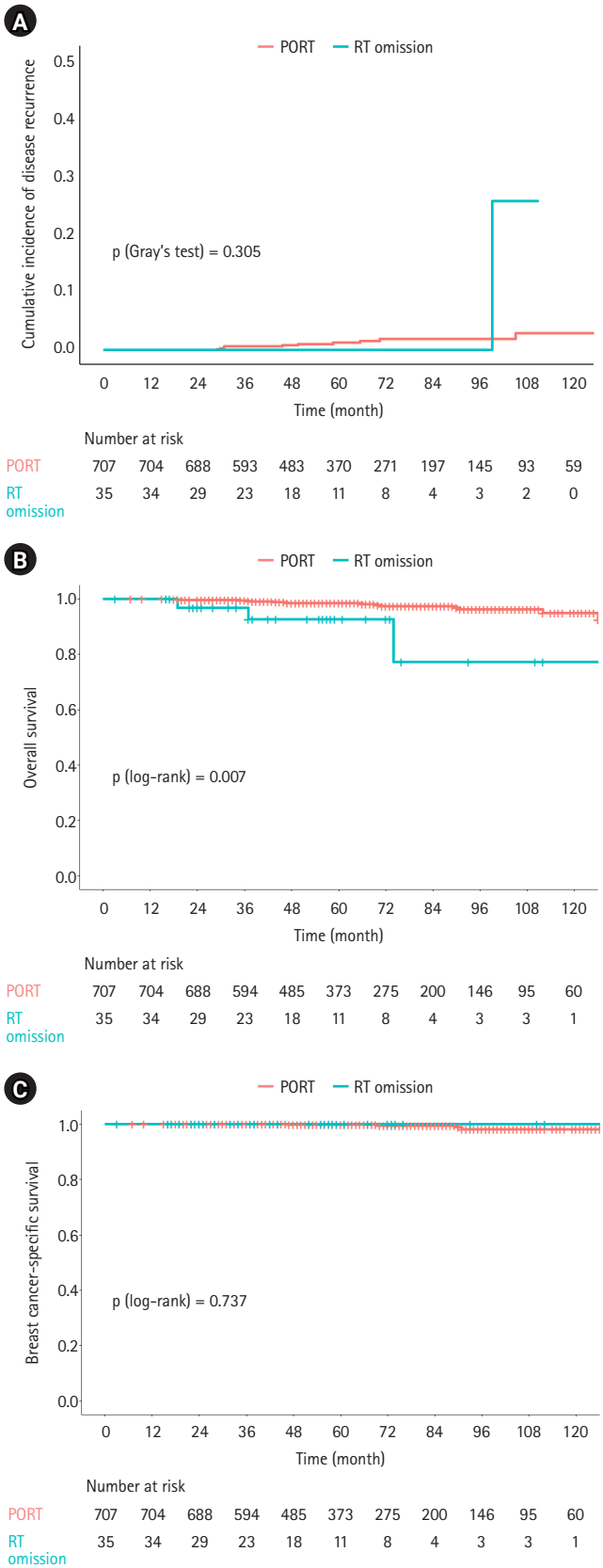

Fig. 2. Outcomes in the unmatched cohort. (A) Cumulative incidence of disease recurrence. (B) Overall survival. (C) Breast cancer-specific survival rates. PORT, postoperative radiation therapy; RT, radiotherapy.

Table 3. Univariate analyses of prognostic factors for cumulative incidence of disease recurrence

Variable	sHR (95% CI)	p-value
RT status		
RT omission (vs. PORT)	2.80 (0.38–20.80)	0.310
Location		
Left (vs. both)	-	0.823[a]
Right (vs. both)	-	0.616[a]
Age	1.05 (0.96–1.15)	0.300
Extent of axillary surgery		
None (vs. SNB)	-	0.780[a]
ALND (vs. SNB)	-	0.981[a]
SNB + ALND (vs. SNB)	-	>0.994[a]
Tumor size (cm)	2.55 (0.86–7.59)	0.092
Histologic grade		
2 (vs. 1)	2.02 (0.25–16.20)	0.510
Nuclear grade		
2 (vs. 1)	-	0.184[a]
Histology		
Mucinous (vs. ductal)	-	0.516[a]
Tubular (vs. ductal)	-	0.426[a]
EIC		
Positive (vs. negative)	0.63 (0.14–2.91)	0.550
Resection margin		
Positive (vs. negative)	-	0.468[a]
Adjuvant endocrine therapy		
Tamoxifen (vs. aromatase inhibitor)	2.24 (0.66–7.61)	0.200

