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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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Acute toxicity and quality of life in postoperative prostate cancer patients treated with ultra-hypofractionated pelvic radiation therapy

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Purpose: This study aimed to report acute toxicity and quality of life (QoL) outcomes in postoperative prostate cancer patients treated with stereotactic body radiation therapy (SBRT) to the prostate bed and pelvic lymph nodes.

Materials and Methods: Patients with prostate cancer who underwent radical prostatectomy and were referred for salvage radiotherapy between January and December 2023 were included. Treatment consisted of 25 Gy to the pelvic nodal areas with a simultaneous integrated boost delivering a total of 30 Gy to the prostate bed, all in 5 fractions, delivered with an empty rectum and comfortably full bladder. Acute gastrointestinal (GI) and genitourinary (GU) toxicities were graded according to Common Terminology Criteria for Adverse Events v5.0. QoL was assessed via phone interview using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-PR25) questionnaire.

Results: A total of 166 patients were treated, of whom 61 had at least 6 months of follow-up. Median age was 65 years, and 77.0% received androgen deprivation therapy. Indications for radiotherapy included biochemical persistence (36.1%), biochemical recurrence (27.9%), local recurrence (21.3%), regional recurrence (6.6%), and combined recurrence (8.2%). All plans met organ-at-risk constraints (mean rectal D1cm^3 [dose to the most irradiated 1 cm^3] 3,000.7 cGy; bowel D1cm^3 2,457.8 cGy). Acute toxicity data was available for 47 patients. No grade ≥3 acute GI or GU toxicity was observed. Grade 2 GI and GU toxicities occurred in 25.5% and 2.1% of patients, respectively. Among the 62.3% who completed the QoL survey, mean symptom scores were low (urinary, 19.1; bowel, 4.2), and sexual functioning averaged 44.4.

Conclusion: Postoperative pelvic SBRT demonstrated low acute toxicity and favorable short-term QoL outcomes, supporting its feasibility and safety for further prospective evaluation.

Keywords: Prostatic neoplasms, Radiosurgery, Toxicity, Quality of life

Introduction

Prostate cancer is the second most commonly diagnosed cancer in men worldwide and the fifth leading cause of cancer-related death in men [1]. In Chile, it is the most frequently diagnosed malignancy among men, with an incidence rate of 56.7 per 100,000 and 8,157 new cases reported in 2020 [1]. Radical prostatectomy (RP) is a standard curative treatment for localized prostate cancer, yet a significant number of patients recur after surgery. Approximately 5%–20% of men have biochemical persistence (detectable prostate-specific antigen [PSA] level post-prostatectomy), indicating residual disease [2]. Additionally, about one-third of men will develop a delayed biochemical recurrence (BCR) within 10 years of surgery [3]. These PSA-defined recurrences can signify local residu-

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al disease in the prostate bed and/or occult metastatic spread to regional lymph nodes. Clinical evidence indicates that the prostate bed is a common site of relapse after surgery, and a considerable subset of patients with post-prostatectomy BCR harbor subclinical nodal metastases in the pelvis [4,5]. Such patterns of failure underscore the rationale for postoperative radiotherapy to eradicate residual local-regional disease.

Salvage radiation therapy (SRT) to the prostate bed is a potentially curative intervention for patients with rising PSA after RP, and its use has been shown to improve long-term outcomes. In the absence of adjuvant or salvage radiotherapy, 10-year biochemical failure rates exceed 60% in men with adverse pathological features, whereas the addition of postoperative radiotherapy roughly halves the risk of recurrence [6-8]. Several studies have established that administering SRT early (at low PSA levels) yields superior disease control and lower all-cause mortality compared to delayed intervention, and current guidelines advocate early SRT in men with BCR after RP [9,10]. Moreover, accumulating evidence supports the inclusion of the pelvic lymph nodes within the salvage radiation field. The recent NRG Oncology SPPORT trial demonstrated that, in men with detectable PSA after prostatectomy, adding short-term androgen deprivation therapy (ADT) and whole-pelvic radiotherapy to prostate bed SRT significantly improved progression-free survival compared to prostate bed irradiation alone [11]. Similarly, in the primary definitive setting, the POP-RT Phase III trial showed that prophylactic whole-pelvis irradiation improved biochemical failure-free and disease-free survival in high-risk prostate cancer relative to prostate-only radiation [12]. This data confirms that targeting sites with potential microscopic nodal disease offers clinical benefit and reinforces the rationale for treating the pelvic lymph nodes in the post-prostatectomy setting when there are risk factors for regional relapse.

Moderately hypofractionated radiation therapy to the prostate bed [13] and pelvic lymph nodes [12,14-17] has emerged as a safe, effective, and convenient alternative to conventional fractionation. Multiple studies [12,14-17] suggest that hypofractionated whole-pelvic radiation therapy (WPRT) can provide favorable disease control with an acceptable toxicity profile.

Building on the success of moderate hypofractionation, there is growing interest in exploring ultra-hypofractionated schedules in the postoperative setting. Ultra-hypofractionation, in the form of stereotactic body radiotherapy (SBRT), delivers a highly conformal radiation dose in five fractions. This extreme hypofractionation offers multiple potential advantages. First, by delivering a high biologically effective dose in a shortened overall treatment time, SBRT can improve patient convenience and resource utilization without compromising efficacy [18]. Second, from a radiobiological perspective, prostate cancer is characterized by a low alpha/beta ratio (~1.5 Gy), indicating greater sensitivity to larger doses per fraction [18]. In the definitive (intact prostate) setting, SBRT has already been validated in clinical trials as a safe and effective treatment, with outcomes comparable to longer courses of radiation [19]. Recent data also support the feasibility of SBRT for WPRT, with excellent regional control and a safe toxicity profile [20,21].

The purpose of this study is to evaluate acute toxicity and quality of life (QoL) outcomes in post-prostatectomy patients treated with ultra-hypofractionated radiation to the prostate bed and pelvic lymph nodes. Reporting the safety profile and patient-reported QoL with stereotactic pelvic radiation contributes to the evidence base supporting this salvage treatment approach and informs future comparative trials.

Materials and Methods

1. Patient selection

A retrospective review was conducted of medical records from patients with histologically confirmed prostate cancer who had previously undergone RP and were referred for salvage radiotherapy between January and December 2023. Eligibility criteria included biochemical persistence, biochemical recurrence, or locoregional recurrence without evidence of distant metastatic disease (M0). All patients underwent restaging with prostate-specific membrane antigen positron emission tomography (PSMA PET) prior to treatment. For the purposes of acute toxicity and quality-of-life analysis, only patients with a minimum follow-up of 6 months were included. No patients had a history of prior pelvic radiation or failed to complete treatment; therefore, no additional exclusion criteria were applied.

2. Treatment planning and delivery

All patients were treated with ultra-hypofractionated radiotherapy to the prostate bed and pelvic lymph nodes using volumetric modulated arc therapy delivered on a Halcyon linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). Simulation was performed using planning computed tomography (CT) on a flat tabletop with an integrated indexing system to ensure reproducible patient positioning throughout treatment. Patients were simulated with a comfortably full bladder and an empty rectum, with rectal preparation using enemas or laxatives as needed according to institutional protocol. The use of intravenous contrast during simulation was determined at the discretion of the treating radiation oncologist.

Target delineation was performed according to institutional protocol, in line with Radiation Therapy Oncology Group consensus guidelines. The clinical target volume (CTV) included the prostate

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bed and pelvic lymph nodes. Common iliac, internal iliac, external iliac, presacral and obturator nodes were included, typically using the lower border of the L5 vertebra to limit the superior extent of the nodal CTV. A 5 mm isotropic margin was added to generate the planning target volume (PTV). Daily image guidance was performed using cone-beam CT (CBCT) with soft-tissue matching to the prostate bed and pelvic anatomy to ensure accurate positioning and reproducibility across fractions. Patients received 25 Gy in 5 fractions to the pelvic nodal PTV, with a simultaneous integrated boost (SIB) delivering a total of 30 Gy to the prostate bed PTV. Pelvic lymph node irradiation was delivered electively. In patients with regional nodal disease identified on PSMA PET imaging, involved lymph nodes were contoured separately and treated with a SIB to 30 Gy. Organ-at-risk (OAR) constraints were standardized according to institutional protocol for five-fraction SBRT regimens.

Dosimetric data were retrospectively collected from clinical treatment records. The following dose–volume parameters were recorded: rectum (D1cm^3 [dose to the most irradiated 1 cm^3], V2900 cGy, [volume receiving at least 2,900 cGy], and V1810 cGy [volume receiving at least 1,810 cGy]), small bowel and sigmoid colon (D1cm^3, D20cm^3 [dose to the most irradiated 20 cm^3]), bladder (V1810 cGy, and V3200 cGy [volume receiving at least 3,200 cGy]), and penile bulb (Dmean [mean dose]). Compliance with institutional dose constraints, based on five-fraction SBRT protocols, was assessed for each patient. Institutional OAR dose constraints are provided in Table 1.

Exploratory analyses were performed to evaluate associations between selected dosimetric parameters and acute toxicity as well as patient-reported quality-of-life outcomes using Kendall's τ-b or Spearman's rank correlation coefficients, as appropriate.

Table 1. Organ-at-risk dosimetric parameters

Dosimetric parameter	Dose constraint	Mean (cGy/%)
Rectum		
D1cm^3	< 3,600 cGy	3,000.68 cGy
V2900 cGy	< 20%	6.30%
V1810 cGy	< 50%	32.57%
Small bowel		
D1cm^3	< 3,000 cGy	2,457.76 cGy
D20cm^3	< 2,500 cGy	1,816.50 cGy
Sigmoid colon		
D1cm^3	< 3,000 cGy	2,539.45 cGy
D20cm^3	< 2,500 cGy	2,152 cGy
Bladder		
V3200 cGy	< 10 cm^3	0.0005 cm^3
V1810 cGy	< 40%	36.81%
Penile bulb		
D50%	< 2,950 cGy	987.38 cGy

D1cm^3, dose to the most irradiated 1 cm^3; V2900 cGy, volume receiving at least 2,900 cGy; V1810 cGy, volume receiving at least 1,810 cGy; D20cm^3, dose to the most irradiated 20 cm^3; V3200 cGy, volume receiving at least 3,200 cGy; D50%, dose received by 50% of the volume.

3. Androgen deprivation therapy

ADT was prescribed at the discretion of the referring multidisciplinary oncological committee. Type and duration of ADT were not standardized and varied based on individual patient risk and physician recommendation.

4. Toxicity and QoL assessment

Acute gastrointestinal (GI) and genitourinary (GU) toxicity were assessed retrospectively through clinical record review. Toxicity was classified according to the Common Terminology Criteria for Adverse Events version 5.0. Acute toxicity was defined as symptoms presenting during treatment or within 60 days after completion of radiotherapy.

QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-PR25), which includes four symptom scales and two functional scales. The official Spanish version was used for this cohort. QoL surveys were administered via structured telephone interviews at the time of last follow-up by either of two medical professionals. To minimize inter-observer variability, a standardized script was used during the interviews.

Results

1. Patient characteristics

Between January and December 2023, a total of 166 patients underwent ultra-hypofractionated pelvic radiation therapy at our center. Sixty-one patients had a minimum follow-up of 6 months and were included in the final analysis. Baseline clinical and pathological characteristics are summarized in Table 2.

The median age at treatment was 65 years (range, 46 to 79 years). Most patients had high-risk or very high-risk features, with 78.7% classified as high-risk, 9.8% as unfavorable intermediate-risk, and 11.5% as favorable intermediate-risk. The most common pathological stage was pT3b (39.4%), followed by pT3a (29.5%) and pT2 (31.1%). Positive surgical margins were reported in 31.1% of cases, and 9.8% of patients had node-positive disease (pN1). The median PSA prior to radiation therapy was 0.36 ng/mL (range, 0.01 to 67.0 ng/mL). Indications for SRT included biochemical persistence (36.1%), BCR (27.9%), local recurrence (21.3%), regional recurrence (6.6%), and combined local and regional recurrence (8.1%). Nine patients (14.8%) had PSMA PET–positive regional nodal disease and received a SIB to involved lymph nodes.

Table 2. Patient baseline characteristics

Clinical/pathological characteristics	Value
Age (year)	65 (46–79)
Pre–radical prostatectomy PSA (ng/mL)	7.72 (3.3–64)
TNM: pT stage	
pT2	19 (31.1)
pT3a	18 (29.5)
pT3b	24 (39.4)
TNM: pN stage	
pN0	55 (90.2)
pN1	6 (9.8)
Surgical margins	
Positive	19 (31.1)
Negative	41 (67.2)
No information	1 (1.7)
Gleason grade group	
1	0 (0)
2	20 (32.8)
3	22 (36.1)
4	10 (16.4)
5	9 (14.7)
Risk group	
Low risk	0 (0)
Favorable intermediate risk	7 (11.5)
Unfavorable intermediate risk	6 (9.8)
High risk or very high risk	48 (78.7)
Indication	
Biochemical persistence	22 (36.1)
Biochemical recurrence	17 (27.9)
Local recurrence	13 (21.3)
Regional recurrence	4 (6.6)
Local and regional recurrence	5 (8.1)
PSA pre-RT (ng/mL)	0.36 (0.01–67.0)
ADT	47 (77.0)
Long term	36 (76.6)
Short term	11 (23.4)
No ADT	14 (23.0)

Values are presented as median (range) or number (%).
PSA, prostate-specific antigen; RT, radiation therapy; ADT, androgen deprivation therapy.

ADT was prescribed in 77.0% of patients, with long-term ADT used in 76.6% of those cases.

2. Dosimetric data

Dosimetric data were available for 60 of 61 evaluable patients (98.4%). All treatment plans met institutional dose constraints across all recorded parameters, with 100% of patients achieving full compliance. The mean rectal D1cm^3 was 3,000.68 cGy, with rectal V2900 cGy and V1810 cGy averaging 6.30% and 32.57%, respectively. Small bowel and sigmoid colon D1cm^3 values remained below 3,000 cGy in all cases, with means of 2,457.76 cGy and 2,539.45 cGy, respectively. Bladder V1810 cGy averaged 36.81%, and penile bulb Dmean was 987.38 cGy. No dosimetric outliers were identified. A detailed summary of dose–volume parameters and constraints is presented in Table 1.

Table 3. Acute toxicity per CTCAE v5.0

Symptom grade	Grade 0	Grade 1	Grade 2	Grade 3
Gastrointestinal toxicity	28 (59.6)	7 (14.9)	12 (25.5)	0 (0)
Genitourinary toxicity	24 (51.1)	22 (46.8)	1 (2.1)	0 (0)

Values are presented as number (%)
CTCAE, Common Terminology Criteria for Adverse Events.

Table 4. EORTC QLQ-PR25 questionnaire

Scale	No. of patients	Mean score
Symptom scales		
Urinary symptoms	38	19.1
Incontinence aid	9	11.1
Bowel symptoms	38	4.2
Functional scales		
Hormonal treatment related symptoms	38	11.7
Sexual activity	38	25.4
Sexual functioning	15	44.4

EORTC QLQ-PR25, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.

3. Acute toxicity

Acute GI and GU toxicity data were available for 47 patients and are summarized in Table 3. No patients experienced grade 3 or higher toxicity.

Grade 2 GI toxicity was observed in 25.5% of patients, while 14.9% experienced grade 1 and 59.6% had no GI symptoms. For GU toxicity, 2.1% of patients experienced grade 2 toxicity, 46.8% experienced grade 1, and 51.1% remained without new GU symptoms. No hospitalizations or treatment interruptions were recorded due to toxicity.

4. Quality of life

QoL was assessed using the EORTC QLQ-PR25 questionnaire in 38 patients (62.3% of the cohort). Results are summarized in Table 4. The mean scores for symptom scales were as follows: 19.1 for urinary symptoms, 11.1 for incontinence aid, 4.2 for bowel symptoms, and 11.7 for hormonal treatment-related symptoms. For functional scales, the mean scores were 25.4 for sexual activity and 44.4 for sexual functioning.

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In this scoring system, lower values for symptom scales indicate lower symptom burden, while lower values for functional scales indicate lower functional status. Overall, these results reflect a low to moderate symptom burden and intermediate sexual function among respondents.

5. Exploratory dose–outcome analyses

Exploratory analyses were performed to assess associations between selected rectal and bladder dose–volume parameters and the occurrence of acute GI and GU toxicity. No statistically significant correlations were observed between acute GI toxicity and rectal D1cm^3, rectal V2900 cGy, or rectal V1810 cGy using either Kendall's τ-b or Spearman correlation analyses. Similarly, no significant associations were identified between acute GU toxicity and bladder V3200 cGy or bladder V1810 cGy. These findings indicate that within the dose constraints applied in this cohort, rectal and bladder dose–volume parameters were not associated with higher rates of acute grade GI or GU toxicity (Supplementary Table S1).

Exploratory analyses were also conducted to evaluate associations between dosimetric parameters and patient-reported quality-of-life domains. No statistically significant correlations were observed between urinary quality-of-life scores and bladder V1810 cGy, nor between bowel quality-of-life scores and rectal D1cm^3, rectal V2900 cGy, or rectal V1810 cGy. Likewise, no significant association was identified between sexual activity scores and mean dose to the penile bulb. However, a significant negative correlation was observed between sexual functioning scores and mean dose to the penile bulb, with lower sexual functioning scores associated with higher penile bulb dose (Spearman $\rho = -0.35$; $p = 0.033$; $n = 37$) (Supplementary Table S2).

Discussion and Conclusion

The decision to irradiate both the prostate bed and pelvic lymph nodes in the salvage setting is supported by growing high-level evidence. The NRG SPPORT trial demonstrated that the addition of short-term ADT and whole-pelvis radiotherapy to salvage prostate bed radiation therapy significantly improved progression-free survival in men with BCR after prostatectomy [11]. More recently, the PEACE V–STORM phase 2 trial further validated the benefit of pelvic nodal irradiation in patients with PET-detected oligorecurrent nodal disease. In that study, elective nodal radiotherapy significantly improved 4-year metastasis-free survival by 13% compared to metastasis-directed therapy alone, without increasing high-grade toxicity [14]. These findings reinforce the oncologic rationale for targeting subclinical nodal disease in the pelvis and support our institutional strategy of combining prostate bed and pelvic lymph node radiation therapy in appropriately selected postoperative patients.

In parallel, fractionation strategies in the postoperative setting have progressively evolved from conventionally fractionated radiotherapy to moderate hypofractionation. The randomized NRG-GU003 trial demonstrated that hypofractionated post-prostatectomy radiotherapy was a well-tolerated regimen, with no sustained increase in GU or GI toxicity at longer follow-up [22]. More recently, prospective data suggest that extreme hypofractionation in the postoperative setting is feasible, with short-course salvage radiotherapy delivered over weeks rather than months without a significant worsening of acute patient-reported toxicity [23]. Additionally, an extreme hypofractionation approach using SBRT offers increased efficiency and convenience. Ultra-hypofractionation significantly reduces overall treatment time compared to conventional fractionation. Standard postoperative radiotherapy typically requires 66–70 Gy in 33–35 fractions over 6.5–7 weeks, which is burdensome for patients and resource-intensive for facilities. In contrast, the SBRT regimen completes treatment in approximately 2 to 3 weeks. This shortened schedule reduces strain on radiotherapy equipment and staff and lowers barriers to patient access. Literature increasingly recognizes the value of such regimens for optimizing resource utilization. A multicenter prospective study reported that extended treatment courses require substantial machine time and personnel effort, potentially limiting access and increasing costs. Ultra-hypofractionated approaches have been shown to decrease equipment use, improve patient convenience, and expand access without compromising efficacy [24].

In this context, characterized by the demonstrated tolerability of postoperative hypofractionation and the potential efficiency benefits of ultra-hypofractionated delivery, our decision to prescribe 30 Gy in 5 fractions to the prostate bed was guided by radiobiological considerations and evidence from conventionally fractionated salvage radiotherapy. Assuming a low α/β ratio for prostate cancer of approximately 1.5 Gy, a dose of 30 Gy delivered in five fractions corresponds to an equivalent dose in 2-Gy fractions of approximately 64 Gy, aligning with the conventional-dose arm of the SAKK 09/10 randomized phase III trial. In that study, salvage radiotherapy to 64 Gy in 32 fractions was non-inferior to dose escalation to 70 Gy with respect to biochemical progression-free survival and was associated with lower GI toxicity [25].

PTV margin selection in the postoperative prostate bed SBRT setting requires particular consideration. The prostate bed is subject to substantial inter-fraction variability driven by bladder and rectal filling as well as surgical bed deformation. In CBCT-guided prostate bed SBRT, most prospective protocols—including SCIMITAR and the UCLA phase II experience—have adopted a 5-mm isotropic CTV-to-PTV expansion [26-28]. In CT/CBCT-guided prostate bed SBRT, pro-

spective series have shown that despite pre- and mid-fraction CBCT, the use of 5-mm margins results in adequate CTV coverage (CTV V95 ≥ 93%) in only approximately 70%–72% of patients or fractions, with loss of coverage primarily related to CTV shape deformation rather than translational setup error [26,27]. Accordingly, a 5-mm isotropic CTV-to-PTV expansion per institutional protocol was applied together with standardized bladder and rectal preparation and daily CBCT soft-tissue matching to account for postoperative geometric uncertainty while maintaining OAR constraints.

Early prospective data support the feasibility and tolerability of ultra-hypofractionated SBRT to the prostate bed in the postoperative setting. The POPART multicenter prospective study evaluated linac-based salvage SBRT delivering 32.5 Gy in five fractions to the prostate bed and reported no acute grade ≥ 2 GU toxicity, with low rates of late grade ≥ 2 GU toxicity (7.5%) and minimal GI toxicity at a median follow-up of 19.6 months [24]. No clinically meaningful deterioration in patient-reported outcomes was observed, and biochemical recurrence-free survival rates were 96.3%, 90.0%, and 85.3% at 6, 12, and 18 months, respectively, supporting both tolerability and short-term oncologic control with postoperative SBRT. Similarly, the SCIMITAR phase II trial demonstrated the feasibility of postoperative SBRT using prostate bed doses in the range of 30–34 Gy delivered in five fractions, with acceptable acute toxicity and preservation of QoL. Although a subset of patients received elective pelvic nodal irradiation and higher prostate bed boost doses, overall acute GI and GU toxicity remained low, further supporting the safety of this dose range in the postoperative SBRT context [28]. In addition, the SHORTER randomized phase II trial evaluated extreme hypofractionation for salvage radiotherapy and demonstrated that delivery of postoperative radiation in 5 fractions was not associated with significantly worse acute patient-reported GU or GI toxicity compared with longer hypofractionated schedules, reinforcing the feasibility of short-course postoperative radiotherapy approaches [23].

The rationale for delivering 25 Gy in five fractions to elective pelvic lymph nodes is primarily derived from prospective SBRT experience in patients with intact prostate cancer. Multiple prospective series and consortium-based analyses have evaluated ultra-hypofractionated pelvic nodal irradiation using 25 Gy in five fractions in combination with prostate SBRT, consistently reporting excellent regional pelvic control and acceptable GI and GU toxicity when delivered with contemporary planning and image guidance. A recent systematic review of pelvic nodal SBRT identified 25 Gy in five fractions as the most commonly adopted elective nodal dose, with acute grade ≥ 2 GI toxicity generally ≤ 10% and late grade ≥ 3 toxicity uncommon across studies [29]. In particular, pooled prospective data from the SHARP consortium [21] demonstrated near-universal pelvic nodal control using this regimen, supporting the biological adequacy of 25 Gy in five fractions for elective nodal irradiation in the ultra-hypofractionated setting. In contrast, evidence supporting ultra-hypofractionated pelvic nodal irradiation in the postoperative setting remains limited. Available prospective postoperative SBRT experiences incorporating elective pelvic nodal irradiation have been restricted to small cohorts and heterogeneous treatment paradigms. Among these, the SCIMITAR multicenter phase II trial included elective pelvic nodal SBRT in a subset of post-prostatectomy patients treated with prostate bed SBRT, demonstrating low rates of acute toxicity and feasibility when delivered with modern image-guided techniques [28]. More recently, Montero et al. [30] reported a prospective postoperative SBRT experience delivering 36.25 Gy in five fractions to the prostate bed with concurrent pelvic nodal irradiation to 26 Gy in five fractions, observing acceptable acute and early-late GI and GU toxicity without unexpected adverse events at a median follow-up of approximately 2 years. Taken together, although direct postoperative data evaluating 25 Gy in five fractions to pelvic lymph nodes remain limited, the consistency of intact-prostate SBRT outcomes and emerging postoperative feasibility data support extrapolation of this nodal dose.

Our findings indicate that ultra-hypofractionated postoperative pelvic radiotherapy (SBRT) yields low acute toxicity and favorable QoL outcomes. Acute GU and GI toxicities were predominantly mild, with few grade 2 events and no severe (grade ≥ 3) complications observed. Patient-reported QoL metrics showed low levels of urinary, bowel, and hormonal symptoms, along with intermediate sexual function scores, reflecting an overall acceptable QoL profile in the short term. The consistent adherence to OAR constraints across nearly all patients further supports the safety of the protocol. All evaluable plans (98.4%) met institutional dose objectives. Mean rectal D1cm^3 remained well below the 36 Gy threshold (3,000.7 cGy), and bowel and bladder exposure was similarly conservative. This uniformity in dose delivery likely contributed to the low observed rates of acute GI and GU toxicity. These results reinforce the tolerability of delivering a high biological dose in a condensed treatment schedule in the post-prostatectomy setting. Our acute toxicity outcomes are consistent with those reported in contemporary postoperative prostate bed SBRT series. In the SCIMITAR multicenter phase II trial, which prospectively evaluated post-prostatectomy SBRT using CT- and magnetic resonance (MR)–guided platforms, acute grade ≥ 2 GI and GU toxicity rates were 5% and 9%, respectively, with improved GI toxicity observed in the MR-guided cohort [28]. However, elective pelvic nodal irradiation was delivered in approximately 27% of patients, and prostate bed boost doses of 36.25–40 Gy were used in a similar proportion, factors that may have contributed to lower acute GI toxicity and

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slightly higher acute GU toxicity compared with our cohort. The POPART study reported very low acute toxicity following postoperative ablative radiotherapy to the prostate bed alone, with no acute grade ≥2 GU toxicity and approximately 5% grade 2 GI toxicity, and no grade ≥3 acute events [24]. The lower GI toxicity observed in POPART is likely, in part, attributable to the absence of elective pelvic nodal irradiation, which limits direct comparability with our treatment volumes. In the intact prostate setting, the SHARP consortium reported low rates of acute toxicity following five-fraction pelvic nodal SBRT in patients with high-risk prostate cancer, with approximately 12% grade 2 GI toxicity and 3% grade 2 GU toxicity, and no grade ≥3 acute events, despite elective nodal irradiation [31]. Although the intact prostate and postoperative settings are not directly comparable, these data provide supportive evidence for the tolerability of pelvic SBRT when delivered with modern planning techniques.

In exploratory dose–outcome analyses, no significant associations were identified between rectal or bladder dose–volume parameters and acute grade ≥2 GI or GU toxicity, suggesting that the applied dose constraints were effective in mitigating early treatment-related toxicity. A single biologically plausible association was observed between higher mean dose to the penile bulb and lower sexual functioning scores. Although exploratory and based on a limited number of evaluable patients, this finding aligns with prior observations regarding the dose sensitivity of erectile structures and supports continued attention to penile bulb dose during treatment planning [32].

Several limitations of this study should be acknowledged. The retrospective design introduces inherent selection biases and relies on the accuracy of medical record documentation. The absence of a prospective trial increases the risk of under-reporting or inconsistencies in toxicity grading and QoL assessment. Regarding baseline GU symptoms, all patients had undergone prostatectomy, and many exhibited pre-existing GU issues such as urinary frequency or incontinence unrelated to radiation. This complicates the distinction between radiation-induced lower urinary tract symptoms and those attributable to the surgical baseline [24]. Consequently, some mild urinary toxicities recorded, such as grade 1 frequency, may reflect ongoing post-surgical dysfunction rather than new treatment-induced symptoms. In addition, the retrospective nature of toxicity reporting precluded precise characterization of symptom onset, peak severity, and duration, as these details were not consistently documented in clinical records. Furthermore, acute toxicity was abstracted from routine clinical documentation rather than prospectively collected at predefined time points, which may have led to underestimation of transient or mild symptoms. It is important to note that QoL was assessed only at the last follow-up, without a pre-treatment baseline for comparison. This limitation restricts the ability to quantify treatment-related changes, and pooling responses introduces heterogeneity in timing. As all patients completed the survey at least 6 months post-treatment, these post-treatment quality-of-life measures can be interpreted in the context of prior prospective studies suggesting that early quality-of-life metrics are broadly reflective of longer-term patient-reported outcomes. In the SATURN trial, which evaluated five-fraction definitive SBRT to the prostate and pelvic lymph nodes, minimal differences in urinary and bowel domain scores were observed between 3 and 24 months post-treatment [33]. A similar trend was observed in the CHHiP QoL substudy [34], which reported little change in patient-reported outcomes between the 6-month and 5-year time points in the intact-prostate setting using moderately hypofractionated radiotherapy. Although the present data are cross-sectional, they provide preliminary support for the tolerability of this approach.

