pISSN 2234-1900
eISSN 2234-3156

Radiation Oncology Journal

ROJ

Vol. 43, No. 4, December 2025

www.e-roj.org

The Korean Society for Radiation Oncology

www.e-roj.org

pISSN 2234-1900
eISSN 2234-3156

ROJ Radiation Oncology Journal

Vol. 43, No. 4, December 2025

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.

The ROJ is free open access journal. All articles published in ROJ are available through http://www.e-roj.org.

Open Access

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher Tae Hyun Kim
Editor-in-Chief Dongryul Oh

Editorial Office
Department of Radiation Oncology, Samsung Medical Center, Proton Therapy Center, B2, 81, Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea
Tel: +82-2-3410-3617 E-mail: rojeditor@gmail.com, roj@kosro.or.kr

The Korean Society for Radiation Oncology
National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang-si, Gyeonggi-do, Republic of Korea
Tel: +82-31-920-0489 E-mail: kosro@kosro.or.kr

Printing Office
M2PI
#805, 26 Sangwon 1-gil, Seongdong-gu, Seoul 04779, Korea
Tel: +82-2-6966-4930 Fax: +82-2-6966-4945 E-mail: support@m2-pi.com

Published on December 31, 2025

© 2025 The Korean Society for Radiation Oncology
This paper meets the requirements of KS X ISO 9706, ISO 9706-1994 and ANSI/NISO Z39. 48-1992 (Permanence of paper)

ROJ Radiation Oncology Journal

Editorial Board

Publisher	Tae Hyun Kim	*National Cancer Center, Korea*
Editor-in-Chief	Dongryul Oh	*Sungkyunkwan University, Korea*
Associate Editor	Jin Hwa Choi	*Chung-Ang University, Korea*
Editorial Board	Zishan Allibhai	*Southlake Regional Health Centre, Canada*
	Sevil Aliyeva Bagaturovna	*N. N. Blokhin Cancer Research Center, Russia*
	Miriam Joy C. Calaguas	*St. Luke's Medical Center, Philippines*
	Yu-Jen Chen	*National Yang-Ming University and MacKay Medical College, Taiwan*
	Jason Chia-Hsien Cheng	*National Taiwan University, Taiwan*
	Jeng-Fong Chiou	*Taipei Medical University, Taiwan*
	Changhoon Choi	*Sungkyunkwan University, Korea*
	Hak Choy	*UT Southweastern Medical Center, USA*
	Mantana Dhanachai	*Mahidol University, Thailand*
	Soehartati Gondhowiardjo	*University of Indonesia, Indonesia*
	Chul Soo Ha	*The University of Texas Health Science Center at San Antonio, USA*
	Ji Hong Hong	*Chang Gung Memorial Hospital, Taiwan*
	Jea-Uk Jeong	*Chunnam National University, Korea*
	JinHong Jung	*Ulsan University, Korea*
	Byoung Hyuck Kim	*SMG-SNU Boramae Medical Center, Korea*
	Donghyun Kim	*Pusan National University, Korea*
	Jin Sung Kim	*Yonsei University, Korea*
	Kyubo Kim	*Seoul National University Bundang Hospital, Korea*
	Sup Kim	*Chungnam National University, Korea*
	Woong Sub Koom	*Yonsei University, Korea*
	Vedang Murthy	*Tata Memorial Centre, India*
	O Kyu Noh	*Ajou University, Korea*
	Jae Won Park	*Yeungnam University, Korea*
	Won Park	*Sungkyunkwan University, Korea*
	Umberto Ricardi	*University of Torino, Italy*
	Vinay Sharma	*University of the Witwatersrand, South Africa*
	Tarek Shouman	*Cairo University, Egypt*
	Chang Won Song	*University of Minnesota, USA*
	Jin-Ho Song	*Catholic University, Korea*
	Ekkasit Tharavichitkul	*Chiang Mai University, Thailand*
	Dang Huy Quoc Thinh	*HCMC Oncology Hospital, Vietnam*
	Joseph Tien-Seng Wee	*National Cancer Center, Singapore*
	Zhao Chong Zeng	*Fudan Univerisity, China*
	Eduardo H. Zubizarreta	*International Atomic Energy Agency, Austria*
Editorial Assistant	Horim Yang	*KOSRO, Korea*
Manuscript Editor	Soo-Hee Chang	*Infolumi, Korea*

ROJ Radiation Oncology Journal

Radiat Oncol J
pISSN 2234-1900 eISSN 2234-3156

Vol. 43, No. 4, December 2025

Editorial

163 Radiotherapy omission in low-risk hormone receptor–positive breast cancer: insights from a Korean single-center cohort
Haeyoung Kim

Original Articles

165 Systemic immune-inflammation index prior to postoperative radiotherapy as a tool for outcome prediction in thymic epithelial tumors
Alper Kahvecioglu, Mervenur Bay, Pervin Hurmuz, Mustafa Cengiz

172 Postmastectomy radiation therapy for patients with pT1-2N1 breast cancer over 2 decades in Korea: Korean Radiation Oncology Group 14-21
Mi Sun Kim, Seung Do Ahn, Yong Bae Kim, Won Park, Shin-Hyung Park, Ik Jae Lee, Byung-Ock Choi, Juri Kim, Sung Ja Ahn, Won Sup Yoon, Jin-hee Kim, Jong Hoon Lee, Donghyun Kim, Hye Li Park, Yeon-Joo Kim, Sun Young Lee, Kyung Ran Park, Division for Breast Cancer, Korean Radiation Oncology Group

181 Can lymphocytic toxicity be induced by radiation dose to the bowel bag in whole pelvic radiotherapy?
Min Kyun Ko, Kyu Hye Choi, Wonmo Sung, Ji Hyun Hong, Seok Hyun Son, Young-nam Kang, Byung-Ock Choi, Yeon-Sil Kim, HongSeok Jang

188 Efficacy and safety of high-dose hypofractionated palliative radiotherapy (40 Gy in 10 daily fractions) for non–small cell lung cancer
James C. H. Chow, Jeffrey C. F. Lui, Chris K. C. Tong, Anthony H. P. Tam, Jeffrey C. H. Chan, Jeannie Y. K. Chik, Gavin T. C. Cheung, Ka Man Cheung, Luke T. Y. Lee, Kam Hung Wong, Kwok Hung Au

195 Machine learning–based prediction of severe oral mucositis from head and neck cancer radiation therapy
Kanyapat Buasawat, Sasikarn Chamchod, Todsaporn Fuangrod, Sawanee Suntiwong, Kiattiyot Chantarak, Pasit Jarutatsanangkoon, Thiansin Liamsuwan

206 Histopathological risk stratification for early-stage endometrial cancer patients receiving adjuvant vaginal brachytherapy
Hae Sol Lim, Won Park, Won Kyung Cho, Jeong-Won Lee, Chel Hun Choi, Tae-Joong Kim, Yoo-Young Lee

Case Report

214 Radiation therapy in a ductal carcinoma in situ patient with ornithine transcarbamylase deficiency: a case report
Iris Kang, Justin Park, Christine Yang, Aster Kim, Mary Tang, Kaye Lu, Azadeh Carr, Stephen F. Sener, Rachel McGowan, Shoji Yano, Stella K. Yoo

ⓒ 2025 The Korean Society for Radiation Oncology

ROJ Radiation Oncology Journal

Editorial

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2025;43(4):163-164
https://doi.org/10.3857/roj.2025.00836

Radiotherapy omission in low-risk hormone receptor–positive breast cancer: insights from a Korean single-center cohort

Haeyoung Kim

Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Received: December 1, 2025
Accepted: December 8, 2025

Correspondence:
Haeyoung Kim
Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea
Tel: +82-2-3410-2612
E-mail: haeyoung0131.kim@samsung.com, hykim0131@skku.edu
ORCID:
https://orcid.org/0000-0003-1808-7573

Breast-conserving surgery (BCS) followed by radiotherapy has long represented the standard of care for early-stage breast cancer, supported by randomized trials and meta-analyses that have demonstrated substantial reductions in ipsilateral breast tumor recurrence and modest improvements in breast cancer mortality [1,2]. As our understanding of tumor biology has evolved and endocrine therapy has become more widely adopted, interest has grown in identifying subsets of patients with truly low-risk, hormone receptor (HR)–positive disease for whom postoperative radiotherapy might be omitted. However, despite decades of research, no clinicopathological subgroup has been conclusively demonstrated to achieve a sufficiently low recurrence risk to omit the local control benefit of radiotherapy. Evidence from the Early Breast Cancer Trialists' Collaborative Group meta-analysis, the NSABP B-21 trial, CALGB 9343, and PRIME II consistently demonstrated that even among patients considered lowest risk, omitting radiotherapy is associated with increased local recurrence than with radiotherapy [1-4]. Accordingly, although treatment de-escalation is an important goal, radiotherapy omissions continue to require thoughtful consideration.

In this issue of *Radiation Oncology Journal*, Song et al. [5] presented an important early Korean report evaluating radiotherapy omission in a narrowly selected, low-risk cohort. Using their single-center hospital's database, the investigators identified postmenopausal women with pT1N0/Nx, grade 1–2, HR-positive/human epidermal growth factor receptor 2–negative tumors and Ki-67 ≤ 20% who underwent BCS and endocrine therapy. Among the 742 eligible patients treated between 2010 and 2020, 707 received radiotherapy and 35 did not. With a median follow-up of less than 6 years in the omission group, no locoregional recurrences were observed, and the overall recurrence rates remained low in both cohorts after propensity score matching. These findings suggest that within highly structured clinical settings, radiotherapy omission may be feasible for a very small, stringently selected subset of patients with biologically favorable disease. In Song et al.'s cohort [5], routine preoperative magnetic resonance imaging, strict clinicopathologic selection, and high adherence to endocrine therapy likely contributed to excellent outcomes, despite omitting radiotherapy.

Despite these favorable outcomes, caution should be exercised. This study was conducted at a single tertiary institution, which limits its generalizability across diverse clinical environments. The retrospective design also introduced selection bias that could not be fully eliminated, as radiotherapy decisions are influenced by age, comorbidity, and physician judgment. Another important limitation was the small number of patients who did not receive radiotherapy (n = 35). Although no recurrences were observed, the omission cohort was too small to draw firm conclusions, and the absence of

Copyright © 2025 The Korean Society for Radiation Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

events in such a limited sample cannot be interpreted as evidence of long-term safety. The relatively short follow-up period warrants further consideration. HR-positive breast cancer is characterized by a sustained risk of late recurrence that extends well beyond 10–15 years [6]. Differences in local recurrence between radiotherapy and no radiotherapy often become more evident with extended observation [2]. These features underscore the need for long-term follow-ups when evaluating the safety of radiotherapy omissions. Another important factor to consider is that all patients in Song et al.'s cohort [5] initiated endocrine therapy and most completed the planned 5-year course. However, in routine practice, adherence tends to be lower. Large population-based studies have reported discontinuation or nonadherence rates approaching 40%–50% within 5 years, with poorer adherence associated with increased recurrence and mortality [7]. Thus, when considering radiotherapy omission, clinicians should recognize that the excellent outcomes reported by Song et al. [5] may not be reproducible in settings with lower endocrine therapy adherence, and should incorporate this into individualized decision-making.

The Korean healthcare system influences the clinical applicability of radiotherapy omission. Radiotherapy is widely accessible in Korea and is associated with low out-of-pocket costs owing to national health insurance coverage. Additionally, nationwide practice trends have shown a rapid increase in partial breast irradiation and hypo-fractionated or ultra-hypofractionated schedules, with hypofractionation increasing from approximately one-third of breast radiotherapy in 2017 to nearly 90% in 2022 [8]. Importantly, radiotherapy substantially reduces the risk of locoregional recurrence, thereby lowering the likelihood of salvage mastectomy or other reinterventions. These features of treatments in Korea—and the availability of contemporary 1–2-week regimens—are important considerations when assessing whether radiotherapy omission is genuinely warranted for Korean patients with low-risk HR-positive breast cancer.

The growing interest in biologically guided de-escalation reflects the recognition that clinicopathological features alone may not adequately capture the recurrence risk. Early studies such as LUMINA and IDEA are encouraging but remain limited by single-arm designs and relatively short follow-up periods [9,10]. Ongoing trials including PRIMETIME, EXPERT, DEBRA, and PRECISION are testing similar strategies in broader prospective settings. Long-term data are ultimately needed to determine whether biological selection can reliably support the omission of radiotherapy.

Taken together, the findings of Song et al. [5] provide an early Korean insight suggesting that radiotherapy omission may be feasible in carefully selected postmenopausal women with favorable HR-positive disease. However, the single-center design, retrospective nature, small cohort, and relatively short follow-up period underscore the need for caution. Further multicenter Korean studies with long-term follow-up and the integration of molecular profiling are crucial to determine when radiotherapy can be safely omitted.

Conflict of Interest

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

References

1. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347:1233–41.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG); Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378:1707–16.
3. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med 2004;351:971–7.
4. Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM. Breast-conserving surgery with or without irradiation in early breast cancer. N Engl J Med 2023;388:585–94.
5. Song Y, Lee SB, Kim SS, Ahn SD, Lee JW, Jung J. Radiotherapy omission in low-risk, early-stage breast cancer: a single-center, real-world comparative analysis. Radiat Oncol J 2025;43:151–60.
6. Pan H, Gray R, Braybrooke J, et al. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med 2017;377:1836–46.
7. Hershman DL, Kushi LH, Shao T, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. J Clin Oncol 2010;28:4120–8.
8. Park HJ, Kim K, Kim YB, Chang JS, Shin KH; Division for Breast Cancer, Korean Radiation Oncology Group. Patterns and longitudinal changes in the practice of breast cancer radiotherapy in Korea: Korean Radiation Oncology Group 22-01. J Breast Cancer 2023;26:254–67.
9. Whelan TJ, Smith S, Parpia S, et al. Omitting radiotherapy after breast-conserving surgery in luminal A breast cancer. N Engl J Med 2023;389:612–9.
10. Jagsi R, Griffith KA, Harris EE, et al. Omission of radiotherapy after breast-conserving surgery for women with breast cancer with low clinical and genomic risk: 5-year outcomes of IDEA. J Clin Oncol 2024;42:390–8.

 https://doi.org/10.3857/roj.2025.00836

ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2025;43(4):165-171
https://doi.org/10.3857/roj.2025.00143

Systemic immune-inflammation index prior to postoperative radiotherapy as a tool for outcome prediction in thymic epithelial tumors

Alper Kahvecioglu, Mervenur Bay, Pervin Hurmuz, Mustafa Cengiz

Department of Radiation Oncology, Hacettepe University Faculty of Medicine, Ankara, Türkiye

Received: March 11, 2025
Revised: May 25, 2025
Accepted: June 2, 2025

Correspondence:
Pervin Hurmuz
Department of Radiation Oncology, Hacettepe University Faculty of Medicine, 06100 Sıhhiye, Ankara, Türkiye
Tel: +90-312-305-29-00
E-mail: phurmuz@yahoo.com
ORCID:
https://orcid.org/0000-0003-1221-9192

Purpose: The systemic immune-inflammation index (SII) is a prognostic biomarker in various solid tumors. However, the prognostic role of SII in thymic epithelial tumors (TETs) receiving adjuvant radiotherapy (RT) has not yet been explored. This study aims to assess the prognostic role of pre-RT SII in TET patients undergoing adjuvant RT.

Materials and Methods: A retrospective analysis was conducted on 37 patients treated with adjuvant RT for TETs between 2004 and 2023. The median adjuvant RT dose was 54 Gy (range, 50 to 70) delivered over 25–35 fractions. SII was calculated based on hemogram parameters within the two weeks preceding the start of RT, and its prognostic role was evaluated.

Results: Median follow-up was 90 months (range, 12 to 230). The 5-year overall survival (OS) and disease-free survival (DFS) rates were 97.1% and 90.7%, respectively. The receiver operating characteristic analysis determined an optimal SII cut-off value of 916 for predicting recurrence (specificity, 67%; sensitivity, 71%). In univariate analysis, patients with an SII ≥916 had significantly lower 5-year OS (92.3% vs. 100%, p=0.028) and DFS (73.1% vs. 100%, p=0.011) compared to those with a SII below 916. In multivariable analysis, no variable remained statistically significant, likely due to limited events and small sample size.

Conclusion: Postoperative, pre-RT SII may have potential prognostic relevance in patients with TETs undergoing adjuvant RT. Elevated SII levels could be explored as a biomarker to help guide more individualized treatment and follow-up strategies; however, further studies are needed to validate these findings.

Keywords: Inflammation, Radiotherapy, Thymoma, Thymic carcinoma

Introduction

Thymic epithelial tumors (TETs) are rare malignancies originating from thymic epithelial cells, displaying a range of behaviors from indolent to highly aggressive. This heterogeneity is evident in their histological subtypes and staging, which greatly influence prognosis and treatment approaches [1]. Complete surgical resection is the primary treatment for early-stage TETs. However, for cases with adverse postoperative pathological features, a multimodal approach, including adjuvant radiotherapy (RT) and sometimes chemotherapy, is recommended to improve outcomes [2,3]. Despite advancements in management of TETs, predicting recurrence and long-term survival remains difficult, as traditional indicators like histopathology and staging may not fully capture disease complexity. This highlights the need for reliable biomarkers to better stratify patients by prognosis. Recently, inflammatory markers, including the systemic immune-inflammation index (SII), have gained interest as prognostic tools in oncology research, with high SII levels linked to poor outcomes in multiple tumors [4]. Elevated SII levels are thought to reflect a pro-tumor inflammatory state, which can

Copyright © 2025 The Korean Society for Radiation Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

drive tumor progression and metastasis. While the prognostic significance of pre-operative SII has been demonstrated in patients with resected thymomas, the impact of its value in the postoperative, pre-RT period on prognosis has not yet been investigated [5]. This study aims to assess the prognostic significance of postoperative, pre-RT SII in patients with resected TETs receiving adjuvant RT.

Materials and Methods

1. Study design and patients

This retrospective study evaluated adult patients (≥ 18 years) diagnosed with thymic malignancies who underwent adjuvant RT after surgical resection. Patients were treated between 2004 and 2023 at our institution. Data were collected from patient records and the hospital's electronic medical system. Inclusion criteria were as follows: (1) histopathologically confirmed TET, (2) completion of surgical resection prior to adjuvant RT, and (3) available hematological data from the two weeks preceding RT. Patients with initially unresectable tumors, those who received neoadjuvant or definitive RT, and individuals with non-epithelial thymic tumors (e.g., lymphomas and germ cell tumors) or incomplete blood parameter data were excluded. The study was approved by the institutional review board, and the ethical principles outlined in the Declaration of Helsinki were followed.