sHR, subdistribution hazard ratio; CI, confidence interval; RT, radiotherapy; PORT, postoperative radiation therapy; SNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; EIC, extensive intraductal component.
[a]Calculated using Gray's test.

adjuvant RT following BCS in women aged 70 years and older with stage I estrogen receptor-positive tumors, there was a significant difference in terms of locoregional recurrence (10-year locoregional recurrence-free survival rate, 98% in the tamoxifen + RT group vs. 90% in the tamoxifen only group) [11]. The following PRIME II trial reported comparable results, with a 10-year local recurrence rate of 0.9% in the RT group vs. 9.5% in the no-RT group [13] (Supplementary Table S1). Consequently, local recurrence remains a major concern for patients undergoing BCS. Although salvage treatments such as repeat lumpectomy or mastectomy are available, the psychological distress associated with recurrence and the necessity for additional interventions should not be underestimated. In this context, the omission of adjuvant RT becomes a challenging clinical decision, particularly when considering the potential tenfold increase in the risk of locoregional recurrence despite no observed difference in survival. This issue is especially pertinent in Korea, where cancer treatment costs are largely covered by the National

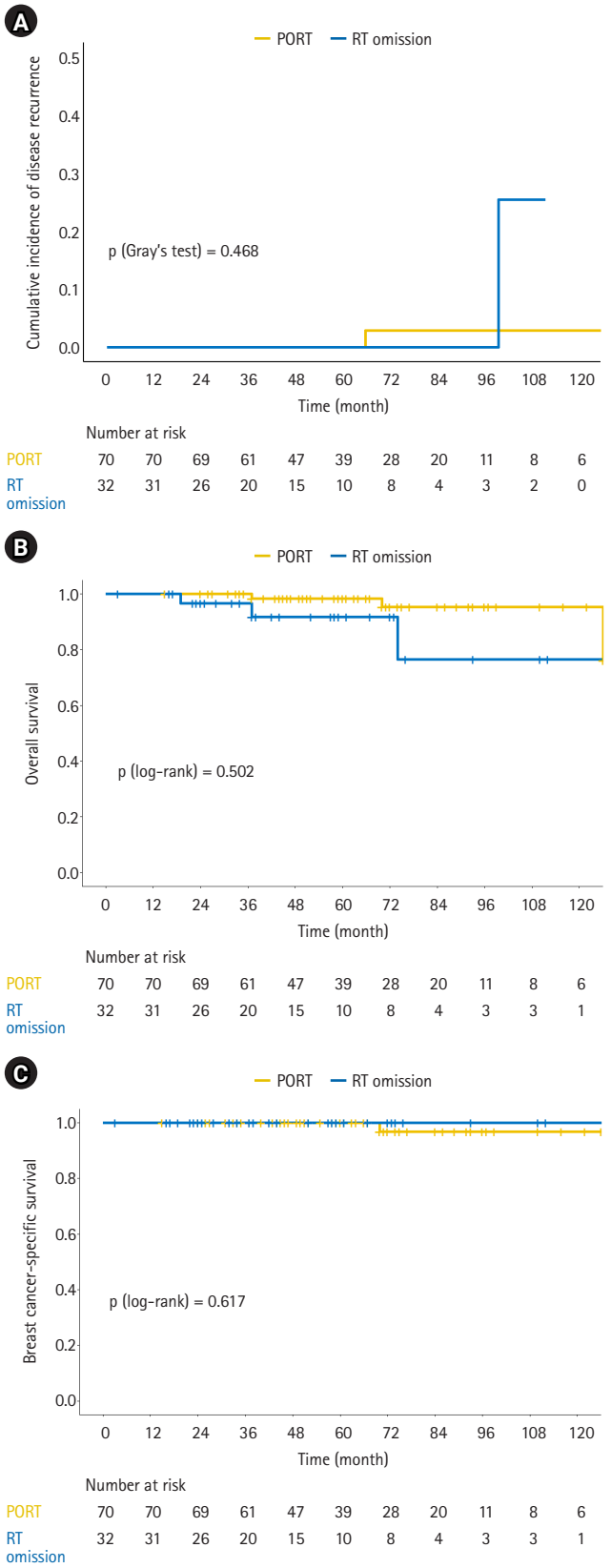

Fig. 3. Outcomes in the propensity score-matched cohort. (A) Cumulative incidence of disease recurrence. (B) Overall survival. (C) Breast cancer-specific survival rates. PORT, postoperative radiation therapy; RT, radiotherapy.

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Health Insurance Service and access to healthcare is exceptionally convenient, thereby minimizing the burden on patients. Our findings, particularly the absence of locoregional recurrence in the RT omission group, suggest that the omission of adjuvant RT in carefully selected patients may not adversely affect oncologic outcomes. This finding may be attributed to several factors. First, the stringent patient selection criteria applied in our study—such as smaller tumor size, favorable histologic subtypes, lower histologic