In addition, the widespread use of ADT in this cohort represents a potential confounding factor for patient-reported urinary, hormonal, and sexual outcomes. ADT was administered to 77.0% of patients, with variable duration and timing relative to radiotherapy. ADT is known to independently affect sexual function, hormonal symptoms, and (to a lesser extent) urinary quality-of-life domains, which limits the ability to attribute patient-reported outcomes solely to radiation treatment [35]. Accordingly, quality-of-life results should be interpreted in the context of combined-modality therapy rather than as isolated radiation effects.

Within these limitations, this study provides one of the largest contemporary postoperative experiences combining prostate bed and elective pelvic nodal SBRT. Our results demonstrate that this approach can be delivered with low acute toxicity, acceptable QoL, and consistent adherence to OAR constraints. Together with emerging prospective data, these findings support the tolerability of postoperative pelvic SBRT and provide a robust foundation for our ongoing prospective study, which will further characterize toxicity and quality-of-life outcomes in this patient population.

Ultra-hypofractionated radiotherapy to the prostate bed and pelvic lymph nodes using SBRT appears to be a well-tolerated and feasible salvage strategy in the postoperative setting. In this cohort, acute toxicity was low and short-term QoL outcomes were acceptable, with minimal symptom burden and preserved functional scores. All treatment plans met predefined OAR constraints, underscoring the technical feasibility of safely delivering combined prostate bed and pelvic nodal SBRT using contemporary planning and image guidance. While these findings should be interpreted in the context of the retrospective design and limited follow-up, they contribute meaningful real-world evidence supporting ultra-hypof-

ractionated postoperative pelvic radiotherapy. An ongoing prospective study at our institution incorporating standardized longitudinal toxicity and quality-of-life assessment is currently underway and will further clarify long-term safety, patient-reported outcomes, and oncologic efficacy of this approach.

Statement of Ethics

This study was approved by the regional ethics committee corresponding to our clinical center (Comité de Ética Científico Adultos del Servicio de Salud Metropolitano Oriente, Chile; approval code: SMOriente100625-1). Written informed consent was waived by the committee due to the study's retrospective nature.

Conflict of Interest

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

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Author Contributions

Conceptualization, IK, CG; Data curation, IK, CG, CC, JS; Formal analysis, IK; Supervision, CG; Writing of the original draft, IK; Writing of the review and editing, CG, CC, JS.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2025.00738.

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A retrospective analysis for early-stage non-endometrioid endometrial cancers

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Purpose: This study aimed to investigate treatment outcomes and explore optimal adjuvant treatment options for patients with early-stage uterine serous carcinoma (USC) and clear cell carcinoma (CCC).

Materials and Methods: We retrospectively reviewed the records of 63 patients diagnosed with stage I–II (2009 International Federation of Gynecology and Obstetrics [FIGO]) USC or CCC. Survival outcomes were estimated using the Kaplan-Meier method, and comparisons between groups were performed with the log-rank test.

Results: Among the 63 patients, 36 (57.1%) had USC and 25 (39.7%) had CCC. According to the revised 2023 FIGO staging system, 23 patients (36.5%) were stage IC, and 40 (63.5%) were stage IIC. Adjuvant treatment included no adjuvant therapy (23.8%), chemotherapy alone (39.7%), radiotherapy alone (28.6%), and combined chemotherapy plus radiotherapy (8.0%). After a median follow-up of 54 months (range, 5 to 227 months), the 5-year progression-free survival (PFS) and overall survival (OS) for the entire cohort were 89.5% and 85.7%, respectively. Patients with CCC had a 5-year PFS of 95.8% and OS of 92.3%, whereas those with USC had a 5-year PFS of 85.1% and OS of 81.4%. Most recurrences (7/63, 11.1%) were distant, occurring predominantly in USC cases (6/7) and 2023 stage IIC (7/7).

Conclusion: In this retrospective study, early-stage USC and CCC had very favorable PFS and survival outcomes. Thus, future randomized clinical trial or large cohort study is necessary to determine the optimal adjuvant treatments in these patients.

Keywords: Endometrial neoplasms, Neoplasm staging, Retrospective studies, Prognosis, Survival analysis

Introduction

Endometrial cancer is the sixth most common gynecologic malignancy worldwide and the incidence continues to rise [1]. While the majority of endometrial cancers are of endometrioid histology and generally have a favorable prognosis, non-endometrioid subtypes are known for their aggressive behavior [2]. Non-endometrioid endometrial cancers including uterine serous carcinoma (USC), clear cell carcinoma (CCC), and carcinosarcomas, account for approximately 10%–15% of all endometrial cancers, but contribute to approximately 40%–50% of endometrial cancer-related deaths [3,4]. These subtypes are characterized by their distinct molecular pro-

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files, rapid progression, and tendency for early metastasis, even in early-stage disease [5,6].

In the revised 2023 International Federation of Gynecology and Obstetrics (FIGO) system, USC and CCC are grouped as "aggressive histologic types," and staging differs from that of non-aggressive endometrioid type tumors [7]. Specifically, USC and CCC confined to the endometrium are classified as stage IC, while any degree of myometrial invasion is categorized as stage IIC, regardless of invasion depth. Given their high recurrence rates, adjuvant therapy is commonly considered for early-stage USC and CCC. However, owing to the rarity of these subtypes, most evidence regarding adjuvant treatment comes from small retrospective studies, and published findings have been inconsistent [4,8-12]. Some research suggests that surgery alone may be sufficient for certain stage I patients [13], whereas others demonstrate improved loco-regional control with adjuvant radiotherapy [14]. Furthermore, given the propensity for distant metastasis, many clinicians advocate incorporating adjuvant chemotherapy [15].

In light of these uncertainties, we conducted a retrospective analysis to investigate treatment outcomes and explore optimal adjuvant treatment strategies for early-stage USC and CCC.

Materials and Methods

1. Patient

From January 2001 to December 2020, we retrospectively identified 63 patients diagnosed with stage I–II (FIGO 2009) USC or CCC who underwent total hysterectomy and bilateral salpingo-oophorectomy at our institution. Pelvic and para-aortic lymphadenectomy, and peritoneal washings were performed at the surgeon's discretion. Staging was conducted according to both the 2009 and the revised 2023 FIGO systems.

2. Adjuvant treatment

Adjuvant treatment was individualized based on tumor characteristics, patient preferences, and physician judgment. The choice between external beam radiotherapy (EBRT) and vaginal brachytherapy was based on risk factors including depth of myometrial invasion, lymphovascular space invasion (LVSI), tumor size, and treating radiation oncologist's assessment. Platinum-based chemotherapy (primarily carboplatin and paclitaxel) was administered for 3–6 cycles. EBRT was delivered to the whole pelvis at a dose of 45–50.4 Gy in 25–28 fractions. Vaginal brachytherapy was delivered as high-dose-rate intracavitary radiation at 30 Gy in 6 fractions or 21 Gy in 3 fractions. For concurrent chemoradiation, weekly cisplatin was administered.

3. Follow-up and outcomes

Progression-free survival (PFS) was defined as the time from surgery to the first documented recurrence or death from any cause. Overall survival (OS) was defined as the time from surgery to death from any cause or last follow-up. Loco-regional recurrence was defined as a recurrence at vaginal stump, pelvic or para-aortic lymph nodes, and distant recurrence was defined as metastases outside the pelvis/abdomen or peritoneal seeding. Patients were followed up at regular intervals, typically every 3 months for the 5 years after surgery. Follow-up evaluations included physical examinations, serum tumor marker assessments, and imaging studies including chest and abdomen-pelvis computed tomography scans.

4. Statistical analysis

Survival outcomes were estimated using the Kaplan-Meier method, and differences between groups were compared using the log-rank test. All statistical analyses were conducted using SPSS version 28 (IBM Corp., Armonk, NY, USA).

Results

1. Patient characteristics

Among the 63 patients included, the median age at diagnosis was 65 years (range, 43 to 84). A total of 36 patients (57.1%) had USC, 25 (39.7%) had CCC, and two (3.2%) had mixed histology. According to the 2009 FIGO staging system, 45 patients (71.4%) were stage IA, 13 (20.6%) were stage IB, and five (7.9%) were stage II. Under the revised 2023 FIGO system, 23 patients (36.5%) were stage IC, and 40 (63.5%) were stage IIC. LVSI was observed in 12 patients (19.0%). There was no significant difference in tumor characteristics between the USC and CCC groups (Table 1).

2. Treatment

All patients underwent total hysterectomy and bilateral salpingo-oophorectomy. Pelvic lymphadenectomy was performed in 59 patients (93.7%), and para-aortic lymphadenectomy was performed in 30 patients (47.6%). Adjuvant treatment regimens varied: 15 patients (23.8%) received no adjuvant therapy, 25 (39.7%) received chemotherapy alone, 18 (28.6%) received radiotherapy alone, and five (8.0%) received combined chemotherapy and radiotherapy. Among those with CCC, 44% did not receive adjuvant therapy. In contrast, among those with USC, 24 patients (66.7%) underwent chemotherapy ($p < 0.001$) (Table 1). Peritoneal washing cytology was performed in 56 patients (88.9%) and was positive in three patients. Omentectomy was conducted in nine patients, consistent with institutional practice during which omental assessment was performed selectively based on surgeon discretion and

Table 1. Patient characteristics

Characteristic	Serous (n = 36)	Clear cell (n = 25)	Mixed (n = 2)	p-value
Age (year)	58.5 (43–84)	59 (48–83)	69.5 (63–76)	0.353
2009 FIGO stage				0.308
IA	23 (63.9)	21 (84.0)	1 (50.0)	
IB	9 (25.0)	3 (12.0)	1 (50.0)	
II	4 (11.1)	1 (4.0)	0 (0)	
2023 FIGO stage				0.498
IC	12 (33.3)	11 (44.0)	0 (0)	
IIC	24 (66.7)	14 (56.0)	2 (100)	
Tumor size (mm)				0.210
≤ 20	14 (38.9)	15 (60.0)	1 (50.0)	
> 20	22 (61.1)	10 (40.0)	1 (50.0)	
Lymphovascular invasion				0.444
Negative	27 (75.0)	22 (88.0)	2 (100)	
Present	8 (22.2)	3 (12.0)	0 (0)	
Unknown	1 (2.8)	0 (0)	0 (0)	
Lymphadenectomy				0.323
Not done	3 (8.3)	1 (4.0)	0 (0)	
Pelvic	13 (36.1)	14 (56.0)	2 (100)	
Pelvic + para-aortic	20 (55.6)	10 (40.0)	0 (0)	
Adjuvant treatment				< 0.001
No treatment	4 (11.1)	11 (44.0)	0 (0)	
VBT	5 (13.9)	4 (16.0)	0 (0)	
VBT + CT	2 (5.6)	0 (0)	0 (0)	
EBRT	3 (8.3)	6 (24.0)	0 (0)	
EBRT + CT	1 (2.8)	1 (4.0)	1 (50.0)	
CT	21 (58.3)	3 (12.0)	1 (50.0)	

Values are presented as median (range) or number (%).
FIGO, International Federation of Gynecology and Obstetrics; VBT, vaginal brachytherapy; CT, chemotherapy; EBRT, external beam radiation therapy.

intraoperative findings rather than routinely for all early-stage cases.

Of the patients receiving chemotherapy, the most common regimen was carboplatin plus paclitaxel (24 patients, 80% of those receiving chemotherapy), with a median of 4 cycles (range, 3 to 6). Among the patients receiving radiotherapy, 12 underwent EBRT and 11 received vaginal brachytherapy.

3. Survival outcomes and prognostic factors

The median follow-up duration was 54 months (range, 5 to 227). During follow-up, seven patients (11.1%) experienced disease recurrence, and 11 (17.5%) died. The 5-year PFS and OS rates for the entire cohort were 89.5% and 85.7%, respectively. Stratified by histology, patients with USC had a 5-year PFS of 85.1% and a 5-year OS of 81.4%, while patients with CCC had a 5-year PFS of 95.8% and a 5-year OS of 92.3% (Fig. 1). Most recurrences (5/7, 71.4%) were distant only, with one case being regional plus distant and one being loco-regional and distant (Table 2).

Univariate analysis identified that age ≥ 70 years (p = 0.025) and stage IIC disease by the 2023 FIGO system (indicating myometrial invasion, p = 0.035) were associated with worse PFS (Table 3). No significant prognostic factors were found for OS. Multivariate analysis was not feasible due to the small number of patients and events.

Table 4 describes the characteristics of patients who experienced recurrence. Of the seven patients who experienced recurrence, six had USC and one had CCC. All of these patients had myometrial invasion (2023 FIGO IIC). Three out of the seven patients exhibited LVSI, the adjuvant treatments they received were varied: two received vaginal brachytherapy (VBT) alone, two received VBT combined with chemotherapy, two received chemotherapy alone, and one received no adjuvant treatment. The most frequent site of distant metastases was lung, occurring in three of the seven patients.

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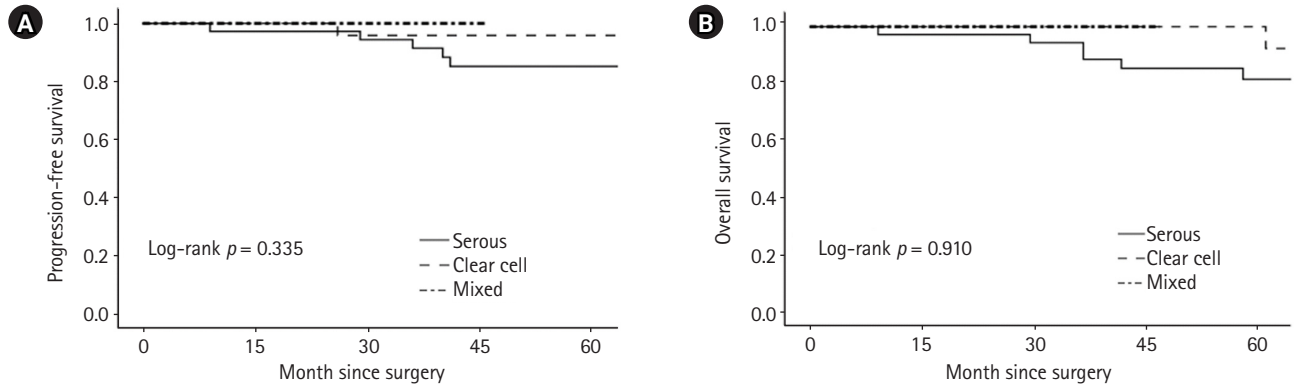

Fig. 1. Kaplan-Meier curves for progression-free survival and overall survival in patients with early-stage uterine serous carcinoma and clear cell carcinoma.

Table 2. Patterns of the first recurrence

	Serous (n = 36)	Clear cell (n = 25)	Total
Regional and distant	1	0	1
Distant	4	1	5
Local, regional, and distant	1	0	1
Total	6	1	7

Discussion and Conclusion

This retrospective study evaluated treatment outcomes and adjuvant strategies for early-stage (2009 FIGO I–II) non-endometrioid endometrial cancers, specifically USC and CCC. A significant finding was the difference in outcomes between these two histologic subtypes. Patients with CCC demonstrated a superior 5-year PFS of 95.8%, compared to 85.1% for those with USC, despite almost half of the CCC group not receiving adjuvant treatment. The recurrence rate for CCC was 4%, versus 16.7% for USC, supporting earlier studies that suggest CCC has a lower recurrence rate—one-third that of USC [16-18].

One of the largest studies on early USC, by Kurnit et al. [14], included 737 patients. They performed a subgroup analysis assessing the impact of adjuvant treatment in those USC confined to the endometrium (without myometrial invasion). Of the 250 patients with endometrium-confined USC, no adjuvant therapy demonstrated a significant difference in recurrence-free survival compared to observation alone. However, vaginal cuff brachytherapy was associated with improved OS compared to observation alone (hazard ratio, 0.46; 95% confidence interval, 0.23 to 0.94) [14]. Armbruster et al.'s study [19], the largest on early-stage CCC, included 112 patients. In this study, OS approached 10 years for early-stage CCC patients. Adjuvant treatment was not associated with survival, but age over 70 and LVSI were the only factors associated with worse survival [19].

Table 3. Univariate analysis for progression-free survival and overall survival

Variable	No.	Progression-free survival		Overall survival	
		5-Year (%)	p-value	5-Year (%)	p-value
Age (year)					
40–69	53	93.4	0.025	87.2	0.164
≥ 70	10	70.0		78.8	
Histology type					
Serous	36	85.1	0.335	81.4	0.910
Clear cell	25	95.8		92.3	
Mixed	2	100		100	
2009 FIGO stage					
IA	45	92.6	0.140	91.0	0.205
IB	13	71.4		59.3	
II	5	100		75.0	
Tumor size (mm)					
0–20	30	95.7	0.080	88.3	0.489
> 20	33	83.9		82.6	
2023 FIGO stage					
IC	23	100	0.035	100	0.051
IIC	40	83.4		77.0	
Lymphovascular invasion					
Absent	51	93.3	0.201	87.8	0.277
Present	11	71.6		72.7	
Unknown	1	-		-	
Radiotherapy					
No	40	94.6	0.195	90.1	0.707
Yes	23	79.4		75.7	
Chemotherapy					
No	33	90.1	0.546	88.4	0.474
Yes	30	88.8		81.7	

FIGO, International Federation of Gynecology and Obstetrics.

Table 4. Clinical characteristics for patients with recurrence (n = 7)

Patient no.	Age (year)	Histology	2009 FIGO	2023 FIGO	LVSI	Adjuvant treatment	DFI	Pattern of recurrence	Final status
1	55	Serous	IA	IIC	–	VBT	22	Distant (neck node)	DOD
2	51	Serous	IB	IIC	+	VBT + CT	12	Distant (bone)	DOD
3	84	Serous	IB	IIC	+	Refuse	7	Locoregional and distant (peritoneal seeding)	DOD
4	53	Serous	IB	IIC	+	CT	37	Distant (lung)	FU loss
5	60	Serous	IA	IIC	–	CT	45	Regional and distant (peritoneal seeding)	DOD
6	83	Clear cell	IA	IIC	–	VBT (refuse EBRT)	15	Distant (lung)	AWD
7	75	Serous	IA	IIC	–	VBT + CT	16	Distant (lung)	DOD

FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular invasion; DFI, disease-free interval; VBT, vaginal brachytherapy; DOD, died of disease; CT, chemotherapy; FU, follow-up; EBRT, external beam radiation therapy; AWD, alive with disease.

In our study cohort, there were 23 cases of 2023 FIGO stage IC (confined to the endometrium), comprising 12 cases of USC and 11 of clear cell CCC as detailed in Table 1. Within this IC subgroup, adjuvant treatment included chemotherapy alone in seven patients (six with USC, one with CCC), concurrent chemoradiotherapy in one patient with USC, VBT alone in three patients, and no adjuvant therapy in 12 patients (data not shown). Notably, all recurrent cases had stage IIC (myometrial invasion) and none of IC patients developed recurrence regardless of adjuvant treatment or histologic type (Table 4). This observation supports the utility of the revised 2023 FIGO staging system, which classifies high-risk histology based on the presence of myometrial invasion.

Regarding prognostic factors for survival, older age (>70) and stage IIC were significant factors for PFS. However, we could not conduct a multivariate analysis due to the small number of patients and events. Previous studies have reported that LVSI and tumor size are associated with survival [14,20,21]. In our study, those with LVSI and larger tumor size had numerically lower survival rates, although this was not statistically significant. Furthermore, we did not identify significance in PFS among the various adjuvant treatment groups; however, this finding should be interpreted cautiously given the study's retrospective design, small sample size, and heterogeneous adjuvant therapies. The patients who received radiotherapy or chemotherapy even had numerically worse PFS compared with those who did not receive such adjuvant treatment (Table 2). This may reflect treatment selection bias, whereby patients with higher-risk features were more likely to be offered adjuvant therapy. Due to the limited sample size and event numbers, multivariate analysis could not be performed to adjust for these confounding variables.

Our study has several limitations, including its retrospective nature, small sample size, and potential for selection bias. The heterogeneity in adjuvant treatments and the extended study period may have introduced confounding factors. Despite these limitations, our findings contribute to the limited body of evidence on early-stage non-endometrioid endometrial cancers. Specifically, the favorable survival outcomes observed in CCC may indicate a relatively indolent disease course, though the role and intensity of adjuvant therapy in these patients remain to be clarified. In contrast, the higher rate of distant failure in USC suggests a potential need for effective systemic treatment strategies. Additionally, given that no recurrence was observed among patients with 2023 FIGO stage IC, further investigation is warranted to determine whether additional treatment might confer clinical benefits regardless of histological subtype at this stage.

In conclusion, this retrospective analysis suggests that patients with early-stage CCC generally demonstrate favorable outcomes, whereas those with USC more frequently experienced distant recurrences, particularly in the presence of myometrial invasion. These findings highlight the importance of considering histologic subtype and myometrial invasion when tailoring adjuvant treatment strategies and are consistent with the rationale of the revised 2023 FIGO staging system, which incorporates depth of invasion in aggressive histologies. Given the retrospective design and limited sample size of this study, the results should be interpreted with caution, and further large-scale prospective studies are warranted to elucidate the optimal adjuvant treatment approach for early-stage USC and CCC.

Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board of Samsung Medical Center, Seoul, Republic of Korea (approval number: 2025-04-007). Written informed consent was waived due to the retrospective nature of this study.

Conflict of Interest

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

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Author Contributions

Conceptualization, EL; Design, EL; Data collection, EL; Data curation, YYL, CHC, TJK; Analysis, EL; Project administration, WKC, JWL; Methodology, WP; Supervision, WKC, JWL, WP; Validation, YYL, CHC, TJK; Writing of the original draft:, EL; Writing of the review and editing, WKC, JWL, WP, YYL, CHC, TJK.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to institutional policy and patient privacy regulations, the datasets are not publicly available.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2025.00724.

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Efficacy and safety of single-fraction radiosurgery in vestibular schwannoma: a 10-year experience

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Purpose: This study aimed to evaluate long-term tumor control, safety, and prognostic factors following single-fraction stereotactic radiosurgery (SRS) for vestibular schwannoma (VS).

Materials and Methods: In this retrospective single-institution study, 68 patients with VS were treated with photon-based single-fraction SRS (mean dose, 13.1 Gy; range, 12 to 15 Gy). Treatment planning was based on computed tomography–magnetic resonance imaging (MRI) fusion with organ-at-risk sparing and a planning target volume margin of 0–2 mm. The primary endpoint was local control (LC). Secondary endpoints included toxicity and predictors of treatment failure.

Results: After a median follow-up of 68 months, LC was maintained in 95.6% of patients. Actuarial LC rates at 5 and 10 years were both 98.5%. MRI showed tumor shrinkage in 41.2% and stability in 57.4% of cases. Treatment was well tolerated. Acute adverse events were infrequent and mild. Localized alopecia occurred acutely in one patient (1.5%) and did not persist into late follow-up. Vertigo and tinnitus were analyzed as disease-related symptoms rather than treatment-related toxicities. Severe toxicity (grade ≥ 3) was rare (<3%). Cox regression revealed no statistically significant predictors of local failure, though trends suggested higher risk after prior surgery and with doses ≥14 Gy.

Conclusion: Single-fraction SRS provides durable long-term LC of VS with a favorable toxicity profile, supporting its role as a primary treatment modality. Optimal outcomes appear to be associated with lower prescription doses (<14 Gy) and treatment of de novo tumors.

Keywords: Vestibular schwannoma, Acoustic neuroma, Stereotactic radiosurgery, Radiation injuries, Treatment outcome

Introduction

Vestibular schwannoma (VS), also termed acoustic neuroma, is a benign tumor arising from Schwann cells of the vestibulocochlear nerve. Despite its non-malignant histology, the tumor's location within the cerebellopontine angle can lead to considerable morbidity, including hearing loss, tinnitus, vertigo, and brainstem compression [1]. Management strategies for VS have evolved substantially over recent decades and currently encompass active surveillance, microsurgical resection, and stereotactic radiosurgery (SRS). The choice of approach depends on tumor size, growth kinetics, and patient-specific factors such as age, comorbidities, and func-

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tional hearing status [2].

SRS has emerged as a standard treatment for small- to medium-sized VS, offering high local tumor control rates while minimizing invasiveness and preserving neurological function [3]. Long-term series consistently report tumor control rates exceeding 90% at 10 years, establishing SRS as a first-line alternative to microsurgery in appropriately selected patients [4]. Importantly, SRS is also associated with lower rates of cranial nerve morbidity and faster recovery compared with surgical resection [5,6].

Nevertheless, several clinically relevant questions remain. First, the optimal prescription dose continues to be debated. Early protocols using 16–20 Gy achieved high tumor control but carried substantial risks of hearing loss and cranial neuropathies [2,3,5,7]. Contemporary practice has shifted toward lower doses of 12–13 Gy to improve safety; however, concerns persist regarding long-term efficacy in larger or previously resected tumors [6,8]. Second, several potential prognostic factors—such as tumor size, prior surgery, and cochlear dose—have been proposed, although evidence regarding their independent clinical impact remains limited and sometimes inconsistent across studies [9]. Finally, late toxicity—including hearing decline, facial nerve palsy, and trigeminal neuropathy—continues to affect quality of life, underscoring the importance of careful long-term outcome evaluation [10,11].

Against this background, we report our single-institution experience with photon-based single-fraction SRS for VS with long-term follow-up. Our objectives were threefold: (1) to evaluate long-term local and out-of-field tumor control, (2) to characterize acute and late toxicity profiles, and (3) to explore potential clinical and dosimetric factors associated with treatment outcomes. By providing long-term real-world data from a contemporary linear accelerator (LINAC)–based SRS cohort, this study aims to complement existing literature and further characterize the safety and effectiveness of single-fraction SRS in patients with VS.

Materials and Methods

1. Study design and patient population

This retrospective, single-center study included 68 consecutive patients with VS who underwent SRS at the Department of Radiotherapy and Radiation Oncology of a tertiary referral center in Germany between 2005 and 2023. Clinical, radiological, and dosimetric data were obtained from electronic medical records and the radiotherapy (RT) planning database.

Eligibility criteria were as follows: (1) radiologically confirmed sporadic VS, (2) treatment with single-fraction photon-based SRS, and (3) a minimum radiological follow-up of ≥ 12 months. Patients with neurofibromatosis type 2 (NF2) were excluded. Baseline characteristics included age, sex, tumor laterality, prior treatment, and indication for SRS. SRS was delivered as primary treatment in 55 patients (80.9%), whereas 13 patients (19.1%) received SRS for residual disease following partial microsurgical resection.

2. Treatment planning and delivery

Patients were immobilized using a stereotactic thermoplastic mask. Thin-slice (1–2 mm) planning computed tomography scans were acquired and rigidly fused with contrast-enhanced T1- and T2-weighted magnetic resonance imaging (MRI). The gross tumor volume was defined as the contrast-enhancing lesion on MRI. The planning target volume (PTV) was generated by applying a margin of 0–2 mm to account for setup uncertainties. The mean PTV volume was 1.29 cm^3 (range, 0.05 to 5.00 cm^3).

The brainstem and ipsilateral cochlea were routinely contoured as organs at risk (OARs) in accordance with institutional and international dose-constraint guidelines. Particular attention was paid to cochlear dose exposure due to its clinical relevance for hearing preservation.

Treatment planning was performed using commercial planning systems (Eclipse, Varian Medical Systems, Palo Alto, CA, USA; Pinnacle, Philips Medical Systems, Fitchburg, WI, USA). Intensity-modulated stereotactic treatment plans were optimized to achieve at least 95% PTV coverage of the prescribed dose while respecting OAR dose constraints. The mean prescribed dose was 13.14 Gy (range, 12 to 15 Gy). Most patients (75%) received a prescription dose of < 14 Gy, while 25% received ≥ 14 Gy. For exploratory analyses, patients were stratified according to prescription dose (< 14 Gy vs. ≥ 14 Gy), reflecting institutional treatment practice and commonly used dose ranges reported in the literature for single-fraction SRS in vestibular schwannoma. The prescription dose was typically delivered to the 80%–90% isodose line in accordance with institutional SRS planning protocols. SRS was delivered using either a Varian TrueBeam linear accelerator (47.1%) or a conventional linear accelerator system (52.9%), both equipped with high-definition multileaf collimators and stereotactic image guidance. For exploratory purposes, treatment delivery platforms were categorized as TrueBeam versus conventional LINAC to evaluate whether different stereotactic delivery systems influenced treatment outcomes.