2. Treatment

Patients received adjuvant RT based on institutional protocols, with treatment techniques evolving over time. Techniques included two-dimensional RT, three-dimensional conformal RT, and intensity-modulated RT. Target volumes were defined based on the pre-operative tumor bed, with added margins as needed based on imaging and clinical findings. Daily fractions of 1.8 to 2 Gy were administered, 5 days per week. Although the decision to administer chemotherapy was ultimately at the discretion of the treating physician, specific clinical indications guided its use in most cases. Neoadjuvant chemotherapy was administered in five patients with potentially resectable tumors at the time of diagnosis. Concurrent and adjuvant chemotherapy was given in two patients who underwent R2 resection and in two patients with thymic carcinoma histology. In the remaining two patients, adjuvant chemotherapy was initiated following R1 resection, based on the clinical judgment of the treating physician. The chemotherapy regimens administered were cisplatin, doxorubicin, and cyclophosphamide (n = 6, 54.5%) and carboplatin/paclitaxel (n = 5, 45.5%).

3. SII calculation

Complete blood count parameters, including neutrophil, lymphocyte, and platelet counts, were obtained from blood samples taken within two weeks before the initiation of RT. The SII was calculated using the formula: [(Neutrophil × Platelet)/Lymphocyte] [6].

4. Follow-up

After completion of RT, all patients were monitored according to a standardized follow-up schedule: every 3 months during the first 2 years, every 6 months for the subsequent 3 years, and annually thereafter. Radiological evaluations, including computed tomography and/or magnetic resonance imaging of the thorax, were performed for disease monitoring.

5. Statistical analysis

All statistical analyses were conducted using the SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, overall survival (OS), and disease-free survival (DFS) were calculated. Local recurrence was defined as recurrence in the tumor bed, regional recurrence as involvement of perithymic or mediastinal lymph nodes, and distant metastasis as pleural or hematogenous spread. The follow-up period and all time-dependent events were measured from the start of RT to the last follow-up, death, or recurrence, whichever occurred first. OS was defined as the interval from the initiation of RT to death from any cause, while DFS was defined as the time from RT initiation to either disease recurrence or death from any cause. Survival analyses were performed using the Kaplan-Meier method, with group comparisons assessed by the log-rank test. The optimal cut-off value for the SII was determined through receiver operating characteristic (ROC) analysis. This method was applied to assess the sensitivity and specificity of the SII in predicting patient outcomes, allowing for the identification of a threshold value that optimized both parameters. Variables with a potential significance level of $p < 0.1$ in univariate analysis were further evaluated using a multivariate Cox proportional hazards model, with hazard ratios (HR) and 95% confidence intervals reported. Statistical significance for all tests was set at $p < 0.05$.

Results

The cohort consisted of 13 (35.1%) male and 24 (64.9%) female patients. The median age of the patients was 56 years (range, 25 to 75 years). Remaining patient, tumor, and treatment characteristics are summarized in Table 1. Based on the American Joint Committee on Cancer/Union for International Cancer Control 8th edition staging system, 72.9% (n = 27) were classified as stage group I, 16.3% (n = 6) as stage group II, and 10.8% (n = 4) as stage group IIIA. All patients with stage group I disease received adjuvant RT due to adverse postoperative risk factors such as capsular invasion

https://doi.org/10.3857/roj.2025.00143

Table 1. Patient, tumor, and treatment characteristics

Characteristic	SII < 916 (n = 22)	SII ≥ 916 (n = 15)	Total (n = 37)	p-value
Age (year)	56 (31–75)	56 (25–74)	56 (25–75)	0.975
Sex				0.081
Male	5 (22.7)	8 (53.3)	13 (35.1)	
Female	17 (77.3)	7 (46.7)	24 (64.9)	
Myastenia gravis				0.122
No	8 (36.3)	11 (73.3)	19 (51.3)	
Yes	14 (63.7)	4 (26.7)	18 (48.7)	
WHO tumor type				0.437
A	1 (4.5)	2 (13.4)	3 (8.1)	
AB	2 (9.1)	5 (33.3)	7 (18.9)	
B1	7 (31.9)	2 (13.4)	9 (24.3)	
B2	8 (36.3)	1 (6.6)	9 (24.3)	
B3	2 (9.1)	5 (33.3)	7 (18.9)	
Thymic carcinoma	2 (9.1)	-	2 (5.5)	
AJCC stage groups				0.256
I	18 (81.8)	9 (60.0)	27 (72.9)	
II	3 (13.7)	3 (20.0)	6 (16.3)	
IIIA	1 (4.5)	3 (20.0)	4 (10.8)	
Masaoka stage groups				0.810
I	2 (9.1)	-	2 (5.5)	
II	18 (81.8)	9 (60.0)	27 (72.9)	
III	2 (9.1)	6 (40.0)	8 (21.6)	
Resection status				0.238
R0	9 (41.0)	10 (66.7)	19 (51.3)	
R1	12 (54.5)	4 (26.7)	16 (43.2)	
R2	1 (4.5)	1 (6.6)	2 (5.5)	
RT technique				0.832
2DRT	10 (45.4)	-	10 (27.1)	
3DCRT	6 (27.3)	2 (13.3)	8 (21.6)	
IMRT/VMAT	6 (27.3)	13 (86.7)	19 (51.3)	
RT dose (Gy)	54 (50–66)	54 (50–70)	54 (50–70)	0.674
Chemotherapy				0.420
Yes	6 (27.3)	5 (33.3)	11 (29.7)	
No	16 (72.7)	10 (66.7)	26 (70.3)	

Values are presetned as median (range) or number (%).
SII, systemic immune-inflammation index; WHO, World Health Organization; AJCC, American Joint Committee on Cancer; RT, radiotherapy; 2DRT, two-dimensional radiotherapy; 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; VMAT, volmetric modulated arc therapy.

or positive surgical margins.

Prior to RT, the median neutrophil count was 5.6 × 10^3/μL (range, [1.2 to 19.3] × 10^3/μL), median lymphocyte count was 1.9 × 10^3/μL (range, [0.6 to 8.2] × 10^3/μL), and median platelet count was 279 × 10^3/μL (range, [105–675] × 10^3/μL). The median SII was calculated to be 722 (range, 398 to 6,672).

The median follow-up was 90 months (range, 12 to 230). A total of 35 patients (94.5%) had a follow-up duration of more than 1 year, and 31 patients (83.7%) were followed for more than 2 years. During the follow-up period, one patient (2.7%) experienced local recurrence, one (2.7%) had regional recurrence in the perithymic lymph nodes, and three patients (8.1%) developed distant metastasis, all of which were pleural metastases. Table 2 summarizes the characteristics of patients who experienced disease recurrence. The 5- and 10-year OS rates were 97.1% and 92.7%, respectively, while the DFS rates were 90.7% at both 5 and 10 years.

The ROC analysis identified an optimal SII cut-off value of 916, with an area under the curve of 0.74, specificity of 67%, and sensi-

Table 2. Patients with recurrence

Age (year)/Sex	WHO tumor type	Resection status	Stage group	RT dose/fractions	RT technique	Chemotherapy	Pre-RT SII	Recurrence pattern	Last status
56/F	Type A	R1	IIIA	60 Gy/30 fractions	3DCRT	Yes	988	RR	AWD
70/F	Type B1	R1	I	56 Gy/28 fractions	IMRT	No	1,403	LR	AWD
50/F	Type AB	R0	IIIA	50.4 Gy/28 fractions	IMRT	Yes	1,019	DM	Exitus
74/F	Type AB	R0	I	50 Gy/25 fractions	IMRT	No	1,256	DM	Exitus
62/M	Type B3	R2	II	70 Gy/35 fractions	IMRT	Yes	2,248	DM	AWD

WHO, World Health Organization; RT, radiotherapy; SII, systemic immune-inflammation index; F, female; 3DCRT, three-dimensional conformal radiotherapy; RR, recurrence rate; AWD, alive with disease; IMRT, intensity-modulated radiotherapy; LR, local recurrence; DM, distant metastasis; M, male.

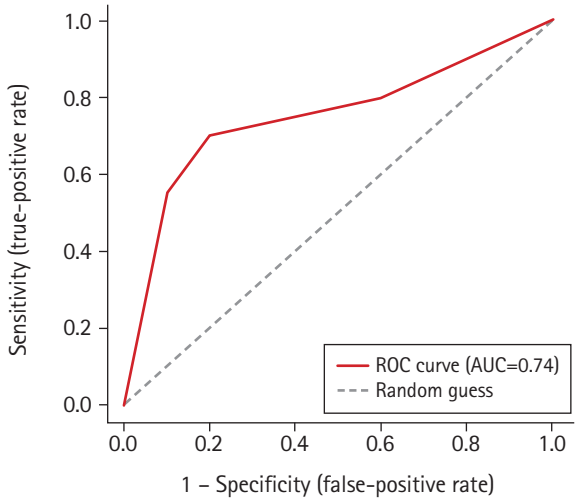

Fig. 1. Receiver operating characteristic (ROC) curve for systemic immune-inflammation index predicting disease recurrence. AUC, area under the curve.

tivity of 71% for predicting recurrence (Fig. 1). In results of univariate analysis, patients with an SII ≥916 showed significantly lower 5-year OS (92.3% vs. 100%, p=0.028) and DFS (73.1% vs. 100%, p=0.011) compared to those with an SII <916 (Fig. 2). Additionally, univariate analysis demonstrated that early Masaoka stage, and the presence of myasthenia gravis at diagnosis were also significant positive prognostic factors for DFS (Table 3). To further evaluate the independent prognostic impact of SII and other relevant variables, we performed multivariable Cox regression analysis. However, none of the included variables—including SII—retained statistical significance, likely due to the limited number of events and small sample size (Table 4).

No grade 3 or higher acute toxicities were observed. Grade 1 acute esophagitis was noted in four patients (10.8%), and grade 2 acute esophagitis in one patient (2.7%). Subacute-late toxicity included grade 2 radiation pneumonitis in three patients (8.1%), with no cases of grade 3 or higher late toxicities reported.

Discussion and Conclusion

This single-center retrospective study indicates that postoperative, pre-RT SII may be associated with survival outcomes in patients with TETs receiving adjuvant RT, suggesting a potential prognostic role that warrants further investigation. TETs are rare neoplasms that generally exhibit higher survival rates compared to other thoracic malignancies, with 5-year survival rates reaching up to 90% even in advanced stages after complete resection [7,8]. Additionally, cases of recurrence often respond favorably to salvage treatments, with a significant proportion of patient mortality attributed to non-tumor-related factors, such as myasthenia gravis [9]. Despite these encouraging survival rates, TETs represent a heterogeneous patient group; even among patients with similar clinicopathological profiles and receiving standardized treatment regimens, some display more aggressive disease course and higher disease-specific mortality rates. This highlights a substantial need for biomarkers that can more accurately stratify TET patients by prognosis, going beyond traditional prognostic factors.

The link between cancer prognosis and inflammation has emerged as a key focus in recent oncology research. Inflammation is recognized as a multifaceted driver in both tumor development and progression, with inflammatory responses in the tumor microenvironment significantly influencing patient outcomes [10]. The SII, derived from peripheral blood parameters, provides an easily accessible and cost-effective biomarker that may serve as an indicator of systemic inflammation. Initially described in 2014, SII has been shown to hold prognostic value, with higher SII values consistently associated with poorer outcomes across multiple cancer types [6,11-18].

Despite its increasing relevance in other malignancies, most studies on SII have not included TETs. Only a limited number of studies have assessed the prognostic implications of SII specifically in TET patients. For instance, a retrospective analysis by Veraar et al. [19], involving 184 surgically treated TET patients, demonstrated that elevated pre-operative SII values were associated with lower

https://doi.org/10.3857/roj.2025.00143

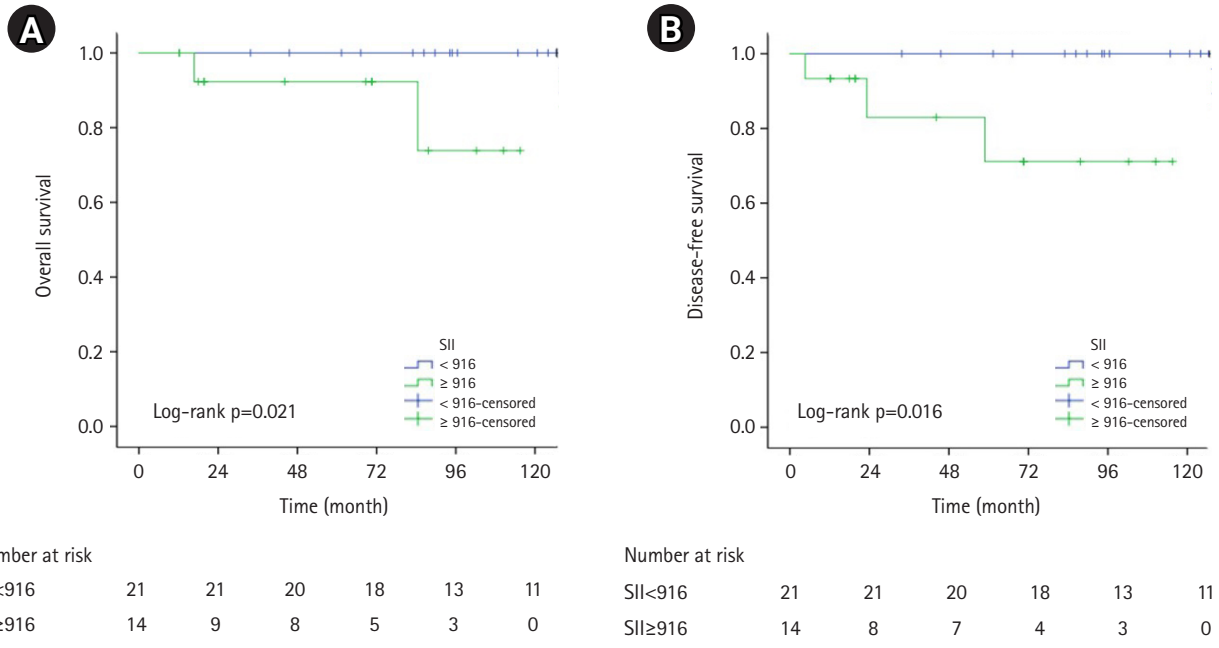

Fig. 2. Kaplan-Meier survival curves of overall survival (A) and disease-free survival (B) stratified by the systemic immune-inflammation index (SII).

Table 3. Results of univariate analysis for OS and DFS rates

Variable	5-Year OS (%)	p-value	5-Year DFS (%)	p-value
Age (< 56 [n = 19] vs. ≥ 56 years [n = 18])	94.4 vs. 100	0.828	91.7 vs. 89.2	0.657
Sex (male [n = 13] vs. female [n = 24])	100 vs. 95.8	0.362	100 vs. 87.1	0.267
Myasthenia gravis (yes [n = 18] vs. no [n = 19])	100 vs. 94.1	0.064	100 vs. 78.7	0.047
AJCC stage (I [n = 27] vs. II/III [n = 6])	100 vs. 88.9	0.336	95.5 vs. 77.1	0.068
Masaoka stage (I/II [n = 29] vs. III [n = 8])	100 vs. 85.7	0.266	95.7 vs. 70.0	0.025
WHO tumor type (A/AB/B1 [n = 19] vs. B2/B3/thymic carcinoma [n = 18])	100 vs. 94.6	0.092	100 vs. 83.7	0.099
Resection status (R0 [n = 19] vs. R1/2 [n = 18])	100 vs. 94.6	0.881	94.7 vs. 86.5	0.511
SII (< 916 [n = 22] vs. ≥ 916 [n = 15])	100 vs. 92.3	0.028	100 vs. 73.1	0.011
Chemotherapy (yes [n = 11] vs. no [n = 26])	100 vs. 90.9	0.521	79.5 vs. 95.0	0.124
RT technique (2DRT/3DCRT [n = 18] vs. IMRT [n = 19])	94.5 vs. 100	0.712	94.5 vs. 84.7	0.431

OS, overall survival; DFS, disease-free survival; AJCC, American Joint Committee on Cancer; WHO, World Health Organization; SII, systemic immune-inflammation index; RT, radiotherapy; 2DRT, two-dimensional radiotherapy; 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

cancer-specific survival rates. Similarly, Li et al.'s retrospecive study [5] of 425 surgically treated TET patients revealed that higher pre-operative SII values correlated with worse OS. However, in the first of these two studies, 60% of the patients were reported to have received adjuvant therapy, whereas the second study did not provide details on adjuvant therapy. Since adjuvant RT is widely used in routine practice and is known to improve oncological outcomes for TETs, the prognostic significance of the pre-operative SII value may theoretically vary based on whether patients receive adjuvant RT [20]. Notably, no studies to date have investigated the prognostic value of postoperative, pre-RT SII in patients requiring adjuvant RT due to adverse pathological risk factors, to the best of our knowledge. This study is therefore the first to address this gap, examining the prognostic role of postoperative, pre-RT SII in a cohort of TET patients receiving adjuvant RT. Our findings reveal that patients with elevated postoperative, pre-RT SII values exhibit significantly poorer 5-year OS and DFS rates. These results suggest that SII may serve as a meaningful prognostic biomarker, potentially elucidating some of the heterogeneity observed within TET patient populations undergoing adjuvant RT and aiding in more refined prognostic stratification. Although our univariate analysis demonstrated a significant association between elevated SII and

Table 4. Results of multivariate analysis for overall survival and disease-free survival rates

	HR	95% CI	p-value
Overall survival			
Myasthenia gravis (yes vs. no)	1 vs. 5.9	0.03–12	0.425
WHO tumor type (A/AB/B1 vs. B2/B3/thymic carcinoma)	1 vs. 13	0.01–28	0.615
SII (<916 vs. ≥916)	1 vs. 18	0.01–31	0.392
Disease-free survival			
Myasthenia gravis (yes vs. no)	1 vs. 5.8	0.6–58	0.211
AJCC stage (I vs. II/III)	1 vs. 1.3	0.1–5.9	0.937
Masaoka stage (I/II vs. III)	1 vs. 1.8	0.1–4.8	0.988
WHO tumor type (A/AB/B1 vs. B2/B3/thymic carcinoma)	1 vs. 12	0.1–23	0.610
SII (<916 vs. ≥916)	1 vs. 14	0.1–4.8	0.425

HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; SII, systemic immune-inflammation index; AJCC, American Joint Committee on Cancer; WHO, World Health Organization.

poorer survival outcomes, this finding did not retain statistical significance in the multivariable model. This may be attributed to the inherent limitations of our cohort, particularly the small sample size and low number of events, which likely reduced the statistical power to detect independent prognostic effects. Nonetheless, the consistent directionality of HRs and the biological plausibility of SII as a marker of tumor-promoting inflammation support its continued investigation as a potential prognostic biomarker in TETs. Larger, multi-institutional studies are needed to validate these preliminary observations.