and nuclear grades, and a predefined Ki-67 threshold—may have contributed to the low recurrence rates. In addition, the routine use of preoperative breast MRI may have enabled more accurate staging and facilitated the exclusion of hidden malignancies. Of note, no locoregional recurrences were observed even among patients in the RT omission group with positive margins, and further studies are warranted to clarify the clinical implications of margin status in patients with low-risk, early-stage breast cancer.

Avoiding unnecessary radiation offers multiple advantages, such as reducing healthcare costs and patient inconvenience, while elim-

Table 4. Characteristics of the PORT and RT omission groups before and after propensity score matching

	Before matching			After matching		
	PORT (n = 707)	RT omission (n = 35)	SMD	PORT (n = 70)	RT Omission (n = 32)	SMD
Age (year)	62 (55–87)	76 (68–85)	2.48	74 (68–87)	75 (68–85)	0.30
Location			0.05			0.04
Left	342 (48.4)	16 (45.7)		32 (45.7)	14 (43.8)	
Right	353 (49.9)	19 (54.3)		37 (52.9)	18 (56.2)	
Both	12 (1.7)	0 (0)		1 (1.4)	0 (0)	
Extent of axillary surgery			0.31			0.17
None	6 (0.8)	1 (2.9)		1 (1.4)	1 (3.1)	
SNB	696 (98.5)	33 (94.2)		68 (97.2)	30 (93.8)	
ALND	2 (0.3)	0 (0)		1 (1.4)	0 (0)	
SNB + ALND	3 (0.4)	1 (2.9)		0 (0)	1 (3.1)	
Tumor size (cm)	1.1 (0.1–2.0)	1.1 (0.2–2.0)	0.26	1.1 (0.1–2.0)	1.1 (0.2–2.0)	0.18
Histologic grade			0.16			0.16
1	101 (14.3)	7 (20.0)		11 (15.7)	7 (21.9)	
2	606 (85.7)	28 (80.0)		59 (84.3)	25 (78.1)	
Nuclear grade			0.05			0.01
1	69 (9.8)	4 (11.4)		9 (12.9)	4 (12.5)	
2	638 (90.2)	31 (88.6)		61 (87.1)	28 (87.5)	
Histology			0.48			0.30
Ductal carcinoma	656 (92.8)	28 (80.0)		62 (88.6)	25 (78.1)	
Mucinous carcinoma	28 (4.0)	6 (17.1)		5 (7.1)	6 (18.8)	
Tubular carcinoma	23 (3.2)	1 (2.9)		3 (4.3)	1 (3.1)	
EIC			0.20			0.28
Negative	488 (71.0)[a]	28 (80.0)		45 (65.2)[b]	25 (78.1)	
Positive	199 (29.0)	7 (20.0)		24 (34.8)	7 (21.9)	
Resection margin			0.09			0.13
Negative	656 (93.8)	32 (91.4)		61 (89.7)	30 (93.8)	
Positive	43 (6.2)[c]	3 (8.6)		7 (10.3)[d]	2 (6.2)	
Adjuvant endocrine therapy			0.84			0.24
Aromatase inhibitor	567 (80.2)	16 (45.7)		41 (58.6)	15 (46.9)	
Tamoxifen	140 (19.8)	19 (54.3)		29 (41.4)	17 (53.1)	