An illustrative example of target and OAR delineation, including the corresponding dose-volume histogram, is shown in Fig. 1.

3. Dosimetric analysis

Dosimetric parameters were extracted from the RT planning system and included PTV volume as well as OAR volumes and dose metrics. For the brainstem and ipsilateral cochlea, mean, maximum, and

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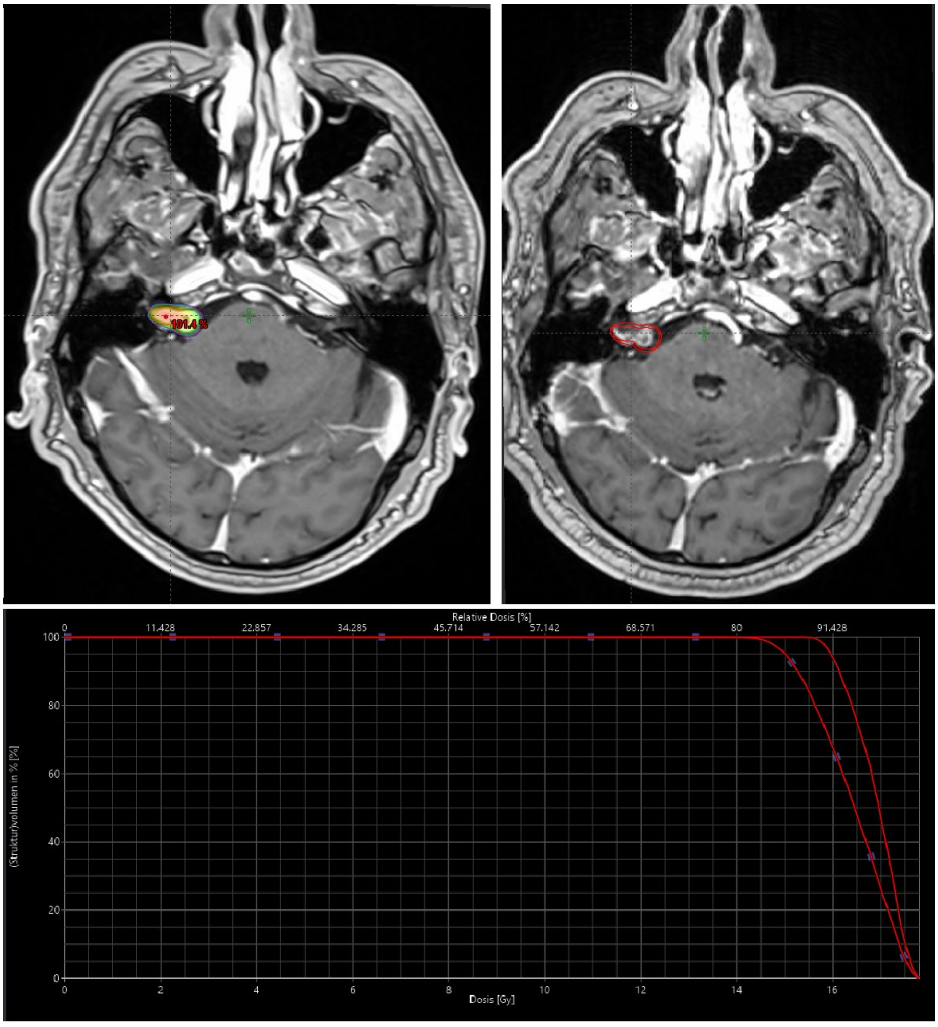

Fig. 1. Axial magnetic resonance imaging (MRI) before radiotherapy (upper left) and 6 years after single-fraction radiosurgery with 14 Gy at 80% isodose (upper right), demonstrating stable disease without progression. The gross tumor volume (red contour) and planning target volume (outer contour) are delineated on the pretreatment image. The MRI on the upper right confirms stability at 6-year follow-up. The corresponding dose-volume histogram is shown below.

minimum doses were recorded. Institutional dose constraints aimed to limit the maximum brainstem dose to ≤ 12 Gy and to minimize cochlear dose exposure whenever feasible, with particular attention to the mean cochlear dose during treatment planning.

Due to incomplete contour availability, brainstem volume data were available for 56 patients, while brainstem and cochlear dose parameters were available for 54 patients.

4. Follow-up and outcome measures

Patients underwent clinical and radiological follow-up starting 3–6 months after SRS and subsequently at intervals of 6–12 months. Follow-up evaluations included neurological examination, audiometric testing when applicable, and MRI imaging. Local control (LC) was defined as the absence of in-field progression (IFP), which was characterized by an increase in the maximum tumor diameter of ≥ 20% or unequivocal radiological progression. To differentiate true tumor progression from pseudoprogression, radiological progression was defined as sustained tumor enlargement on consecutive MRI examinations and/or the requirement for salvage treatment. Radiological response was categorized as stable disease or tumor shrinkage.

Treatment-related toxicities were documented and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Acute toxicities were defined as events occurring within 6 weeks after treatment, whereas late toxicities were defined as those occurring thereafter. Second primary tumors detected during follow-up were documented separately and were not considered VS progression events.

5. Statistical analysis

Descriptive statistics were used to summarize baseline patient characteristics, treatment parameters, and outcomes. Kaplan-Meier estimates were generated for LC and overall survival (OS). Univariate Cox proportional hazards regression analyses were performed to evaluate potential predictors of LC, including sex, tumor laterality, prior surgery, prescribed dose (< 14 Gy vs. ≥ 14 Gy), and treatment platform. Hazard ratios (HRs) with corresponding 95% confidence intervals were calculated. Given the limited number of local failure events, these analyses were considered exploratory. Dosimetric variables were not included in the Cox regression analyses due to incomplete data availability. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 29 (IBM Corp., Armonk, NY, USA).

Results

1. Patient and treatment characteristics

A total of 68 patients with VS were treated with single-fraction SRS. Baseline patient and treatment characteristics are summarized in Table 1. The mean patient age was 60.5 years, with a near-equal sex distribution (47.1% male and 52.9% female). Tumors were more frequently right-sided (55.9%). SRS was administered as primary treatment in 55 patients (80.9%), whereas 13 patients (19.1%) received SRS for residual disease following partial microsurgical resection.

The mean prescription dose was 13.14 Gy (range, 12 to 15), with the majority of patients (75%) receiving < 14 Gy. Treatments were delivered using either a TrueBeam linear accelerator (47.1%) or a conventional linear accelerator system (52.9%). Detailed dosimetric planning parameters are presented in Table 2.

The mean PTV was 1.29 cm^3 (range, 0.05 to 5.00). Brainstem volume data were available for 56 patients, with a mean volume of 22.97 cm^3. Brainstem dose parameters were available for 54 patients, with a mean dose of 0.73 Gy, a mean maximum dose of 7.09 Gy, and a mean minimum dose of 0.04 Gy. Cochlear volume and dose parameters were also available for 54 patients; the mean cochlear volume was 0.46 cm^3. The mean cochlear dose was 8.87 Gy, with a mean maximum dose of 12.90 Gy and a mean minimum dose of 5.01 Gy. All treatment plans fulfilled institutional dose constraints for OARs while maintaining adequate target coverage.

2. Tumor control and survival outcomes

After a median radiological follow-up of 68 months (range, 12 to 184), excellent tumor control was observed. LC, defined as the absence of IFP, was achieved in 65 patients (95.6%). Only three patients (4.4%) developed IFP during follow-up, and subsequently required salvage treatment. One patient developed a meningioma outside the irradiated field during follow-up, which was considered a second primary tumor rather than VS progression.

The actuarial LC rates were 100% at 1 year and 98.5% at both 5 and 10 years (Fig. 2). Radiological assessment on follow-up MRI demonstrated stable disease in 39 patients (57.4%) and tumor shrinkage in 28 patients (41.2%). A summary of oncological outcomes is provided in Table 3. The mean IFP-free survival was 62.1 months. The mean OS was 75.7 months. No disease-related deaths were observed at the last follow-up.

Table 1. Patient characteristics

Variable	Value
Total patients	68
Sex	
Male	32 (47.1)
Female	36 (52.9)
Mean age at RT (year)	60.49 ± 13.15
Tumor location	
Right-sided tumors	38 (55.9)
Left-sided tumors	30 (44.1)
Treatment	
No prior treatment	55 (80.9)
Partial resection + RT	13 (19.1)
RT	
Single dose RT (< 14 Gy)	51 (75.0)
Single dose RT (≥ 14 Gy)	17 (25.0)
TrueBeam treatment	32 (47.1)
Conventional linac treatment	36 (52.9)

Values are presented as number (%) or mean ± standard deviation.
RT, radiotherapy.

Table 2. Planning and dosimetric parameters

Parameter	Mean ± SD	Range (min–max)
PTV volume (cm^3)	1.29 ± 1.18	0.05–5.00
Brainstem volume (cm^3)	22.97 ± 5.45	11.30–35.20
Brainstem mean dose (Gy)	0.73 ± 0.57	0.05–2.40
Brainstem maximum dose (Gy)	7.09 ± 4.41	0.25–15.60
Brainstem minimum dose (Gy)	0.04 ± 0.03	0.00–0.17
Cochlea volume (cm^3)	0.46 ± 0.54	0.01–1.90
Cochlea mean dose (Gy)	8.87 ± 4.03	0.03–15.80
Cochlea maximum dose (Gy)	12.90 ± 3.35	0.05–18.00
Cochlea minimum dose (Gy)	5.01 ± 3.83	0.03–12.60

PTV: n = 68; brainstem volume n = 56, dose n = 54; cochlea n = 54.
PTV, planning target volume; SD, standard deviation.

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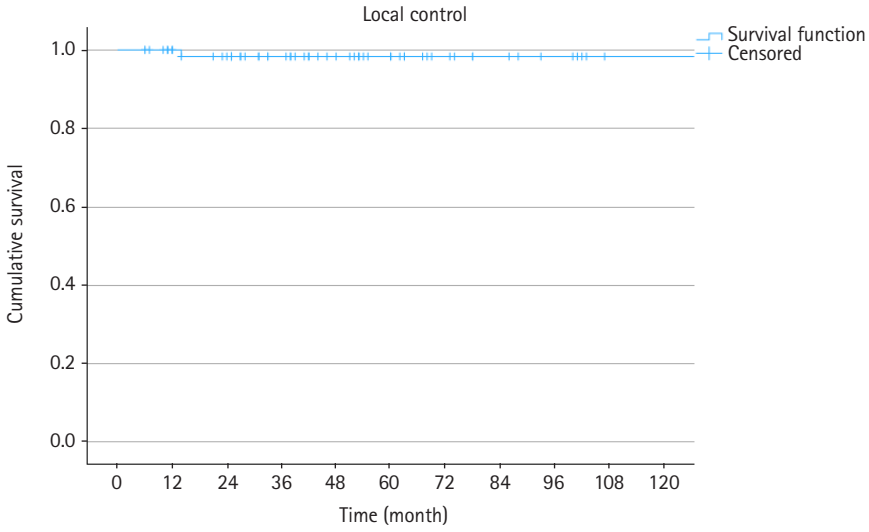

Fig. 2. In patients with vestibular schwannoma treated with stereotactic radiosurgery, the local control rate was 100% at 1 year, and 98.5% at both 5 and 10 years of follow-up.

Table 3. Treatment outcomes

Outcome	Value
No in-field progression	65 (95.6)
In-field progression	3 (4.4)
Stable MRI	39 (57.4)
Shrinkage on MRI	28 (41.2)
Mean IFP-free survival (mo)	62.10 ± 50.56
Mean radiological FU (mo)	67.97 ± 61.60
Mean overall survival (mo)	75.66 ± 62.82

Values are presented as number (%) or mean ± standard deviation.
MRI, magnetic resonance imaging; IFP, in-field progression; FU, follow-up.

3. Prognostic factors

Univariate Cox proportional hazards regression analysis did not identify any statistically significant predictors of local failure. Given the very small number of local failure events (n = 3), the results of these analyses should be interpreted cautiously.

Patients with a history of prior partial microsurgical resection showed an increased estimated hazard for recurrence (HR, 598.06), although this did not reach statistical significance (p = 0.493). This extremely large HR likely reflects statistical instability related to the low number of events rather than a precise estimate of effect size.

Similarly, a prescribed dose of ≥ 14 Gy showed a numerically higher estimated risk of local failure compared with doses < 14 Gy (HR, 3.83; p = 0.282).

No associations were identified between local failure and patient sex, tumor laterality, or treatment platform. Detailed results of the univariate analysis are summarized in Table 4.

4. Treatment-related toxicity

SRS was generally well tolerated. Acute toxicities occurring within 6 weeks after treatment were predominantly mild and included headache (8.8%), nausea (4.4%), fatigue (4.4%), and localized alopecia in one patient (1.5%) (Table 5).

Vertigo, tinnitus, and ataxia were considered disease-related symptoms of VS rather than treatment-related toxicities and were therefore analyzed separately.

Late toxicities, defined as those occurring beyond 6 weeks post-SRS, were infrequent and remained largely low-grade. No cases of persistent alopecia were observed during late follow-up. Facial nerve paresis was observed in nine patients (13.2%) at late follow-up.

Importantly, four patients (5.9%) presented with facial nerve paresis prior to SRS. Accordingly, only new-onset facial nerve paresis developing after treatment was considered treatment-related toxicity. Based on this definition, five patients (7.4%) developed new facial nerve paresis attributable to SRS.

None of these cases were associated with tumor progression at the time of symptom onset. The median time to onset of facial nerve paresis after treatment was approximately 8 months (range, 3 to 18). During follow-up, partial or complete clinical improvement was observed in several patients, indicating that these deficits were often transient.

No high-grade (CTCAE ≥ 3) facial nerve toxicity was observed. Severe adverse events (CTCAE grade ≥ 3) were rare, occurring in fewer than 3% of patients. One patient developed trigeminal neuralgia during follow-up (1.5%). The symptoms improved with conservative medical management during subsequent follow-up.

Table 4. Cox regression analysis – local control

Variable	Category coding	B	SE	Wald	df	p-value	HR (Exp(B))	95% CI for HR
Sex	0: female, 1: male	0.963	1.537	0.392	1	0.531	2.619	0.129–53.307
Site	0: left, 1: right	0.358	1.470	0.059	1	0.808	1.430	0.080–25.493
Pre-treatment	0: none, 1: partial resection + RT	6.394	9.332	0.469	1	0.493	598.057	0.000–5.24 × 10^{10}
SRS dose	0: < 14 Gy, 1: ≥ 14 Gy	1.342	1.247	1.158	1	0.282	3.828	0.332–44.129
Device	0: TrueBeam, 1: conventional LINAC	1.997	4.133	0.233	1	0.629	7.366	0.002–24,287.39

B, regression coefficient (log hazard ratio); SE, standard error; Wald, Wald chi-square statistic; df, degrees of freedom; HR (Exp(B)), hazard ratio (exponential of B); CI, confidence interval; RT, radiotherapy; SRS, stereotactic radiosurgery; LINAC, linear accelerator.

Table 5. Acute and late treatment-related toxicity

Symptom	Acute toxicity (≤ 6 weeks)	Late toxicity (> 6 weeks)
Headache	6 (8.8)	0 (0)
Nausea	3 (4.4)	2 (2.9)
Vomiting	0 (0)	1 (1.5)
Fatigue	3 (4.4)	0 (0)
Facial nerve paresis	Not observed	5 (7.4)
Trigeminal neuralgia	Not observed	1 (1.5)
Alopecia	1 (1.5)	0 (0)

Values are presented as number (%).

5. Evolution of disease-related symptoms after SRS

Disease-related symptoms, including vertigo, tinnitus, ataxia, and hearing impairment, were evaluated separately from treatment-related toxicities. These symptoms primarily reflect the natural history of VS rather than radiation-induced effects.

Hearing impairment was defined based on clinical documentation and available audiometric reports; standardized classifications such as Gardner–Robertson were not consistently available in this retrospective cohort.

A comparison of symptoms before and after treatment is presented in Table 6. Overall, no clinically meaningful long-term deterioration in disease-related symptoms was observed. While a transient increase in vertigo was noted during the acute post-treatment phase, symptoms generally stabilized or improved over time.

6. Statistical analysis of symptom evolution

Statistical analyses exploring changes in disease-related symptoms and functional status over time are summarized in Table 7. Given the retrospective study design and the limited number of events, these analyses should be considered descriptive and exploratory rather than confirmatory.

A statistically significant increase in vertigo was observed during the acute phase ($p < 0.001$), consistent with transient post-radiosurgical effects. No statistically significant changes were detected in late follow-up with respect to hearing impairment, tinnitus, ataxia, facial nerve function, trigeminal neuralgia, or Karnofsky performance status (all $p > 0.05$).

Although the overall number of patients reporting vertigo slightly decreased at late follow-up (Table 6), a transient increase in vertigo symptoms was observed during the acute post-treatment phase (≤ 6 weeks). This early post-treatment exacerbation explains the statistically significant Wilcoxon test result reported in Table 7, despite the absence of a sustained increase in vertigo at later follow-up.

Table 6. Disease-related symptoms before and after stereotactic radiosurgery

Symptom	Before treatment	After treatment	Change
Hearing impairment	61 (89.7)	60 (88.2)	–1
Tinnitus	28 (41.2)	24 (35.3)	–4
Vertigo	31 (45.6)	28 (41.2)	–3
Ataxia	8 (11.8)	5 (7.4)	–3

Values are presented as number (%).

Table 7. Wilcoxon and McNemar test results for acute (≤6 weeks) and late (>6 weeks) toxicities after single-fraction radiotherapy

Period	Symptom/ Score	Test	p-value	Interpretation
Acute (≤ 6 weeks)	Karnofsky score	Wilcoxon	0.248	Performance preserved
Acute (≤ 6 weeks)	Vertigo	Wilcoxon	< 0.001	Transient increase
Late (> 6 weeks)	Hearing impairment	McNemar	> 0.99	No significant change
Late (> 6 weeks)	Tinnitus	McNemar	0.424	No significant change
Late (> 6 weeks)	Ataxia	McNemar	0.453	No significant change
Late (> 6 weeks)	Facial nerve paresis	McNemar	0.727	No significant change

Discussion and Conclusion

VS, although histologically benign, often cause significant morbidity due to their location in the cerebellopontine angle and proximity

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to critical neurovascular structures. Our study of 68 patients treated with single-fraction SRS adds long-term real-world data supporting the established efficacy and safety of this treatment modality. We observed a local control rate of 95.6% at a mean follow-up of 62.1 months, which is in line with contemporary series reporting 90–98% long-term tumor control after SRS [3,6,7]. A detailed comparison of our outcomes with major contemporary studies is provided in Table 8 [3,12-15]. These outcomes support SRS as a first-line option for small- to medium-sized tumors, particularly when the preservation of neurological function and quality of life (QoL) is prioritized [1,8,9].

The mechanisms underlying VS control after SRS are thought to involve both direct tumor cell DNA damage and radiation-induced vascular changes. High-dose single-fraction irradiation induces DNA double-strand breaks that overwhelm repair mechanisms in the slowly proliferating Schwann cells [2]. In addition, radiation-induced endothelial apoptosis and subsequent hyalinization of intratumoral vessels further contribute to tumor control [5]. In our series, 41.2% of tumors demonstrated radiographic shrinkage, consistent with previously reported regression rates of 30%–50% [6,10,16]. Importantly, transient tumor expansion (pseudoprogression) was not uncommon and has been well characterized in prior studies, typically resolving within 2–3 years [10,16]. Thus, early post-treatment enlargement should not be misinterpreted as treatment failure.

The optimal radiation dose for VS remains an area of active discussion. Our institutional practice of prescribing 12–15 Gy (mean, 13.14 Gy) reflects the global shift from earlier high-dose protocols (16–20 Gy) toward lower-dose regimens to reduce cranial nerve toxicity [6,17,18].

In our exploratory analyses, doses ≥ 14 Gy showed a numerically higher estimated risk of local failure, although this finding did not reach statistical significance and should be interpreted with caution given the very small number of failure events in our cohort (n = 3).

Our findings align with Hasegawa et al. [3], who reported excellent tumor control with 12–13 Gy and lower complication rates compared to higher-dose treatments. Current consensus suggests that doses < 12 Gy may compromise tumor control in larger tumors [19,20], while doses above 13–14 Gy may increase toxicity without significant gain in efficacy [6,21].

Hearing preservation remains a critical outcome metric in VS management. In our cohort, the mean cochlear dose (8.87 Gy) exceeded the 4–14 Gy range reported to correlate with better hearing preservation [4,8,9]. This likely reflects the inclusion of earlier treatment plans predating routine cochlear dose constraints. Contemporary practice emphasizes maintaining a mean cochlear dose ≤ 4–5 Gy when hearing preservation is a goal [11,12,19,22]. Emerging strategies such as cochlear-sparing planning and hypofractionated regimens (e.g., 25 Gy in 5 fractions) have demonstrated promising results in improving hearing outcomes without compromising local control [11,19,22,23].

However, standardized audiometric classifications such as Gardner-Robertson or American Academy of Otolaryngology–Head and Neck Surgery were not systematically available in this retrospective cohort, which limits formal evaluation of hearing preservation outcomes and direct comparison with published series.

The management of VS after prior subtotal resection presents unique challenges. In our exploratory analysis, prior subtotal resection was associated with a markedly elevated estimated HR for local failure (HR, 598.057). Given that only three local failures occurred in the entire cohort, this extremely large HR should be interpreted cautiously and likely reflects statistical instability rather than a precise estimate of effect size. Nevertheless, this observation is broadly consistent with prior reports suggesting that residual tumor after surgery may exhibit altered radiosensitivity [17] or represent more aggressive tumor biology [24]. Postoperative changes

Table 8. Comparison of the current studies of radiosurgery of vestibular schwannoma

Study	No.	Dose (Gy)	Mean F/U (month)	Local control (%)	Hearing preservation (%)	Facial nerve toxicity (%)	Trigeminal toxicity (%)	Tumor shrinkage (%)
Present study	68	12–15 (mean 13.14)	67.97	98.5 at 5 years	Not systematically available[a]	10.3	1.5	41.2
Hasegawa et al. (2013) [3]	440	12.8 (median)	150	93 at 5 years, 92 at 10 years	NR	1	1	NR
Kim et al. (2007) [12]	59	11–13	60	97 at 5 years	33	0	0	NR
Johnson et al. (2019) [13]	307	12–13	91	95 at 7 years	68.8 at 5 years	NR	NR	NR
De Leo et al. (2024) [14]	139	12.5	60	90 at 5 years	NR	0.9	NR	NR
Teyateeti et al. (2021) [15]	58	12–14	96	92–96 at 10 years	72 at 5 years, 39 at 10 years	3.5	NR	NR

F/U, follow-up; NR, not reported.
[a]Hearing preservation data in the present study were not systematically assessed using standardized audiometric classifications such as Gardner-Robertson or American Academy of Otolaryngology–Head and Neck Surgery.

also complicate target delineation and dose delivery [25]. In such cases, the literature supports either definitive upfront SRS for residual disease or a surgical strategy aiming for gross total resection when feasible [17,26].

The toxicity profile in our series was acceptable and compares favorably with surgical series. Localized alopecia was rare and transient, occurring acutely in only one patient (1.5%) and resolving without persistence into late follow-up.

When pre-existing facial nerve deficits were excluded, new-onset facial nerve paresis attributable to SRS was observed in only five patients (7.4%), which remains substantially lower than the 15%–40% rates typically reported after microsurgery [8,9,26], and trigeminal neuropathy occurred in only 1.5%, comparable to modern SRS outcomes [3,6,27]. Our results emphasize the importance of careful dose planning to minimize radiation exposure to the brainstem and cranial nerves [18,28].

Most tumors in our series either remained stable (57.4%) or regressed (41.2%) on follow-up imaging. Transient enlargement, reported in up to 30% of cases [10,16], underscores the importance of cautious interpretation of post-SRS imaging. Our mean follow-up of ~68 months was sufficient to differentiate pseudoprogression from true recurrence.

The benign and localized nature of sporadic VS was further supported by the absence of true out-of-field tumor progression [21,29]. One patient developed a meningioma outside the irradiated field, which was considered a second primary tumor rather than VS progression; nevertheless, such findings warrant continued clinical vigilance, particularly in younger patients, to exclude underlying genetic predisposition such as NF2 [24].

In our cohort, outcomes were comparable between TrueBeam and conventional LINAC platforms, suggesting that adherence to dosimetric principles is more critical than platform selection [20,30,31]. Nevertheless, newer delivery systems with improved image guidance and shorter treatment times may further optimize therapeutic ratios [18]. Our mean PTV dimension of 1.29 cm^3 reflects modern standards, though some centers advocate for sub-millimeter margins enabled by high-resolution MRI and advanced immobilization techniques [32,33].

Although formal QoL measures were not assessed in this study, the low rate of significant toxicity suggests that most patients maintain good functional outcomes after SRS. This is consistent with prospective QoL studies showing superior balance and facial function outcomes compared with microsurgery [1,9,12]. Future multicenter prospective studies incorporating standardized QoL and audiometric outcomes are needed to confirm these findings [1,9].

Advances in imaging (diffusion tensor imaging, tractography, and functional MRI) may further improve target delineation and cranial nerve preservation [33]. Radiogenomic profiling holds potential for individualized dose prescription and outcome prediction [34]. Additionally, hypofractionated regimens (3–5 fractions) may offer an improved therapeutic window for larger tumors or lesions abutting critical structures [11,20,23,35].

Our institutional experience provides additional long-term real-world evidence supporting single-fraction SRS as a safe and effective treatment for vestibular schwannoma, achieving durable tumor control with low treatment-related morbidity. Prognostic analyses in this cohort were exploratory and limited by the very small number of failure events. Continued technological advances, improved dose constraints, and prospective studies incorporating standardized functional and audiometric outcomes will be important to further refine patient selection and optimize treatment strategies.

Statement of Ethics

The study was approved by the ethics committee of the Philipps University Marburg (Nr. 24-138-RS at 03.06.2024) and was carried out in accordance with the Declaration of Helsinki, and the requirement for informed consent was waived because of the retrospective design.

Conflict of Interest

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

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Author Contributions

Conceptualization, methodology, project administration: SA, AG. Investigation and data curation: MF. Formal analysis: KTT. Writing of the original draft: KTT. Writing of the review and editing: KTT, MF, PL, FFS, ES, KR, KZ, HV, SA, AG.

Data Availability Statement

The data are not publicly available due to privacy or ethical restrictions but are available from the corresponding author upon reasonable request.

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Trends in radiotherapy fractionation for bone metastases: a multi-center study of practice patterns before, during, and after COVID-19

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Purpose: Trials show similar pain outcomes for hypofractionated and multi-fraction regimens in bone metastases, yet clinical adoption of hypofractionation remains limited. The coronavirus disease 2019 (COVID-19) pandemic may have increased hypofractionation to minimize hospital visits and optimize resources. This study evaluated fractionation patterns before, during and after COVID-19 and compared pain outcomes between regimens in routine practice.

Materials and methods: Data on treatment regimens for bone metastases between 2018 and 2022 were collected from 11 of 22 Dutch radiotherapy departments. Trends in utilization of hypofractionated (1–2 times 8 Gy) and multi-fraction (≥5 fractions) regimens were analyzed. For a subset of patients (n = 278), self-reported pain scores were collected at baseline, 4 and 8 weeks, and 3 months. Pain scores and pain response were compared for hypofractionated and multiple-fraction regimens, with complete (pain score 0) or partial (reduction ≥2 points) response classified as responders.

Results: A total of 17,336 patients were included, receiving 31,677 treatment regimens. The majority of the regimens were hypofractionated (n = 25,790, 81.4%). The use of hypofractionated regimens ranged from 33.6% to 98.9% between radiotherapy departments. A statistically significant increase in hypofractionated regimens was observed since the onset of the COVID-19 pandemic in 2020 ($p < 0.001$). In an exploratory analysis of patients with available pain scores, pain response in the three months post-treatment did not differ significantly between hypofractionated and multi-fraction regimens (56% vs. 63%, $p = 0.406$).

Conclusion: This study demonstrates a high adoption of hypofractionated regimens, with a slight increase since the COVID-19 pandemic, though considerable variation remains between departments. Pain outcomes were comparable between hypofractionated and multi-fraction regimens, suggesting equal palliation and less treatment burden with hypofractionation.