While our study is the first to specifically investigate the prognostic significance of postoperative, pre-RT SII in patients with TETs undergoing adjuvant RT, it is important to acknowledge several limitations. The retrospective nature of the study may inherently introduce selection biases, potentially affecting the robustness of our findings. Additionally, the small sample size and low incidence of disease-related events in our cohort may limit the statistical power and affect the ability to detect subtler associations. However, given the challenges of designing prospective studies due to the rarity of TETs, our study plays a valuable role in filling a significant gap in the literature.

In conclusion, this study suggests that elevated postoperative, pre-RT SII values may be associated with poorer OS and DFS in patients with TETs undergoing adjuvant RT. Given the heterogeneity of TETs, SII may aid in identifying patients who could benefit from more personalized and potentially intensified treatment and follow-up strategies. However, these findings should be interpreted with caution, and validation through larger prospective studies is warranted.

Statement of Ethics

This research involving human data was conducted in accordance with the principles outlined in the Declaration of Helsinki. The study received ethical approval from the Hacettepe University Health Sciences Research Ethics Committee under approval number SBA 24/1179, granted on 16 December 2024. Written informed consent was obtained from all individual participants included in the study.

Conflict of Interest

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

Funding

None.

Author Contributions

Conception and design of the study, AK, PH; Data collection, MB; Analysis and interpretation of results, AK; Writing the first draft, AK; Supervision, PH, MC; All authors approved the final version of the manuscript.

Data Availability Statement

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

 https://doi.org/10.3857/roj.2025.00143

References

1. Marx A, Chan JK, Coindre JM, et al. The 2015 World Health Organization classification of tumors of the thymus: continuity and changes. J Thorac Oncol 2015;10:1383–95.
2. Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485–92.
3. Rico M, Flamarique S, Casares C, et al. GOECP/SEOR radiotherapy guidelines for thymic epithelial tumours. World J Clin Oncol 2021;12:195–216.
4. Tian BW, Yang YF, Yang CC, et al. Systemic immune-inflammation index predicts prognosis of cancer immunotherapy: systemic review and meta-analysis. Immunotherapy 2022;14:1481–96.
5. Li Q, Pu Y, Gong Z, et al. Preoperative systemic immune-inflammation index for predicting the prognosis of thymoma with radical resection. Thorac Cancer 2023;14:1192–200.
6. Hu B, Yang XR, Xu Y, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res 2014;20:6212–22.
7. Zhao Y, Shi J, Fan L, Hu D, Yang J, Zhao H. Surgical treatment of thymoma: an 11-year experience with 761 patients. Eur J Cardiothorac Surg 2016;49:1144–9.
8. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg 2003;76:878–84.
9. Huang J, Detterbeck FC, Wang Z, Loehrer PJ Sr. Standard outcome measures for thymic malignancies. J Thorac Oncol 2010;5:2017–23.
10. Zhao H, Wu L, Yan G, et al. Inflammation and tumor progression: signaling pathways and targeted intervention. Signal Transduct Target Ther 2021;6:263.
11. Cheng HW, Wang T, Yu GC, Xie LY, Shi B. Prognostic role of the systemic immune-inflammation index and pan-immune inflammation value for outcomes of breast cancer: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 2024;28:180–90.
12. Li M, Li Z, Wang Z, Yue C, Hu W, Lu H. Prognostic value of systemic immune-inflammation index in patients with pancreatic cancer: a meta-analysis. Clin Exp Med 2022;22:637–46.
13. Li X, Zhang S, Lu J, Li C, Li N. The prognostic value of systemic immune-inflammation index in surgical esophageal cancer patients: an updated meta-analysis. Front Surg 2022;9:922595.
14. Meng L, Yang Y, Hu X, Zhang R, Li X. Prognostic value of the pretreatment systemic immune-inflammation index in patients with prostate cancer: a systematic review and meta-analysis. J Transl Med 2023;21:79.
15. Qiu Y, Zhang Z, Chen Y. Prognostic value of pretreatment systemic immune-inflammation index in gastric cancer: a meta-analysis. Front Oncol 2021;11:537140.
16. Wang Y, Li Y, Chen P, Xu W, Wu Y, Che G. Prognostic value of the pretreatment systemic immune-inflammation index (SII) in patients with non-small cell lung cancer: a meta-analysis. Ann Transl Med 2019;7:433.
17. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of systemic immune-inflammation index in cancer: a meta-analysis. J Cancer 2018;9:3295–302.
18. Yang Y, Li J, Wang Y, Luo L, Yao Y, Xie X. Prognostic value of the systemic immune-inflammation index in lung cancer patients receiving immune checkpoint inhibitors: a meta-analysis. PLoS One 2024;19:e0312605.
19. Veraar C, Janik S, Thanner J, et al. Clinical prognostic scores for patients with thymic epithelial tumors. Sci Rep 2019;9:18581.
20. Jackson MW, Palma DA, Camidge DR, et al. The impact of postoperative radiotherapy for thymoma and thymic carcinoma. J Thorac Oncol 2017;12:734–44.

ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2025;43(4):172-180
https://doi.org/10.3857/roj.2025.00052

Postmastectomy radiation therapy for patients with pT1–2N1 breast cancer over 2 decades in Korea: Korean Radiation Oncology Group 14–21

Mi Sun Kim[1], Seung Do Ahn[2], Yong Bae Kim[3], Won Park[4], Shin-Hyung Park[5], Ik Jae Lee[6], Byung-Ock Choi[7], Juri Kim[8], Sung Ja Ahn[9], Won Sup Yoon[10], Jin-hee Kim[11], Jong Hoon Lee[12], Donghyun Kim[13], Hye Li Park[14], Yeon-Joo Kim[15], Sun Young Lee[16], Kyung Ran Park[17], Division for Breast Cancer, Korean Radiation Oncology Group

[1]*Department of Radiation Oncology, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea*
[2]*Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea*
[3]*Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea*
[4]*Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*
[5]*Department of Radiation Oncology, Kyungpook National University School of Medicine, Daegu, Republic of Korea*
[6]*Department of Radiation Oncology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea*
[7]*Department of Radiation Oncology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea*
[8]*Department of Radiation Oncology, Cheil General Hospital, Seoul, Republic of Korea*
[9]*Department of Radiation Oncology, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea*
[10]*Department of Radiation Oncology, Korea University College of Medicine, Seoul, Republic of Korea*
[11]*Department of Radiation Oncology, Keimyung University Dongsan Medical Center, Daegu, Republic of Korea*
[12]*Department of Radiation Oncology, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, Republic of Korea*
[13]*Department of Radiation Oncology, Pusan National University School of Medicine, Busan, Republic of Korea*
[14]*Department of Radiation Oncology, Jeonju Jesus Hospital, Jeonju, Republic of Korea*
[15]*Department of Radiation Oncology, Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea*
[16]*Department of Radiation Oncology, Jeonbuk National University Hospital, Jeonju, Republic of Korea*
[17]*Department of Radiation Oncology, Kosin University College of Medicine, Busan, Republic of Korea*

Received: January 27, 2025
Revised: June 9, 2025
Accepted: July 3, 2025

Correspondence:
Kyung Ran Park
Department of Radiation Oncology, Kosin University College of Medicine, 262 Gamcheon-ro, Seo-gu, Busan 49267, Republic of Korea
Tel: +82-51-990-6399
E-mail: krparkia@gmail.com
ORCID:
https://orcid.org/0000-0002-9163-0707

Seung Do Ahn
Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea
Tel: +82-2-3010-4436
E-mail: sdahn@amc.seoul.kr
ORCID:
https://orcid.org/0000-0003-4153-4191

Purpose: This study investigates patterns of postmastectomy radiation therapy (PMRT) use in patients with pT1–2N1 breast cancer treated with mastectomy in Korea over 2 decades.

Materials and Methods: Data from 700 patients treated at 16 institutions across three decades (1990, 2000, and 2010) were retrospectively reviewed.

Results: Overall, 10.0% of patients received PMRT, with utilization rates of 7.4%, 8.8%, and 11.1% in 1990, 2000, and 2010, respectively. The use of PMRT varied substantially among the hospitals (0%–87.5%). The two-dimensional radiotherapy was used in 1990, but the adoption of tangential beam three-dimensional conformal radiotherapy increased in subsequent decades. Axillary irradiation was performed in all patients in 1990 but was omitted in some cases starting in the 2000s (performed in 72.7% of cases in 2000, 84.1% in 2010). The inclusion of axillary levels, internal mammary nodes, and supraclavicular nodes decreased over time. The 10-year overall survival (OS) and recurrence-free survival (RFS) rates for all patients were 81.3% and 76.3%, respectively. Locoregional recurrence rates were significantly lower in the PMRT group (1.4%) compared to the no-PMRT group (8.1%, p=0.043). However, no significant differences were observed in 10-year OS, RFS, or distant metastasis–free survival rates between the two groups.

Conclusion: PMRT was performed in approximately 10% of patients with pT1–2N1 breast cancer after mastectomy, with minimal changes in utilization rates over two decades. The use and extent of regional nodal irradiation has declined over time. Further research is needed to reflect the latest patterns of practice.

Keywords: Breast neoplasms, Physicians' practice patterns, Radiotherapy, Mastectomy

Copyright © 2025 The Korean Society for Radiation Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

Postmastectomy radiotherapy (PMRT) plays an important role in the management of locoregionally advanced breast cancer. Multiple clinical trials have shown treatment benefits of PMRT in locoregional control, disease-free survival, and overall survival (OS) in patients with four or more positive axillary lymph nodes (LN) (N2 or higher) or T3–4 disease [1,2]. Despite the publication of the American Society of Clinical Oncology (ASCO) guideline and other similar guidelines over two decades ago, the benefit of PMRT in patients with a tumor size of 5 cm or smaller and metastasis to 1–3 axillary LN(s) (T1–2N1) remains unclear [3-6]. It is very challenging to determine the usefulness of PMRT since no randomized study has been conducted to assess the therapeutic value of PMRT for T1–2N1 breast cancer patients, and the patient characteristics between the PMRT and no-PMRT groups were not comparable in the retrospective studies. Most guidelines and consensus statements published in the 2000s indicate that there is insufficient evidence to support the routine use of PMRT for treating T1–2N1 disease and recommend its use exclusively for patients with poor prognostic factors [7-9]. Therefore, in the previously published studies, PMRT was performed according to each physician's preference and institutional policy [10-13]. In Korea, there is no consensus of PMRT for T1–2N1 breast cancer. Nationwide surveys conducted by the Korean Radiation Oncology Group (KROG) have shown considerable variations in patterns of PMRT [14,15].

This study was to investigate practice patterns of PMRT for T1–2N1 breast cancer and longitudinal changes over 2 decades (1990, 2000, and 2010) in Korea, enabling us to establish the future treatment guidelines for T1–2N1 breast cancer.

Materials and Methods

1. Patients

The KROG authorized this study protocol (protocol No. KROG 14-21). Using three independent patient cohorts from the years of 1990, 2000, and 2010, we collected the data of T1–2N1 breast cancer patients who were treated with mastectomy at 15 institutions in Korea. The institutional review board of each institution approved this study. Patients who were pathologically diagnosed with T1–2N1 stage breast cancer were considered eligible for this study. Patients were excluded from the study if they met the following criteria: (1) had received neoadjuvant chemotherapy, (2) had a past history of other cancers except for thyroid/skin/uterine cervix cancer and distant metastasis, or (3) were male. Finally, a total of 700 selected patients were reviewed retrospectively.

2. Data collection

Patients' data related to the following pathologic features were obtained: pathological type, nuclear grade, histological grade, tumor size, resection margin, lympho-vascular invasion, status of hormone receptors, HER2/neu status, Ki-67 expression, number and size of positive axillary LN, and extracapsular extension of axillary LN, the recurrence pattern, and the date and cause of death. Treatment information including surgical technique used for axillary LN, radiotherapy (RT), adjuvant chemotherapy, and hormonal therapy was carefully reviewed.

3. Statistical analysis

The medians and distributions were compared using the chi-square and Student's t-tests. The OS and recurrence-free survival (RFS) were estimated using the Kaplan-Meier method. Multivariate logistic regression analyses were used to assess the correlation between the variables and survival. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA).

Results

1. Patients' characteristics

The patients and their tumor characteristics stratified by the study year are presented in Table 1. The numbers of patients receiving mastectomy in the years 1990, 2000, and 2010 were 54, 251, and 395, respectively. The median age was 48 (interquartile range [IQR], 42 to 56) of all patients. In 1990, the proportions of premenopausal and postmenopausal patients were similar, whereas the proportion of premenopausal patients increased in 2000 and 2010. The proportion of patients with more advanced features, such as T2 disease, three positive LNs, or LN size of ≥ 10 mm, significantly decreased in recent years. While the molecular subtypes in 2000 and 2010 were comparable, 1990 showed a notable difference due to a higher proportion of cases categorized as not available.

Axillary LN dissection was performed in all patients. Sentinel lymph node biopsy (SLNB) was not adopted in the 1990 patient cohort. SLNB was conducted in 6.3% and 73.1% of the patients from the 2000 and 2010 cohorts, respectively. Number of dissected LNs has decreased over time. Adjuvant chemotherapy was given to 83.3%, 95.6%, and 91.9% of patients in 1990, 2000, and 2010, respectively. Majority of the patients (95.6%) received CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) in 1990; however, the use of CMF reduced significantly thereafter. Anthracycline-based chemotherapy was performed in 38.8% and 93.4% of the patients in 2000 and 2010, respectively. Use of hormone therapy increased over the study years. The test for HER2/neu status was

https://doi.org/10.3857/roj.2025.00052

Table 1. Patients and tumor characteristics

	Year				p-value
	Total (n = 700)	1990 (n = 54)	2000 (n = 251)	2010 (n = 395)	
No. of patients					
Age (year)					0.132
Median (range)	48 (25-84)				
< 40	126 (18.0)	11 (20.4)	54 (21.5)	61 (15.4)	
≥ 40	574 (82.0)	43 (79.6)	197 (78.5)	334 (84.6)	
Menopause (n = 689)					< 0.001
Premenopause	418 (60.7)	26 (54.2)	169 (67.9)	223 (56.9)	
Postmenopause	271 (39.3)	22 (45.8)	80 (32.1)	169 (43.1)	
Pathology					0.321
IDC	656 (93.7)	53 (98.1)	236 (94.0)	367 (92.9)	
Others	44 (6.3)	1 (1.9)	15 (6.0)	28 (7.1)	
T category					< 0.001
T1	277 (39.6)	13 (24.1)	84 (33.5)	180 (45.6)	
T2	423 (60.4)	41 (75.9)	167 (66.5)	215 (54.4)	
No. of positive nodes					0.031
1	378 (54.0)	28 (51.9)	127 (50.6)	223 (56.5)	
2	213 (30.4)	12 (22.2)	77 (30.7)	124 (31.4)	
3	109 (15.6)	14 (25.9)	47 (18.7)	48 (12.2)	
Node size (mm) (n = 330)					< 0.001
< 10	243 (73.6)	-	3 (15.0)	240 (77.4)	
≥ 10	87 (26.4)	-	17 (85.0)	70 (22.6)	
Ki-67 (%)					< 0.001
< 30	155 (22.1)	1 (1.9)	8 (3.2)	146 (37.0)	
≥ 30	79 (11.3)	0 (0)	10 (4.0)	69 (17.5)	
NA	466 (66.6)	53 (98.1)	233 (92.8)	180 (45.5)	
HER2/neu					< 0.001
(+)	175 (25.0)	0 (0)	64 (25.5)	111 (28.1)	
(–)	382 (54.6)	1 (1.9)	125 (49.8)	256 (64.8)	
NA	143 (20.4)	53 (98.1)	62 (24.7)	28 (7.1)	
Molecular subtype					< 0.001
Luminal	492 (70.3)	9 (16.7)	172 (68.5)	311 (78.7)	
HER2/neu	63 (9.0)	0 (0)	18 (7.2)	45 (11.4)	
TNBC	56 (8.0)	0 (0)	26 (10.4)	30 (7.6)	
NA	89 (12.7)	45 (83.3)	35 (13.9)	9 (2.3)	
Postmastectomy radiotherapy					0.497
Yes	70 (10.0)	4 (7.4)	22 (8.8)	44 (11.1)	
No	630 (90.0)	50 (92.6)	229 (91.2)	351 (88.9)	
Surgical methods for axillary LN					< 0.001
ALND	393 (56.1)	54 (100.0)	236 (94.0)	103 (26.1)	
SLNB ± ALND	307 (43.9)	0 (0)	15 (6.0)	292 (73.9)	
No. of dissected nodes					0.002
< 10	98 (14.0)	3 (5.6)	24 (9.6)	71 (18.0)	
≥ 10	602 (86.0)	51 (94.4)	227 (90.4)	324 (82.0)	
Adjuvant chemotherapy (n = 648)					
CMF	181 (27.9)	43 (95.6)	129 (53.75)	9 (2.5)	
Anthracycline-based	433 (66.8)	1 (2.2)	93 (38.75)	339 (93.4)	
Others	34 (5.3)	1 (2.2)	18 (7.5)	15 (4.1)	
Hormone therapy (n = 492 with hormone receptor–positive)					0.012
Yes	472 (95.9)	7 (77.8)	163 (94.8)	302 (97.1)	
No	18 (3.7)	2 (22.2)	9 (5.2)	7 (2.3)	
NA	2 (0.4)	0 (0)	0 (0)	2 (0.6)	
Trastuzumab (n = 175 with HER2/neu (+))					< 0.001
Yes	78 (44.6)	0 (0)	0 (0)	78 (70.3)	
No	97 (55.4)	0 (0)	64 (100)	33 (29.7)	

IDC, intraductal carcinoma; NA, not available; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; LN, lymph node; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; CMF, cyclophosphamide, methotrexate, and fluorouracil.

performed in only one patient from the patient cohort of 1990; however, its trend increased significantly during the subsequent study years. Seventy-eight of 175 patients (44.6%) with a positive HER2/neu status received treatment with trastuzumab.