Values are presented as number (%) or median (range).
PORT, postoperative radiation therapy; RT, radiation therapy; SMD, standard mean difference; SNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; EIC, extensive intraductal component.
[a]Data were not available for 20 patients.
[b]Data was not available for 1 patient.
[c]Data were not available for 8 patients.
[d]Data were not available for 2 patients.

inating RT-related toxicities that may compromise cosmesis, diminish quality of life, or lead to serious health complications. The primary challenge lies in accurately identifying the very low-risk patients who can safely forgo RT while still achieving excellent outcomes with minimal physical, psychological, and financial burdens. Traditionally, clinicopathologic factors such as patient age, tumor size, and tumor grade have been utilized to predict the risk of local recurrence following BCS. Over the past decade, growing evidence has highlighted the molecular heterogeneity of early-stage breast cancer, emphasizing the need for personalized treatment strategies. Several clinical trials have sought to refine patient selection for RT omission based on molecular markers, even among younger patients. The LUMINA trial, which included patients with a Ki-67 index of ≤13.25%, reported a 5-year local recurrence rate of only 2.3% [21]. Similarly, the IDEA study used the Oncotype DX Breast Recurrence Score to guide decisions regarding RT omission (Supplementary Table S1) [22]. Other trials, such as PRECISION (NCT02653755) and PRIMETIME (ISCTRN41579286), have integrated clinical and biological factors, including the Prosigna PAM50 assay or the IHC4+-Clinical biomarker, to further refine risk stratification. Additionally, two ongoing randomized trials—EXPERT (NCT02889874) and DEBRA (NCT04852887)—are investigating the role of endocrine therapy alone in patients selected through genomic profiling. Collectively, if these studies confirm that biomarkers can reliably predict local recurrence risk, they could significantly advance more personalized approaches to RT omission.

The limitations of our study highlight the need for a larger, nationwide study to validate our results and provide more generalizable evidence. First, its retrospective, single-center design introduces inherent selection biases. Second, the non-randomized treatment allocation resulted in a significant imbalance in patient numbers and baseline characteristics between groups. While this reflects the real-world clinical landscape, where RT omission remains infrequent and, when implemented, is typically reserved for patients older than those outlined in current guidelines [23], we attempted to mitigate these imbalances through propensity score matching. Additionally, the follow-up time differed between the two groups, with the PORT group having a longer follow-up duration both before and after matching. Although time-to-event analyses such as Kaplan-Meier estimation and Fine-Gray competing-risk models were used to adjust for this difference, the shorter follow-up in the RT omission group may still have limited the detection of late recurrences. This temporal imbalance should be taken into account when interpreting our findings. Moreover, the oncologic safety observed after RT omission must be interpreted in light of the universal and sustained use of adjuvant endocrine therapy. In our study, the planned five-year course of tamoxifen or aromatase inhibitor was initiated by all patients and completed by the vast majority, likely underpinning the absence of locoregional recurrence despite RT omission. However, real-world adherence to endocrine therapy is suboptimal, with 5-year persistence rates of only 60%–80% in HR-positive survivors [24]. Because discontinuation has been associated with higher locoregional recurrence, clinicians should adopt a cautious, individualized approach when considering RT omission for patients in whom long-term endocrine therapy is uncertain. Finally, while most patients (98.6%) in the PORT group of our study underwent WBI, PBI has increasingly been adopted in selected early-stage breast cancer patients [25-28]. The ongoing EUROPA trial (NCT04134598) reflects this evolving paradigm by comparing single-modality RT, primarily short-course PBI, with endocrine therapy alone in women aged ≥ 70 years with T1N0, luminal A-like tumors. Interim results suggest better quality of life and fewer adverse events in the RT arm (Supplementary Table S1) [29]. While our study explored the feasibility of RT omission in well-selected low-risk patients receiving standard endocrine therapy, future research should broaden the comparison to include PBI alone, with comprehensive evaluation not only of oncologic outcomes but also of patient convenience and cost-effectiveness. Collectively, these combined efforts may help inform more individualized treatment strategies.