Keywords: Palliative care, Radiation dose hypofractionation, COVID-19, Pain

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Introduction

Bone metastases are a common cause of pain in patients with metastatic cancer, negatively impacting their quality of life [1,2]. Palliative radiotherapy is one of the main treatment options for pain relief in bone metastases. Trials have shown that single-fraction radiotherapy (1×8 Gy) is an appropriate and effective alternative to longer regimens for pain relief in bone metastases [3]. These studies have consistently shown equal pain response rates and toxicity with single fraction versus multi-fraction regimens. As a result, single-fraction radiotherapy has become the internationally recommended treatment for bone metastases [4-6].

Several factors favor the use of hypofractionated regimens consisting of one or two fractions over longer regimens. Given the limited survival of many patients with bone metastases, hypofractionated regimens may benefit patients and their families by reducing the treatment burden, and the time and indirect costs spent on treatment [7], allowing them to spend their remaining time in more meaningful ways. In addition, shorter treatment regimens allow radiotherapy departments to use resources more efficiently.

Despite these benefits and the evidence supporting hypofractionated regimens, studies have shown wide variations in the uptake of hypofractionated regimens, with some countries adopting hypofractionation more routinely while others continue to rely predominantly on conventional fractionation schedules [8,9]. However, evidence on recent trends in the uptake of hypofractionated treatment regimens in daily clinical practice, particularly since the coronavirus disease 2019 (COVID-19) pandemic, remains limited. During the pandemic, radiotherapy practices shifted considerably globally, including increased use of telemedicine, reduced patient volumes, postponement of treatments, and a push toward shorter treatment schedules [10,11]. The use of hypofractionated regimens was specifically advocated to reduce hospital visits and optimize the use of limited resources [12], and the pandemic may therefore have further accelerated their adoption [12]. In the Netherlands, the use of one or two fractions of 8 Gy as a substitute for longer regimens (e.g., 5×4 Gy or 10×3 Gy) was advised by the Dutch Society for Radiotherapy and Oncology [13]. Therefore, this study aimed to evaluate trends in fractionation patterns including data from multiple radiotherapy departments in the Netherlands before, during, and after the COVID-19 pandemic. Moreover, we performed an exploratory analysis in a subset of the total cohort to assess pain response in patients treated with hypofractionated palliative regimens versus those receiving multi-fraction regimens in daily clinical practice.

Materials and Methods

1. Study population and data

Eleven out of the 22 academic and non-academic radiotherapy departments in the Netherlands participated in this study. Data on all treatment regimens for bone metastases between 2018 and 2022 were collected from the local registration systems, including age at time of treatment, sex, performance status, primary tumor localization, treatment site, and radiotherapy treatment details (total dose, number of fractions, technique, previous radiation to the same site). Stereotactic treatment regimens with high ablative total doses were excluded either through the variable indicating the radiotherapy technique when available or, when absent, by identifying stereotactic dose-fractionation schedules based on expert opinion of a senior radiation oncologist (YML). Pain outcome data were collected for all patients from the total study cohort who were previously enrolled in the PRospective Evaluation of interventional StudiEs on boNe meTastases (PRESENT) cohort. All adult patients with bone metastases undergoing radiotherapy were eligible for inclusion in the PRESENT study and had to provide informed consent. Exclusion criteria were mentally incompetent patients and a life expectancy of <1 year. More detailed inclusion and exclusion criteria for enrollment in the PRESENT cohort were described previously [14]. The pseudonymized data were combined and collected in a central database at the Netherlands Comprehensive Cancer Organisation (IKNL). As the initiators of the study, IKNL and Leiden University Medical Centre (LUMC) obtained approval from the Scientific Committee of the Department of Radiotherapy at LUMC. The study was exempted from review by the Medical Research Ethics Committee of the LUMC and the Amsterdam University Medical Centers because the Medical Research Involving Human Subjects Act did not apply to the study.

2. Definitions

Treatment regimens were categorized as hypofractionated (1×8 or 2×8 Gy) or multi-fraction (≥5 fractions). A small proportion of the regimens (2%) consisted of <5 fractions but other than 1×8 Gy or 2×8 Gy and were excluded from the analyses. Localization of the primary tumor was categorized into lung, prostate, breast, other, or unknown. Since the treatment site was recorded as open text data, artificial intelligence (AI: GPT-4o-Mini) was used to categorize it into one of the following groups: cervical spine, thoracic spine, lumbar spine, ribs, sacrum (including os coccygis), pelvis, proximal femur/acetabulum, humerus, or other. After categorization by AI, the first 100 observations per radiotherapy department were manually checked. This showed a correct categorization in approximately 95% of the cases. In about a quarter of the regimens, the

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treatment site consisted of a combination of these categories, most commonly (1) a larger treatment area in the spine, (2) spine and/or pelvis and/or sacrum, (3) pelvis and/or sacrum and/or proximal femur/acetabulum, and (4) spine and ribs. These categories were added to the original nine categories. The distribution of the treatment sites of the included treatment regimens across these categories is shown in Supplementary Table S1. For the analyses, the treatment site was grouped into five broader categories, namely spine, pelvic region, extremities, ribs, or other. Data on re-irradiation were available at two centers and were categorized as yes or no based on whether a patient had received a previous course of radiotherapy to the same treatment site. Performance status was grouped into Eastern Cooperative Oncology Group (ECOG) 0, 1, ≥ 2, or unknown. If performance status was documented as Karnofsky performance status (KPS), it was converted to ECOG (KPS 90–100 to ECOG 0, KPS 70–80 to ECOG 1, KPS 10–60 to ECOG ≥ 2) [15]. Pain scores were self-reported using the Brief Pain Inventory at baseline (a maximum of plus or minus 7 days from date of first fraction), and 4 and 8 weeks and 3 months after treatment. The outcome measure was the worst pain a patient experienced in the previous 3 days, measured on the Numeric Rating Scale ranging from 0 (no pain) to 10 (worst pain imaginable).

3. Statistical analyses

Characteristics of the study population were analyzed descriptively. Trends in the use of hypofractionated (1 × 8 or 2 × 8 Gy) and multi-fraction (≥ 5 fractions) regimens were analyzed over time for the entire cohort and stratified by radiotherapy department to assess variation. Trends in fractionation patterns were additionally stratified into 1 × 8 Gy, 2 × 8 Gy, 5 × 4 Gy, 10 × 3 or 13 × 3 Gy, or other multi-fraction (≥ 5). To evaluate trends in hypofractionation use over time and account for demographic shifts (e.g., aging population), a logistic regression was performed including year of treatment, age, sex, and primary tumor site. Logistic regression analyses were also performed to assess factors independently associated with hypofractionation. First, univariable analyses were performed for the variables age, sex, radiotherapy department, primary tumor localization, treatment site, and re-irradiation. Variables significantly associated with hypofractionation in the univariable analyses ($p < 0.1$) were included in a multivariable model. A separate multivariable model was performed in the subset of patients with information on re-irradiation (n = 3,893). Because most variables had very few missing observations (< 1%), complete-case analyses were used for all regression models. Since performance status was missing frequently, and not at random due to systematic differences in registration between radiotherapy departments, it was excluded from the regression analyses.

An exploratory analysis of pain outcomes was performed in patients for whom pain scores were available through inclusion in the PRESENT cohort. Mean pain scores and pain response were calculated over the 3-month post-treatment period for patients with baseline pain scores ≥ 2. Pain response was based on the difference between baseline pain scores and pain scores at week 4, week 8, and 3 months, irrespective of changes in analgesic use, as no data on this were available. Therefore, calculations of pain response could not be fully performed according to the international consensus criteria [16]. Patients who achieved a complete (pain score 0) or partial (reduction ≥ 2 points) response were classified as responders; others were classified as non-responders. Mean pain scores were compared between hypofractionated and multi-fraction regimens using the Wilcoxon rank sum tests. Pain response was compared using chi-squared tests. Statistical analyses were performed using Stata version 17.0 software (Stata Corp., College Station, TX, USA). A two-tailed p-value of < 0.05 was considered statistically significant.

Results

1. Cohort characteristics

A total of 17,336 patients were included in this study, receiving 31,677 treatment regimens. During the study period, 9,545 patients (55.1%) received one radiotherapy treatment, 4,249 patients (24.5%) two treatments, and 3,542 patients (20.4%) three or more treatments. At the time of first treatment, the median age of patients was 70 years (interquartile range, 61 to 76 years), and most patients were male (57.5%) (Table 1). The most frequent primary tumor was lung cancer (26.6%), followed by prostate cancer (21.3%) and breast cancer (17.2%), and 34.5% had another primary tumor. Across all treatment regimens, the most common treatment site was the spine (40.9%), followed by the pelvic region (26.1%). Across the radiotherapy departments, the number of patients treated for bone metastases during the study period ranged from 637 to 2,977. Moreover, lung, prostate, and breast cancer were the most common primary tumor localizations across all departments.

2. Trends in radiotherapy fractionation for bone metastases

Among all 31,677 radiotherapy treatment regimens, 81.4% were hypofractionated (n = 25,790), while 18.6% were multi-fraction regimens (n = 5,887). The use of hypofractionated regimens increased slightly from the onset of the COVID-19 pandemic in 2020 onwards (77.9%–79.0% before COVID-19 vs. 82.5%–83.9% since COVID-19, $p < 0.001$) (Fig. 1A). This trend remained significant

Table 1. Patient and treatment characteristics of the study cohort (2018–2022)

	No. (%)
Patient characteristics (n = 17,336)	
Age (year)	70 (61–76)
Sex	
Male	9,955 (57.5)
Female	7,372 (42.5)
Unknown	9 (0.0)
Performance score (WHO)	
0	507 (2.9)
1	1,355 (7.8)
≥ 2	1,772 (10.3)
Unknown	13,702 (79.0)
Localization primary tumor	
Lung	4,612 (26.6)
Prostate	3,695 (21.3)
Breast	2,983 (17.2)
Other	5,982 (34.5)
Unknown	64 (0.4)
No. of treatment regimens received in study period	
1	9,545 (55.1)
2	4,249 (24.5)
≥ 3	3,542 (20.4)
Treatment characteristics (n = 31,677)	
Treatment site	
Spine	12,923 (40.8)
Pelvic region	8,241 (26.0)
Extremities	4,228 (13.3)
Ribs	2,277 (7.1)
Other	3,939 (12.4)
Unknown	69 (0.4)

Values are presented as median (interquartile range) or number (%).
WHO, World Health Organization

Table 2. Multivariable regression analysis of factors associated with receiving hypofractionated regimens (1×8 Gy or 2×8 Gy) for bone metastases (n = 31,292)

Variable	OR (95% CI)	p-value
Sex		
Male	Reference	
Female	0.95 (0.88–1.03)	0.289
Age (year)		
< 50	Reference	
50–75	1.12 (1.00–1.26)	0.046
> 75	1.61 (1.41–1.83)	< 0.001
Radiotherapy department		
1	Reference	
2	0.44 (0.39–0.50)	< 0.001
3	0.49 (0.44–0.55)	< 0.001
4	1.72 (1.53–1.94)	< 0.001
5	0.79 (0.71–0.88)	< 0.001
6	1.27 (1.10–1.46)	0.001
7	0.08 (0.07–0.09)	< 0.001
8	18.70 (10.26–34.08)	< 0.001
9	2.24 (1.89–2.65)	< 0.001
10	0.97 (0.81–1.16)	0.794
11	0.62 (0.55–0.71)	< 0.001
Localization primary tumor		
Lung	Reference	
Prostate	1.09 (0.97–1.21)	0.136
Breast	0.66 (0.59–0.73)	< 0.001
Other	0.63 (0.58–0.69)	< 0.001
Treatment site		
Spine	Reference	
Pelvic region	1.01 (0.93–1.09)	0.800
Extremities	0.88 (0.80–0.96)	0.009
Ribs	1.70 (1.47–1.96)	< 0.001
Other	0.68 (0.62–0.75)	< 0.001

OR, odds ratio; CI, confidence interval.

when controlling for age, sex, and primary tumor localization ($p < 0.001$) (Supplementary Table S2). A single fraction of 8 Gy was the most commonly used hypofractionated regimen (72.0%–75.9% over the years) (Fig. 1B). The use of 2 fractions of 8 Gy increased slightly (4.9%–9.2% over the years). In total, 5 fractions of 4 Gy was the most commonly provided multi-fraction regimen, with a slight decrease over the years (16.1% to 11.7% over the years). Between radiotherapy departments, the use of hypofractionated regimens ranged from 33.6% to 98.9% (Fig. 2).

3. Factors associated with receipt of hypofractionated regimens

Age, radiotherapy department, localization of the primary tumor, and treatment site were independently associated with hypofractionation (Table 2). Older patients had higher odds of receiving hypofractionated treatment regimens compared to younger patients (> 75 years; odds ratio [OR], 1.61; 95% confidence interval [CI], 1.41 to 1.83; $p < 0.001$). Patients with a primary tumor in the breast were less likely to receive hypofractionated regimens (OR, 0.66; 95% CI, 0.59 to 0.73; $p < 0.001$). Bone metastases in the spine and pelvic region had similar odds of being treated with hypofractionated regimens. The odds of hypofractionation were slightly lower when the treatment site was the extremities (OR, 0.88; 95% CI, 0.80 to 0.96; $p = 0.009$) and higher when the treatment site was the ribs (OR, 1.70; 95% CI, 1.47 to 1.96; $p < 0.001$). The likelihood of hypofractionation was also higher in case of re-irradiation of a previously treated site (Supplementary Table S3).

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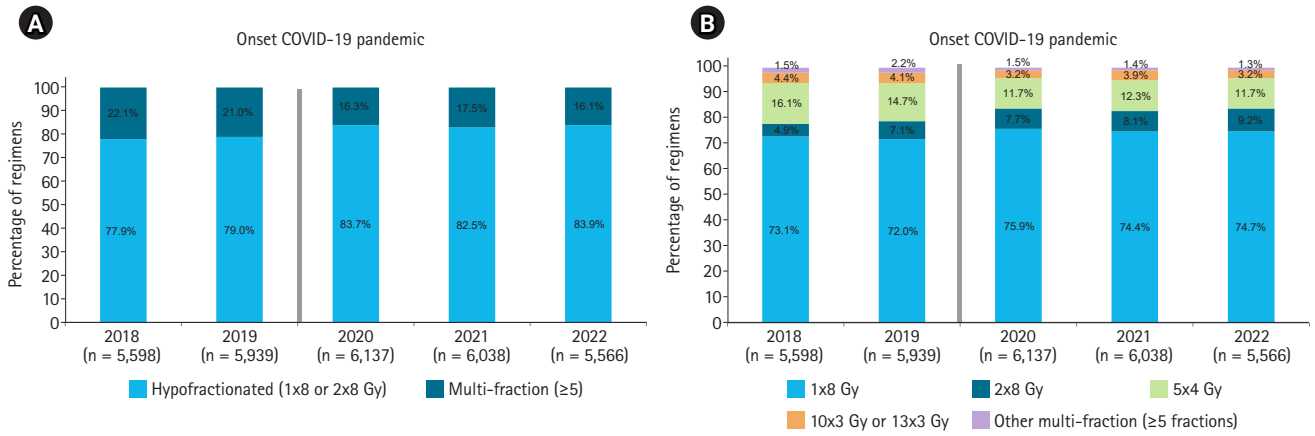

Fig. 1. Trends in fractionation patterns over the period 2018–2022. Hypofractionated versus multi-fraction regimens (A) and further stratification of treatment regimens (B). COVID-19, coronavirus disease 2019.

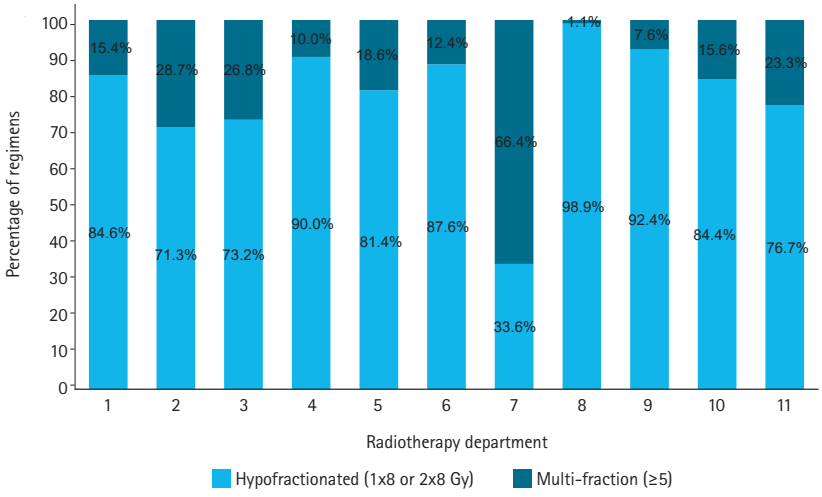

Fig. 2. Use of hypofractionated (1×8 or 2×8 Gy) and multi-fraction (≥5) regimens during the period 2018–2022 stratified by radiotherapy department.

4. Pain

Pain scores at baseline were available in a subset of 278 patients. These patients had a median age of 69 years, were predominantly male (65.1%), and most commonly had a primary tumor in the prostate (32.0%), followed by the lung (26.2%) (Supplementary Table S4). Compared to the total study cohort, these patients were more often male, more likely to have prostate cancer, and more frequently treated with multi-fraction schedules. The majority of these patients received hypofractionated regimens (n = 204, 73.3%). Mean pain scores did not differ significantly between hypofractionated and multi-fraction regimens over the 3-month post-treatment period. Scores declined from 6.5 to 4.0 in the hypofractionated group and from 6.3 to 3.4 in the multi-fraction group (Fig. 3). Pain response at week 4, week 8 and 3 months was similar between patients receiving hypofractionated and multi-fraction regimens (month 3, 55.6% vs. 63.0%; p = 0.406) (Fig. 4).

Discussion and Conclusion

This study evaluated fractionation patterns of palliative radiotherapy for bone metastases in a large cohort of patients in the Netherlands. Hypofractionated regimens were most commonly used, and a modest but significant increase in hypofractionated regimens was observed since the onset of the COVID-19 pandemic. In an exploratory analysis in a subgroup of patients, comparable mean pain scores and pain responses were observed between patients receiving hypofractionated and multi-fraction regimens in routine clinical practice over the 3-month post-treatment period.

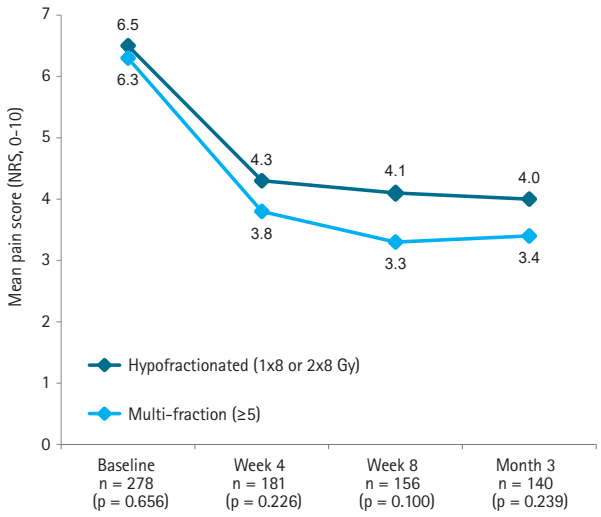

Fig. 3. Mean pain scores at baseline, week 4, week 8, and 3 months after treatment in patients receiving hypofractionated versus multi-fraction (≥5) regimens. NRS, Numeric Rating Scale.

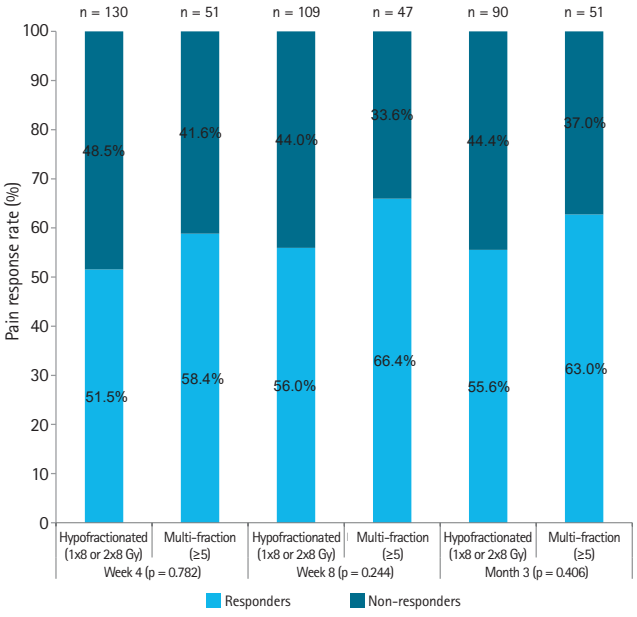

Fig. 4. Pain response at week 4, week 8, and month 3 for patients who received hypofractionated (1×8 Gy or 2×8 Gy) regimens versus multi-fraction (≥5) regimens. Pain response was defined based on differences in pain scores, irrespective of changes in analgesic use.

During the study period, one fraction of 8 Gy was the most commonly used regimen for the palliation of bone metastases, with its use ranging from 72%–76% over the years. Treatment with two fractions of 8 Gy increased from 5% to 9% over the years, which may indicate a replacement of 5 fractions of 4 Gy with 2 fractions of 8 Gy, as the use of 5×4 Gy decreased slightly during the study period. These findings are in line with established clinical guidelines that support the use of hypofractionated regimens as they provide optimal treatment for many patients [4-6]. The use of hypofractionated regimens observed in this study is relatively high compared to international practice patterns, with international literature reviews showing use of single-fraction regimens mostly ranging between 5% and 50% [8,17]. This may be related to extensive research in the Netherlands into the effectiveness of single-fraction radiotherapy combined with a nationally applied evidence-based medicine approach that ensures that these findings are integrated into clinical practice. Additionally, differences in financing may play a role, as reimbursement models in some countries are more dependent on fractionation schedules, potentially incentivizing longer treatment courses [18-20]. The high adoption of hypofractionated regimens also suggests a patient-centered care approach, as hypofractionated regimens reduce the burden of treatment, which can ultimately improve patient wellbeing and quality of life [21,22]. In this study, older patients were more likely to receive hypofractionated regimens, supporting the fact that patient-centered care is being delivered to more frail patients by reducing the intensity of treatment. However, since results from the Dutch Bone Metastasis Study showed that response rates with single- or multi-fraction regimens are independent of age [23], hypofractionated regimens may be just as beneficial for younger patients by reducing the treatment and time burden while maintaining the same level of treatment efficacy if pain response is the treatment goal.

This study showed a slight but significant increase in hypofractionation in the treatment of bone metastases since the onset of the COVID-19 pandemic. Previous studies have shown changes in radiotherapy practices during the pandemic, including the increased use of telemedicine and a decrease in patient volumes, postponement of treatments, and shortages of staff and equipment [10,24]. During the pandemic, it was recommended to increase the use of hypofractionated regimens to reduce hospital visits and optimize the use of limited resources [12]. The slight increase in the use of hypofractionated regimens after 2020 may indicate that these recommendations were at least partially adopted by radiation oncologists and that this effect may have continued after the pandemic.

Despite the overall trend toward hypofractionated regimens, this study observed considerable variation between radiotherapy departments in the uptake of these regimens. This is consistent with the variability observed internationally in the use of hypofractionated regimens [8,9,25]. After adjusting for key patient and disease characteristics (age, sex, primary tumor localization, and localization of bone metastases), the differences between departments remained statistically significant, indicating that case mix alone is

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unlikely to fully account for the observed differences. Previous studies showed that several other factors may contribute to this variability, including beliefs in the clinical evidence surrounding hypofractionation, waiting times at the radiotherapy department, and physician or institutional preferences [25-27]. Individual institutional protocols of the departments may vary in how strongly hypofractionated regimens are advocated, and longstanding departmental practice patterns may shape treatment decisions. These factors likely contribute to the observation that even within a country with a limited number of radiotherapy departments, united within a well-organized national radiotherapy society, the approach to the radiation treatment of bone metastases remains subject to individualization. Although some variation in clinical practice can be an indicator of effective patient-centered care, unwarranted variation in hypofractionation may impede the delivery of affordable and accessible radiotherapy. Therefore, the practice variation observed in this study may serve as valuable information for benchmarking and targeting implementation strategies.

Primary tumor localization and treatment site significantly influenced fractionation patterns. Patients with prostate or lung cancer were more likely to receive hypofractionated regimens than patients with breast cancer. The higher rate of hypofractionated regimens in patients with lung cancer may reflect the relatively poor prognosis of these patients. These patients may have the most to gain in terms of time investment versus life expectancy from hypofractionated regimens. Although both patients with metastatic prostate and breast cancer generally have a better prognosis, there is some evidence that bone metastases from primary breast tumors may have a higher likelihood of pathologic fractures [28,29]. Breast cancer bone metastases are typically osteolytic, which increases the likelihood of pathologic fractures, whereas prostate cancer bone metastases are more likely to be osteoblastic [30]. Since longer treatment regimens may be beneficial in the presence of pathologic fractures [31], this may partly explain the higher rate of multi-fraction regimens in breast cancer patients. Additionally, remineralization has been shown to be significantly higher in breast cancer patients following multi-fraction regimens, contributing to improved bone stabilization [32]. It was also observed that re-irradiation of previously treated metastases was more likely to involve a hypofractionated regimen. This may be related to the fact that physicians are more inclined to retreat after 1 or 2 fractions of 8 Gy [33], and then subsequent re-irradiation is likely to consist of 1 or 2 fractions.

In terms of pain outcomes, the exploratory analysis on pain outcomes in this study showed that mean pain scores and pain response over the 3-month post-treatment period did not differ significantly between hypofractionated and multi-fraction regimens. These results support the generalizability of the clinical trial results showing non-inferiority of hypofractionated regimens for pain relief to real-world settings. It is important to note, however, that selecting an appropriate fractionation schedule can be influenced by expected patient survival, although predicting survival in patients with metastatic disease remains challenging. Several studies have shown that single-fraction regimens are associated with a greater likelihood of re-irradiation compared with multi-fraction regimens [3]. Clinicians may therefore prefer multi-fraction regimens for patients anticipated to live longer to reduce the risk of pain recurrence. However, the rate of re-irradiation likely does not accurately reflect response duration, since it was shown that re-irradiation is carried out earlier and more often after a single 8 Gy treatment, irrespective of response [33]. It may therefore capture clinicians' willingness and the feasibility to retreat after a single fraction, and the ongoing disbelief that 8 Gy is as effective as multiple fractions. As advances in systemic therapies extend life expectancy for patients with metastatic disease, the recent availability of stereotactic regimens may provide a chance of more durable pain control in individuals likely to live longer [34]. However, which patients will benefit from stereotactic radiotherapy is still uncertain. Nevertheless, after a single fraction of 8 Gy, re-irradiation is effective [33,35], and when retreatment is required, a single-fraction for retreatment still results in less cumulative treatment burden than longer multi-fraction regimens [33].

The main strength of this study is the inclusion of a large number of treatment regimens for bone metastases from a variety of radiotherapy departments in the Netherlands, thus providing a representative reflection of treatment patterns in clinical practice. However, some limitations should be noted. First, the use of hypofractionated or multi-fraction regimens for bone metastases may depend on variables that were not available for this study. Most importantly, due to the limited structural registration of spinal cord compression and/or pathologic fractures in radiotherapy databases, we were unable to characterize bone metastases as complicated or uncomplicated, which may affect fractionation patterns, as complicated bone metastases may benefit from longer treatment schedules [31]. Other variables that may influence dose fractionation patterns that were not available in this study include factors such as lesion size, soft tissue involvement, travel distance, and concurrent systemic therapy. Second, data on analgesic use were not available for this study, and therefore pain response could only be assessed based on changes in pain scores. Changes in analgesic use could not be accounted for according to the international consensus criteria [16]. This may have led to an underestimation of the response rates in this study. However, in previous analyses of the Dutch Bone Metastasis Study, the effect of reduced analgesic use

on response rates appeared to be small (in 3% of patients in both the single and multi-fraction group) [33].

This study shows a high overall adoption of hypofractionated radiotherapy regimens for the palliation of bone metastases in the Netherlands, with a slight increase since the COVID-19 pandemic. In the subgroup with available pain scores, pain outcomes between hypofractionated and multi-fraction regimens were comparable. This exploratory analysis suggests equal palliation with lower care burden in case of hypofractionation. However, variation between radiotherapy departments in the use of hypofractionated regimens exists. These observations support the use of hypofractionation in routine practice to promote convenient and accessible radiotherapy for all patients with bone metastases.