2. Postmastectomy radiotherapy

The utilization of PMRT showed a slight increase over time. Of 700 patients, 70 patients (10.0%) received PMRT, which included 7.4%, 8.8%, and 11.1% of the patients from 1990, 2000, and 2010, respectively. However, this increase was not statistically significant. The use of PMRT varied substantially among the hospitals, ranging from 0%–87.5%. Three of the 16 institutions did not perform PMRT throughout the entire study period. Patients from these three institutions exhibit various risk factors including close resection margin, positive LN size of ≥ 2 cm, and high histologic grade, among others.

There were significant differences observed between the PMRT and no-PMRT subgroups. Patients who received PMRT were more likely to exhibit high-risk features such as three positive LNs ($p = 0.015$), positive LN size of ≥ 10 mm ($p = 0.002$), positive or close resection margin ($p = 0.006$), high grade ($p = 0.036$), extensive intraductal component ($p = 0.005$), and high levels of Ki-67 expression ($p = 0.009$) (Table 2).

RT technique stratified by the study year is listed in Table 3. For chest wall irradiation, the reverse hockey stick technique was exclusively used in 1990, but the adoption of tangential beam three-dimensional conformal RT increased in subsequent decades. Chest wall boost was performed in about 28% of the patients in the years 2000 and 2010, and the median boost dose was 9 Gy (range, 8 to 10.8 Gy). While axillary irradiation was administered to all patients in 1990, its use became selective in subsequent years, with 72.7% of patients receiving it in 2000 and 84.1% in 2010. Approximately one-quarter of the patients received a posterior axillary boost, which remained consistent throughout the study periods. The inclusion of axillary LN levels, internal mammary nodes, and supraclavicular nodes decreased over time. The most common radiation dose used was 50.4 Gy (range, 45 to 60 Gy), with a daily dose of 1.8 Gy. Hypofractionated radiation scheme (45 Gy in 15 fractions) was performed for only one patient in 2010.

3. Treatment outcomes

The median follow-up was 58.5 months (IQR, 52.3 to 121.2). The median follow-up for the 1990, 2000, and 2010 cohorts was 96.4 months (IQR, 60.8 to 161.6), 137.5 months (IQR, 83.7 to 151.1), and 54.4 months (IQR, 50.2 to 58.2), respectively. The 10-year OS, RFS, locoregional recurrence–free survival (LRRFS), and distant metastasis–free survival (DMFS) were 81.3%, 76.3%, 89.7%, and

Table 2. Patients and tumor characteristics in patients with or without PMRT

	Total	PMRT	No PMRT	p-value
No. of patients	700	70 (10.0)	630 (90.0)	
Age (year)				0.600
< 40	126	11 (15.7)	115 (18.3)	
≥ 40	574	59 (84.3)	515 (81.7)	
Pathology				0.406
IDC	656	64 (91.4)	592 (94.0)	
Others	44	6 (8.6)	38 (6.0)	
T category				0.487
T1	277	25 (35.7)	252 (40.0)	
T2	423	45 (64.3)	378 (60.0)	
No. of positive node				0.015
1	378	27 (38.6)	351 (55.7)	
2	213	26 (37.1)	187 (29.7)	
3	109	17 (24.3)	92 (14.6)	
Node size (mm) (n = 300)				0.002
< 10	243	15 (50.0)	228 (76.0)	
≥ 10	87	15 (50.0)	72 (24.0)	
Resection margin				0.006
(+)	3	2 (2.9)	1 (0.1)	
Close	90	11 (15.7)	79 (12.5)	
(–)	596	57 (81.4)	540 (85.7)	
NA	10	0 (0.0)	10 (1.6)	
Histologic grade				0.036
I	69	3 (4.3)	66 (10.5)	
II	338	27 (38.6)	311 (49.4)	
III	197	28 (40.0)	169 (26.8)	
NA	96	12 (17.1)	84 (13.3)	
Nuclear grade				0.265
I	44	3 (4.3)	41 (6.5)	
II	283	23 (32.9)	260 (41.3)	
III	187	25 (35.7)	162 (25.7)	
NA	186	19 (27.1)	167 (26.5)	
Extracapsular extension				0.290
(+)	102	10 (14.3)	92 (14.6)	
(–)	365	31 (44.3)	334 (53.0)	
NA	233	29 (41.4)	204 (32.4)	
Extensive intraductal component				0.005
(+)	187	14 (20.0)	173 (27.5)	
(–)	351	29 (41.4)	322 (51.1)	
NA	162	27 (38.6)	135 (21.4)	
Lymphovascular invasion				0.289
(+)	222	22 (31.4)	200 (31.7)	
(–)	342	39 (55.7)	303 (48.1)	
NA	136	9 (12.9)	127 (20.2)	
Ki-67 (%)				0.009
≥ 30	79	14 (20.0)	65 (10.3)	
< 30	155	20 (28.6)	135 (21.4)	
NA	466	36 (51.4)	430 (68.3)	
Molecular subtype				0.050
Luminal	492	47 (67.1)	445 (70.6)	
HER2/neu	63	3 (4.3)	60 (9.5)	
TNBC	56	11 (15.7)	45 (7.1)	
NA	89	9 (12.9)	80 (12.7)	

Values are presented as number (%).
PMRT, postmastectomy radiation therapy; IDC, intraductal carcinoma; NA, not assessable; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer.

https://doi.org/10.3857/roj.2025.00052

Table 3. Postmastectomy radiotherapy

	Total	Year			p-value
		1990	2000	2010	
No. of patients received PMRT	70 (10.6)	4 (9.5)	22 (8.8)	44 (11.8)	0.497
Chest wall RT field					0.318
RH	35 (50.0)	4 (100)	11 (50.0)	20 (45.5)	
Tangential	35 (50.0)	0 (0)	11 (50.0)	24 (54.5)	
Chest wall boost					0.420
Yes	19 (26.1)	0 (0)	7 (31.8)	12 (27.3)	
No	51 (73.9)	4 (100)	15 (68.2)	32 (72.7)	
Axillary node irradiation					0.330
Yes	57 (81.4)	4 (100)	16 (72.7)	37 (84.1)	
No	13 (18.6)	0 (0)	6 (27.3)	7 (15.9)	
Irradiated axillary node level[a)]					0.082
1	19 (33.4)	1 (25.0)	3 (18.8)	15 (40.5)	
2	10 (17.5)	0 (0)	0 (0)	10 (27.0)	
3	28 (49.1)	3 (75.0)	13 (81.2)	12 (32.5)	
Posterior axillary boost					0.979
Yes	17 (24.3)	1 (25.0)	5 (22.7)	11 (25.0)	
No	53 (75.7)	3 (75.0)	17 (77.3)	33 (75.0)	
Internal mammary node irradiation					0.305
Yes	27 (38.6)	3 (75.0)	8 (36.4)	16 (36.4)	
No	43 (61.4)	1 (25.0)	14 (63.6)	28 (63.6)	
Supraclavicular node irradiation					0.330
Yes	57 (81.4)	4 (100)	16 (72.7)	37 (84.1)	
No	13 (18.6)	0 (0)	6 (27.3)	7 (15.9)	

Values are presented as number (%).
PMRT, postmastectomy radiation therapy; RT, radiotherapy; RH, reverse hockey stick.
[a)]Irradiated axillary level means number of irradiated axillary lymph node level. For example, 2 level means axillary level I–II or II–III.

80.0%, respectively. In the 1990 cohort, the pathological and molecular data were not available for a relatively large number of patients and most of patients received CMF chemotherapy, rather than anthracycline or taxane-based chemotherapy. In addition, in the 2000 cohort, all patients with HER2/neu (+) did not receive trastuzumab. Therefore, we conducted a survival analysis by era (Table 4). Except for the 10-year OS, all other treatment outcomes demonstrated improvement over the study period.

The available follow-up data for 700 patients revealed that 116 patients (16.6%) experienced recurrence. Recurrence at locoregional and distant sites decreased significantly over the study years: 24 (44.4%), 59 (23.5%), and 33 (8.4%) patients in 1990, 2000, and 2010, respectively ($p < 0.001$). The first recurrence site was locoregional recurrence (LRR) in 29 (25.0%), distant metastasis (DM) in 66 (56.9%), and LRR and DM in 21 (18.1%). Nine (12.9%) of 70 patients with PMRT and 107 (17.0%) of 630 patients without PMRT exhibited recurrences. Of nine patients with recurrences in PMRT group, LRR at their first recurrence was observed in one patient (1.4%). The LRR site was supraclavicular LN. In patients without PMRT, LRR at their first recurrence was present in 49 patients (7.8%). LRR was significantly lower in the PMRT group compared to the no-PMRT group ($p = 0.043$). In the PMRT group, 13 patients (18.6%) did not receive axillary irradiation. Among them, four patients had recurrence as DM (1 bone metastasis, 1 liver metastasis, and 2 lung metastases). There was no LRR. Detailed information on the recurrence sites in the PMRT group and the no-PMRT group is provided in Supplementary Table 1.

The 10-year LRRFS showed a trend toward improvement in the PMRT group compared to the no-PMRT group (98.6% vs. 88.8%, $p = 0.055$). However, there was no significant difference in 10-year OS, RFS, or DMFS between PMRT and no-PMRT groups (Table 5). Given the substantial differences in treatment approaches between patients in the 1990s and 2000s and those in more recent years, we further analyzed the impact of PMRT within the 2010 cohort. In 2010 cohort, PMRT was not associated with a significant survival benefit (Supplementary Table 2).

Table 4. Treatment outcomes by study era

	1990 (n = 54)	2000 (n = 251)	2010 (n = 395)	p-value
Recurrence				< 0.001
No	30 (55.6)	192 (76.5)	360 (91.1)	
Yes	24 (44.4)	59 (23.5)	33 (8.4)	
NA	0 (0)	0 (0)	2 (0.5)	
Locoregional recurrence	13 (24.1)	22 (8.8)	17 (4.3)	< 0.001
Distant metastasis rate	18 (33.3)	51 (20.3)	25 (6.4)	< 0.001
10-Year OS (%)	54.0	85.0	91.9[a]	0.077[b]
10-Year RFS (%)	54.7	75.1	89.8[a]	< 0.001[b]
10-Year LRRFS (%)	73.5	90.5	94.3[a]	0.049[b]
10-Year DMFS (%)	62.9	78.6	92.7[a]	0.002[b]

Values are presented as number (%) unless otherwise indicated.
OS, overall survival; RFS, recurrence-free survival; LRRFS, locoregional recurrence–free survival; DMFS, distant metastasis–free survival.
[a]Because the median follow-up period of the 2010 cohort was approximately 54 months (range, 2 to 69), the survival analysis results of the 2010 cohort are 5-year results.
[b]The p-value is for comparing the combined 1990 and 2000 cohorts against the 2010 cohort.

Table 5. Treatment outcomes by postmastectomy radiotherapy

	PMRT (n = 70)	No PMRT (n = 630)	p-value
Locoregional recurrence	1 (1.4)	51 (8.1)	0.043
Distant metastasis rate	8 (11.4)	86 (13.7)	0.598
10-Year OS (%)	79.0	81.6	0.738
10-Year RFS (%)	83.0	75.6	0.508
10-Year LRRFS (%)	98.6	88.8	0.055
10-Year DMFS (%)	84.3	79.6	0.754

Values are presented as number (%) unless otherwise indicated.
PMRT, postmastectomy radiotherapy; OS, overall survival; RFS, recurrence–free survival; LRRFS, locoregional recurrence–free survival; DMFS, distant recurrence–free survival.

In the current study, chemotherapy regimen was related to survival outcomes of the participating patients. Anthracycline-based chemotherapy significantly reduced the rates of LRR and DM compared to CMF chemotherapy ($p < 0.001$ and $p = 0.001$) (Table 6). Additionally, it led to significant improvements in 10-year OS, RFS, and LRRFS ($p < 0.001$, $p = 0.003$, and $p < 0.001$). Of 175 patients with positive HER2/neu status, treatment with trastuzumab improved 10-year RFS (94.7% vs. 66.2%, $p = 0.040$). There was no significant difference in 10-year OS for trastuzumab and no-trastuzumab groups (93.3% vs. 86.5%, $p = 0.609$).

Treatment-related complications were analyzed separately in the PMRT group and the no-PMRT group. Among the 70 patients who received PMRT, PMRT-related complications were evaluable in 63 patients: three patients (75.0%) in 1990, 20 patients (90.9%) in 2000, and 40 patients (90.9%) in 2010. In the 1990 cohort, PMRT-related complications was not observed. In the 2000 cohort, one patient (4.5%) developed grade 3 lymphedema. In the 2010 cohort, five patients (11.4%) experienced lymphedema (three with grade 1, while the remaining two had no reported grade information), and two patients developed grade 1 radiation pneumonitis. The most common PMRT-related complication was lymphedema. Axillary LN dissection, the number of dissected LNs, axillary LN irradiation, and the irradiated axillary node level were not associated with the development of lymphedema ($p = 0.999$, $p = 0.997$, $p = 0.999$, and $p = 0.995$, respectively).

In the no-PMRT group, treatment-related complications were evaluable in 398 patients: 39 patients (78.0%) in 1990, 125 patients (54.6%) in 2000, and 234 patients (66.7%) in 2010. No treatment-related complications were reported in the 1990 cohort. In the 2000 cohort, nine patients (7.2%) experienced treatment-related complications, including lymphedema in six patients (one with grade 2 and five with grade 1), neutropenia in three patients (one with grade 3, one with grade 2, and one with grade 1), and grade 3 nausea in one patient. In the 2010 cohort, treatment-related complications occurred in 30 patients (12.8%), including lymphedema in 23 patients (three with grade 2, 18 with grade 1, and two with no reported grade information), neutropenia in two patients (one with grade 1 and one with no reported grade information), cardiac complications associated with herceptin in two patients (both grade 2), web syndrome (grade 1) in one patient, pulmonary fibrosis in one patient (no reported grade information), and chest wall swelling in one patient (no reported grade information). The most common treatment–related complication was lymphedema. Axillary LN dissection and the number of dissected LNs were not associated with the development of lymphedema ($p = 0.306$ and $p = 0.998$, respectively).

https://doi.org/10.3857/roj.2025.00052

Table 6. Treatment outcomes by chemotherapy

	No CTx (n = 52)	CMF (n = 181)	Anthracycline-based CTx (n = 433)	p-value
Locoregional recurrence	6 (11.5)	26 (14.4)	17 (3.9)	< 0.001
Distant metastasis rate	8 (15.4)	39 (21.5)	43 (9.9)	0.001
10-Year OS (%)	54.7	75.3	91.2	< 0.001[a]
10-Year RFS (%)	63.8	72.5	78.3	0.003[a]
10-Year LRRFS (%)	83.5	84.6	94.1	< 0.001[a]
10-Year DMFS (%)	72.9	78.4	78.5	0.110[a]

Values are presented as number (%) unless otherwise indicated.
CTx, chemotherapy; CMF, cyclophosphamide, methotrexate, and fluorouracil; OS, overall survival; RFS, recurrence–free survival; LRRFS, locoregional recurrence–free survival; DMFS, distant metastasis–free survival.
[a]The p-value is for comparing CMF and anthracycline-based chemotherapy.

Discussion and Conclusion

We investigated the use of PMRT in patients with T1–2N1 breast cancer treated with mastectomy at 16 institutions in Korea over 2 decades. The number of patients for this study markedly increased in recent years, which represented the rise of incidence of breast cancer in Korea. PMRT was performed in about 10% of patients in the entire study population. The proportion of patients who received PMRT did not change significantly over 2 decades; however, PMRT utilization was profoundly varied (ranging from 0%–87.5%) among the participating institutions. PMRT was preferred for the patients with high-risk factors according to each institution's criteria. Radiation field and technique were different among the radiation oncologists. The majority of patients received anthracycline-based chemotherapy (66.8%) or CMF (27.9%). Despite the presence of high-risk features in patients receiving PMRT, 10-year LRRFS was higher in the PMRT group.

The benefits of PMRT in patients with T1–2N1 breast cancer following mastectomy remain controversial because of undetermined significance on the patient's survival and potential concerns of morbidity [4,6,16]. Several challenges complicate the assessment of PMRT outcomes. (1) Including this study, the patients who received PMRT were more likely to exhibit high-risk features; however, the definition of high-risk features varies across institutions, and the institutional criteria for administering PMRT in patients with a limited number of involved LNs remain unstandardized. (2) RT field and technique vary significantly institutions. While some institutions irradiate the chest wall and comprehensive LN area (axillary, supraclavicular, and internal mammary LN), others limit the treatment field to the chest wall alone or the chest wall with select LNs area. (3) Breast cancer is a disease with a long natural history. Based on Early Breast Cancer Trialists' Collaborative Group review on the effect of PMRT in the patients with N1 disease, who were followed up for 20 years, LRR in patients with N1 disease was shown to increase steadily for 10 years after mastectomy and RT reduced both recurrence and breast cancer mortality [17]. They reported that approximately one breast cancer-related death was avoided in the 20 years after RT for every 1.5 recurrences of any type (either locoregional or distant) avoided during the first 10 years after RT. Therefore, it is necessary to long-term follow-up for more than 10 years to determine the beneficial effects of PMRT on the survival outcomes in the patients with T1–2N1 breast cancer. Furthermore, a large number of subjects is required to draw a meaningful conclusion in the era of modern multimodality therapy.

Lately, the proportion of patients with more advanced features, such as T2 disease, three positive LNs, or LN size of ≥ 10 mm, have decreased significantly, and increased use of anthracycline-based chemotherapy over CMF has yielded favorable results. It has been shown that the emerging treatment strategies for breast cancer, such as taxane-based chemotherapy, endocrine therapy, and immune-oncologic agents tailored to subtype are associated with superior and more effective results [10,18]; therefore, the effect of PMRT on survival might be expected to decrease in the modern multimodal treatment era. Consistent with this, PMRT did not provide any survival benefit in the 2010 cohort (Supplementary Table 2).

In order to determine the patient groups that can truly benefit from RT, several investigators have attempted to identify the risk factors associated with the recurrence after mastectomy in the patients who did not receive PMRT. Young age and three positive LNs were associated with a significantly high risk of LRR, implying that PMRT may also be favorable to this group [11,19-21]. Furthermore, there might be patients with molecular features that are at high risks of LRR after mastectomy, and they may benefit from PMRT. The 21-gene recurrence score (RS) assay has been validated as an independent prognosticator of LRR, distant recurrence, and OS in women with node-positive estrogen receptor (ER)–positive breast cancer [22-24]. The 21-gene RS assay may therefore be useful as a predictive marker for potential OS benefit from PMRT in women

with T1–2N1 ER-positive breast cancer. Now, the Canadian Tailor RT trial (CCTG MA.39, NCT03488693) is underway on women with T1–2N1 disease and documented low RS who underwent breast-conserving surgery or mastectomy randomizing to either regional radiation or no regional radiation, with breast cancer recurrence-free interval as the primary objective. This trial can provide clarity regarding the value of RS as a predictor of the value of RT in women with T1–2 N1 breast cancer.