In conclusion, our study suggests that postmenopausal women with T1N0, grade 1–2, HR-positive, HER2-negative tumors with a Ki-67 index of ≤20% who received adjuvant endocrine therapy exhibit comparable disease recurrence and survival rates, regardless of their post-BCS RT status. These findings support the feasibility of RT omission in carefully selected patients receiving endocrine therapy. However, further studies by the Korean Radiation Oncology Group are necessary to confirm these preliminary results and refine the selection criteria for RT omission in low-risk, early-stage breast cancer.

Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board of Asan Medical Center (approval no. 2024-0974). As this study was a retrospective analysis, a waiver of the requirement for informed consent was granted by the Institutional Review Board of Asan Medical Center.

Conflict of Interest

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

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Author Contributions

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Data Availability Statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2025.00269.

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Letter to the Editor

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Optimizing palliative radiotherapy for breast cancer with skin involvement: technical and methodologic considerations

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We read with great interest the recent article by Min et al. [1] addressing the efficacy of palliative radiotherapy (RT) for breast cancer patients with skin involvement. The authors should be commended for presenting valuable real world data on a challenging clinical subset where symptom control remains paramount. However, while the study offers important insights, we would like to raise several methodological concerns and offer constructive suggestions for future research.

The evaluation of the skin dose and associated toxicity is critically dependent on the treatment planning algorithms and delivery devices used [2,3]. Unfortunately, insufficient information is provided about the RT planning systems, dose calculation algorithms (e.g., anisotropic analytical algorithm, Monte Carlo), and linear accelerator models. These factors are known to influence surface dose distribution and may significantly impact local control and skin toxicity outcomes. Although bolus use was reported in 25.6% of patients, details regarding its thickness, frequency, and placement were not provided. In addition, no target delineation criteria were described, which limits reproducibility, particularly for lesions close to the skin [4]. Respiratory motion, especially in free breathing settings, may also affect target coverage and skin dose if not properly managed. Addressing these technical variables would strengthen the interpretability of the findings.

Although the study broadly refers to the treatment as "palliative," the therapeutic intent for individual cases is not clearly specified. Several patients had extended follow up durations and received high biologically effective doses (BEDs; > 100 Gy), which may indicate heterogeneous clinical scenarios, potentially including consolidative or long term disease control strategies. Without a clear delineation of treatment goals, whether symptom relief, local control, or curative intent, the interpretation of survival and tumor control outcomes becomes less straightforward. Distinguishing between strictly palliative, symptom oriented RT and potentially curative or consolidative RT is crucial, especially given the diverse prognoses of patients with skin involvement. Providing more detailed stratification according to treatment intent, Eastern Cooperative Oncology Group performance status, and systemic therapy history would enrich the clinical context.

A pivotal conclusion of the study hinges on the dichotomization of the BED at 75 Gy, which was determined via receiver operating characteristic curve analysis. However, essential statistical details for this cut-off are lacking, such as area under the curve, sensitivity, specificity, and confidence interval information [5]. Without these metrics, the robustness of this threshold remains questionable. We

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recommend presenting these parameters to support the clinical applicability of BED stratification.

In conclusion, this study makes a meaningful contribution to the understanding of the role of RT in skin-involved breast cancer. However, further refinements in methodology, technical reporting, and statistical transparency would strengthen its implications. Future studies could benefit from prospective designs, standardized bolus protocols, and the integration of patient reported outcomes to better capture the real impact of RT in this unique and underserved patient population.

Conflict of Interest

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

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Initiative	Type of study	Source
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