Statement of Ethics

The Netherlands Comprehensive Cancer Organisation (IKNL) and Leiden University Medical Centre (LUMC) obtained approval from the Scientific Committee of the Department of Radiotherapy at LUMC. The study was exempted from review by the Medical Research Ethics Committee of the LUMC and the Amsterdam University Medical Centers because the Medical Research Involving Human Subjects Act did not apply to the study. Informed consent was not obtained for this study, as the majority of patients had deceased at the time of data collection. The study used pseudo-anonymized treatment data and did not involve directly identifiable patient information. In accordance with the Dutch Medical Treatment Contracts Act (WGBO), specific informed consent was therefore not required.

Conflict of Interest

R. Gal and J.M. van der Velden report receiving research grants from the Dutch Cancer Society (KWF). J.M. van der Velden also serves on the Data Safety Monitoring Board for the BRENAR trial and is a member of the Dutch National Guideline Committee for Spinal Metastases. M. Mast reports serving as Chair of the ESTRO Focus Group on Positioning & Immobilization. J.G.H. van Nes reports being Secretary of the National Platform for Radiotherapy for Benign Conditions. P.G. Westhoff reports receiving payment for a presentation from Longkankernet and an honorarium for membership in the Dutch Guideline Committee on Bone Metastases. N.J.H. Raijmakers reports serving as Chair of the Foundation of Palliative Care Research in the Netherlands. Y.M. van der Linden reports receiving trial grants from ZonMW, and participating in teaching courses, lectures, and expert testimony for the Guideline on Bone Metastases.

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Author Contributions

Conceptualization, ES, HPF, NJHR, YML; Methodology, ES; Formal analysis, ES; Visualization, ES; Project administration, ES; Supervision, HPF, NJHR, YML; Resources, RG, JMV, EJBJ, IC, JNAD, MEM, JGHN, PGW, EV, KW, EDW, YML; Writing of the original draft: ES; Writing of the review & editing, HPF, RG, JMV, EJBJ, IC, JNAD, MEM, JGHN, PGW, EV, KW, EW, NJHR, YML.

Data Availability Statement

The data used in this study were provided by individual radiotherapy departments and shared with the Netherlands Comprehensive Cancer Organisation (IKNL) solely for the purposes of this study. As data ownership remains with the original institutions, IKNL is not authorized to share the combined dataset. Data may be available upon reasonable request from the respective departments, subject to their approval.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2026.00038.

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Lower-neck involvement and post–concurrent chemoradiotherapy response predict distant metastasis in head and neck cancer

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Purpose: This study aimed to evaluate whether lower-neck involvement and post–concurrent chemoradiotherapy (CCRT) response predict distant metastasis (DM) in patients with head and neck squamous cell carcinoma (HNSCC) treated with definitive intensity-modulated radiotherapy (IMRT)–based CCRT.

Materials and Methods: We retrospectively analyzed 210 patients with non-metastatic HNSCC treated with definitive IMRT-based CCRT between 2009 and 2020. Lower-neck involvement was defined as radiologic involvement of inferior cervical lymph nodes. Post-treatment response was categorized as complete response (CR) versus non-CR. Logistic and Cox regression models were used to identify predictors of DM and survival outcomes.

Results: At a median follow-up of 59.8 months, DM developed in 51 patients (24.3%). In multivariable logistic analysis, lower-neck involvement (odds ratio [OR], 2.32; 95% confidence interval [CI], 1.18 to 4.54; p = 0.014) and non-CR (OR, 2.57; 95% CI, 1.31 to 5.05; p = 0.006) independently predicted DM. In Cox analyses, lower-neck involvement was associated with inferior distant metastasis-free survival (DMFS) (hazard ratio [HR], 2.07; 95% CI, 1.15 to 3.75; p = 0.016) and progression-free survival (PFS) (HR, 1.93; 95% CI, 1.19 to 3.14; p = 0.008), whereas non-CR predicted worse DMFS (HR, 2.71; 95% CI, 1.49 to 4.95; p = 0.001), PFS (HR, 3.77; 95% CI, 2.25 to 6.33; p < 0.001), and overall survival (HR, 5.08; 95% CI, 1.94 to 13.34; p < 0.001).

Conclusion: Lower-neck involvement and post-CCRT response independently predict DM after definitive CCRT for HNSCC and may improve risk stratification for systemic failure.

Keywords: Head and neck neoplasms, Squamous cell carcinoma, Distant metastasis, Lymph nodes, Chemoradiotherapy, Risk factors

Introduction

Head and neck squamous cell carcinoma (HNSCC) remains a major cause of cancer-related morbidity and mortality worldwide. For locally advanced disease, definitive concurrent chemoradiotherapy (CCRT) is the standard treatment based on randomized trials demonstrating improved outcomes compared with radiotherapy (RT) alone [1-3]. With the widespread adoption of intensity-modulated radiotherapy (IMRT), locoregional control has improved substantially. Despite advances in multimodality treatment and IMRT, distant metastasis (DM) remains a leading cause of treatment failure in HNSCC [4,5].

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To reduce systemic dissemination, induction chemotherapy (IC) was explored, and docetaxel-based regimens improved response rates in randomized trials [6,7]. However, subsequent studies have not consistently demonstrated a durable survival benefit or a clear reduction in DM with IC prior to CCRT [8,9]. Accordingly, evaluation of patients treated with definitive IMRT-based CCRT without IC provides a clearer framework for assessing intrinsic risk factors for DM.

Cervical lymph node (LN) involvement is a well-established risk factor for DM. Both advanced nodal stage and the anatomic distribution of metastatic nodes have been associated with increased systemic risk [10-14]. In particular, involvement of the lower neck (level IV, level Vb, and supraclavicular regions) may reflect biologically advanced regional spread. Given the proximity of these nodal stations to major lymphatic and venous drainage pathways, lower-neck involvement may serve as a clinically identifiable marker of systemic access rather than simply indicating nodal stage.

In addition, HNSCC demonstrates preferential metastatic involvement of specific organs, most commonly the lung, followed by bone and liver [7,9]. However, the clinical implications of site-specific distribution in homogeneous IMRT-treated cohorts remain unclear. Furthermore, early post-treatment response may reflect intrinsic tumor biology and could be linked to subsequent systemic dissemination.

Accordingly, we aimed to evaluate DM in a homogeneous cohort of patients with HNSCC treated with definitive IMRT-based CCRT without IC. Specifically, we examined the association between lower-neck LN involvement and the development of DM, characterized patterns of metastatic dissemination including organ-specific and multi-site involvement within the cohort, and assessed the prognostic significance of early post-treatment response as a marker of systemic risk.

Materials and Methods

1. Study design and patient population

This retrospective cohort study included patients with HNSCC who underwent definitive CCRT at a university-affiliated tertiary medical center (institution name withheld for peer review) between January 2009 and December 2020. A total of 210 consecutive patients meeting the eligibility criteria were included in the final analysis.

Patients were eligible if they had histologically confirmed squamous cell carcinoma, no evidence of DM (M0) on pre-treatment computed tomography (CT)/magnetic resonance imaging (MRI) or positron emission tomography–computed tomography (PET-CT), received definitive IMRT-based CCRT delivering 66–70 Gy in conventional fractions, and had availability of at least 6 months of clinical follow-up. Patients were excluded if they underwent adjuvant RT following upfront surgery, or salvage RT for recurrent disease, evidence of DM before initiation of CCRT, non-squamous histology (e.g., adenocarcinoma, salivary gland carcinoma, sinonasal malignancies), or failure to complete planned definitive CCRT.

2. Imaging evaluation and staging

All patients underwent baseline staging with neck CT or MRI and chest CT, with PET-CT performed when clinically indicated. Tumor staging was reassigned according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system [15]. Nasopharyngeal carcinoma was staged according to the nasopharynx-specific system. For all other subsites, including oropharyngeal cancer, the non–p16-based staging system was uniformly applied regardless of biomarker status to maintain consistency across the cohort. Human papillomavirus (HPV; p16) status was assessed when available; however, due to incomplete data, it was not incorporated into the multivariable analysis.

Follow-up evaluations were generally performed every 3–6 months during the first 2 years and at longer intervals thereafter. Imaging studies, including neck CT or MRI and chest CT, were performed at regular intervals or when clinically indicated. PET-CT was not routinely performed but was used selectively based on clinical suspicion.

3. Clinical and treatment characteristics

All patients received definitive CCRT. RT was delivered primarily using IMRT, predominantly with Tomotherapy systems; a small proportion of earlier cases were treated with conventional step-and-shoot IMRT. The prescribed RT regimen consisted of daily fractions of 2.0–2.2 Gy, administered five days per week, to a total dose of 66–70 Gy. Target volume delineation followed standard institutional and international guidelines and included the gross tumor volume, clinical target volume, and planning target volume. Elective nodal regions and anatomically contiguous areas at risk were treated with 54–60 Gy, depending on clinical stage, radiologic extent, and anatomical considerations. CCRT consisted of cisplatin-based regimens administered during the RT course. Most patients received weekly cisplatin at a dose of 40 mg/m^2, while a minority were treated with high-dose cisplatin (100 mg/m^2) administered every three weeks. Only chemotherapy delivered during the definitive CCRT course was considered in the analysis; systemic therapies administered after disease progression for salvage or palliative purposes were not included in the analysis. For clinical variable definition, cervical LN involvement was assessed based on pretreatment imaging. Radiologic nodal involvement was determined by size and morphologic criteria on CT/MRI and/or focal flu-

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orodeoxyglucose uptake on PET-CT, as interpreted by dedicated head and neck radiologists. The lower neck was anatomically defined as level IV, level Vb, and supraclavicular LN regions. Lower-neck involvement was considered present when pretreatment CT, MRI, or PET-CT demonstrated radiologically abnormal lymphadenopathy or definite nodal tumor infiltration in these regions. This definition was applied irrespective of overall N stage.

4. Treatment-related time factor

To assess the impact of treatment duration on outcomes, overall treatment time (OTT) was evaluated. OTT was defined as the total elapsed time from the start to the completion of RT. Based on radiobiological evidence indicating accelerated tumor repopulation after approximately 4 weeks and an increased risk of locoregional control deterioration with treatment durations exceeding 7–8 weeks (49–56 days) [16,17], an OTT >8 weeks (56 days) was classified as prolonged.

5. Response assessment

Treatment response was evaluated using CT, MRI, or PET-CT performed after completion of RT. The timing of the first response assessment was defined as the interval between the first post-treatment simulation CT and the earliest subsequent imaging study, regardless of imaging modality. In cases where multiple simulation CT scans were performed, the first simulation CT was used as the reference time point.

For analytic purposes, response was dichotomized into complete response (CR) versus non-CR. CR was defined as the absence of radiologic evidence of residual disease at the primary site and regional lymph nodes on post-treatment imaging; all other responses were classified as non-CR. Post-treatment response was treated as an early clinical marker for subsequent systemic failure in multivariable survival analyses.

6. Follow-up and outcome definitions

Patients were followed every 1–3 months during the first two years and every 6–12 months thereafter. Follow-up evaluations included neck CT or MRI and chest CT. Abdominal imaging (CT or ultrasonography) and PET-CT were performed when clinically indicated or when DM was suspected. DM was defined as radiologic or pathologic evidence of metastatic disease beyond the locoregional extent of the primary tumor and regional lymphatics [16]. Distant metastasis-free survival (DMFS) was defined as the time from initiation of RT to the first occurrence of DM. Progression-free survival (PFS) was defined as the time from RT initiation to locoregional recurrence, DM, or death from any cause. Overall survival (OS) was defined as the time from RT initiation to death from any cause. Site-specific DM incidence was defined as the occurrence of metastatic involvement at each organ site at any time during follow-up, regardless of whether multiple sites were involved. Local and regional recurrences were assessed independently; thus, patients could contribute more than one recurrence category. Locoregional recurrence was defined as recurrence involving both the primary site and regional LNs, either simultaneously or sequentially, during follow-up.

7. Statistical analysis

Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were summarized as medians with ranges. Univariable logistic regression analyses were performed to explore factors associated with DM as a binary outcome. Variables deemed clinically relevant or showing $p < 0.10$ in univariable analyses were entered into multivariable logistic regression models. To minimize overfitting, a multivariable model including a limited number of clinically relevant variables was constructed. Given the potential collinearity between N stage and lower-neck involvement, an exploratory model incorporating N stage was additionally evaluated to assess their independent contributions. Odds ratios (ORs) and hazard ratios (HRs) were reported with 95% confidence intervals (CIs). Site-specific DM incidence was analyzed within the overall cohort based on whether metastatic involvement at each organ site occurred at any time during follow-up. Patients with metastases at multiple sites were allowed to contribute to more than one organ-specific category. DMFS, PFS, and OS were estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariable Cox proportional hazards regression models were constructed to evaluate independent prognostic factors for time-to-event outcomes, incorporating clinically relevant covariates. Only patients with complete data for variables included in each model were analyzed. A two-sided p-value < 0.05 was considered statistically significant. All statistical analyses were performed using Python 3.10 (Python Software Foundation, Wilmington, DE, USA).

Results

Baseline characteristics and treatment parameters are summarized in Table 1. The median age was 63 years (range, 20 to 82 years), and 89.5% of patients were male. The most common primary sites were nasopharynx (27.6%), oropharynx (24.8%), and larynx (24.8%). Advanced-stage disease was prevalent: 37.6% of patients had T3–4 tumors, 49.5% had N2–3 disease, and 50.0% were classified as AJCC stage IVA–IVB. Lower-neck LN involvement was present in 39.5% of patients. Weekly cisplatin (40 mg/m^2) was administered to 81.9% of patients, whereas 18.1% received high-

Table 1. Baseline characteristics, treatment parameters, and key oncologic outcomes (n = 210)

Variable	Value
Patient characteristics	
Age (year)	63 (20–82)
Sex	
Male	188 (89.5)
Female	22 (10.5)
Tumor characteristics	
Primary site	
Oropharynx	52 (24.8)
Hypopharynx	41 (19.5)
Larynx	52 (24.8)
Oral cavity	7 (3.3)
Nasopharynx	58 (27.6)
T stage	
T1	46 (21.9)
T2	85 (40.5)
T3	45 (21.4)
T4	34 (16.2)
N stage	
N0	53 (25.2)
N1	53 (25.2)
N2	94 (44.8)
N3	10 (4.8)
Clinical stage (AJCC 8th)	
Stage I–II	45 (21.4)
Stage III	60 (28.6)
Stage IVA–IVB	105 (50.0)
Lower-neck LN involvement	
Yes	83 (39.5)
No	127 (60.5)
Treatment characteristics	
Radiotherapy	
OTT (days)	51 (41–73)
OTT > 8 weeks	51 (24.3)
Chemotherapy	
Weekly cisplatin (40 mg/m^2)	172 (81.9)
3-Weekly cisplatin (100 mg/m^2)	38 (18.1)
Cumulative cisplatin ≥ 200 mg/m^2	197 (93.8)
Treatment response	
CR	126 (60.0)
Non-CR	84 (40.0)
Oncologic outcomes	
DM	51 (24.3)

Values are presented as median (range) or number (%).
AJCC, American Joint Committee on Cancer; OTT, overall treatment time; CR, complete response; DM, distant metastasis.

dose cisplatin every 3 weeks. A cumulative cisplatin dose ≥ 200 mg/m^2 was achieved in 93.8% of patients. The median OTT was 51 days (range, 41 to 73 days), and OTT > 8 weeks occurred in 24.3% of patients. Following CCRT, 126 patients (60.0%) achieved a CR, whereas 84 (40.0%) had a non-CR. The median time to first response assessment after CCRT was 19.9 weeks (range, 5.9 to 93.4 weeks). The median follow-up duration was 59.8 months. During follow-up, local recurrence occurred in 30 patients (14.3%), regional recurrence in 34 (16.2%), and DM in 51 (24.3%). To identify baseline factors associated with overall DM occurrence, univariable logistic regression analysis (Table 2) showed that N stage (N2–3 vs. N0–1; OR, 2.85; 95% CI, 1.46 to 5.57; p = 0.002), lower-neck LN involvement (OR, 2.86; 95% CI, 1.49 to 5.46; p = 0.001), and post-CCRT response (non-CR vs. CR; OR, 3.10; 95% CI, 1.62 to 5.95; p < 0.001) were significantly associated with increased odds of DM, whereas OTT > 8 weeks showed a borderline association (OR, 1.84; 95% CI, 0.92 to 3.68; p = 0.086). In the multivariable model, only lower-neck LN involvement (OR, 2.32; 95% CI, 1.18 to 4.54; p = 0.014) and post-CCRT response (OR, 2.57; 95% CI, 1.31 to 5.05; p = 0.006) remained independently associated with DM.

Overall, the lung was the most common site of DM (27.7% in LN+ vs. 14.2% in LN–), followed by bone (12.0% vs. 2.4%) and liver (9.6% vs. 3.9%), whereas brain and other sites were relatively uncommon (Table 3). As shown in Table 3, DM occurred in 16.5% of patients without lower-neck involvement (LN–) and 36.1% of those with lower-neck involvement (LN+) (OR, 2.86; 95% CI, 1.49 to 5.47; p = 0.002). Lung metastasis developed in 14.2% of LN– patients and 27.7% of LN+ patients (OR, 2.32; 95% CI, 1.16 to 4.62; p = 0.020), and bone metastasis in 2.4% and 12.0%, respectively (OR, 5.66; 95% CI, 1.50 to 21.20; p = 0.007). Differences in liver metastasis (3.9% vs. 9.6%, p = 0.141), brain metastasis (1.6% vs. 1.2%, p > 0.99), pleural or mediastinal metastasis (1.6% vs. 6.0%, p = 0.116), distant LN metastasis (2.4% vs. 7.2%, p = 0.159), and other sites (0.8% vs. 3.6%, p = 0.303) were not statistically significant. Multi-site metastasis occurred more frequently in lower neck LN+ patients (18.1% vs. 6.3%; OR, 3.28; 95% CI, 1.32 to 8.17; p = 0.012).

Kaplan-Meier analysis demonstrated significantly inferior DMFS and PFS in patients with lower-neck involvement compared with those without (both log-rank p < 0.001), whereas the difference in OS did not reach statistical significance (log-rank p = 0.068) (Fig. 1).

In univariable Cox regression analyses (Table 4), lower-neck LN involvement and post-CCRT non-CR status were significantly associated with inferior DMFS and PFS, while post-CCRT non-CR status was also strongly associated with worse OS. T stage (T3–4 vs. T1–2) was associated with inferior PFS but did not show a significant association with DMFS or OS. In multivariable Cox regression analysis incorporating post-CCRT response (Table 4), lower-neck LN involvement independently predicted inferior DMFS (HR, 2.07; 95% CI,

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Table 2. Univariable and multivariable logistic regression for predictors of DM (n = 210)

Variable	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value
Age (per 10 years)	1.12 (0.82–1.52)	0.481	-	-
Sex (male vs. female)	0.84 (0.31–2.27)	0.730	-	-
T stage (T3–4 vs. T1–2)	1.51 (0.80–2.87)	0.207	-	-
N stage (N2–3 vs. N0–1)	2.85 (1.46–5.57)	0.002	-	-
Lower-neck LN involvement (yes vs. no)	2.86 (1.49–5.46)	0.001	2.32 (1.18–4.54)	0.014
Cisplatin regimen (weekly vs. q3wk)	1.25 (0.53–2.93)	0.608	-	-
Post-CCRT response (non-CR vs. CR)	3.10 (1.62–5.95)	<0.001	2.57 (1.31–5.05)	0.006
OTT >8 weeks (yes vs. no)	1.84 (0.92–3.68)	0.086	-	-

DM, distant metastasis; OR, odds ratio; CI, confidence interval; LN, lymph node; q3wk, every 3 weeks; CCRT, concurrent chemoradiotherapy; CR, complete response; OTT, overall treatment time.

Table 3. Comparison of metastatic site distribution according to lower-neck involvement

Outcome	No. (%)		OR (95% CI)	p-value
	LN– (n = 127)	LN+ (n = 83)		
Any DM	21 (16.5)	30 (36.1)	2.86 (1.49–5.47)	0.002
Lung	18 (14.2)	23 (27.7)	2.32 (1.16–4.62)	0.020
Bone	3 (2.4)	10 (12.0)	5.66 (1.50–21.20)	0.007
Liver	5 (3.9)	8 (9.6)	-	0.141
Brain	2 (1.6)	1 (1.2)	-	>0.99
Pleura/mediastinum	2 (1.6)	5 (6.0)	-	0.116
Distant LN	3 (2.4)	6 (7.2)	-	0.159
Other	1 (0.8)	3 (3.6)	-	0.303
Multi-site	8 (6.3)	15 (18.1)	3.28 (1.32–8.17)	0.012

ORs and p-values were calculated using univariate analysis.
Patients may have multiple metastatic sites (n = 51).
LN, lymph node; OR, odds ratio; CI, confidence interval; DM, distant metastasis.

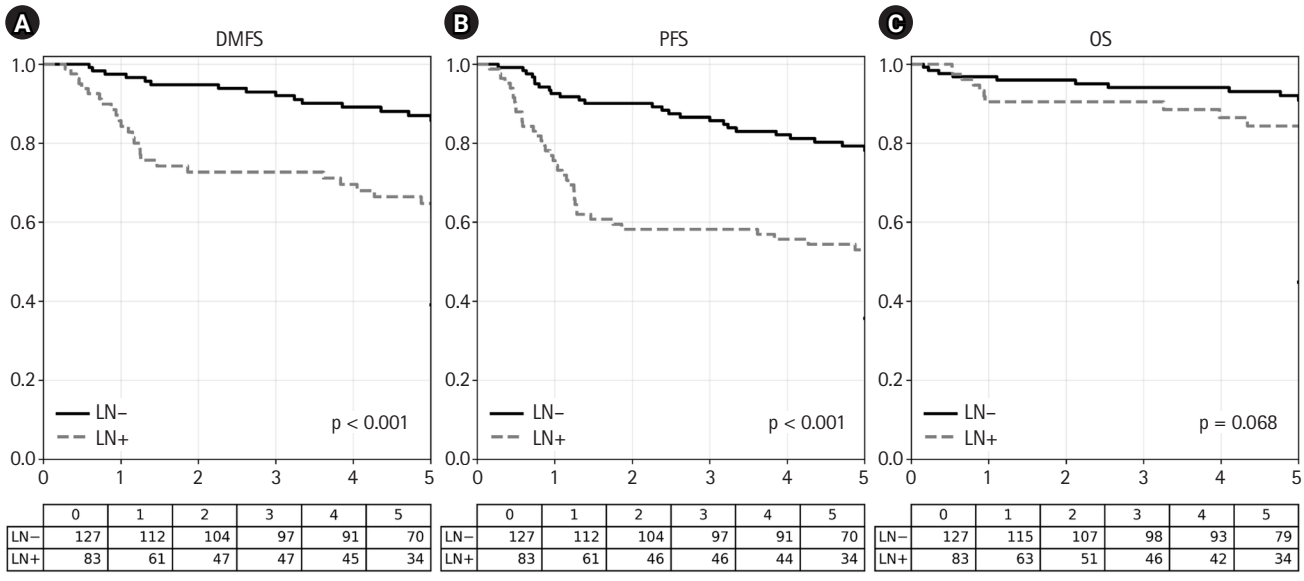

Fig. 1. Distant metastasis-free survival (DMFS) (A), progression-free survival (PFS) (B), and overall survival (OS) (C) according to lower-neck lymph node (LN) involvement. Kaplan-Meier curves for DMFS, PFS, and OS stratified by lower-neck LN involvement. p-values were calculated using the log-rank test, and the numbers at risk are provided below each plot.

Table 4. Univariable and multivariable Cox regression analysis for DMFS, PFS, and OS

Variable	HR (95% CI)					
	DMFS		PFS		OS	
	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
Age (per 10 years)	1.15 (0.86–1.54)	1.10 (0.82–1.48)	1.14 (0.89–1.44)	1.06 (0.84–1.35)	1.59 (1.00–2.54)	1.47 (0.92–2.36)
p-value	0.351	0.510	0.300	0.610	0.051	0.106
T stage (T3–4 vs. T1–2)	1.66 (0.96–2.89)	1.10 (0.61–1.97)	1.67 (1.06–2.64)	1.07 (0.66–1.73)	1.27 (0.55–2.95)	1.01 (0.42–2.40)
p-value	0.071	0.754	0.028	0.781	0.577	0.985
Lower-neck involvement (+)	2.81 (1.61–4.91)	2.07 (1.15–3.75)	2.67 (1.68–4.24)	1.93 (1.19–3.14)	2.11 (0.93–4.81)	1.64 (0.70–3.81)
p-value	< 0.001	0.016	< 0.001	0.008	0.075	0.253
OTT > 8 weeks	1.78 (0.99–3.19)	1.33 (0.72–2.45)	1.48 (0.90–2.45)	1.10 (0.65–1.84)	1.36 (0.56–3.31)	1.14 (0.47–2.79)
p-value	0.053	0.357	0.122	0.731	0.496	0.767
Post-CCRT response (non-CR vs. CR)	3.48 (1.98–6.12)	2.71 (1.49–4.95)	4.57 (2.80–7.45)	3.77 (2.25–6.33)	6.10 (2.40–15.55)	5.08 (1.94–13.34)
p-value	< 0.001	0.001	< 0.001	< 0.001	< 0.001	< 0.001

DMFS, distant metastasis-free survival; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; OTT, overall treatment time; CCRT, concurrent chemoradiotherapy; CR, complete response.

1.15 to 3.75; p = 0.016) and PFS (HR, 1.93; 95% CI, 1.19 to 3.14; p = 0.008), but not OS (HR, 1.64; 95% CI, 0.70 to 3.81; p = 0.253). In contrast, non-CR status was strongly associated with worse outcomes across all endpoints, including DMFS (HR, 2.71; 95% CI, 1.49 to 4.95; p = 0.001), PFS (HR, 3.77; 95% CI, 2.25 to 6.33; p < 0.001), and OS (HR, 5.08; 95% CI, 1.94 to 13.34; p < 0.001). OTT > 8 weeks was not significantly associated with DMFS, PFS, or OS.

Discussion and Conclusion

In this study, we evaluated DM in a homogeneous cohort of patients with HNSCC treated with definitive IMRT-based CCRT without IC. Three principal findings emerged. First, DM remained a major mode of failure in the contemporary IMRT era. Second, lower-neck LN involvement was independently associated with increased odds of DM and inferior DMFS and PFS. Third, non-CR after CCRT was strongly associated with inferior DMFS, PFS, and OS. Notably, when post-CCRT response was incorporated into survival models, the association between lower-neck involvement and OS was attenuated (Table 4).

Despite favorable overall outcomes, with a 5-year OS of 88.5% (Fig. 1), DM occurred in 24.3% of patients (Table 1) and was consistently associated with inferior survival endpoints. These findings are consistent with prior IMRT-era data demonstrating that improvements in locoregional control have not eliminated systemic relapse as a major determinant of long-term outcome [9,10]. Favorable OS in this cohort may be partly explained by improved locoregional control with IMRT and the potential for effective salvage treatment. In addition, cohort characteristics and follow-up structure, including patient selection and censoring, may have contributed to the relatively high observed survival rates. Five-year OS also varied across subsites, with relatively favorable outcomes in nasopharyngeal carcinoma (93.1%) and oropharyngeal cancer (92.3%) compared to hypopharyngeal cancer (78.0%). These differences likely reflect distinct tumor biology, including greater radiosensitivity and more favorable treatment response, particularly in HPV-associated oropharyngeal cancer.

Lower-neck LN involvement emerged as a robust marker of systemic risk. In multivariable analyses, inferior nodal extension remained significantly associated with DM and adverse time-to-event outcomes (Table 4). When N stage was included in the model, the magnitude of association decreased. This finding suggests partial biological overlap between overall nodal burden and inferior nodal extension, consistent with prior studies linking nodal extent and distribution to systemic dissemination [11-14]. To further explore this relationship, we performed analyses stratified by N stage. In N-stage–stratified analyses, lower-neck involvement showed a consistent direction of association with adverse outcomes across subgroups. The effect was more pronounced in patients with N2–3 disease, in whom lower-neck involvement remained significantly associated with both DM (OR, 2.81; 95% CI, 1.15 to 6.85; p = 0.024) and PFS (HR, 2.59; 95% CI, 1.31 to 5.12; p = 0.006). In contrast, in patients with N0–1 disease, a similar trend was observed, although statistical significance was not reached for either DM (OR, 1.33; 95% CI, 0.38 to 4.63; p = 0.650) or PFS (HR, 2.02; 95% CI, 0.90 to 4.50; p = 0.087), likely due to the limited number of events. These findings support that inferior nodal extension may represent a distinct marker of systemic dissemination risk, rather than merely reflecting overall nodal burden.

Anatomically, level IV, Vb, and supraclavicular LNs are closely connected to major lymphatic and venous drainage pathways. Thus, involvement of these regions may reflect more advanced re-

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gional disease with increased potential for systemic dissemination, as suggested in prior studies. This interpretation is consistent with prior studies suggesting that inferior nodal extension is associated with an increased risk of systemic dissemination [13,14].