In summary, PMRT utilization in patients with T1–2N1 breast cancer following mastectomy did not change significantly over two decades in Korea. Despite the presence of high-risk features in those receiving PMRT, there was an improvement in the 10-year LRRFS of the PMRT group. Prospective randomized study with a large number of patients and long-term follow-up is necessary to determine the impact of PMRT on the survival outcomes and for the selection of the patients who may benefit from PMRT. Further research is needed to reflect the latest patterns of practice.

Statement of Ethics

This study protocol was reviewed and approved by the Korean Radiation Oncology Group (protocol No. KROG 14-21). The need for patients' informed consent was waived by each institutional review board because of the retrospective nature of the study.

Conflict of Interest

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

Funding

None.

Author Contributions

Data collection, MSK, SD, YBK, WP, SHP, IJL, BOC, JK, SJA, WSY, JHK, JHL, DK, HLP, YJK, SYL; Formal analysis and writing, MSK; Review and of the review and editing, KRP, SDA.

Data Availability Statement

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

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2025.00052.

References

1. Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol 2006;24:2268–75.
2. Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst 2005;97:116–26.
3. Cosar R, Uzal C, Tokatli F, et al. Postmastectomy irradiation in breast in breast cancer patients with T1-2 and 1-3 positive axillary lymph nodes: is there a role for radiation therapy? Radiat Oncol 2011;6:28.
4. Gilmore RC, Sebai ME, Psoter KJ, et al. Analysis of breast cancer patients with T1-2 tumors and 1-3 positive lymph nodes treated with or without postmastectomy radiation therapy. Sci Rep 2020;10:9887.
5. Kayali M, Abi Jaoude J, Tfayli A, El Saghir N, Poortmans P, Zeidan YH. Post-mastectomy radiation therapy in breast cancer patients with 1-3 positive lymph nodes: no one size fits all. Crit Rev Oncol Hematol 2020;147:102880.
6. Verma R, Chandarana M, Barrett J, Anandadas C, Sundara Rajan S. Post-mastectomy radiotherapy for women with early breast cancer and one to three positive lymph nodes. Cochrane Database Syst Rev 2023;6:Cd014463.
7. Eifel P, Axelson JA, Costa J, et al. National Institutes of Health Consensus Development Conference Statement: adjuvant therapy for breast cancer, November 1-3, 2000. J Natl Cancer Inst 2001;93:979–89.
8. Recht A, Edge SB, Solin LJ, et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001;19:1539–69.
9. Taylor ME, Haffty BG, Rabinovitch R, et al. ACR appropriateness criteria on postmastectomy radiotherapy expert panel on radiation oncology-breast. Int J Radiat Oncol Biol Phys 2009;73:997–1002.
10. Kim YJ, Park W, Ha B, et al. Postmastectomy radiotherapy in patients with pT1-2N1 breast cancer treated with taxane-based chemotherapy: a retrospective multicenter analysis (KROG 1418).

Cancer Res Treat 2017;49:927–36.
11. Moo TA, McMillan R, Lee M, et al. Selection criteria for postmastectomy radiotherapy in t1-t2 tumors with 1 to 3 positive lymph nodes. Ann Surg Oncol 2013;20:3169–74.
12. Macdonald SM, Abi-Raad RF, Alm El-Din MA, et al. Chest wall radiotherapy: middle ground for treatment of patients with one to three positive lymph nodes after mastectomy. Int J Radiat Oncol Biol Phys 2009;75:1297–303.
13. Kong M, Hong SE. Which patients might benefit from postmastectomy radiotherapy in breast cancer patients with t1-2 tumor and 1-3 axillary lymph nodes metastasis? Cancer Res Treat 2013;45:103–11.
14. Park HJ, Kim K, Kim YB, Chang JS, Shin KH; Division for Breast Cancer, Korean Radiation Oncology Group. Patterns and longitudinal changes in the practice of breast cancer radiotherapy in Korea: Korean Radiation Oncology Group 22-01. J Breast Cancer 2023;26:254–67.
15. Park HJ, Oh DH, Shin KH, et al. Patterns of practice in radiotherapy for breast cancer in Korea. J Breast Cancer 2018;21:244–50.
16. Yang J, Zhang X, Ye Y, Lin Y, Yang Q, Cai H. Postmastectomy radiation therapy can improve survival for breast cancer patients with 1-3 positive axillary lymph nodes: a retrospective cohort study using the SEER database. Transl Cancer Res 2021;10:1984–2001.
17. McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014;383:2127–35.
18. McBride A, Allen P, Woodward W, et al. Locoregional recurrence risk for patients with T1,2 breast cancer with 1-3 positive lymph nodes treated with mastectomy and systemic treatment. Int J Radiat Oncol Biol Phys 2014;89:392–8.
19. Jagsi R, Pierce L. Postmastectomy radiation therapy for patients with locally advanced breast cancer. Semin Radiat Oncol 2009;19:236–43.
20. Sharma R, Bedrosian I, Lucci A, et al. Present-day locoregional control in patients with t1 or t2 breast cancer with 0 and 1 to 3 positive lymph nodes after mastectomy without radiotherapy. Ann Surg Oncol 2010;17:2899–908.
21. Truong PT, Olivotto IA, Kader HA, Panades M, Speers CH, Berthelet E. Selecting breast cancer patients with T1-T2 tumors and one to three positive axillary nodes at high postmastectomy locoregional recurrence risk for adjuvant radiotherapy. Int J Radiat Oncol Biol Phys 2005;61:1337–47.
22. Mamounas EP, Tang G, Fisher B, et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. J Clin Oncol 2010;28:1677–83.
23. Mamounas EP, Liu Q, Paik S, et al. 21-Gene recurrence score and locoregional recurrence in node-positive/ER-positive breast cancer treated with chemo-endocrine therapy. J Natl Cancer Inst 2017;109:djw259.
24. Woodward WA, Barlow WE, Jagsi R, et al. Association between 21-gene assay recurrence score and locoregional recurrence rates in patients with node-positive breast cancer. JAMA Oncol 2020;6:505–11.

ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2025;43(4):181-187
https://doi.org/10.3857/roj.2025.00220

Can lymphocytic toxicity be induced by radiation dose to the bowel bag in whole pelvic radiotherapy?

Min Kyun Ko[1], Kyu Hye Choi[1], Wonmo Sung[2], Ji Hyun Hong[1], Seok Hyun Son[1], Young-nam Kang[1], Byung-Ock Choi[1], Yeon-Sil Kim[1], HongSeok Jang[1]

[1]*Department of Radiation Oncology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea*
[2]*Department of Biomedical Engineering and Biomedicine and Health Science, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea*

Received: April 8, 2025
Revised: July 15, 2025
Accepted: July 28, 2025

Correspondence:
Kyu Hye Choi, MD, PhD
Department of Radiation Oncology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Republic of Korea
Tel: +82-2-2258-1526
E-mail: kyuhye@catholic.ac.kr
ORCID:
https://orcid.org/0000-0001-6446-6377

Purpose: Lymphocytopenia is a known side effect of radiation exposure to the bone marrow. However, the hematological impact of irradiating the bowel bag—a highly vascularized region containing numerous mesenteric lymph nodes—remains poorly understood. This study aimed to examine whether radiation to the bowel bag leads to a decrease in absolute lymphocyte count (ALC) during pelvic radiotherapy.

Materials and Methods: We retrospectively analyzed 168 patients with prostate, bladder, gynecologic, and gastrointestinal cancers who received whole pelvic radiotherapy (45–60 Gy) without concurrent chemotherapy between October 2016 and November 2022. Dose-volume parameters (V5, V10, V15, V20, and V30) representing the percentage of bowel bag volume receiving ≥x Gy were calculated. The primary endpoint was grade 3 lymphocytopenia (ALC 200–500/μL) measured at 3 weeks post-treatment initiation. Logistic regression analysis evaluated associations between bowel bag dosimetric parameters and severe lymphocytopenia.

Results: The overall lymphocytopenia rate was 92.3%, with 23.8% developing grade 3 toxicity. Logistic regression analysis demonstrated that higher radiation doses to the bowel bag at V5, V10, and V15 significantly increased the risk of grade 3 lymphocytopenia (odds ratios, 3.0 to 5.9, all $p < 0.01$).

Conclusion: Radiation dose to the bowel bag independently predicts severe lymphocytopenia during pelvic radiotherapy. These findings suggest that dose constraints to the bowel bag should be considered alongside bone marrow sparing techniques to preserve hematopoietic function. Prospective validation and development of bowel bag dose-volume guidelines are warranted.

Keywords: Absolute lymphocyte count, Radiotherapy, Bowel bag, Lymphocytopenia, Pelvic region

Introduction

Whole pelvic radiotherapy (RT) plays a crucial role in cancer treatment, and is mainly used to treat cervical, prostate, and bladder cancers. According to the National Comprehensive Cancer Network guidelines, definitive RT is a standard treatment option for patients with locally advanced cervical cancer and is often combined with chemotherapy. In prostate cancer, RT is a key component of curative-intent treatment across various risk groups, including as an alternative to surgery. In bladder cancer, RT is used as part of bladder preservation strategies in selected patients. Given the wide use of RT across these malignancies, understanding and managing radiation-induced toxicities such as lymphocytopenia is becoming increasingly important.

Various studies have emphasized the need to minimize organs-at-risk (OARs) toxicity during pelvic RT, with particular attention to lymphocytopenia as a significant adverse effect [1]. Although the transition from conformal techniques to intensity-modulated ra-

Copyright © 2025 The Korean Society for Radiation Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

diotherapy (IMRT) has reduced many treatment-related toxicities, lymphocyte depletion remains a persistent issue [2,3]. Given the growing recognition of the role of lymphocyte preservation in maintaining immune function and enabling potential future use of immunotherapy, pelvic RT-associated lymphocytopenia should not be overlooked.

In patients with cervical cancer treated with pelvic RT, a correlation between higher radiation dose to the pelvic bone marrow (BM) and lymphocytopenia has been reported [4]. However, due to the abundance of blood vessels and proximity to mesenteric lymph nodes, irradiation of the bowel bag may also influence lymphocyte counts [5]. Previously reported articles have shown a relationship between the irradiated dose to the bowel bag and the development of acute diarrhea [6]. However, studies on the hematological effects of the radiation dose on the bowel bag are limited. Therefore, this study aimed to investigate how lymphocyte counts decrease based on the amount of irradiation to the bowel bags during pelvic RT.

Although RT planning may differ depending on the cancer type and target location, bowel bag delineation within the pelvic region follows a generally consistent approach. The bowel bag typically includes all bowel loops and mesenteric structures encompassed by the RT field. Previous studies have shown a relationship between pelvic BM dose and lymphocytic toxicity following concurrent chemoradiotherapy (CCRT) [7]. These studies suggest that lower radiation dose to pelvic BM is associated with reduced risk of lymphocytopenia. Given the rich vascularization and immunologic relevance of the bowel bag and adjacent mesenteric lymph nodes, it is plausible that radiation to this region may similarly influence lymphocyte counts. Therefore, this study aimed to investigate the relationship between bowel bag dosimetric parameters and the incidence of grade ≥ 3 lymphocytopenia during pelvic RT.

Materials and Methods

1. Patients

This was a retrospective study that included patients who underwent RT in the pelvic area at Seoul St. Mary's Hospital between October 2016 and November 2022. All patients were pathologically diagnosed with cancer. The inclusion criteria included: (1) patients undergoing whole pelvic RT of ≥ 45 Gy, (2) patients with a Karnofsky Performance Status score of ≥ 70, and (3) blood tests routinely conducted before treatment, during treatment at weekly intervals, and within 1 month after treatment completion. The exclusion criteria comprised: (1) patients who received chemotherapy or RT within 3 months prior to or following RT, (2) patients who had interruptions in RT exceeding 1 week for any reason, (3) patients with secondary primary tumors, and (4) patients whose baseline (pre-RT) absolute lymphocyte count (ALC) was < 1,000/μL were excluded.

2. Radiotherapy

RT was delivered using a conventional fractionation scheme with a total dose ranging from 45 to 60 Gy, administered over 20 to 31 fractions. The fraction size varied between 1.8 Gy and 2.5 Gy per day, delivered once daily, five times per week. Treatment planning was performed using simulation computed tomography, and all patients were treated using the IMRT technique.

All patients were treated with whole pelvic RT. The clinical target volume (CTV) encompassed the gross tumor (if applicable) and regional lymphatic areas, depending on tumor type. The planning target volume was defined by adding appropriate margins to the CTV. The superior border of the radiation field was generally set at the L4–L5 junction, and the inferior border was placed at or 2–3 cm below the level of the symphysis pubis, adjusted slightly based on anatomical and target volume considerations. OARs, including the bowel bag, femoral heads, and pelvic BM, were contoured in all cases.

Among the 40 patients with gynecologic malignancies who received whole pelvic RT, three patients (7.5%) also received intracavitary brachytherapy following external beam RT. Brachytherapy was delivered at 25 Gy in 5 fractions for two patients, and 30 Gy in 6 fractions for one patient. As the brachytherapy component was limited in both number and dose contribution, and was not included in the treatment planning system used for dose-volume histogram analysis, only external beam RT plans were used for dosimetric evaluation in this study.

3. Dosimetric parameters of the BM and bowel bag

BM contouring included the lower lumbar level (L4–5), sacrum, and ilium. The contouring of the bowel bag involves the superior border at the L3–4 junction and the inferior border extending to the bladder and coccyx, encompassing all bowel and mesenteric structures in between. Volume dosimetric parameters (Vx) represent the percentage of a given radiation dose (x Gy) occupying a certain volume (V) relative to the total volume. For instance, V5 indicates the percentage of the total volume that is received in a dose of 5 Gy. Similarly, V10, V15, V20, V25, and V30 represent the corresponding percentages of the total volume that received doses of 10, 15, 20, 25, and 30 Gy, respectively. In addition to that, the mean radiation doses received by the bowel bags (Dmean) were also calculated.

4. Lymphocyte count

Lymphocyte counts were determined using a complete blood count. The ALC measured at 3 weeks after initiation of RT was used to define the lowest ALC and assess lymphocyte toxicity. Toxicity grades

https://doi.org/10.3857/roj.2025.00220

were assigned based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0: grade 1 (800–1,000/μL), grade 2 (500–800/μL), grade 3 (200–500/μL), and grade 4 (≤200/μL). Grade 0 represents the absence of an adverse event, defined as normal lymphocyte count (>1,000/μL).

5. Statistical analysis

We compared the mean dose of each dosimetric factor between groups using independent sample t-tests. Cutoff values for each dosimetric variable (e.g., Dmean, Vx) were determined using the Youden index derived from the receiver operating characteristic (ROC) curve. After dichotomizing patients based on these cutoff values, we performed logistic regression analysis to assess the association between each dosimetric parameter and the risk of developing grade 3 lymphocytopenia. Odds ratios (ORs) represent the odds of developing grade 3 lymphocytopenia in patients with dosimetric values above the cutoff compared to those below the cutoff. The 95% confidence intervals were calculated using the standard error of the log OR. Data analysis was conducted using the SPSS software version 23.0 (SPSS IBM Corp., Armonk, NY, USA). Statistical significance was attributed to all values with a significance level of $p < 0.05$.

Results

1. Patient characteristics

Based on these criteria, 168 patients were included in this study with a median age of 70 years (range, 29 to 91). The median pre-RT ALC was 1360.8, and all patients exhibited a baseline ALC grade of 0, defined as ALC >1,000/μL according to CTCAE version 5.0. The overall lymphocytic toxicity rate was 92.3%; among them, the grade 3 lymphocytic toxicity rate was 23.8%. There was no patient with grade 4 lymphocytic toxicity. Table 1 shows the patients characteristics. For the purpose of comparative analysis, patients were stratified into two groups based on the lowest ALC measured 3 weeks after initiating RT: those with grade 0–2 lymphocytopenia and those with grade ≥3.

2. Comparison of dosimetric factors by lymphocytopenia severity

Patients were grouped based on the severity of lymphocytopenia, as determined by the ALC measured 3 weeks after the start of RT: those exhibiting toxicity of grade 3 and those showing toxicity of grade 2 or lower. When conducting independent t-tests based on the variables Dmean, V5, V10, V15, V20, V25, and V30, we found significant differences in all continuous variables except for V25. The following Table 2 shows the results of independent t-tests for dosimetric parameters of bowel bag between ALC grades 0–2 and grade 3 patients.

3. Area under the curve and cutoff determination

ROC curves were generated for dosimetric parameters, and the endpoint was the presence of grade 3 ALC. Table 3 and Fig. 1 show the area under the curve and corresponding cutoff values for Dmean, V5, V10, V15, V20, V25, and V30 in patients grouped by ALC grade 3 and those grouped by ALC grade 2 or lower. Significant results were observed when the dose exceeded the cutoff value for Dmean, V5, V10, and V15 ($p < 0.05$).

4. Association between dosimetric parameters and grade 3 lymphocytopenia

Using these cutoff values, multivariate logistic regression analysis was then performed to evaluate the association between each dosimetric parameter and the risk of developing grade 3 lymphocytopenia. Table 4 summarizes the results that higher values of Dmean, V5, V10, V15, and V25 were significantly associated with an increased risk of grade 3 lymphocytopenia. ORs for these parameters ranged from 3.0 to 5.9, all with p-values < 0.01. These results suggest that specific bowel bag dose-volume thresholds may serve as

Table 1. Patients characteristics

Characteristic	Value
Age (year)	70 (29–91)
<70	81 (48.2)
≥70	87 (51.8)
Sex	
Male	124 (73.8)
Female	44 (26.2)
Primary	
Prostate	118 (70.2)
Bladder	8 (4.8)
Gynecologic organ	41 (24.4)
Gastrointestinal tract	1 (0.6)
BM volume (cm^3)	934 (544.7–1,300.3)
BB volume (cm^3)	1,757 (677.3–3,586.2)
Whole pelvic dose (cGy)	5,040 (4,500–6,000)
Lymphocytotoxicity grade[a]	
0 (normal)	13 (7.7)
1	27 (16.1)
2	88 (52.4)
3	40 (23.8)
4	0 (0)

Values are presented as median (range) or number (%).
BM, bone marrow; BB, bowel bag.
[a]Lymphocyte toxicity was categorized into grades 1–4 according to the Common Terminology Criteria for Adverse Events version 5.0.