Regarding metastatic distribution, the lung was the most frequent site of DM, followed by bone and liver (Table 3), consistent with previous reports [7-10]. Although the incidence of lung and bone metastases was higher in patients with lower-neck involvement, the overall distribution pattern—lung predominance followed by bone and liver—remained consistent across groups. This indicates that lower-neck involvement influences the probability of developing DM, rather than determining the metastatic organ site [18].

Post-CCRT response showed the strongest association with survival outcomes (Table 4). Patients with non-CR had substantially higher risks of DM and death. Notably, when post-treatment response was included in the survival model, the association between lower-neck involvement and OS was attenuated. This finding suggests that early treatment response may partly mediate the impact of inferior nodal extension on survival.

Lower-neck involvement and post-CCRT response represent two complementary aspects of disease biology at different time points. Lower-neck involvement reflects baseline systemic risk at diagnosis, whereas post-CCRT response reflects the realized treatment effect and residual disease after therapy. In this framework, lower-neck involvement identifies patients with an inherent predisposition to systemic dissemination, while non-CR indicates persistent or treatment-resistant disease. Together, these variables provide a more comprehensive assessment of systemic failure risk by capturing both baseline risk and treatment response. From a practical standpoint, both lower-neck LN involvement and early post-CCRT response are readily assessable in routine care. Patients exhibiting both inferior nodal extension and non-CR may represent a clinically identifiable subgroup with particularly elevated systemic risk. Such patients could be considered candidates for closer surveillance or future trials evaluating intensified systemic strategies.

Our study has several limitations. This study was retrospective and conducted at a single institution.

Primary tumor subsites were heterogeneous, and both the biological behavior and baseline risk of DM are known to vary across subsites, which may influence the clinical interpretation of lower-neck involvement. DM rates varied across primary tumor subsites in our cohort, with hypopharyngeal cancer showing higher rates and oropharyngeal cancer lower rates, consistent with known biological differences among HNSCC subsites. However, these subsite-specific differences did not account for our main findings, as the association between lower-neck involvement and DM remained consistent across analyses. In addition, HPV and Epstein-Barr virus (EBV) status were incomplete, potentially affecting subsite-specific outcomes. Due to incomplete biomarker data, p16/HPV status was not included in the multivariable analysis. While biomarker distributions (p16 in oropharyngeal cancer and EBV in nasopharyngeal carcinoma) were descriptively assessed, no further subsite-specific analyses were performed due to limited sample sizes. The limited number of DM events restricted detailed subgroup analyses.

In sensitivity analyses excluding nasopharyngeal carcinoma and oropharyngeal cancer, the association between lower-neck involvement and adverse time-to-event outcomes remained generally consistent. Lower-neck involvement remained associated with worse DMFS (HR, 2.24; 95% CI, 0.97 to 5.19; $p = 0.060$) and significantly worse PFS (HR, 2.39; 95% CI, 1.18 to 4.87; $p = 0.016$). Similar patterns were observed after excluding nasopharyngeal carcinoma and p16-positive oropharyngeal cancer, with lower-neck involvement remaining associated with worse DMFS (HR, 2.10; 95% CI, 0.98 to 4.54; $p = 0.058$) and PFS (HR, 2.16; 95% CI, 1.14 to 4.10; $p = 0.018$). These findings suggest that the observed effect may not be solely explained by subsite-specific biological differences. Furthermore, although p16 status is an established prognostic factor in oropharyngeal carcinoma, non–p16-based staging was applied in the present study due to incomplete biomarker data and the retrospective nature of the cohort. This approach allowed for consistent staging across the entire study population and avoided substantial case exclusion. Nevertheless, we acknowledge that this may limit subsite-specific interpretation and should be considered when generalizing the results.

Several additional nodal factors, such as bilateral involvement, extranodal extension, and nodal size, are known to be associated with metastatic risk and were not individually evaluated in this study due to the limited number of events. However, lower-neck involvement often reflects more extensive nodal disease and may serve as a simple clinical marker capturing multiple high-risk nodal features. The consistent associations observed in our analyses suggest that lower-neck involvement itself carries additional prognostic information beyond these factors.

Additionally, systemic therapies administered after recurrence were not standardized and may have influenced OS. Although OTT >8 weeks occurred in nearly one-quarter of patients, this likely reflected calendar-day calculation and institutional non-treatment days rather than treatment-related toxicity. Nevertheless, the consistency of associations across logistic and time-to-event models supports the internal validity of the findings.

In an IMRT-treated cohort of patients with HNSCC, DM remained a major determinant of long-term outcome. Lower-neck LN involvement and non-CR after CCRT independently identified patients at increased risk of systemic dissemination. These clinically

accessible factors may improve risk stratification.

Statement of Ethics

This study was approved by the Institutional Review Board of Pusan National University Hospital (approval No. 2306-019-128). The requirement for informed consent was waived 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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Author Contributions

Conceptualization, DK (Donghyun Kim), WK; Methodology, DK (Dongchan Kim), DK (Donghyun Kim), JN; Data curation, DK (Dongchan Kim), KL; Formal analysis, DK (Dongchan Kim), DK (Donghyun Kim), YK, JJ; Writing of the original draft, DK (Dongchan Kim); Writing of the review and editing, all authors; Approval of the final manuscript, all authors.

Data Availability Statement

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

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Radiation therapy increases long-term gonadotropin deficiency, hypothalamic-pituitary dysfunction, and brainstem necrosis in pediatric patients with brain tumor

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Purpose: No comprehensive nationwide population-based cohort study has been conducted to fully evaluate the impact of radiotherapy (RT) on late side effects in pediatric patients with brain tumor in a nationwide population, including endocrinopathies, late-delayed complications, and late cerebrovascular complications.

Materials and Methods: This population-based, retrospective cohort study included 815 pediatric patients with brain tumor receiving RT (RT group) and 1,630 matched controls without RT (non-RT group), extracting all data from the National Health Insurance Research Database of Taiwan.

Results: RT group patients exhibited 1.172-fold and 1.796-fold higher risk of long-term endocrinopathies and late-delayed complications, respectively, than did non-RT group patients. In addition to older age (0.270–0.248-fold), prior surgery (1.856-fold), or chemotherapy (1.679-fold), the risk of overall late side effects in the RT group was 1.173-fold (95% confidence interval, 1.063 to 1.430) higher than that in the non-RT group. Patients with RT had 1.602-fold and 1.120-fold higher risk for gonadotropin deficiency and hypothalamic pituitary dysfunction, respectively, and 3.208-fold higher risk for brain stem necrosis than their non-RT counterparts.

Conclusion: In addition to prior surgery or chemotherapy, RT is an independent predictor of increased risk of late side effects in pediatric patients with brain tumor, particularly in patients who are younger at tumor diagnosis. Gonadotropin deficiency, hypothalamic-pituitary dysfunction, and brainstem necrosis are the main RT-related late side effects in pediatric patients with brain tumor. Frequency of these deficits increases with time, warranting long-term surveillance.

Keywords: Brain neoplasms, Long term adverse effects, Pediatrics, Radiotherapy

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Introduction

Radiotherapy (RT) is widely used to effectively treat primary and metastatic brain tumors in adult and pediatric patients [1]. The clinical differences between brain tumors in adults and children are striking. Compared with brain tumors in adults, pediatric tumor types (mostly glial and neuronal) are more sensitive to RT [2]. RT is the most effective nonsurgical treatment for pediatric gliomas, resulting in 5-year progression-free survival estimates exceeding 80% [3].

To optimize the therapeutic efficacy, RT strategies have been modified dramatically in recent decades, developing various RTs, such as intensity modulated RT, volumetric modulated arc therapy, and proton beam RT. Modified RTs were reported to improve long-term survival of brain tumor patients [4]; however, RT-related late side effects, including neurocognitive, neuroendocrine dysfunction, cerebrovascular complications, and hearing deficits were often observed in pediatric patients with glioma [5-8].

Late-delayed treatment increases the likelihood of developing brain complications and permanent neurologic disability [9]. Consequently, alteration or even discontinuation of the antineoplastic treatment plan may be required to prevent further neurologic injury. As a result, early identification of pediatric patients at high risk for developing late brain injury is essential. In addition, the development of neuroprotective strategies that modify existing antineoplastic treatment regimens is clinically significant. However, no nationwide population-based cohort study has been performed to fully assess the extent to which RT affects overall late side effects in pediatric patients with brain tumor in a nationwide population, including endocrinopathies (e.g., hypothalamic pituitary dysfunction, gonadotropin deficiency, and hypothyroidism), late-delayed complications (e.g., post-RT brain stem necrosis, sensorineural hearing loss, and RT-induced non-senile cataracts), and late cerebrovascular complications (e.g., cavernous/arteriovenous malformation, transient cerebral ischemia, and stroke). Therefore, the present study aimed to fully evaluate associations between RT and late side effects in pediatric patients with brain tumors in the nationwide population of Taiwan.

Materials and Methods

1. Data source

All data for the present study were extracted from the National Health Insurance Research Database (NHIRD) in Taiwan, of the Taiwan National Health Insurance Program, which was established in 1995 and currently covers more than 99% of the 23 million Taiwanese population [10]. The NHIRD contains complete demographic and clinical data for outpatient and inpatient claims data, where all clinical diagnoses and procedures are recorded based on the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes. Additionally, the NHIRD is subjected to periodic quality control audits, and is also overseen by an advisory board run by the National Public Health Association.

2. Study design and sample

Fig. 1 depicts the study population selection for this population-based, retrospective cohort study. A total of 34,092 patients with brain cancer were initially selected from the NHIRD (2000–2015). Patients aged > 18 years; those with a brain tumor diagnosed before the index date; those with late effects before tracking; patients without tracking and those with unknown sex were excluded. After exclusions, a cohort of pediatric patients with brain tumor (n = 3,292) was established, identifying patients by using ICD-9-CM 191 (malignant neoplasm of brain), 192.0 (malignant cranial nerve tumor), 192.1 (malignant cerebral meninges tumor), 194 (malignant neoplasm of other endocrine glands and related structures), or 239.6 (neoplasm of unspecified nature of brain). Among 3,292 pediatric patients with brain tumor, 815 cases received RT (ICD-9-CM V58.0) but 2,477 patients did not undergo RT. Then, two-fold matching by age, sex, and the year of the index date was performed to select 1,630 matched cases without RT, selecting 815 cases with RT and 1,630 matched cases without RT who represented the final analytic sample. For all hospitals and medical centers in Taiwan, the brain tumor was diagnosed according to guidelines of the Taiwan Society of Neuro-Oncology, while the RT exposure procedure, exposure dose and exposure location were based on guidelines of the Taiwan Society of Therapeutic Radiology and Oncology.

3. Main outcomes

The overall late side effects of RT are classified into three categories, endocrinopathies, late-delayed complications, and late cerebrovascular complications. Endocrinopathies consist of hypothyroidism (ICD-9-CM 244), hypothalamic pituitary dysfunction (ICD-9-CM 253), growth hormone (GH) deficiency (ICD-9-CM 259.4 and 259.8), cortisol deficiency (ICD-9-CM 255.4 and 255.5), gonadotropin deficiency (ICD-9-CM 259.0, 259.1, 259.4 and 259.8), delay milestone (ICD-9-CM 783.42), and short stature (ICD-9-CM 783.43). Late-delayed complications include late effects of radiation (ICD-9-CM 909.2), sensorineural hearing loss (ICD-9-CM 389.10), stroke (ICD-9-CM 437), post-RT necrosis of brain stem (ICD-9-CM OP31.1 and OP31.2), visual field defects (ICD-9-CM 368.4), myopia (ICD-9-CM 367.1), astigmatism (ICD-9-CM 367.2), RT-induced non-senile cataract (ICD-9-CM 366.0), nasogastric

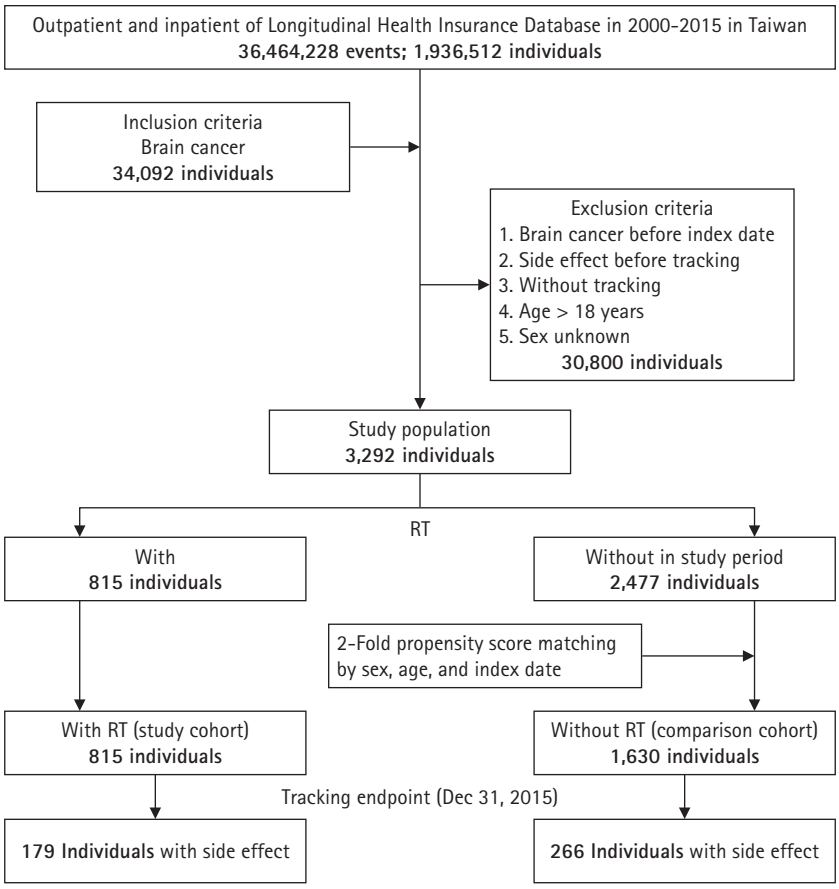

Fig. 1. Flowchart of study population selection. RT, radiotherapy.

tube insertion (ICD-9-CM OP44.99), and gastrostomy (ICD-9-CM OP44.19). Late cerebrovascular complications contain cavernous/arteriovenous malformation (ICD-9-CM 747.81), stroke (ICD-9-CM 434, 436, 437), cerebral atrophy (ICD-9-CM 331.7, 331.89, 331.9), and transient cerebral ischemia (ICD-9-CM 437.5). These late side effects were assessed and diagnosed by all hospitals in Taiwan according to the follow-up of regular outpatients, routine blood tests, routine imaging (computed tomography/magnetic resonance imaging [MRI]) examinations, clinical assessment (neurological symptoms), histopathology, or assessment of growth and development, according to the guidelines of the major Medical Societies in Taiwan.

The independent variables were age, sex, salary-based insurance premium, prior chemotherapy (ICD-9-CM V58.1), prior brain surgery (ICD-9-CM OP01, OP02, OP04), location of residence, urbanization level, hospital care level, and the revised Charlson comorbidity index (CCI_R). CCI_R was defined as "Charlson Comorbidity Index (CCI) without brain tumor excision and stroke." The CCI was used to assess the level of general comorbid conditions, as previously described [11].

4. Statistical analysis

Categorical variables are expressed as counts and percentages, and were compared using the chi-squared test. In contrast, continuous variables are presented as mean ± standard deviation, and were compared using the Student's t-test. Possible confounding variables ($p < 0.05$) among baseline variables were adjusted for subsequent statistical analyses. Multivariable Cox proportional hazards regression analysis was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of late side effects in the RT cohort compared with the non-RT cohort. Kaplan-Meier analysis was used to measure the cumulative incidence of late side effects for both study cohorts, and the log-rank test was used to evaluate differences between the two cumulative incidence curves. All statistical analyses were carried out using IBM SPSS statistical software version 22 for Windows (IBM Corp., Armonk, NY, USA). A 2-tailed p-value of less than 0.05 was established as statistical significance.

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Results

1. Patients' characteristics

A total of 2,445 pediatric patients with brain tumors were included in this study, consisting of 815 patients with RT and 1,630 patients without RT (Table 1, Fig. 1). No significant differences in age, sex, salary-based insured premium, and location of residence were found between the two groups at baseline and endpoint (all $p > 0.05$); however, CCI_R, prior chemotherapy, prior brain surgery, urbanization level at baseline and the hospital level of medical care were significantly different between the two groups (all $p < 0.05$) (Table 1).

Table 1. Characteristics of study population at endpoint

	Total (n = 2,445)	RT (n = 815)	Non-RT (n = 1,630)	p-value
Late effects				0.001*
Without	2,000 (81.8)	636 (78.0)	1,364 (83.7)	
With	445 (18.2)	179 (22.0)	266 (16.3)	
Sex				0.999
Male	1,475 (60.1)	490 (60.1)	980 (60.1)	
Female	970 (39.9)	325 (39.9)	650 (39.9)	
Age (year)	10.83 ± 5.94	10.95 ± 5.32	10.77 ± 6.22	0.489
Age groups (year)				0.007*
< 1	15 (0.6)	3 (0.4)	12 (0.7)	
1–6	695 (28.4)	202 (24.8)	493 (30.2)	
7–12	924 (37.8)	341 (41.8)	583 (35.8)	
13–18	811 (33.2)	269 (33.0)	542 (33.3)	
Insured premium (NT$)				0.462
< 18,000	2,431 (99.4)	811 (99.5)	1,620 (99.4)	
18,000–34,999	11 (0.5)	4 (0.5)	7 (0.4)	
≥ 35,000	3 (0.1)	0 (0)	3 (0.2)	
CCI_R	0.54 ± 1.06	1.50 ± 1.21	0.06 ± 0.89	< 0.001*
Prior chemotherapy				< 0.001*
Without	1,487 (60.8)	333 (40.9)	1,154 (70.8)	
With	958 (39.2)	482 (59.1)	476 (29.2)	
Prior brain surgery				< 0.001*
Without	1,928 (78.9)	704 (86.4)	1,224 (75.1)	
With	517 (21.1)	111 (13.6)	406 (24.9)	
Location				0.126
Northern Taiwan	1,359 (55.6)	476 (58.4)	883 (54.2)	
Middle Taiwan	495 (20.2)	148 (18.2)	347 (21.3)	
Southern Taiwan	487 (19.9)	155 (19.0)	332 (20.4)	
Eastern Taiwan	100 (4.1)	36 (4.4)	64 (3.9)	
Outlets islands	4 (0.2)	0 (0)	4 (0.2)	
Urbanization level				0.053
1 (highest)	1,038 (42.5)	321 (39.4)	717 (44.0)	
2	1,209 (49.4)	435 (53.4)	774 (47.5)	
3	52 (2.1)	16 (1.96)	36 (2.2)	
4 (lowest)	146 (6.0)	43 (5.3)	103 (6.3)	
Level of care				0.036*
Medical center	1,932 (79.0)	668 (82.0)	1,264 (77.6)	
Regional hospital	426 (17.4)	124 (15.2)	302 (18.5)	
Local hospital	87 (3.6)	23 (2.8)	64 (3.9)	

Values are presented as number (%) or mean ± SD.
RT, radiotherapy; CCI_R, revised Charlson comorbidity index; SD, standard deviation.
*$p < 0.05$.

2. Associations between patients' characteristics and incidence of RT-related late side effects

The incidence of late side effects increased significantly in the RT group compared with that in the non-RT group (21.96% vs. 16.32%, p < 0.05) (Table 1). After adjusting for possible confounding variables, multivariable Cox regression analysis revealed that the risk of late side effects in the RT group was approximately 1.173-fold (adjusted HR [aHR], 1.173; 95% CI, 1.063 to 1.430; p < 0.05) (Table 2) higher than that in the non-RT group. In addition, high CCI_R (aHR, 1.032; 95% CI, 1.004 to 1.060), prior chemotherapy (aHR, 1.679; 95% CI, 1.299 to 2.170), prior brain surgery (aHR, 1.856; 95% CI, 1.466 to 2.350), and high level of care were also

Table 2. Cox-regression analysis of factors associated with RT-related late side effects

Variable	Crude HR (95% CI)	p-value	aHR[a] (95% CI)	p-value
RT				
Without	Reference		Reference	
With	1.260 (1.059–1.504)	0.006*	1.173 (1.063–1.430)	0.003*
Sex				
Male	0.987 (0.817–1.193)	0.894	1.002 (0.794–1.165)	0.692
Female	Reference		Reference	
Age groups (year)				
< 1	Reference		Reference	
1–6	0.315 (0.100–0.990)	0.048*	0.355 (0.113–1.120)	0.077
7–12	0.236 (0.074–0.749)	0.014*	0.270 (0.085–0.860)	0.027*
13–18	0.208 (0.066–0.657)	0.007*	0.248 (0.078–0.784)	0.018*
Insurance premium (NT$)				
< 18,000	Reference		Reference	
18,000–34,999	1.423 (0.457–4.434)	0.543	1.369 (0.431–4.348)	0.594
≥ 35,000	-	-	-	-
CCI_R	1.069 (1.046–1.094)	0.014*	1.032 (1.004–1.060)	< 0.001*
Prior CT				
Without	Reference		Reference	
With	1.633 (1.283–2.079)	< 0.001*	1.679 (1.299–2.170)	< 0.001*
Prior brain surgery				
Without	Reference		Reference	
With	1.971 (1.570–2.473)	< 0.001*	1.856 (1.466–2.350)	< 0.001*
Location				
Northern Taiwan	Reference		Multicollinearity with urbanization level	
Middle Taiwan	0.772 (0.603–0.989)	0.040*	Multicollinearity with urbanization level	
Southern Taiwan	1.009 (0.795–1.281)	0.943	Multicollinearity with urbanization level	
Eastern Taiwan	0.681 (0.411–1.129)	0.136	Multicollinearity with urbanization level	
Outlets islands	-	-	Multicollinearity with urbanization level	
Urbanization level				
1 (highest)	2.320 (1.393–3.861)	0.001*	0.787 (0.426–1.456)	0.445
2	1.966 (1.183–3.267)	0.009*	0.808 (0.268–2.441)	0.706
3	0.706 (0.236–2.113)	0.534	0.862 (0.459–1.619)	0.644
4 (lowest)	Reference		Reference	
Level of care				
Medical center	9.084 (2.915–28.310)	< 0.001*	8.889 (2.721–29.040)	< 0.001*
Regional hospital	3.496 (1.087–11.241)	0.036*	3.506 (1.080–11.379)	0.037*
Local hospital	Reference		Reference	

RT, radiotherapy; HR, hazard ratio; CI, confidence interval; aHR, adjusted hazard ratio; CCI_R, revised Charlson comorbidity index; CT, computed tomography.
*p < 0.05.
[a]Adjusted for variables listed in the table.

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associated with an elevated risk of late side effects, while older age (≥ 1 year) was associated with a decreased risk of late side effects (all $p < 0.05$) (Table 2). After stratifying by the variables listed in Table 2, multivariable Cox regression analysis adjusted for these variables disclosed that each subgroup among patients with RT had a higher risk of late side effects than did subgroups among patients without RT (all $p < 0.05$) (Supplementary Table S1), except for the older age subgroup, suggesting associations between age and RT-related late side effects.

Kaplan-Meier plot and log-rank tests showed that the RT group also had a high risk of late side effects compared with that of the non-RT group across ≥ 7 years of tracking (all $p < 0.05$) (Fig. 2A). Furthermore, high insurance premium, high urbanization level, and high hospital level of care were also associated with incident RT-related late side effects (all $p < 0.05$) (Table 2).

3. Associations between RT and specific late side effects

Compared to the non-RT group, the RT group had higher proportion of long-term endocrinopathies (13.3% vs. 9.8%, $p < 0.05$) and late-delayed complications (8.1% vs. 4.5%, $p < 0.05$) and a slightly lower proportion of late cerebrovascular complications (2.2% vs. 2.6%, $p > 0.05$) (Supplementary Table S2) than the non-RT group. For long-term endocrinopathies, the proportion of hypothalamic pituitary dysfunction (10.1% vs. 7.5%, $p < 0.05$) and gonadotropin deficiency (1.7% vs. 0.8%, $p < 0.05$) was also higher in the RT group than in the non-RT group. For late-delayed complications, the proportion of stroke (and other and ill-defined cerebrovascular disease) (1.1% vs. 0.4%, $p < 0.05$) and post-RT necrosis of the brain stem (4.8% vs. 2.0%, $p < 0.05$) was also higher in the RT group than in the non-RT group. For late cerebrovascular complications, the proportion of cavernous/arteriovenous malformation (0.3% vs. 1.0%, $p < 0.05$) was lower in the RT group than that in the non-RT group.

Among the results of multivariate Cox regression analysis after adjusting for the variables listed in Table 2, the RT group exhibited 1.172-fold (95% CI, 1.020 to 1.398) and 1.796-fold (95% CI, 1.250 to 2.578) higher risk of long-term endocrinopathies and late-de-

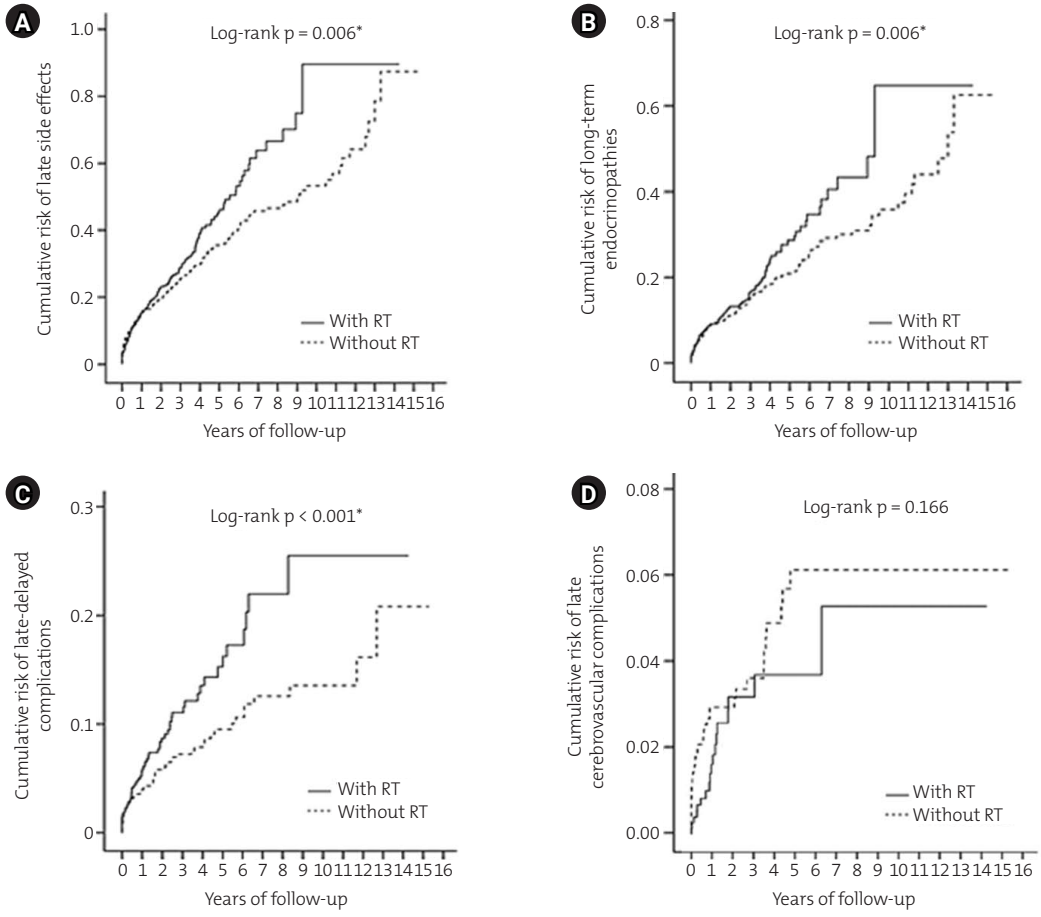

Fig. 2. Kaplan-Meier plot for cumulative incidence of late effects in patients with (solid line) and without radiotherapy (RT) (dotted line). (A) Overall late effects. (B) Long-term endocrinopathies. (C) Late-delayed complications. (D) Late cerebrovascular complications. *$p < 0.05$.

layed complications, respectively, than did the non-RT group (all p < 0.05) (Table 3). However, no significant differences were found in late cerebrovascular complications between the two groups. For long-term endocrinopathies, the RT group had 1.602-fold (1.010–3.718) and 1.120-fold (1.005–1.548) higher risk for gonadotropin deficiency and hypothalamic pituitary dysfunction, respectively, than did the non-RT group (all p < 0.05). For late-delayed complications, the RT group had 3.208 (1.953–5.297)-fold higher risk for post-RT necrosis of the brain stem than did the non-RT group (p < 0.05).