Table 2. Independent t-tests for dosimetric parameters of bowel bag between ALC grades 0–2 and grade 3 patients

BB dose	Mean	SD	t-value	p-value
Dmean				
0–2	14.270	4.177	–3.471	0.001
3	17.080	5.312		
V5				
0–2	0.511	0.151	–3.895	< 0.001
3	0.625	0.193		
V10				
0–2	0.466	0.140	–3.500	0.001
3	0.561	0.176		
V15				
0–2	0.401	0.127	–3.147	0.002
3	0.477	0.154		
V20				
0–2	0.321	0.120	–2.281	0.024
3	0.374	0.150		
V25				
0–2	0.246	0.107	–1.685	0.098
3	0.285	0.133		
V30				
0–2	0.186	0.088	–2.013	0.046
3	0.220	0.110		

ALC, absolute lymphocyte count; BB, bowel bag; SD, standard deviation; Dmean, mean dose; Vx, volume dosimetric parameters (Vx), the percentage of a given radiation dose (x Gy) occupying a certain volume (V) relative to the total volume.

potential predictors of grade 3 lymphocytopenia during pelvic RT.

5. Summary

Independent t-tests for dosimetric parameters of bowel bag between ALC grades 0–2 and grade 3 patients revealed significant differences between the two groups for Dmean, V5, V10, V15, V20, and V30, with p-values less than 0.05. When deriving ROC curves and cutoff values, significant differences between the two groups were observed for Dmean, V5, V10, and V15. Using the cutoff values obtained from the ROC curves, we divided the data for Dmean, V5, V10, V15, V20, V25, and V30 into two groups and compared their ORs. This comparison yielded significant results for Dmean, V5, V10, V15, and V25 ($p < 0.05$). Consequently, we confirmed a significant association between the reduction in ALC and the dosimetric parameters of the bowel bag for Dmean, V5, V10, and V15, as these parameters showed significant results across all three statistical analyses.

Table 3. ROC curves and cutoff values

BB dose	AUC	SD	p-value	Cutoff value (Gy or %)
Dmean	0.654	0.051	0.003	17.840
V5	0.689	0.053	0.000	0.624
V10	0.670	0.052	0.001	0.510
V15	0.645	0.051	0.006	0.433
V20	0.591	0.053	0.082	0.378
V25	0.570	0.053	0.180	0.369
V30	0.575	0.053	0.154	0.232

ROC, receiver operating characteristic; BB, bowel bag; AUC, area under the curve; SD, standard deviation; Dmean, mean dose; Vx, volume dosimetric parameters (Vx), the percentage of a given radiation dose (x Gy) occupying a certain volume (V) relative to the total volume.

Table 4. Logistic regression analysis of bowel bag dosimetric parameters based on ROC-derived cutoff values for predicting grade 3 lymphocytopenia

	OR	95% CI	p-value
Dmean			
Group 1 (< 17.84 Gy)	1		
Group 2 (≥ 17.84 Gy)	3.549	1.668–7.554	0.001
V5			
Group 1 (< 62.4%)	1		
Group 2 (≥ 62.4%)	5.885	2.738–12.648	0.001
V10			
Group 1 (< 51.0%)	1		
Group 2 (≥ 51.0%)	4.113	1.886–8.968	0.001
V15			
Group 1 (< 43.3%)	1		
Group 2 (≥ 43.3%)	3.036	1.434–6.425	0.003
V20			
Group 1 (< 37.8%)	1		
Group 2 (≥ 37.8%)	1.99	0.965–4.107	0.061
V25			
Group 1 (< 36.9%)	1		
Group 2 (≥ 36.9%)	3.545	1.377–9.128	0.006
V30			
Group 1 (< 23.2%)	1		
Group 2 (≥ 23.2%)	1.889	0.908–3.943	0.089

ROC, receiver operating characteristic; OR, odds ratio; CI, confidence interval; Dmean, mean dose; Vx, volume dosimetric parameters (Vx), the percentage of a given radiation dose (x Gy) occupying a certain volume (V) relative to the total volume.

Discussion and Conclusion

Radiotherapy for tumors located within the pelvis can induce hematological side effects. Studies have shown the potential hematologic challenges posed by irradiation to the BM [8]. Particularly, a

https://doi.org/10.3857/roj.2025.00220

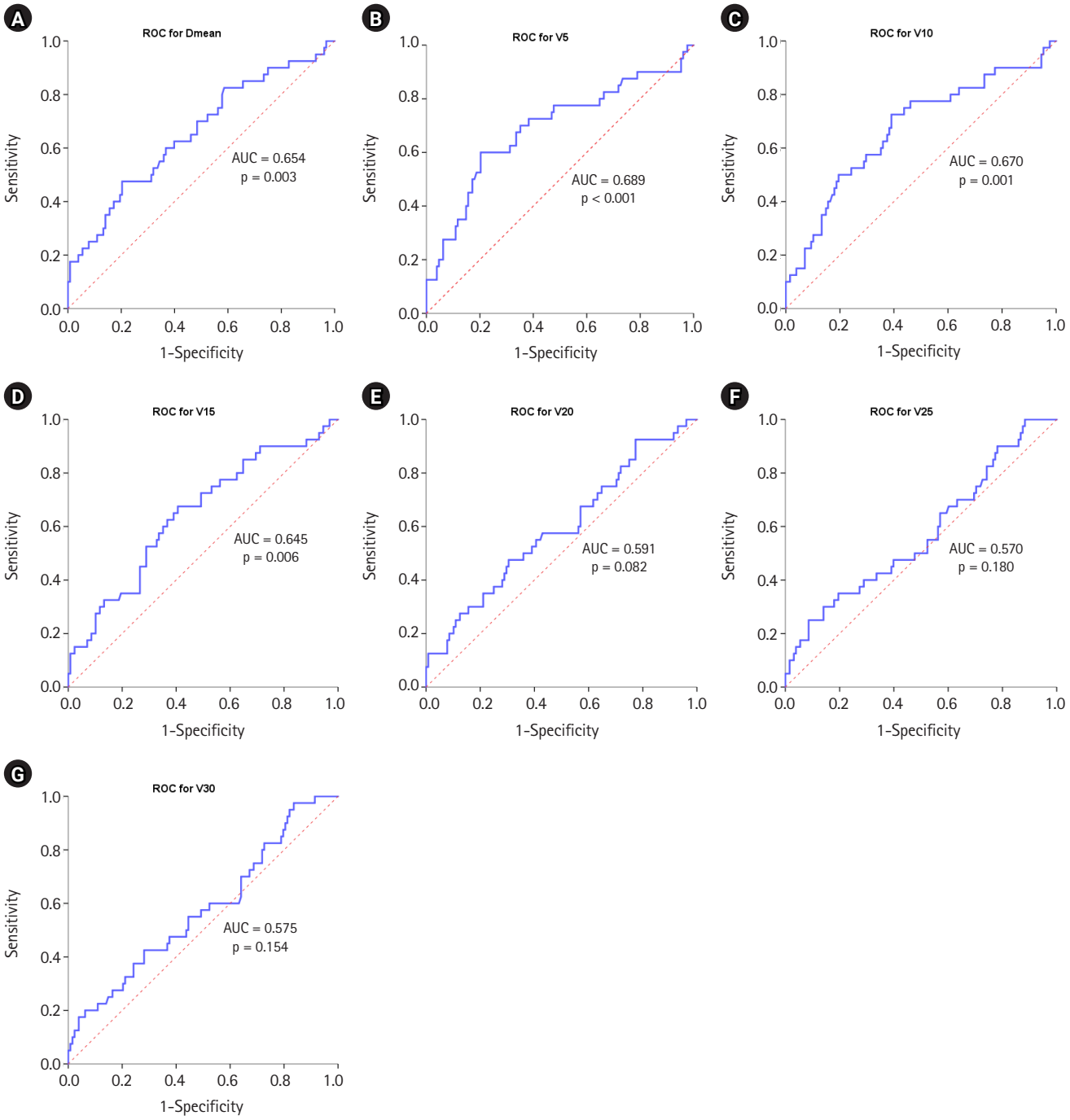

Fig. 1. ROC curves for the dosimetry parameters. ROC for Dmean (A), V5 (B), V10 (C), V15 (D), V20 (E), V25 (F), and V30 (G). ROC, receiver operating characteristic; Dmean, mean dose; Vx, volume dosimetric parameters (Vx), the percentage of a given radiation dose (x Gy) occupying a certain volume (V) relative to the total volume; AUC, area under the curve.

significant reduction in the number of lymphocytes can affect the intensity and duration of RT, potentially undermining the intended therapeutic effect [9]. Lymphocytes are pivotal in the human immune system and are essential for combating tumor cells [10,11]. Their participation in inducing cell apoptosis, cytotoxicity, and antitumor responses, notably through CD8+ and CD4+ T cells and cytokine secretion, highlights the importance of maintaining normal lymphocyte counts for effective tumor treatment [12-15].

Consequently, preserving patients' lymphocyte levels is critical, underscoring the need to modulate the irradiated doses to the normal tissues. Because a substantial portion of the active BM resides in the pelvis and lumbar spine, regulating the irradiated dose to the

pelvis is an effective approach for managing the hematologic side effects potentially induced by BM irradiation [16]. Considering such aspects, it can be inferred that exposure to radiation in the blood within the bowel bag or mesenteric lymph nodes may also lead to a decrease in lymphocyte counts, such as the radiation investigated in the pelvic bones.

Recent studies investigating the link between pelvic BM and lymphocyte toxicity during CCRT in patients with pelvic tumor have shown that adjusting the radiation dose to the bowel bag may alleviate lymphocytic toxicity. However, specific findings regarding the effect of RT alone on lymphocyte toxicity when directed to the bowel bag remain uncertain. Investigating this is important for understanding the minimal irradiated dose to the normal tissues that is necessary to maintain lymphocyte counts. Against this backdrop, we examined the correlation between dosimetric parameters of the bowel bag and lymphocyte toxicity during pelvic tumor RT. Our findings suggest that dosimetric modulation of RT may help mitigate lymphocyte toxicity, although further studies are warranted.

Previous research has claimed an association between the radiation dose administered to the BM and lymphocytopenia. This is likely attributed to the meticulous exclusion of pelvic bone from the contour, possibly owing to the increased utilization of IMRT in recent times for planning RT. Similarly to the outcomes of CCRT for cervical cancer, this suggests that even when RT is administered without concurrent chemotherapy, careful attention should be paid to minimizing unnecessary low-to-intermediate dose exposure to the BM.

In our study, BM was contoured and included in the dosimetric analysis to evaluate its potential association with lymphocytopenia. However, the independent t-test results showed no statistically significant differences in BM dosimetric parameters (Dmean, V5–V30) between patients with grade 0–2 and grade 3 ALC toxicity (Supplementary Table S1). This may be attributed to the relatively low BM radiation dose in our cohort, likely resulting from the use of modern IMRT planning techniques that effectively spare the pelvic bones. These findings suggest that, in settings where chemotherapy is not administered and IMRT is utilized, the contribution of BM irradiation to lymphocytopenia may be minimal. Based on the lack of significant association between BM dose and lymphocytopenia in our cohort, the potential for confounding bias between bowel bag dose and BM dose is unlikely. Nevertheless, future prospective studies incorporating multivariate analyses are warranted to further evaluate potential interactions between bowel bag and BM doses.

Our study had certain limitations. Given that this was a retrospective study, prospective validation is needed to confirm the findings. In addition, we did not adjust for pelvic BM radiation dose, which is a well-established predictor of lymphocyte depletion. This confounding factor may have influenced the observed association between bowel bag dose and lymphocytic toxicity. Furthermore, our estimation of bowel bag blood volume and the number of mesenteric lymph nodes may not precisely reflect physiological conditions.

In conclusion, during pelvic RT, low-dose radiation exposure to the bowel bag may be associated with the development of high-grade lymphocytopenia. However, given the retrospective design and the lack of BM dosimetry adjustment, further prospective studies are needed to clarify the independent impact of bowel bag irradiation.

Statement of Ethics

This retrospective study was reviewed and approved by the Institutional Review Board (IRB) of Seoul St. Mary's Hospital, The Catholic University of Korea (No. KC22RISI0715). The requirement for informed consent was waived by the IRB due to the retrospective nature of the study.

Conflict of Interest

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

Funding

This study was supported by the Research Fund of Seoul St. Mary's Hospital, The Catholic University of Korea.

Author Contributions

Conceptualization, MKK; Investigation and methodology, MKK, KHC, SHS; Resources, MKK, KHC, WS, JHH, YNK; Supervision, KHC, WS, BOC, YSK, HJ; Writing of the original draft, MKK; Writing of the review and editing, MKK, KHC, WS; Formal analysis, MKK, KHC, WS, JHH. Data curation, MKK, KHC. All the authors have proofread the final version.

Data Availability Statement

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

https://doi.org/10.3857/roj.2025.00220

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2025.00220.

References

1. Fiorino C, Valdagni R, Rancati T, Sanguineti G. Dose-volume effects for normal tissues in external radiotherapy: pelvis. Radiother Oncol 2009;93:153–67.
2. Klopp AH, Yeung AR, Deshmukh S, et al. Patient-reported toxicity during pelvic intensity-modulated radiation therapy: NRG Oncology-RTOG 1203. J Clin Oncol 2018;36:2538–44.
3. Nicholas S, Chen L, Choflet A, et al. Pelvic radiation and normal tissue toxicity. Semin Radiat Oncol 2017;27:358–69.
4. Kumar T, Schernberg A, Busato F, et al. Correlation between pelvic bone marrow radiation dose and acute hematological toxicity in cervical cancer patients treated with concurrent chemoradiation. Cancer Manag Res 2019;11:6285–97.
5. Li J, Chen Q, Liu Z, Xu Y, Ji S. Predictive value of bowel dose-volume for severe radiation-induced lymphopenia and survival in cervical cancer. Front Immunol 2024;15:1459206.
6. Chopra S, Dora T, Chinnachamy AN, et al. Predictors of grade 3 or higher late bowel toxicity in patients undergoing pelvic radiation for cervical cancer: results from a prospective study. Int J Radiat Oncol Biol Phys 2014;88:630–5.
7. Zhang BZ, Li Y, Xu LM, et al. The relationship between the radiation dose of pelvic-bone marrow and lymphocytic toxicity in concurrent chemoradiotherapy for cervical cancer. Radiat Oncol 2023;18:12.
8. Chang Y, Yang ZY, Li GL, et al. Correlations between radiation dose in bone marrow and hematological toxicity in patients with cervical cancer: a comparison of 3DCRT, IMRT, and rapidARC. Int J Gynecol Cancer 2016;26:770–6.
9. Abu-Rustum NR, Lee S, Correa A, Massad LS. Compliance with and acute hematologic toxic effects of chemoradiation in indigent women with cervical cancer. Gynecol Oncol 2001;81:88–91.
10. Fogar P, Sperti C, Basso D, et al. Decreased total lymphocyte counts in pancreatic cancer: an index of adverse outcome. Pancreas 2006;32:22–8.
11. Thiangphak E, Pruegsanusak K, Buhachat R. Pretreatment lymphocyte count as independent prognostic factor in patients with locally advanced cervical cancer treated with concurrent chemoradiotherapy. Int J Gynaecol Obstet 2022;159:672–8.
12. Asrir A, Tardiveau C, Coudert J, et al. Tumor-associated high endothelial venules mediate lymphocyte entry into tumors and predict response to PD-1 plus CTLA-4 combination immunotherapy. Cancer Cell 2022;40:318–34.
13. Martinez-Lostao L, Anel A, Pardo J. How do cytotoxic lymphocytes kill cancer cells? Clin Cancer Res 2015;21:5047–56.
14. Oh DY, Kwek SS, Raju SS, et al. Intratumoral CD4(+) T cells mediate anti-tumor cytotoxicity in human bladder cancer. Cell 2020;181:1612–25.
15. Seliger B, Massa C. Modulation of lymphocyte functions in the microenvironment by tumor oncogenic pathways. Front Immunol 2022;13:883639.
16. Rose BS, Liang Y, Lau SK, et al. Correlation between radiation dose to (1)(8)F-FDG-PET defined active bone marrow subregions and acute hematologic toxicity in cervical cancer patients treated with chemoradiotherapy. Int J Radiat Oncol Biol Phys 2012;83:1185–91.

ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2025;43(4):188-194
https://doi.org/10.3857/roj.2025.00346

Efficacy and safety of high-dose hypofractionated palliative radiotherapy (40 Gy in 10 daily fractions) for non–small cell lung cancer

James C. H. Chow[1], Jeffrey C. F. Lui[1], Chris K. C. Tong[1], Anthony H. P. Tam[1], Jeffrey C. H. Chan[1], Jeannie Y. K. Chik[1], Gavin T. C. Cheung[2], Ka Man Cheung[1], Luke T. Y. Lee[1], Kam Hung Wong[1], Kwok Hung Au[1]

[1]*Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong SAR, China*
[2]*Department of Oncology, United Christian Hospital, Hong Kong SAR, China*

Received: June 11, 2025
Revised: July 31, 2025
Accepted: August 4, 2025

Correspondence:
James C. H. Chow
Department of Clinical Oncology, Queen Elizabeth Hospital, Room 1116, 11/F, Block R, Queen Elizabeth Hospital, 30 Gascoigne Road, Kowloon, Hong Kong SAR, China
Tel: +852-35067394
E-mail: cch932@ha.org.hk
ORCID:
https://orcid.org/0000-0001-5305-4342

Purpose: Palliative thoracic radiotherapy plays a crucial role in the management of patients with non–small cell lung cancer (NSCLC). Conventional dose-fractionation schemes often yield modest and short-lived tumor responses. This study aims to evaluate the efficacy and safety of a high-dose hypofractionated radiotherapy regimen of 40 Gy in 10 daily fractions in NSCLC.

Materials and Methods: Consecutive NSCLC patients who underwent palliative thoracic radiotherapy using the 40 Gy in 10 daily fractions regimen between January 2017 and December 2022 were identified from institutional databases of two tertiary oncology centers. Treatment responses were assessed using the Response Evaluation Criteria in Solid Tumor criteria. Local tumor control rate was estimated using cumulative incidence function, considering death as a competing event. The rates of radiation pneumonitis and esophagitis were assessed.

Results: Sixty-two eligible patients were included. Median age was 72.6 years, with 52 patients (83.4%) having Eastern Cooperative Oncology Group performance status of ≥2. Radiotherapy was given to 33 patients (53.2%) with locally advanced primary NSCLC and 29 patients (47.8%) with oligopersistent or oligoprogressive NSCLC. Fifty-three tumors (85.4%) were considered unsuitable for stereotactic radiotherapy by location or size. With a median follow-up of 4.1 years, the overall response rate was 69.3%. Local control rates at 1 and 3 years were 96.7% and 76.9%, respectively. Grade 1–2 radiation pneumonitis and esophagitis occurred in 46.7% and 8.1% of patients. One case of grade 3 esophagitis was observed.

Conclusion: The 40 Gy in 10 daily fractions regimen demonstrates high local tumor control rate and a favorable safety profile, representing an effective and safe palliative option for NSCLC patients.

Keywords: Non-small cell lung carcinoma, Radiotherapy, Radiotherapy dosage, Palliative care

Introduction

Over half of patients with non–small cell lung cancer (NSCLC) present with locally advanced or metastatic disease [1]. Current practices in conventional palliative radiotherapy for NSCLC vary significantly across clinicians and institutions, with common regimens ranging from 8–10 Gy in a single fraction to 30 Gy delivered in 10 fractions [2,3]. While these regimens are effective in alleviating symptoms, the resulting tumor response is often modest and short-lived. Higher-dose regimens, such as 39 Gy in 13 fractions, has been shown to improve overall survival compared with conventional schedules, at the expense of a slightly higher incidence of radiation-induced esophagitis [4]. Aggregate data from a systematic review also suggest a modest survival advantage survival with

Copyright © 2025 The Korean Society for Radiation Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

radiotherapy schedules with biologically effective dose of ≥ 35 Gy [5]. Evidence for further dose escalation to 50–70 Gy in 10–25 fractions exists, but the studies were primarily focused on patients with early-stage disease with relatively small tumor sizes [6,7].

As the prognosis of NSCLC continues to improve with breakthroughs in molecularly targeted agents and immune checkpoint inhibitors, there is a growing demand for more effective local therapies, driven by the need to optimize local primary tumor control and to address oligometastatic diseases [8]. The advent of stereotactic body radiotherapy (SBRT) has allowed effective ablation of primary tumors and lung metastases. Nevertheless, factors such as tumor size and location may limit its applicability. The general upper limit of tumor diameter considered acceptable for SBRT is 5 cm, delivering high ablative radiation to targets beyond this size limit is dosimetrically challenging [9]. Tumors with endobronchial involvement and patients on anticoagulation are also considered not suitable for SBRT. Given these considerations, there remains a room to explore effective and safe non-SBRT palliative radiotherapy regimens for patients with NSCLC, with an aim to palliate symptoms and attain local tumor control.

Over the past decade, our group employed a high-dose hypofractionated regimen of 40 Gy in 10 daily fractions as palliative radiotherapy for selected patients with NSCLC. This represents a dose escalation from the conventional regimen of 30 Gy in 10 daily fractions. By utilizing hypofractionation at 4 Gy per fraction, we aim to increase the biologically effective dose, potentially enhancing local tumor control while maintaining an acceptable profile of radiation-related toxicities. The brief two-week treatment course is chosen to optimize patient compliance and convenience, including elderly patients and those with suboptimal performance status. The current study reports on the efficacy and toxicity outcomes of this radiotherapy regimen from a jointed cohort of consecutively treated patients.

Materials and Methods

This is a joint retrospective cohort study conducted in two tertiary oncology centers (Queen Elizabeth Hospital and United Christian Hospital, Hong Kong). Approval has been granted by the research ethics committee (reference number: CIRB-2025-101-2), patient consent was waived. Consecutive NSCLC patients who underwent palliative thoracic radiotherapy using the 40 Gy in 10 daily fractions regimen between January 2017 and December 2022 were identified from institutional databases. Patients without cross-sectional images for response assessment were excluded. The disease was staged using American Joint Committee on Cancer/Union for International Cancer Control 8th edition TNM classification.

All patients were treated in the supine position, immobilized using a wing board with bilateral hand grips. Simulation was performed using computed tomography (CT) with intravenous contrast, images were co-registered with positron emission tomography images wherever available. The use of 4-dimensional CT (4DCT) was not mandatory. Gross tumor volume was delineated using lung window. Isocentric expansion of 5–8 mm was used to generate the clinical target volume, followed by anatomic editing according to natural barriers. A 5 mm isotropic planning target volume (PTV) margin was used if 4DCT simulation was in place, otherwise a differential expansion (5–7 mm axially and 10–12 mm superoinferiorly) was used to account for both respiratory motion and set-up error. Radiotherapy plans were optimized either by 3-dimensional conformal radiotherapy (3DCRT) or volumetric modulated arc radiotherapy (VMAT) techniques. The PTV received 40 Gy in 10 daily fractions, with treatment delivered five fractions per week. The organs at-risk included lungs, heart, esophagus, spinal cord, and brachial plexus. Their respective dose constraints were detailed in Supplementary Table S1. Treatment verification was performed using kV orthogonal on-board imaging or cone-beam CT. No concurrent systemic therapy was given during the course of radiotherapy. An example case was illustrated in Fig. 1.

Treatment responses were evaluated by diagnostic CT using the Response Criteria in Solid Tumors (RECIST) 1.1 criteria. Local tumor control rate was estimated using the cumulative incidence function with death assigned as a competing event. A sensitivity analysis was conducted, censoring data at the time of changes in systemic therapy. Subgroup comparisons were conducted using Gray's test. Overall survival (OS) was estimated using the Kaplan-Meier method, calculated from the start of radiotherapy to death or last follow-up. Multivariable analyses were conducted using the Fine-Gray subdistribution hazard model and Cox regression. The rates of radiation pneumonitis and esophagitis were graded in accordance with Common Terminology Criteria for Adverse Events version 6.0. Statistical analyses were conducted using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA) and Stata version 10 (Stata Corp., College Station, TX, USA).

Results

A total of 62 eligible NSCLC patients were identified during the study period, all of whom completed the 40 Gy in 10 daily fractions palliative regimen to the thorax (Table 1). The median age of the cohort was 72.6 years, with 52 patients (83.4%) having Eastern Cooperative Oncology Group performance status of ≥ 2. Adenocarcinoma (75.8%) and squamous cell carcinoma (17.8%) were the predominant histology types. Actionable alterations were identified

https://doi.org/10.3857/roj.2025.00346

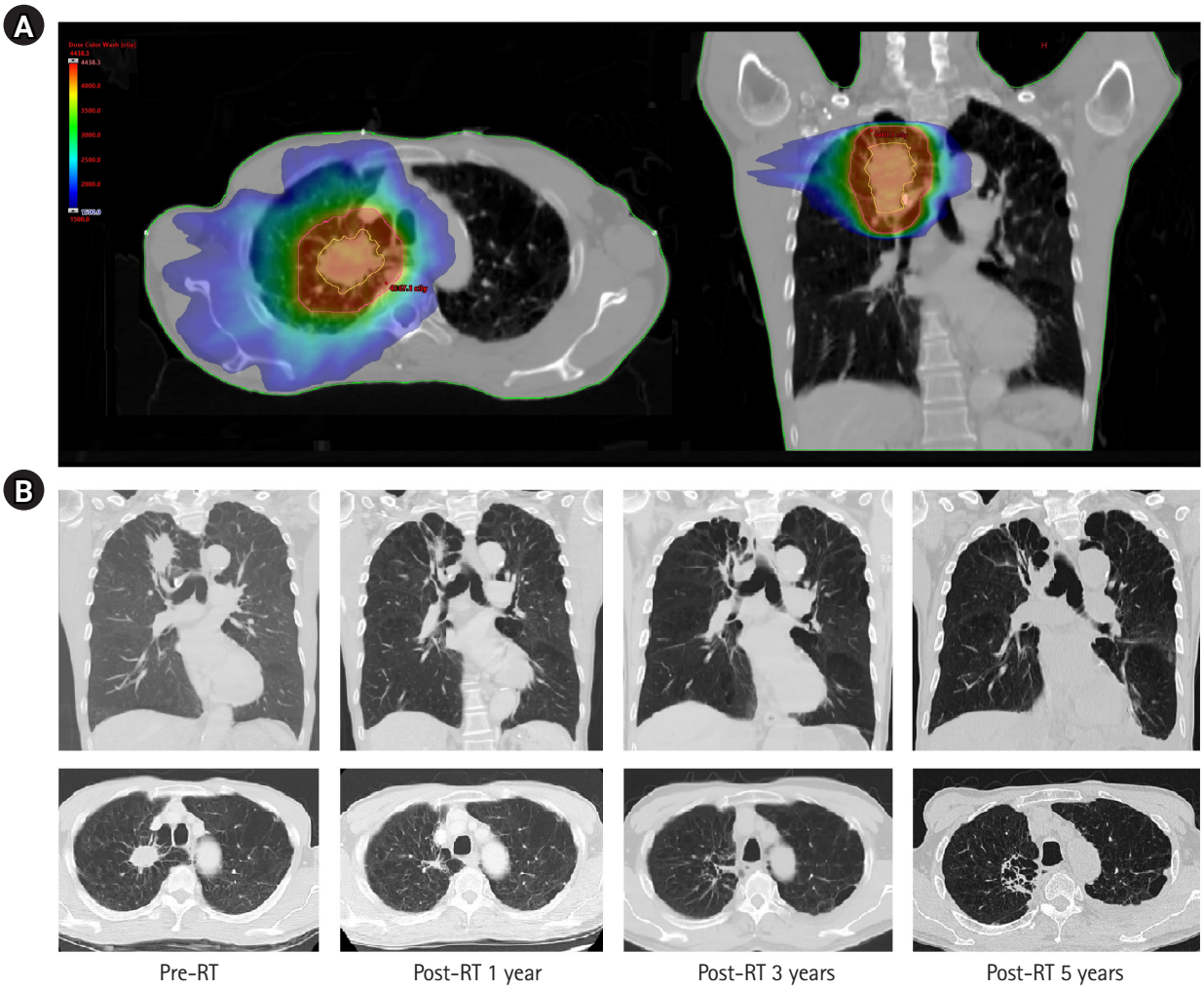

Fig. 1. An example of a radiotherapy (RT) plan using 40 Gy in 10 daily fractions for a 75-year-old man diagnosed with cT2bN0M0 adenocarcinoma of the lung. The 4.7 cm tumor in the right upper lobe was located adjacent to the trachea. (A) Palliative RT was delivered using the volumetric modulated arc radiotherapy technique. The gross tumor volume is indicated in yellow, while the planning target volume is shown in red. The isodose color-wash ranges from 15 Gy to 44.4 Gy. (B) Serial computed tomography images illustrate the continual tumor response and local control over time.

in 50.0% of patients, mostly sensitizing epidermal growth factor receptor mutations. Of the entire cohort, radiotherapy was given to 33 patients (53.2%) with treatment-naïve locally advanced primary NSCLC and 29 patients (47.8%) with oligopersistent or oligoprogressive NSCLC following systemic therapy. Most of the treated tumors were considered unsuitable for SBRT due to large tumor size (n = 34, 54.8%) or ultracentral location (n = 19, 30.6%) with respect to the trachea or the proximal bronchial tree. In the cohort, 29.0% (18/62) of the patients had a change in systemic therapy after radiotherapy, at a median interval of 4.8 months. The distribution of subsequent systemic therapies were tyrosine kinase inhibitors (n = 8), chemotherapy (n = 6), immunotherapy (n = 3), and chemo-immunotherapy (n = 1).

Radiotherapy was delivered using VMAT and 3DCRT in 54 patients (87.1%) and eight patients (12.9%), respectively. 4DCT simulation was employed in 39 patients (62.9%). The median PTV was 168.8 cm^3 (interquartile range [IQR], 100.1 to 266.5). The median PTV V100% was 98.8% (IQR, 97.4% to 99.6%) with a median Dmax of 44.0 Gy (IQR, 43.2 to 44.6). Radiation dose-volume data of the organs at-risk (OARs) were summarized in Table 2. The median lung and heart doses were 6.6 Gy (IQR, 5.4 to 8.8) and 2.2 Gy (IQR, 0.7 to 6.9), respectively. Pre-specified radiation dose constraints were fulfilled in all radiotherapy plans.

With a median follow-up of 4.1 years, the overall response rate of the 40 Gy in 10 daily fractions palliative regimen was 69.3%. The response rates for locally advanced primary tumor and oligometastatic diseases were 78.8% (26/33) and 58.6% (17/29), respectively (p = 0.086). The local control rates at 1-year and 3-year

Table 1. Demographics and treatment details

Characteristic	Value
Age (year)	72.6 (66.8–80.3)
Sex	
Male	36 (58.1)
Female	26 (41.9)
ECOG performance status	
0–1	10 (16.1)
2	45 (72.6)
3	7 (11.3)
Smoking status	
Never smoker	29 (46.8)
Current/ex-smoker	33 (53.2)
Histology	
Adenocarcinoma	47 (75.8)
Squamous cell carcinoma	11 (17.8)
Lymphoepithelioma-like carcinoma	3 (4.8)
Non-small cell lung cancer, NOS	1 (1.6)
Actionable mutations	
EGFR mutation	28 (45.2)
ALK fusion	2 (3.2)
KRAS G12C mutation	1 (1.6)
None	24 (38.7)
Not assessed	7 (11.3)
Indication for radiotherapy	
Local control for primary tumor	33 (53.2)
Oligoprogression	23 (37.1)
Oligopersistence	6 (9.7)
PET-CT before radiotherapy	
Yes	57 (91.9)
No	5 (8.1)
Tumor size (cm)	5.2 (3.4–6.5)
T category[a]	
T1	8 (12.9)
T2	33 (53.2)
T3	16 (25.8)
T4	5 (8.1)
N category[a]	
N0	34 (54.8)
N1	8 (12.9)
N2	15 (24.2)
N3	5 (8.1)
M category[a]	
M0	31 (50.0)
M1	31 (50.0)
Radiotherapy planning technique	
Volumetric modulated arc radiotherapy	54 (87.1)
3-Dimensional conformal radiotherapy	8 (12.9)

Values are presented as median (IQR) or number (%).
ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; KRAS, Kirsten rat sarcoma virus; PET-CT, positron emission tomography computed tomography; IQR, interquartile range.
[a]Cancer stage assessed at the time of palliative radiotherapy.

Table 2. Radiation dose-volume metrics of target volumes and organs at-risk

Structure	Metric	Median (IQR)
GTV	Volume (cm^3)	30.7 (10.0–56.3)
	V100% (%)	100.0 (100.0–100.0)
PTV	Volume (cc)	168.8 (100.1–266.5)
	V100% (%)	98.8 (97.4–99.6)
	Dmax (Gy)	44.0 (43.2–44.6)
Spinal cord	Dmax (Gy)	18.2 (12.6–24.8)
Spinal cord PRV	Dmax (Gy)	22.7 (15.4–30.5)
Total lung (minus GTV)	Dmean (Gy)	6.6 (5.4–8.8)
	V16 Gy (%)	14.3 (10.0–18.9)
	V4.5 Gy (%)	33.8 (22.6–43.2)
Heart	V19.5 Gy (%)	0.6 (0.0–6.3)
	Dmean (Gy)	2.2 (0.7–6.9)
	V39 Gy (%)	0.0 (0.0–0.2)
Esophagus	Dmean (Gy)	6.0 (3.8–8.5)

IQR, interquartile range; GTV, gross tumor volume; PTV, planning target volume; V100%, the relative volume of structure received 100% of prescription dose; Dmax, maximal dose; PRV, planning organ at risk volume; Dmean, mean dose; Vx Gy, the relative volume of structure received x Gy.

of the whole cohort were 96.7% and 76.9% (sensitivity analysis censoring data at the time of changes in systemic therapy, 96.7% and 73.4%), respectively (Fig. 2, Supplementary Fig. S1). No significant difference in local control was observed by tumor size (> 5 cm vs. ≤ 5 cm; 1-year rates, 96.9% vs. 96.6%; p = 0.383) or indication of radiotherapy (locally advanced primary tumor vs. oligometastasis; 1-year rates, 93.8% vs 100.0%; p = 0.188) (Supplementary Fig. S2). Over half of the patients (56.4%) developed subsequent distant progression. The 1-year OS was 88.6% and the 3-year OS was 61.4%, respectively. No statistically significant associations were found between local control or OS and patient age, sex, tumor size, treatment indication, or radiotherapy technique (Supplementary Tables S2, S3).

The crude incidences of grade 1–2 radiation pneumonitis and esophagitis were 46.7% and 8.1%, respectively. One patient developed grade 3 esophagitis that subsided 2 months after radiotherapy with supportive medications. In the radiotherapy plan for this index patient, approximately 5 cm length of the esophagus overlapped with the PTV. The maximal dose (Dmax) and mean dose (Dmean) of the esophagus were 42.4 Gy and 14.4 Gy, respectively.

Discussion and Conclusion

To the best of our knowledge, this study represents the first report of efficacy and safety data of radiotherapy for NSCLC using 40 Gy in 10 daily fractions. With a high overall response rate of 69.3%

https://doi.org/10.3857/roj.2025.00346

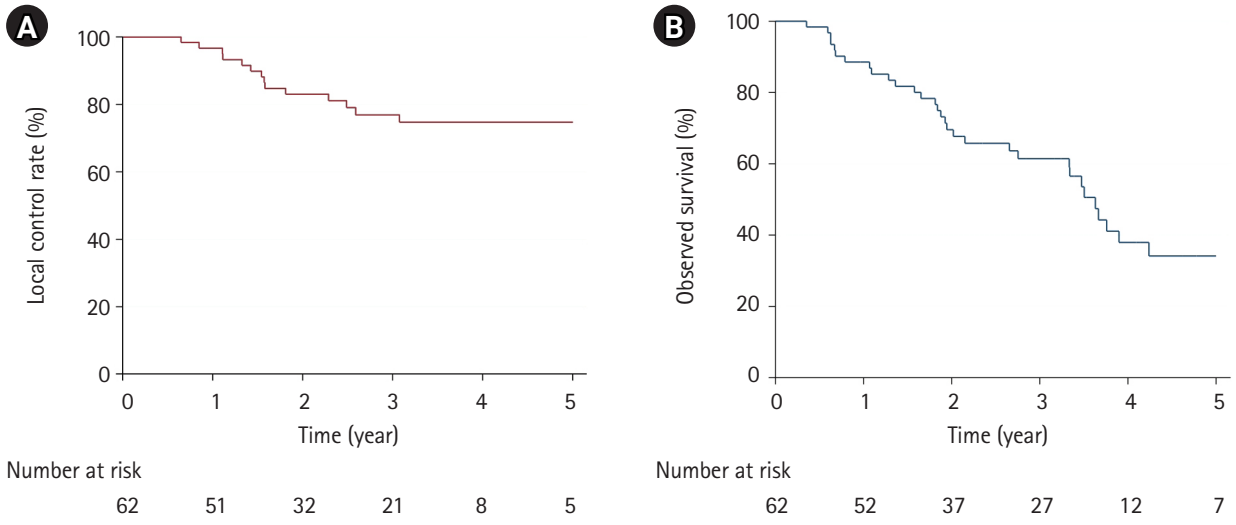

Fig. 2. (A) Local control rate and (B) overall survival of the cohort.

and an encouraging 1-year local control rate of 96.7%, this regimen represents a simple and effective radiotherapy scheme in attaining local tumor control.