Kaplan-Meier plot and log-rank tests revealed that the RT group also had a higher risk of long-term endocrinopathies and late-delayed complications, respectively, than did the non-RT group across ≥ 8 years of tracking (all p < 0.05) (Fig. 2B, 2C, Supplementary Tables S3, S4). No significant differences were found in the risk of late cerebrovascular complications between the two groups across all years of tracking (all p > 0.05) (Fig. 2D, Supplementary Table S5).

Discussion and Conclusion

Results of the present study demonstrated associations between RT and the profile of overall late side effects in pediatric patients with brain tumors in the national population of Taiwan. The key finding was that the RT group had higher risk of late side effects compared to the non-RT group, except for those with older age and prior surgery or chemotherapy. In these late side effects, the risk of long-term endocrinopathies and late-delayed complications were higher in the RT group than in the non-RT group, however, no significant differences were found in the risk of late cerebrovascular complications between the two groups. Associations were also noted between age and the presence of RT-related late side effects. For long-term endocrinopathies, the RT group had higher risk of gonadotropin deficiency and hypothalamic pituitary dysfunction than did the non-RT group. For late-delayed complications, the RT group had higher risk for post-RT necrosis of brain stem than did the non-

Table 3. Multivariable Cox-regression analysis of RT-related late side effects subgroup

Subgroup	RT vs. Non-RT	
	aHR[a] (95% CI)	p-value
Long-term endocrinopathies	1.172 (1.020–1.398)	0.018*
Hypothyroidism	1.434 (0.635–3.248)	0.364
Hypothalamic pituitary dysfunction	1.120 (1.005–1.548)	0.045*
Growth hormone deficiency	-	-
Cortisol deficiency	0.667 (0.261–1.699)	0.423
Gonadotropin deficiency	1.602 (1.010–3.718)	0.031*
Delay milestone	-	-
Short stature	1.055 (0.348–2.124)	0.789
Late-delayed complications	1.796 (1.250–2.578)	0.002*
Late effect of radiation	-	-
Sensorineural hearing loss	-	-
Stroke (other and ill-defined cerebrovascular disease)	2.785 (0.906–8.589)	0.077
Post-RT necrosis of brain stem	3.208 (1.953–5.297)	< 0.001*
Visual field defects	0.903 (0.387–2.104)	0.853
Myopia	0.394 (0.139–1.121)	0.094
Astigmatism	1.446 (0.270–7.726)	0.655
RT-induced non-senile cataract	-	-
Nasogastric tube insertion	-	-
Gastrostomy	-	-
Late cerebrovascular complications	0.817 (0.454–1.471)	0.553
Cavernous/arteriovenous malformation	0.494 (0.104–2.348)	0.403
Stroke (occlusion of cerebral arteries, acute cerebrovascular disease, and other and ill-defined cerebrovascular disease)	1.018 (0.492–2.114)	0.928
Cerebral atrophy	1.374 (0.240–7.849)	0.714
Moyamoya disease	0.982 (0.048–20.089)	0.998

RT, radiotherapy; aHR, adjusted hazard ratio; CI, confidence interval.
*p < 0.05.
[a]Adjusted for variables listed in Table 2.

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RT group.

Treatment strategies for pediatric brain tumor often include a combination of surgery, RT, and chemotherapy. Nevertheless, many pediatric brain tumor survivors are at significant risk for late side effects, which can be attributed to direct neurologic damage to the developing brain caused by surgery on the central nervous system [12]. Chemotherapy or RT may lead to late side effects, including possible neurocognitive and endocrine effects [13,14]. Similarly, the results of the present study exhibited that not only RT (aHR, 1.173) but also prior surgery (aHR, 1.856) or chemotherapy (aHR, 1.679) were independent predictors for increased risk of late side effects, suggesting that late side effects are not solely attributable to RT, and that prior chemotherapy and surgical interventions also may constitute significant risk factors, potentially exceeding the contribution of RT. In addition, the contemporary precision RT techniques (e.g., intensity-modulated RT, volumetric modulated arc therapy, or proton therapy) have recently become more widely adopted in pediatric brain tumor [15], enabling substantial sparing of normal organs, hence the actual incidence of late side effects in clinical practice attributable to RT may be considerably lower than that observed in the present cohort.

Higher radiation doses (36 Gy) correlate with greater late cognitive decline [14]. Furthermore, previous studies have reported that younger children are more sensitive to RT, which may complicate their risk for late side effects such as neurocognitive decline [7,16]. The impact of age also exceeded that of the radiation dose; patients younger than 5 years experienced the greatest decline in cognition [7]. Shalitin et al. [8] also reported that pediatric patients with brain tumors undergoing RT were at increased risk of late endocrine side effects, particularly those treated with cranial radiation and diagnosed at a younger age. Avadiappan et al. [17] also observed that younger patients receiving RT were at a greater risk of developing cerebrovascular complications. Compared to those studies, findings of the present study have added further evidence that, among pediatric patients, patients with young age (< 1 year) and undergoing RT were at an increased risk of overall late side effects when compared to patients with older age (≥ 1), supporting the association between pediatric age and RT-related overall late side effects, with a cut-off value of age 1-year. On the basis of these findings, we recommend that pediatric patients with brain tumors and undergoing RT require regular monitoring and frequent neurologic evaluations to ensure normal development. Moreover, additional educational support is essential for patients' recovery.

Cerebral radiation necrosis is a well-characterized toxicity associated with RT, as first described in adult patients [18]. However, little data is available regarding the incidence and risk of radiation necrosis in pediatric patients. Plimpton et al. [19] observed that pediatric patients undergoing RT for brain tumors may have an increased likelihood of developing cerebral radiation necrosis compared to adult counterparts. Furthermore, recent studies have revealed that brainstem injury is a rare complication of photon therapy [20,21]. Results of the present study demonstrate further that pediatric patients with brain tumors and undergoing RT had a higher (3.208-fold) risk of post-RT necrosis of the brain stem than did pediatric patients not receiving RT, which may worsen cerebral cellular injury and vascular damage leading to tissue hypoxia. Radiation necrosis has been reported to begin as acute cellular injury, in which endothelial cell death causes platelet aggregation and thrombus formation, ultimately leading to occlusion of microvessels [18,22]. Therefore, we hypothesized that the aforementioned mechanism may possibly be responsible for RT-related brainstem necrosis in pediatric patients with brain tumors. Those cellular and physiological alterations may further lead to cerebral atrophy, causing mass lesions, resulting in confusion, seizures, and other significant neurologic effects [23]. Helton et al. [24] indicated that late-delayed cerebral radiation necrosis occurs 6-12 months to years after RT. Therefore, our recommendation is to routinely perform MRI monitoring for post-RT brain- stem injury in pediatric patients within this time period. Various approaches such as corticosteroids [25], bevacizumab [26], hyperbaric oxygen therapy [27], anticoagulation [28], and oral vitamin E [29] may be recommended for treatment of cerebral radiation necrosis.

Late endocrine side effects also occur frequently and are often severe in pediatric patients with brain tumors [8]. The most common late endocrine side effects is GH deficiency, which may occur as soon as the first year after the initiation of RT [5]. It occurs in nearly 100% of patients who receive a radiation dose of 36 Gy or more to the pituitary region, and is less common with radiation doses of 18–24 Gy, but may not become evident until 10 years after treatment [12]. Laughton et al. [30] reported that around 1.8 years after RT, 84% of pediatric patients with embryonal brain tumors were diagnosed with GH deficiency, and 10% of patients developed thyroid-stimulating hormone (TSH) deficiency. Furthermore, the 4-year cumulative incidence rates for GH and TSH deficiency were 93% and 23%, respectively [30]. Bahl et al. [31] showed that the 5-year cumulative incidence rate was 68% for GH deficiency and 52% for hypothyroidism in pediatric patients with medulloblastomas (MB) who underwent RT. The present study further demonstrated that, in up to 16 years of tracking, the majority of pediatric patients with brain tumors and RT had 1.120-fold higher risk for hypothalamic pituitary dysfunction than did their counterparts without RT. In response to this finding, we suggest that the goal here is to prevent radiation-induced hyposuppression of the hypothalamic-pituitary-adrenal (HPA) axis, but not to reduce

the radiation dose, since radiation-induced toxicity in the HPA axis was not reduced by lower RT doses in low-risk MB patients [32].

Vatner et al. [33] reported that the 4-year actuarial rate for gonadotropin deficiencies was 4.1% in pediatric and young adult patients with brain tumor after RT. In a large cohort of 748 pediatric patients with brain tumor and RT, the estimated 40-year cumulative incidence of gonadotropin deficiency was 24.4% [34]. In particular, the present study further pointed that pediatric patients with RT had a 1.602-fold higher risk for gonadotropin deficiency than those without RT, implying that the risk of gonadotropin deficiencies is increasing steadily over time even long after the completion of RT. Thus, despite improved long-term survival of pediatric patients with brain tumor and RT, the RT-related gonadotropin deficiency may substantially affect their quality of life and medical expenditures later [35].

Both short and long-term cerebrovascular complications may arise following RT. Cerebral microbleeds can be detected as early as eight months after RT, while cavernous malformations and atherosclerosis can present decades later [6,36]. However, in the present study, after 16-year tracking, no significant differences were found in late cerebrovascular complications, including cavernous/arteriovenous malformation, stroke, cerebral atrophy, and moyamoya disease, between RT and non-RT groups. Cerebral microbleeds are RT-induced small vessel vasculopathies that are associated with poorer executive function, poor working memory, cognitive decline, and stroke in pediatric patients with brain tumors [37,38]. Hence, we still recommend that clinicians must monitor these potential late cerebrovascular complications continuously after using RT to treat pediatric patients with brain tumor.

Beyond the survivorship challenges commonly encountered within the broader pediatric oncology population, pediatric brain tumor survivors face a pronounced risk of enduring endocrinopathies, particularly GH deficiency. Fischer et al. [12] demonstrated that GH deficiency was present in nearly all patients who received radiation doses of ≥ 36 Gy targeting the pituitary region. Nevertheless, GH deficiency can be ameliorated through growth hormone replacement therapy (GHRT) [39]. However, given the established role of GH in tumorigenesis [40], concerns have been raised regarding the potential causal relationship between GHRT and tumor recurrence or the emergence of secondary malignancies. Evidence to date reassures, however, that GHRT does not elevate the risk of tumor recurrence or secondary malignancies in pediatric brain tumor survivors [41]. Although such patients exhibit an increased incidence of meningiomas, the increase is likely attributable to prior cranial irradiation rather than to GHRT administration. Further investigation is needed to determine the risk of tumor occurrence or secondary malignancies in pediatric patients with brain tumor after RT.

The present study was strengthened by the analysis of data from the longitudinal NHIRD, which represents a nationwide population in Taiwan. Nevertheless, this study has several limitations, including, first, the data were extracted from an administrative database, so the possibility of selection bias cannot be ruled out and the observational study design does not allow inferences of causation. Also, due to the insurance claim limit, patients' follow-up time is necessarily restricted and since no appropriate ICD-9-CM codes for the classification of neurocognitive decline are available in the administrative database, we were not able to assess it in the present study, and because most patients with pediatric brain tumor receive combined therapy (RT, chemotherapy, and surgery) rather than RT alone, the late side effects are likely to be caused by combined therapy, even though multivariate Cox regression analysis was adjusted by these variables. The NHIRD also does not provide detailed information on possible brain tumor- or RT-related risk factors such as smoking, diet, genetic variants, structural birth defects, types of tumors, location of tumors, brain surgery, radiation dose, treatment volume, fraction size, and image guidance, which could be potential confounding factors and these factors could not be evaluated, necessitating prospective multicenter studies to confirm results of the present study.

RT, in addition to prior surgery or chemotherapy, is an independent predictor for increased risk of late side effects in pediatric patients with brain tumors, particularly in patients who are younger at tumor diagnosis. RT-related late side effects, including gonadotropin deficiency, hypothalamic pituitary dysfunction, and brainstem necrosis increase over time. Lifelong medical surveillance and close follow-up for potential RT-related late side effects are essential in young pediatric patients, thereby reducing morbidity and mortality.

Statement of Ethics

To protect patient privacy, all personal patient information from the NHIRD is encrypted before being released to the public, including researchers. Therefore, all data for the present study were de-identified and were analyzed anonymously, precluding signed informed consent. The study protocol was approved by the Ethics Review Board of Tri-Service General Hospital (No. TSGHIRB. B-109-27).

Conflict of Interest

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

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Author Contributions

Conceptualization, FCL, WCC, CCC; Methodology, SKH; Data curation, FCL, CHC, SFL, WCC; Formal analysis, CHC, SFL, WCC, CCC; Writing of the original draft preparation, FCL, WCC, CCC; Writing of the review & editing, FCL, CHC, SFL, WFK, SKH, HC, PCH, WCC, CCC; Approval of the final version for submission, all authors.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on request.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2025.00885.

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Feasibility of surface-guided radiotherapy for detecting patient instability during prostate radiotherapy

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Purpose: Maintaining patient immobility during radiotherapy is essential for accurate dose delivery; however, patients may experience discomfort during treatment, leading to involuntary movement. Continuous imaging to detect intrafractional changes is not routinely feasible in conventional fractionation due to radiation exposure. This study aimed to evaluate the feasibility of knee-based surface-guided radiotherapy (SGRT) as a real-time method for detecting subtle patient motion during prostate radiotherapy.

Material and Methods: A total of 125 patients undergoing prostate intensity-modulated radiation therapy (2,527 fractions) were monitored using an SGRT system with the knees as the region of interest. Mean and maximum displacement per fraction were analyzed. Clinical factors, including bladder volume, age, International Prostate Symptom Score, laxative use, and overactive bladder medication, were evaluated. A displacement threshold of ≥4 mm was defined as an operational level to identify notable motion events.

Results: Displacement ≥4 mm was observed in 357 of 2,527 fractions (14.1%). Larger displacements were more frequent in the latter half of sessions and were often suggestive of urinary urgency. In a single case, motion improved following verbal instruction. Bladder volume was significantly associated with both mean displacement ($p = 0.025$) and the proportion of fractions with displacement ≥4 mm ($p = 0.004$), whereas other factors were not consistent predictors. Knee motion monitoring allowed real-time detection of patient movement requiring clinical attention.

Conclusion: Knee-based SGRT appears to be a feasible, non-invasive method for monitoring patient motion. While not a surrogate for prostate displacement, it may help identify patient instability and support timely clinical responses.

Keywords: Surface-guided radiotherapy, Motion monitoring, Intrafractional motion, Prostatic neoplasms

Introduction

Radiotherapy requires accurate and reproducible patient positioning to ensure precise dose delivery. Although it is generally assumed that patients remain immobile during irradiation, involuntary movement may occur due to various factors, including discomfort, anxiety, or physiological conditions. Such movement during treatment has the potential to compromise treatment accuracy, even when careful setup and image guidance are performed prior to irradiation.

In prostate radiotherapy, particular attention is given to organ motion, as the prostate may shift due to changes in bladder and rectal filling or pelvic muscle activity [1-7]. To minimize these effects, image-guided techniques such as cone-beam computed to-

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mography (CBCT) or fiducial markers are commonly used for patient setup. However, continuous monitoring during irradiation is not routinely performed in conventional fractionation due to concerns regarding additional radiation exposure. As a result, unexpected patient movement during treatment may go undetected.

Surface-guided radiotherapy (SGRT) is a non-invasive technique that enables real-time monitoring of patient surface motion without additional radiation exposure. It is widely used for the management of respiratory motion, particularly in techniques such as deep inspiration breath-hold (DIBH) for breast and thoracic radiotherapy [8-10]. Its application for monitoring non-respiratory body motion during irradiation remains limited, and the application of SGRT in prostate radiotherapy has not been well established. Several studies have reported the use of SGRT primarily for patient setup in prostate radiotherapy [11-13]. In clinical practice, however, patients undergoing prostate radiotherapy are often treated under full bladder conditions, which may lead to urinary urgency and associated discomfort during treatment. This may result in involuntary body movement that is difficult to detect using conventional monitoring methods such as closed-circuit television (CCTV) cameras. Initially, we attempted to track the pelvic region using the thermal surface camera. However, respiratory motion interfered with accurate tracking, resulting in unstable displacement signals (Fig. 1). In this study, we evaluated the feasibility of knee-based SGRT as a real-time method for detecting patient motion during prostate radiotherapy. Importantly, this approach is not intended to serve as a surrogate for prostate displacement, but rather as a practical tool to identify patient instability and detect clinically relevant motion during treatment.

Materials and Methods

1. Preparation for radiotherapy

Patients underwent radiotherapy under near full bladder conditions. They were instructed to drink a fixed volume of water at a consistent time and to maintain regular bowel movements. Bladder and rectal volumes were assessed using low-dose planning computed tomography (CT) scans employing CARE Dose 4D & CARE kV with a Tin filter (SOMATOM go Sim, Siemens AG, Munich, Germany). Once stable bladder and rectal conditions were confirmed, a full planning CT was acquired, and treatment plans were developed using volumetric-modulated arc therapy (VMAT).

2. Radiation therapy

Patients were positioned supine on the treatment couch using a breast board and knee support. Initial positioning was performed using ExacTrac Dynamic (ETD)-SGRT system by aligning the reference contour from the planning CT with the real-time optical surface. Subsequently, CBCT was performed for precise anatomical alignment based on target and organ-at-risk structures. After CBCT verification, 6 MV VMAT beams were delivered. Standard prescriptions were 60 Gy in 20 fractions or 63 Gy in 21 fractions. Each treatment fraction lasted approximately 10 minutes. During treatment, patients were monitored using CCTV and the ETD system, which continuously tracked both knee motion. A displacement threshold of 4 mm was used to define clinically relevant motion. This threshold was selected based on commonly used tolerance levels in clinical SGRT practice, where motion thresholds of approximately 3–5 mm are widely applied. In this study, 4 mm was adopted as a practical cutoff to identify noticeable intrafraction body motion detectable by the external monitoring system [14].

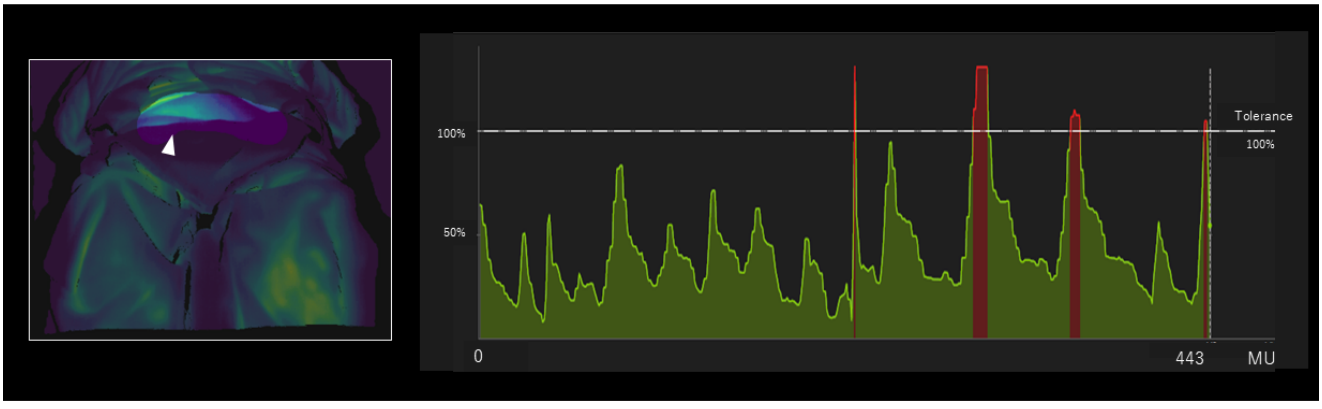

Fig. 1. Respiratory motion interfered with stable tracking of the pelvic region, resulting in fluctuating displacement signals. The region of interest is marked with an arrowhead.

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3. Data analysis

The ETD system logs displacement values at each monitor unit. Displacement was defined as the magnitude of positional deviation detected by the SGRT system rather than directional components (e.g., vertical, longitudinal, and lateral). Using these data, we calculated the mean and maximum displacement per fraction for each patient. The proportion of fractions with displacements ≥ 4 mm was defined as the number of such fractions divided by the total number of evaluated fractions. Associations between displacement metrics (mean displacement, maximum displacement, and proportion of fractions with displacement ≥ 4 mm) and continuous variables (age, bladder volume on planning CT, and International Prostate Symptom Score [IPSS]) were evaluated using Spearman's rank correlation coefficient. Categorical variables, including the use of urinary and bowel medications, were compared using the Mann-Whitney U test. Variables with $p < 0.05$ in univariate analyses were included in multivariable linear regression models to identify independent predictors of displacement. All statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

Results

A total of 140 patients received intensity-modulated radiation therapy for prostate cancer between October 2023 and November 2024, of whom 125 were monitored using ETD. Patient demographics are summarized in Table 1. The median age was 76 years, the median IPSS was 7, and the median bladder volume was 231.5 mL. Medications included α1 blockers (40 patients) and overactive bladder drugs (18 patients). We retrospectively reviewed log files from these 125 patients covering 2,527 treatment fractions. Displacement ≥ 4 mm was detected in 357 treatments (14.1%). Mean displacement per fraction was 0.9 mm (range, 0.06 to 9.52), while mean maximum displacement was 21.5 mm (range, 0.37 to 344.7). The extreme displacement of 344.7 mm occurred in a patient with anxiety and hearing impairment; treatment for this patient was continued after revising the immobilization method. Representative patterns of intrafraction motion are shown in Fig. 2, including stable displacement, late-session motion associated with urinary urgency, and motion reduction following clinical intervention. In univariate analysis, age, IPSS, and laxative use showed weak but statistically significant associations with mean displacement ($p = 0.039$, $p = 0.026$, and $p = 0.040$, respectively). Notably, IPSS demonstrated a weak inverse correlation ($r = -0.20$). Bladder volume was significantly associated with the proportion of fractions exhibiting displacement ≥ 4 mm ($p = 0.044$) (Table 2). Linear regression analysis further demonstrated a weak but statistically significant association between bladder volume and mean displacement ($r^2 = 0.033$) (Fig. 3). All patient characteristics evaluated in the univariate analysis were subsequently included in the multivariable linear regression analysis. Bladder volume emerged as the only consistent predictor for both mean displacement ($p = 0.025$) and the proportion of fractions with displacement ≥ 4 mm ($p = 0.004$). No evaluated factors significantly predicted maximum displacement (Table 3).

Table 1. Patient characteristics (n = 125)

Variable	Value
Age (year)	76 (57–92)
IPSS score	7 (0–32)
Bladder volume (mL)	231.5 (98.4–535.8)
α1 Blocker use	40 (32.0)
OAB medication use	18 (14.4)
BPH medication use	14 (11.2)
Laxative use	42 (33.6)
Dimethicone use	37 (29.6)

Values are presented as median (range) or number (%).
IPSS, International Prostate Symptom Score; OAB, overactive bladder; BPH, benign prostatic hyperplasia.

Discussion and Conclusion

It is well recognized that the correlation between prostate position and external surface motion is limited; therefore, surface-based monitoring cannot be used as a direct surrogate for prostate localization [14]. For this reason, image-guided techniques such as CBCT or fiducial marker-based alignment remain the standard approaches for accurate target positioning prior to irradiation. Once

Table 2. Correlation between patient characteristics and knee displacement

Variable	r-value (p-value)		
	Mean displacement	Maximum displacement	Displacement ≥4 mm (%)
Age	0.185 (0.039)	0.140 (0.122)	0.202 (0.024)
IPSS score	−0.200 (0.026)	−0.075 (0.408)	−0.089 (0.326)
Bladder volume	0.143 (0.113)	0.123 (0.173)	0.181 (0.044)
α1 Blocker use	- (0.605)	- (0.556)	- (0.207)
OAB medication use	- (0.139)	- (0.124)	- (0.115)
BPH medication use	- (0.664)	- (0.434)	- (0.877)
Laxative use	- (0.040)	- (0.136)	- (0.175)
Dimethicone use	- (0.578)	- (0.362)	- (0.578)

r, Spearman's rank correlation coefficient (continuous variables only); IPSS, International Prostate Symptom Score; OAB, overactive bladder; BPH, benign prostatic hyperplasia.

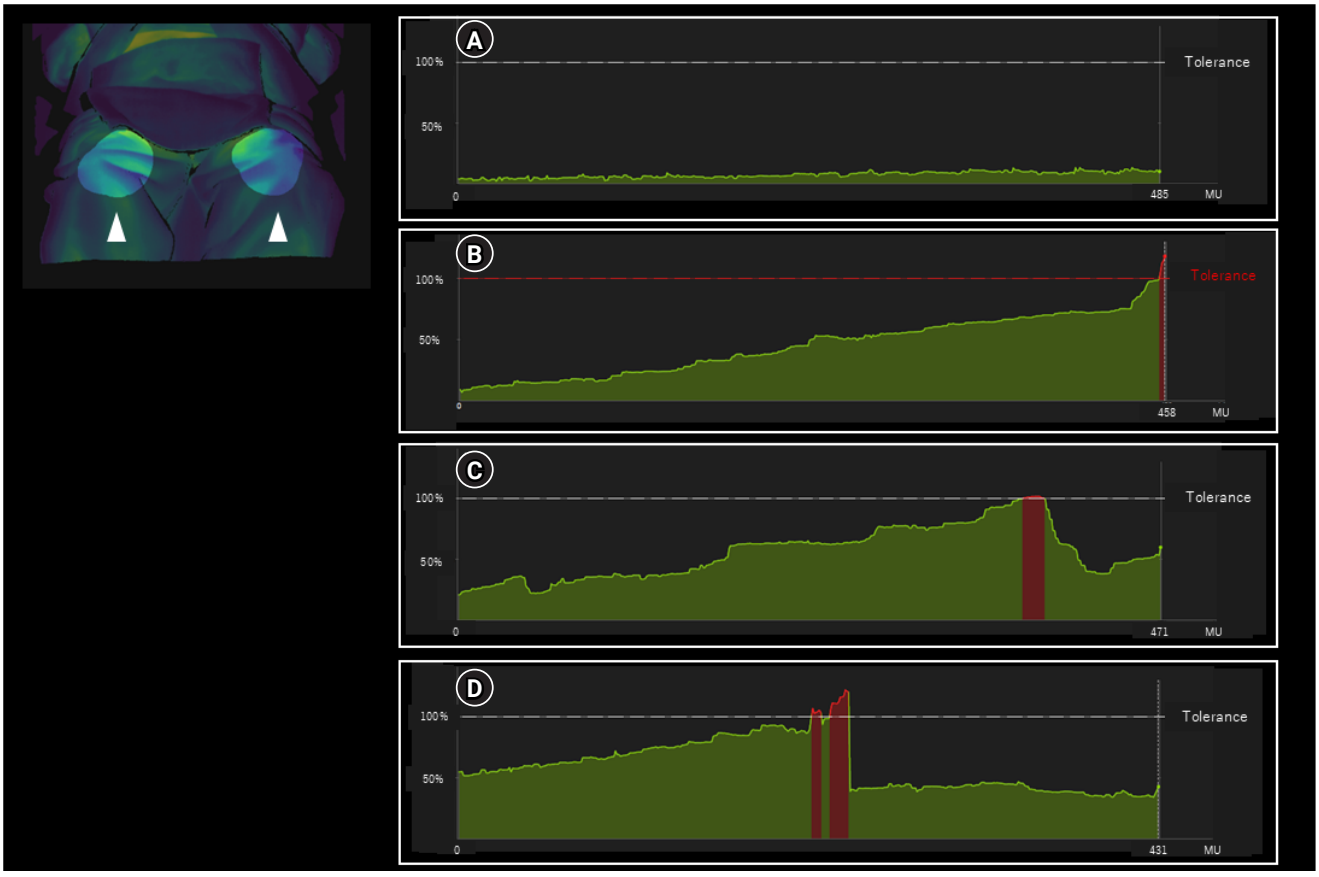

Fig. 2. Representative knee motion patterns during prostate radiotherapy. Regions of interest were placed on both knees to monitor patient motion (arrowheads). (A) Stable condition with displacement maintained within 4 mm. (B) Gradual increase in displacement during the late phase of treatment, associated with urinary urgency. (C) Reduction in motion following notification of treatment completion. (D) Early-session motion prompting patient repositioning using cone-beam computed tomography. Red bars indicate displacement exceeding the predefined threshold (4 mm).

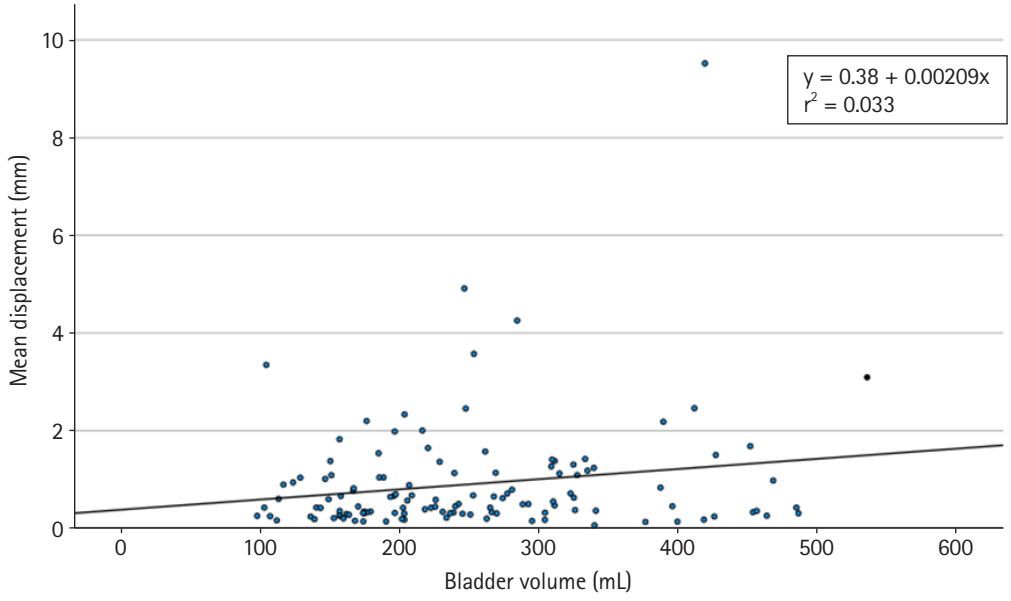

Fig. 3. Scatter plot showing the relationship between bladder volume on planning computed tomography and mean displacement during treatment. Linear regression analysis demonstrated a weak association ($r^2 = 0.033$).

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Table 3. Multivariable linear regression analysis of factors associated with displacement

Variable	p-value		
	Mean displacement	Maximum displacement	Displacement ≥ 4 mm (%)
Age	0.112	0.210	0.089
IPSS score	0.084	0.512	0.401
Bladder volume	0.025	0.331	0.004
α1 blocker use	0.488	0.602	0.198
OAB medication use	0.173	0.201	0.142
BPH medication use	0.721	0.533	0.812
Laxative use	0.067	0.188	0.209
Dimethicone use	0.601	0.444	0.590

IPSS, International Prostate Symptom Score; OAB, overactive bladder; BPH, benign prostatic hyperplasia.

treatment begins, however, continuous monitoring of prostate position is not routinely performed in conventional fractionation due to concerns regarding additional radiation exposure. As a result, unexpected patient movement during irradiation may compromise treatment accuracy despite careful initial setup and contouring.

In this study, we did not aim to establish knee motion as a surrogate for prostate displacement. Instead, we evaluated the feasibility of knee-based SGRT as a practical tool to detect patient instability or discomfort during treatment, which may indicate an increased risk of intrafractional uncertainty. While SGRT is commonly used for managing respiratory motion, such as in DIBH [8-10], the present findings suggest that it may also be useful for detecting subtle and non-respiratory body motion during irradiation.

In prostate radiotherapy, maintaining a full bladder and an empty rectum is commonly recommended to reduce internal organ motion and optimize dose distribution [15,16]. Malygina et al. [15] demonstrated that bladder volume was significantly correlated with dosimetric parameters such as V48Gy and V40Gy, suggesting a potential benefit in reducing urinary toxicity. However, bladder filling is also associated with urinary urgency, which may lead to involuntary patient movement. In our observations, increased knee displacement was frequently accompanied by signs of urinary urgency, such as patient-reported discomfort or an immediate need for voiding after treatment. These findings suggest that knee motion reflects changes in patient condition during irradiation, rather than target motion itself, and may serve as a practical indicator of patient status. Monitoring such involuntary patient movements may provide a practical approach to identifying clinically relevant motion during treatment. Although the pelvis was initially selected as the region of interest (ROI), respiratory motion produced substantial fluctuations in this area. Therefore, the ROI was shifted to the knee, which is less affected by respiration. Although the present study did not directly evaluate the relationship between knee and pelvic motion, the kinetic linkage between the pelvis and lower extremities has been well described [17,18]. From a biomechanical perspective, substantial movement of the lower extremities may reflect a broader pattern of whole-body instability rather than isolated limb motion. Therefore, knee displacement observed in this study is more appropriately interpreted as an indicator of patient instability or discomfort during treatment, rather than a direct surrogate for pelvic or prostate motion. Importantly, knee motion does not directly reflect prostate or pelvic displacement, and the two should be considered independent phenomena.

Detection of substantial knee motion may serve as a practical trigger for additional imaging. Such an approach could help identify potential positional deviations and support more accurate treatment delivery. Further studies are warranted to evaluate the clinical impact of this workflow.

Bladder volume was identified as a significant factor associated with mean displacement ($p = 0.025$), suggesting that urinary urgency due to a full bladder may contribute to increased patient motion during treatment. In contrast, no significant association was observed with the mean of maximum displacement, indicating that sudden and large motion may occur unpredictably. SGRT enables real-time detection of both types of patient motion, potentially facilitating appropriate and timely clinical intervention without additional radiation exposure. These findings may apply to patients who have difficulty remaining still, such as those experiencing severe pain or pediatric patients. For example, in pediatric radiotherapy, minimizing additional radiation exposure is important, and it is well recognized that maintaining complete immobility can be challenging [19]. In non-sedated patients, real-time detection of motion may allow timely verbal intervention, which could help reduce patient movement. In addition, even in sedated patients, continuous monitoring of body motion may provide an additional safety layer by enabling the detection of unexpected movement and facilitating appropriate actions, such as temporary beam interruption when necessary [20,21].

In this context, SGRT-based motion monitoring without additional radiation exposure may offer a clinically useful approach for detecting patient movement, even when direct visualization of the treatment region is limited, such as when immobilization devices are used. Therefore, this approach may have broader applicability beyond prostate radiotherapy, including pediatric settings and proton therapy, where motion management remains a critical challenge.

This study had several limitations. First, since the data were derived from routine clinical practice, CBCT re-setup was not performed for every detected motion event; therefore, the dosimetric

impact of intrafractional motion could not be quantified. Second, although knee motion was consistently observed and used as a practical surrogate for trunk movement, it does not directly represent trunk or prostate motion and may not fully capture intrafractional body movement.

Despite these limitations, knee-based SGRT offers a simple and non-invasive method for monitoring patient condition during treatment. While it does not provide direct information on prostate position, it may serve as a useful adjunct tool to identify patients who require closer observation, reassurance, or intervention during irradiation.

Statement of Ethics

This retrospective study was approved by the Institutional Review Board of Tsukuba Medical Center Hospital (approval number: 2023-0042) and was conducted in accordance with the Declaration of Helsinki. Owing to the retrospective nature of the study, the requirement for written informed consent was waived by the IRB.

Conflict of Interest

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

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Author Contributions

Conceptualization, YK; Methodology: YK; Investigation, YK, MI, RW, DW, YT, YS, MS; Data curation, YK, MI, MH, RW, DW, YT, YS, MS; Formal analysis, YO; Resources, MI, MH, RW, DW, KS, YT, YS, MS; Clinical investigation (patient treatment), MH, KS, YO; Supervision, YO; Project administration, YO; Writing of the original draft, YK; Writing of the review and editing, YO.

Data Availability Statement

The data that support the findings of this study are not publicly available due to institutional and ethical restrictions regarding patient privacy but are available from the corresponding author upon reasonable request and with permission of the institutional review board.

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Case Report

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Boron neutron capture therapy for recurrent pediatric sialoblastoma: the first clinical experience and dosimetric considerations for skeletal safety with 4-year follow-up

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Sialoblastoma is a rare, aggressive pediatric salivary gland tumor often refractory to conventional therapies, which carry significant risks of growth impairment in children. We report the 52-month follow-up of a 6-year-old girl with recurrent sialoblastoma treated with two sessions of boron neutron capture therapy (BNCT). She achieved a 23-month complete response after the first session and a sustained partial response following the second. Dosimetric analysis using a conservative α/β ratio of 2.0 Gy for late-responding tissues showed that the equivalent dose in 2-Gy fractions to the mandible area was approximately 4.3 Gy-Eq. This is substantially below the 15 Gy threshold recognized for skeletal impairment. Our findings suggest that BNCT is a highly selective salvage option that effectively controls refractory pediatric tumors while preserving craniofacial development.

Keywords: Recurrent, Sialoblastoma, Boron neutron capture therapy, Pediatrics, Bone development

Introduction

Sialoblastoma is a rare salivary gland tumor originating from the primitive duct epithelium, with an annual incidence of approximately 0.8 cases per million among individuals aged 0 to 19 years [1,2]. Sialoblastoma is characterized by a high recurrence rate, necessitating aggressive multimodal management. However, both chemotherapy and conventional radiotherapy (RT) pose severe long-term risks to young children, including reduced bone density and permanent impairment of skeletal growth [3,4]. For patients who have already exhausted conventional RT limits, selecting a salvage modality with high therapeutic selectivity is paramount. Boron neutron capture therapy (BNCT) offers a unique biological advantage by delivering localized high–linear energy transfer radiation via the $^{10}B(n,\alpha)^{7}Li$ reaction [5]. This allows for the delivery of curative doses to tumor cells while effectively sparing adjacent healthy skeletal structures and growth centers.

BNCT, an emerging treatment modality, has shown remarkable efficacy in head and neck cancers, and its clinical implementation is increasingly recognized in the East Asian oncology community [6,7]. Notably, BNCT has also exhibited outstanding results in the treatment of salivary gland tumors, with the added benefit of ex-

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tremely low side effects [8]. The underlying mechanism of BNCT enables highly localized radiation delivery, effectively confining damage to tumor cells and significantly minimizing harm to surrounding normal tissues.

This case involves a 6-year-old patient diagnosed with sialoblastoma who underwent multiple surgeries, two chemotherapy courses, and low-dose conventional photon RT. Despite these interventions, the tumor recurred, leading to the selection of BNCT to minimize long-term negative effects on growth and development.

Case Report

A 6-year-old girl presented with a recurrent right facial mass in July 2020. She had been diagnosed with sialoblastoma of the right parotid gland shortly after birth and underwent three surgical resections between 2015 and 2018. Despite postoperative RT (4,500 cGy in 25 fractions) and multiple rounds of chemotherapy (including cisplatin, doxorubicin, and cyclophosphamide), the tumor recurred locally by July 2020. Given the exhaustion of conventional treatment options and the high risk of further radiation-induced skeletal damage, BNCT was proposed as a salvage treatment.

1. Treatment planning and delivery

In this study, patients were administered boronophenylalanine (BPA) as the boron compound via intravenous injection. BPA was prepared by dissolving 6.25 mg of the compound in 250 mL of fructose solution. The administered dose was determined based on the patient's body weight, with a total dosage of 0.5 g/kg.

The boron concentration in the tumor and normal tissues was estimated based on individualized ^{18}F-fluoro-boronophenylalanine positron emission tomography (PET)/computed tomography imaging performed prior to treatment. The tumor-to-normal (T/N) ratio derived from the standardized uptake value (SUV) mean was 3.76 for the first BNCT session and 2.50 for the second session. These ratios were used to calculate the biologically equivalent dose (Gy-Eq) for both the target volume and critical organs at risk.

The neutron source used was from the reactor, which provides a high-quality epithermal neutron beam. The beam hole was tailored to the tumor location on the right cheek (Fig. 1A, 1B). Irradiation time was determined by the treatment planning system to ensure the prescribed dose was delivered while respecting normal tissue constraints, specifically the skin and oral mucosa. The dose prescription principles at our institution integrate the biological selectivity of BNCT with strict anatomical constraints similar to those in conventional RT. The primary objective is to deliver a curative dose to boron-containing tumor cells while minimizing the thermal neutron exposure to critical structures such as the brain and carotid arteries. For pediatric patients, our institutional protocol specifically prioritizes the preservation of growth and development. In this case, the treatment plan was optimized to ensure that the biologically equivalent dose to the skeletal growth centers and the central nervous system remained well below the thresholds for late toxicity, thereby safeguarding the patient's craniofacial symmetry and long-term quality of life.

On the day of irradiation, the blood boron concentration was monitored via inductively coupled plasma atomic emission spectroscopy to adjust the real-time dosimetry.

The biological equivalent dose was calculated by applying tissue-specific factors derived from established models: a compound biological effectiveness (CBE) of 3.8 for the tumor [5], 4.9 for the oral mucosa [9], 2.27 for normal bone [10], and 1.35 for spinal cord [11].

To ensure precise tumor control while safeguarding the skeletal development of the pediatric patient, the biologically equivalent dose was determined by integrating the physical dose components with tissue-specific biological weighting factors. Following the methodology utilized in recent BNCT clinical protocols [12], the total dose was calculated using the following summation (Eq. 1):

$$D_{BNCT} = D_{gamma} + [D_{boron} \times CBE_{organ} + (D_H + D_N) \times RBE_{neutron}] \quad (1)$$

Where D_{gamma} represents the gamma-ray dose, D_{boron} is the physical dose from the ^{10}B and ^{7}Li reaction, and (D_H + D_N) accounts for

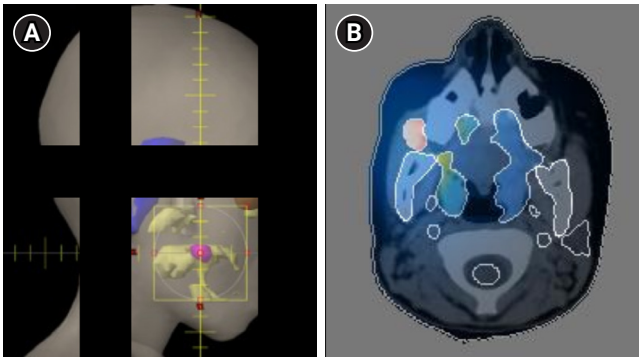

Fig. 1. Boron neutron capture therapy (BNCT) treatment planning and dosimetric analysis. (A) Schematic of neutron beam incidence: The neutron beam enters perpendicularly from the patient's right cheek toward the tumor. This orientation ensures that the primary neutron path avoids critical brain tissues. (B) 2nd BNCT Isodose distribution map: The high-dose regions are highly localized within the tumor tissue and the oral mucosa. Note the significantly lower dose delivered to the bone, reflecting the poor uptake of boronophenylalanine in skeletal structures and the high therapeutic selectivity of BNCT.

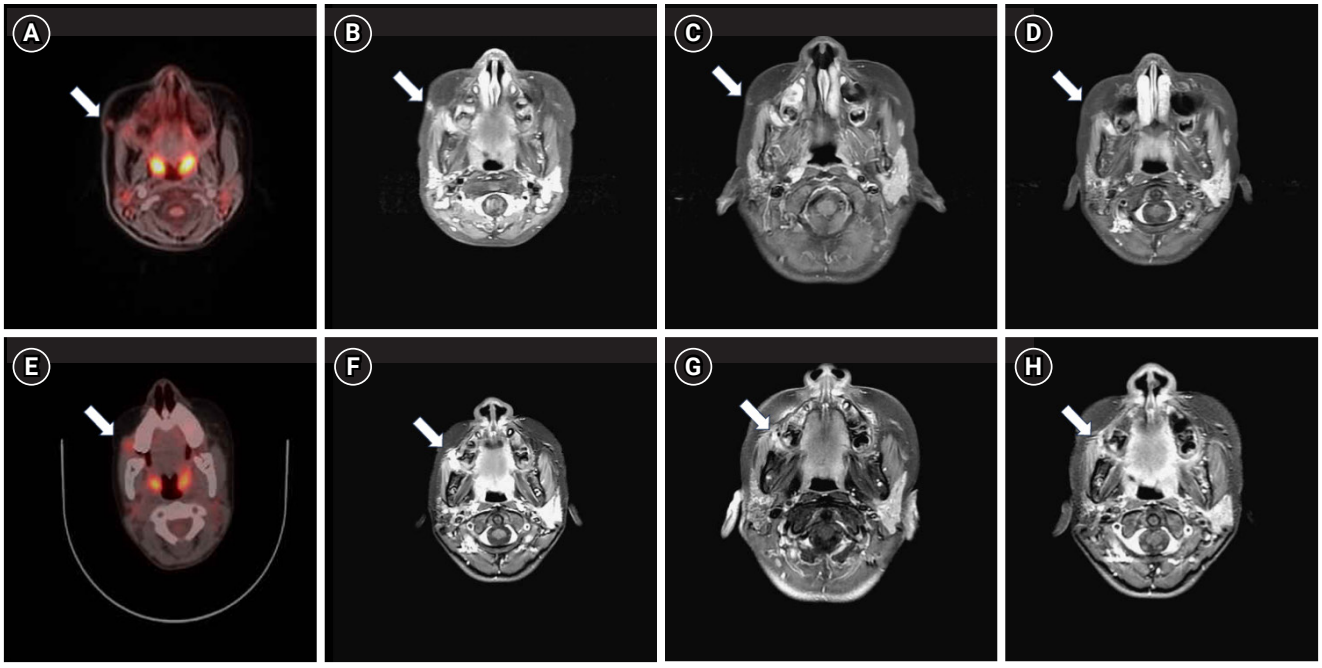

Fig. 2. Imaging follow-up of the patient. (A) Pre-treatment treatment fluorodeoxyglucose (FDG) positron emission tomography (PET) (July 15, 2020) revealing hypermetabolic nodules in the right facial and buccal regions (arrows). (B–D) Sequential magnetic resonance imaging (MRI) follow-up (October 2020 to October 2021) showing a gradual reduction in tumor size (arrows), confirming a complete response after the first boron neutron capture therapy (BNCT) session. (E) Recurrent FDG PET imaging (August 17, 2022) indicating new metabolic activity in the right buccal region (arrows). (F–H) Post-second BNCT MRI series (August 2022 to March 2024) demonstrating sustained partial response and localized tumor control (arrows).

the dose from thermal and fast neutrons. In this study, a fixed relative biological effectiveness (RBE) of 3.2 was applied to the neutron components [5].

Furthermore, to evaluate the safety of the single-session BNCT relative to conventional fractional RT, the equivalent dose in 2-Gy fractions (EQD_2) was derived using the linear-quadratic model [13] (Eq. 2).

$$EQD_2 = D_{BNCT} \times [1 + D_{BNCT}/(\alpha/\beta)]/[1 + 2/(\alpha/\beta)] \quad (2)$$

According to the SIOPE Radiotherapy Working Group consensus, the threshold for clinically observable growth impairment in the pediatric skeleton begins at an EQD_2 of 15–18 Gy [14], with severe developmental risks occurring at doses exceeding 30 Gy. Given that pediatric growth plates and mandibular bone are late-responding tissues, an α/β ratio of 2.0 was considered for the skeletal safety analysis [15]. By maintaining the mean dose to the mandible significantly below the thresholds established by these models, the treatment plan prioritized the prevention of permanent growth arrest and midfacial asymmetry.

2. 1st BNCT and clinical response

On July 15, 2020, routine whole-body fluorodeoxyglucose (FDG) PET imaging revealed two hypermetabolic nodules in the right face and right buccal space with a maximum SUV of 1.6 (Fig. 2A). The patient underwent the first BNCT session on September 2, 2020, with a blood boron concentration of 24.3 ppm measured on the day of irradiation. Table 1 presents the maximum radiation dose delivered to the tumor (25.92 Gy-Eq) and its average dose (Dave = 21.66 Gy-Eq). Among normal tissues, the mucosa received the highest average dose (Dave = 7.39 Gy-Eq), followed by the right submandibular gland (Dave = 3.79 Gy-Eq).

Magnetic resonance imaging (MRI) follow-up showed a gradual reduction in tumor size, eventually leading to complete disappearance and classification as a complete response (Fig. 2B–2D). She remained progression-free for 23 months. During this period, no additional chemotherapy or surgical interventions were administered. Regarding side effects, the patient experienced only Common Terminology Criteria for Adverse Events (CTCAE) grade 2 mucositis [16], which resolved within a few weeks.

3. 2nd BNCT and clinical response

During FDG PET imaging on August 17, 2022 (Fig. 2E), the previously identified right facial nodule had disappeared. However, increased enhancement was observed in the right buccal region (SUV max 3.17). Additionally, an MRI report from August 25, 2022, indi-

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Table 1. 1st and 2nd BNCT radiation dose distribution

	1st BNCT				2nd BNCT			
	Dmax	Dave	Dmin	Volume	Dmax	Dave	Dmin	Volume
Tumor	25.92	21.66	14.80	1.36	27.16	26.39	25.25	1.18
Oral mucosa	18.40	7.39	1.56	26.15	12.94	5.85	2.18	25.71
Muscle	6.15	0.73	0.01	1,670.93	6.58	0.76	0.03	1,882.52
Mandible	6.24	2.21	0.33	47.43	6.38	2.35	0.46	51.99
Skull	5.82	0.64	0.02	643.35	6.32	0.66	0.03	606.97
Parotid Lt	0.66	0.40	0.23	8.23	0.71	0.50	0.34	8.90
Submandibular Rt	5.38	3.79	2.41	4.62	4.60	3.26	2.35	4.90
Submandibular Lt	1.60	1.09	0.70	4.17	1.52	1.13	0.76	3.47
Spinal cord	1.15	0.57	0.08	8.33	1.34	0.62	0.07	15.72

Biological dose calculation: The biologically equivalent dose (Gy-Eq) was determined using the following weighting factors: CBE for tumor, 3.8; CBE for oral mucosa, 4.9; CBE for bone (mandible/skull), 2.27; CBE for spinal cord, 1.35.
BNCT, boron neutron capture therapy; Dmax, maximum dose; Dave, average dose; Dmin, minimum dose; Parotid, parotid gland; Lt, left; Rt, right; Submandibular, submandibular gland; CBE, compound biological effectiveness.

cated increased enhancement and thickening in the right buccal region, retromolar area, and masticator space. A biopsy conducted in October 2022 confirmed recurrent sialoblastoma, and BNCT was administered on November 11, 2022.

During this BNCT session, the tumor received a maximum radiation dose of 27.16 Gy-Eq, with a Dave of 26.39 Gy-Eq. The mucosa received an average dose of 5.85 Gy-Eq, and the right submandibular gland received 3.26 Gy-Eq (Table 1). Subsequent follow-up confirmed a partial response in tumor control (Fig. 2F–2H). The patient experienced only mild mucositis, which resolved spontaneously within a few weeks.

At the latest follow-up (52 months after the first BNCT), the patient was surviving with persistent disease, maintaining a stable partial response. The patient's long-term development was assessed using structured clinical parameters. Growth and physical development were monitored using standardized pediatric growth charts; both her height and weight remained consistently within the 50th–75th percentile, indicating no systemic endocrine or growth impairment. Regarding late toxicity, a mild, asymptomatic fibrosis was noted in the right buccal mucosa, corresponding to a CTCAE v5.0 Grade 1 oral soft tissue fibrosis [16], with no associated pain or restriction in jaw movement. Regarding facial development, clinical symmetry was evaluated by comparing bilateral anatomical landmarks (tragus to commissure of the lips and mandibular angle depth). No significant mandibular hypoplasia or facial asymmetry was observed, despite the cumulative radiation dose to the right cheek. Furthermore, while formal Pediatric Quality of Life Inventory scores were not collected at baseline, retrospective assessment of her school progress reports demonstrated age-appropriate neurocognitive functioning and social integration, with no learning disabilities identified during her primary school years.

Discussion

The management of pediatric head and neck oncology requires a precise balance between local tumor control and the preservation of long-term developmental integrity. In the present case, the patient had already received 45 Gy of prior photon therapy, reaching the biological threshold for skeletal tolerance. The subsequent successful application of BNCT demonstrates the modality's capacity for safe re-irradiation in sensitive pediatric regions.

To rigorously evaluate skeletal safety, we converted the BNCT doses to an EQD_2. We categorized the mandible and its associated growth centers as late-responding tissues with a conservative α/β ratio of 2.0 Gy [15]. Our analysis showed that the average dose to the mandible was 2.35 Gy-Eq; to ensure a worst-case safety estimate, we also evaluated the high-dose submandibular region (Dave, 3.26 Gy-Eq), resulting in an EQD_2 of approximately 4.3 Gy-Eq. This value remains far below the 15–18 Gy threshold recommended by the SIOPE Radiotherapy Working Group (2019) for preventing clinically significant growth retardation [14].

It is important to distinguish between the curative dose delivered to the tumor and the dose received by adjacent normal tissues. In the first BNCT session, the average tumor dose (Dave) reached 21.66 Gy-Eq, while the normal oral mucosa was limited to 7.39 Gy-Eq to prevent severe radiation-induced sequelae. Notably, the subsequent recurrence did not occur on the mucosal surface, but was located in the deeper right buccal region, retromolar area, and masticator space. This suggests that the treatment failure was likely a result of the aggressive biological behavior of the recurrent sialoblastoma and the conservative margins required in a re-irradiation setting, rather than under-dosage to the mucosa.

Clinical evidence at the 52-month follow-up corroborated these

dosimetric findings. The patient maintained facial symmetry and physical growth within the 50th–75th percentiles. Regarding late toxicity, a mild, asymptomatic fibrosis was noted in the right buccal mucosa (CTCAE v5.0 Grade 1) [16], with no associated pain or mandibular hypoplasia. While no clinical evidence of peripheral neurotoxicity was identified at the 52-month follow-up, the potential for delayed neurological sequelae remains a critical consideration for pediatric survivors. Late radiation-induced peripheral nerve injury often results from a combination of direct axonal damage and progressive perineural fibrosis, which may manifest years after the completion of therapy [17,18]. Given that this patient presented with mild, asymptomatic grade 1 oral soft tissue fibrosis, continued long-term monitoring is essential, as progressive fibrotic changes can eventually lead to nerve entrapment or ischemic injury to the peripheral nerves in the masticator space [19]. The high therapeutic selectivity of BNCT may theoretically reduce the risk of such sequelae by sparing the surrounding stromal architecture [11]; however, further studies with extended longitudinal follow-up are required to fully establish the long-term neurotoxicity profile of BNCT in the pediatric population. This case provides robust evidence that BNCT's high T/N tissue ratio enables effective salvage treatment while minimizing the long-term developmental morbidity often associated with conventional photon therapy.

Our 52-month follow-up demonstrates that BNCT is a viable salvage treatment for recurrent pediatric sialoblastoma. By maintaining the biological EQD_2 to the mandible significantly below the SIOPE-recommended 15 Gy threshold—even when utilizing a conservative α/β ratio of 2.0 Gy for growth centers—we achieved robust local control without compromising craniofacial development. Our findings confirm that BNCT's high therapeutic selectivity may enable safe re-irradiation in the pediatric head and neck region, offering a promising alternative to conventional RT for preserving skeletal integrity and quality of life in young survivors.

Statement of Ethics

As BNCT is classified as an emergency medical treatment in our country, this study was approved by the Institutional Review Board of Taipei Veterans General Hospital (approval Nos. 2020-08-E02A and 2022-11-E06C). The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from the patient's legal guardians for the treatment and the publication of this case report, including all accompanying clinical images.

Conflict of Interest

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

Funding

None.

Author Contributions

Conceptualization, HRL; Data curation, HRL; Formal analysis, HRL, STC; Investigation, HRL; Methodology, FIC, JJP, HML; Project administration, YWC; Resources, YYL, CYL, KHL; Supervision, YWC; Visualization, HRL; Writing of the original draft, HRL; Writing of the review and editing, YWC; Approval of final manuscript, all authors.

Data Availability Statement

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy and institutional restrictions, but are available from the corresponding author on reasonable request.

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Instructions for Authors

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

Initiative	Type of study	Source
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Introduction section should contain 1) the background and rationale of the study and 2) the objective of the study. The former part should state background information and references that inform the reader as to why the study was performed. Please avoid an extensive review of the literature. The final paragraph of the introduction should clearly state the hypothesis and the objective of the study.

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Materials and Methods section should include sufficient details of the research design, subjects, and methods. Sufficient details need to be addressed in the methodology section of an experimental study so that it can be further replicated by others. The sources of special chemicals or reagents should be given along with the source location (name of the company, city, state/province, and country). Identify and provide references for all the statistical methods used. Statistical methods should be described meticulously. Software used for the statistical analysis should be stated with the name, manufacturer, and version. For studies using human subjects, the detail of IRB approval and patient informed consent should be stated. For animal experiments, a statement of approval by the institutional animal care committee or appropriate substitute should be provided.

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

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

Book:

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

Conference paper:

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

Online sources:

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

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