A variety of dosing and fractionation schedules for palliative radiotherapy in NSCLC are used in clinical settings. Among the commonly employed regimens are 8–10 Gy in 1 fraction, 16–17 Gy in 2 fractions, 20 Gy in 5 fractions, 30 Gy in 10 fractions, and 36–39 Gy in 12–13 fractions [2]. The biologically effective dose (BED) 10, BED3, and equivalent doses in 2 Gy fractions of these regimens are detailed in Supplementary Table S4. Regarding palliative radiotherapy, the American Society for Radiation Oncology clinical practice guidelines recommend high-dose regimens (30 Gy in 10 fractions equivalent or greater) for NSCLC patients with good performance status [10]. This recommendation is consistent with other clinical guidelines and is primarily based on randomized data suggesting potential survival benefits with higher radiation doses compared to more modest treatment regimens [11]. In a meta-analysis of 13 randomized controlled trials, higher BED10 schedules of 35 Gy were associated with a greater likelihood of symptom improvement and longer survival compared to lower BEDs [5]. In this regard, the 40 Gy in 10 fractions regimen has a BED10 of 46.7 Gy, placing it at the higher end of the palliative thoracic radiotherapy dose spectrum.

Historically, studies evaluating conventional palliative radiotherapy regimens for NSCLC have primarily focused on symptom relief and OS as endpoints, the effect on local tumor control and toxicity outcomes was rarely reported [2,3]. The local control rate observed in our study closely aligns with data from other high-dose hypofractionated schedules for NSCLC, which were primarily investigated in the context of curative intent treatments. Using 3DCRT, Soliman et al. [12] reported long-term results of 118 patients with inoperable stage I–II NSCLC, treated with doses of 48–60 Gy delivered in 12–15 fractions, achieving a 5-year local control rate and OS of 70.1% and 40.0%, respectively. Comparable local control rates of 60%–70% have also been observed with more protracted schedules of 54–60 Gy in 18–20 fractions [13,14]. However, the incidence of grade ≥ 3 pneumonitis with the above schedules was reported to be up to 4–5%, necessitating corticosteroid treatment, and instances of fatal events have been documented. In this context, the clinical outcomes associated with the 40 Gy in 10 fractions regimen reported in the current study demonstrated a favorable balance between efficacy and safety, particularly in patients with suboptimal performance status. In addition to the satisfactory tumor response and control rates, the moderate hypofractionation over a brief 2-week treatment course is also convenient for patients and allows easy integration between cycles of systemic therapies.

The widespread adoption of immunotherapy and molecularly targeted agents has markedly improved the prognosis for patients with recurrent or metastatic NSCLC. Achieving sustained local tumor control with radiotherapy has become increasingly important for oligopersistent or oligoprogressive primary tumors following systemic treatments, as it serves to eradicate resistant tumor clones for potentially improved survival outcomes [15]. Although SBRT is widely recognized as the standard technique in these settings, its application to large or ultracentral tumors necessitates careful consideration of dosimetric feasibility and the potential for treatment-related toxicity. Several prospective studies have investigated SBRT approaches for centrally located NSCLC, reporting promising local control rates of 75%–90% [16-19]. However, the incidence of severe adverse events remain a concern, with grade ≥ 3 and grade 5 toxicities occurring in 7%–20% and 3%–15% of the treated pa-

tients, respectively. In the current cohort of patients treated by the 40 Gy in 10 fractions regimen, nearly one-third of the PTVs abutted the trachea and the proximal bronchial tree. Despite the ultracentral tumor location, no major hemorrhagic events were observed over a median follow-up duration of more than four years. Furthermore, the tumors included in this cohort were notably large, with a median PTV of 168.8 cm^3, corresponding to tumor diameters of approximately 6 to 7 cm. Traditionally, bulky tumors are considered more resistant to radiotherapy and are often underrepresented in SBRT trials. In one retrospective multicenter study of 92 patients with primary NSCLC measuring ≥5 cm treated with SBRT, local control rates at 1 and 2 years were 95.7% and 73.2%, respectively [20]. These outcomes closely align with the 1-year and 3-year local control rates of 96.7% and 76.9% observed in the present cohort, thereby supporting the efficacy of high-dose hypofractionated radiotherapy for achieving tumor control in large NSCLC.

The 40 Gy in 10 daily fractions regimen demonstrated a satisfactory safety profile in patients with NSCLC. The cohort primarily comprised an elderly population with fair performance status, as over half of the patients were aged 70 years or older. With all radiotherapy plans adhered to the pre-specified OAR constraints, the crude incidence of high-grade adverse event was low at 1.6%. Although pneumonitis was observed in 46.7% of patients, all cases were low-grade and primarily manifested as radiological changes in the absence of clinical symptoms. The only high-grade event was one case of grade 3 esophagitis, which occurred in a patient with a central lung tumor that abutted the esophagus, leading to a relatively high esophageal Dmax of 42.4 Gy. In the context of palliative thoracic radiotherapy for large tumors, where long segments of the esophagus may inevitably overlap with the PTV, prioritizing the esophagus during treatment plan optimization may further reduce the risk of symptomatic esophagitis while maintaining survival outcomes, especially when the prescribed radiotherapy dose is high [21]. This approach could be carefully considered in conjunction with the 40 Gy in 10 fractions regimen for patients in whom minimizing esophageal complication is a priority, allowing for a balance between effective tumor control and treatment-related toxicity.

This study has several limitations. First, while tumor response assessment was standardized using the RECIST criteria, accurate measurement of tumor size may be influenced by local tissue fibrosis caused by high-dose radiotherapy. Tumors surrounded by fibrotic scars can sometimes be mistakenly classified as RECIST-progressive diseases if only physical dimensions are considered. Functional imaging techniques, such as positron emission tomography, may provide additional information in evaluating responses in the post-radiation context, but it was not consistently available in our cohort [22]. As a result, our reported response and local control rates may be underestimated. Second, a switch in systemic therapy in any time-point after thoracic radiotherapy may confound response assessment and potentially lead to overestimation of tumor control. To address this, we conducted a separate sensitivity analysis by censoring this event, aiming to provide a more accurate estimation of our primary study endpoint. Third, due to the retrospective nature of this study, comprehensive data adverse events were not available. Certain toxicities, such as long-term chest wall and cardiac complications, were not routinely assessed hence may be underreported.

In conclusion, high-dose hypofractionated radiotherapy of 40 Gy in 10 daily fractions is an effective and safe regimen for local control of NSCLC. It represents a viable dose-fractionation with an aim for local response and control, especially in instances where tumor size or location renders SBRT unsuitable. Prospective evaluation of this regimen, along with careful comparisons to lower dose-fractionation schedules, is warranted to affirm its clinical value.

Statement of Ethics

This study protocol was reviewed and approved by the Central Institutional Review Board of the Hong Kong Hospital Authority (reference number: CIRB-2025-101-2). Waiver of informed consent was granted by the ethics committee due to the retrospective nature of the study.

Conflict of Interest

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

Funding

None.

Author Contributions

Conceptualization, JCHC (James C.H. Chow), JCHC (Jeffrey C.H. Chan), JYKC, GTCC, KMC, LTYL, KHW, KHA; Investigation and methodology, JCHC (James C.H. Chow), JCFL, CKCT, AHPT; Writing of the original draft, JCHC (James C.H. Chow); Reviewing and editing, all authors; Data curation, JCHC (James C.H. Chow), JCFL, CKCT, AHPT; Approval of 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.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2025.00346.

References

1. Ganti AK, Klein AB, Cotarla I, Seal B, Chou E. Update of incidence, prevalence, survival, and initial treatment in patients with non-small cell lung cancer in the US. JAMA Oncol 2021;7:1824–32.
2. Jumeau R, Vilotte F, Durham AD, Ozsahin EM. Current landscape of palliative radiotherapy for non-small-cell lung cancer. Transl Lung Cancer Res 2019;8(Suppl 2):S192–201.
3. King J, Patel K, Woolf D, Hatton MQ. The use of palliative radiotherapy in the treatment of lung cancer. Clin Oncol (R Coll Radiol) 2022;34:761–70.
4. Macbeth FR, Bolger JJ, Hopwood P, et al. Randomized trial of palliative two-fraction versus more intensive 13-fraction radiotherapy for patients with inoperable non-small cell lung cancer and good performance status. Medical Research Council Lung Cancer Working Party. Clin Oncol (R Coll Radiol) 1996;8:167–75.
5. Fairchild A, Harris K, Barnes E, et al. Palliative thoracic radiotherapy for lung cancer: a systematic review. J Clin Oncol 2008;26:4001–11.
6. Hughes RT, Helis CA, Soike MH, Levine BJ, Farris M, Blackstock AW. Moderately hypofractionated radiotherapy alone for stage I-IIB non-small cell lung cancer. Cureus 2019;11:e4969.
7. Rock C, Sood S, Cao Y, Shelton S, Chen RC, Wang F. Ten fraction hypofractionated stereotactic body radiotherapy for the management of ultracentral lung tumors: a retrospective analysis of dosimetry, outcomes, and toxicity. Radiat Oncol 2023;18:128.
8. Stephens SJ, Moravan MJ, Salama JK. Managing patients with oligometastatic non-small-cell lung cancer. J Oncol Pract 2018;14:23–31.
9. Guckenberger M, Andratschke N, Dieckmann K, et al. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. Radiother Oncol 2017;124:11–7.
10. Rodrigues G, Videtic GM, Sur R, et al. Palliative thoracic radiotherapy in lung cancer: an American Society for Radiation Oncology evidence-based clinical practice guideline. Pract Radiat Oncol 2011;1:60–71.
11. The Royal College of Radiologists. Radiotherapy dose fractionation. 4th ed. London: The Royal College of Radiologists; 2024.
12. Soliman H, Cheung P, Yeung L, et al. Accelerated hypofractionated radiotherapy for early-stage non-small-cell lung cancer: long-term results. Int J Radiat Oncol Biol Phys 2011;79:459–65.
13. Bonfili P, Di Staso M, Gravina GL, et al. Hypofractionated radical radiotherapy in elderly patients with medically inoperable stage I-II non-small-cell lung cancer. Lung Cancer 2010;67:81–5.
14. Oh D, Ahn YC, Kim B, Pyo H. Hypofractionated three-dimensional conformal radiation therapy alone for centrally located cT1-3N0 non-small-cell lung cancer. J Thorac Oncol 2013;8:624–9.
15. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. J Clin Oncol 2020;38:2830–8.
16. Bezjak A, Paulus R, Gaspar LE, et al. Safety and efficacy of a five-fraction stereotactic body radiotherapy schedule for centrally located non-small-cell lung cancer: NRG Oncology/RTOG 0813 Trial. J Clin Oncol 2019;37:1316–25.
17. Giuliani ME, Filion E, Faria S, et al. Stereotactic radiation for ultra-central non-small cell lung cancer: a safety and efficacy trial (SUNSET). Int J Radiat Oncol Biol Phys 2024;120:669–77.
18. Levy A, Adebahr S, Hurkmans C, et al. Stereotactic body radiotherapy for centrally located inoperable early-stage NSCLC: EORTC 22113-08113 LungTech phase II trial results. J Thorac Oncol 2024;19:1297–309.
19. Lindberg S, Grozman V, Karlsson K, et al. Expanded HILUS trial: a pooled analysis of risk factors for toxicity from stereotactic body radiation therapy of central and ultracentral lung tumors. Int J Radiat Oncol Biol Phys 2023;117:1222–31.
20. Verma V, Shostrom VK, Kumar SS, et al. Multi-institutional experience of stereotactic body radiotherapy for large (>/=5 centimeters) non-small cell lung tumors. Cancer 2017;123:688–96.
21. Louie AV, Granton PV, Fairchild A, et al. Palliative radiation for advanced central lung tumors with intentional avoidance of the esophagus (PROACTIVE): a phase 3 randomized clinical trial. JAMA Oncol 2022;8:1–7.
22. Pierson C, Grinchak T, Sokolovic C, et al. Response Criteria in Solid Tumors (PERCIST/RECIST) and SUV(max) in early-stage non-small cell lung cancer patients treated with stereotactic body radiotherapy. Radiat Oncol 2018;13:34.

ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2025;43(4):195-205
https://doi.org/10.3857/roj.2025.00416

Machine learning–based prediction of severe oral mucositis from head and neck cancer radiation therapy

Kanyapat Buasawat[1], Sasikarn Chamchod[1,2], Todsaporn Fuangrod[1], Sawanee Suntiwong[2], Kiattiyot Chantarak[1], Pasit Jarutatsanangkoon[1], Thiansin Liamsuwan[1]

[1]*Princess Srisavangavadhana Faculty of Medicine, Chulabhorn Royal Academy, Bangkok, Thailand*
[2]*Department of Radiation Oncology, Chulabhorn Hospital, Chulabhorn Royal Academy, Bangkok, Thailand*

Received: July 11, 2025
Revised: August 12, 2025
Accepted: August 14, 2025

Correspondence:
Thiansin Liamsuwan
Princess Srisavangavadhana Faculty of Medicine, Chulabhorn Royal Academy, 906 Kampangpetch 6 Rd., Talat Bang Khen, Lak Si, Bangkok 10210 Thailand
Tel: +66-25766000
E-mail: thiansin.lia@cra.ac.th
ORCID:
https://orcid.org/0000-0002-7453-3024

Purpose: This study aimed to develop prediction models for severe oral mucositis (OM) (grade ≥ 3) from head and neck cancer (HNC) radiotherapy (RT) using machine learning (ML) techniques and different types of features, including clinical, dose-volume metric, and radiomic features.

Materials and Methods: Retrospective data of 148 HNC RT patients were collected and randomly divided into 80% training and 20% test datasets. Sixteen combinations of feature selection and classification algorithms were used for modeling with different combinations of feature types. The model performance was evaluated using a confusion matrix and the area under the receiver operating characteristic curve (AUROC). The difference in the error rates obtained from any pair of modeling approaches were evaluated with McNemar's test.

Results: The best-performing model was based on the random forest classifier and minimum redundancy maximum relevance feature selection algorithm, achieving the accuracy of 0.930 (95% confidence interval [CI], 0.926 to 0.933) and AUROC of 0.901 (95% CI, 0.897 to 0.905). For this model, $D_{45\%}$ of the oral cavity, subsite, V_{75Gy} of the parotid glands and total dose to the target were found to be the most important features. All modeling approaches achieved the accuracy and AUROC of at least 0.756 and 0.722 and the error rates obtained by all modeling approaches were insignificantly different.

Conclusion: The inclusion of clinical and dose-volumetric features were most promising for ML-based prediction of severe OM, although information obtained prior to dose calculation (clinical or radiomic) may also be used exclusively with insignificantly different error rates.

Keywords: Head and neck neoplasm, Stomatitis, Machine learning, Radiomics

Introduction

Radiotherapy (RT) is an important treatment modality for head and neck cancer (HNC) that can preserve organs, control tumors, and sterilize microscopic tumor lesions spreading beyond surgical margins [1]. Although the goal of RT is to control tumors while sparing normal tissues surrounding the tumors, many patients receive high doses of radiation in large areas, which can cause complications [2]. One of the most common complications from HNC RT is oral mucositis (OM), which impacts on the patient's quality of life and the continuation of treatment [3]. OM, which is an acute toxicity, is a normal tissue injury that can occur when the oral cavity is exposed to radiation doses of around 15–20 Gy of standard fractionated radiotherapy [4]. OM can lead to oral pain, weight loss, dysphagia, feeding tube insertion, hospitalization, and treatment hold [3].

Traditionally, prediction of OM from RT is done using normal tissue complication probability (NTCP) models, which are usually

Copyright © 2025 The Korean Society for Radiation Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

based on dose-volume metric predictors associated with oral cavity dose [5-8] and parotid glands dose [9]. However, other factors may also affect the occurrence of OM due to complex interactions of biological, physical, and clinical factors. Some studies found that factors, such as, age, sex, comorbidities, body mass index (BMI) before radiation, RT technique, and smoking status were important for predicting severe OM [9-15].

In recent years, increase of beneficial clinical data and computation power have led to the growing applications of artificial intelligence (AI) and machine learning (ML) in radiotherapy. Additionally, there is growing interest in using ML to predict toxicity as it has been shown to have higher prediction performance than using traditional mathematical calculation models [16]. Apart from clinical and dose-volume metric features, radiomic features obtained from medical images, such as, computed tomography (CT) and magnetic resonance (MR) images have been shown to be useful in prognostic and predictive modeling [17].

Development of conventional NTCP models for severe OM have been extensively studied [5-7,9-12,14,15]. However, only two ML-based models have been proposed: one using clinical and dose-volume metric features [12] and the other using clinical, dose-volume metric, and radiomic features [14]. The latter study included only 49 samples and only a single classifier and feature selection method was implemented.

In this study, we aimed to develop and compare ML-based prediction models for severe OM (grade ≥ 3) based on different ML-based classifiers and feature selection algorithms using a collection of clinical, dose-volume metric and radiomic features, and also to investigate whether using a single type of features alone (clinical, dose-volumetric, or radiomic features) would be effective for severe OM prediction.

Materials and Methods

1. Patient cohort and endpoint

The flow diagram of this work is shown in Fig. 1. Retrospective data of 148 HNC patients treated with intensity modulated radiation therapy (IMRT) or volumetric modulated arc radiation therapy (VMAT) during 2016–2023 at Chulabhorn Hospital were collected. The study was approved by the Human Research Ethics Committee, Chulabhorn Royal Academy (Project Code EC 026/2566). Patient demographics and characteristics are listed in Table 1. The prescribed dose ranged from 60.00 to 74.24 Gy with 2.0–2.2 Gy per fraction and 30–35 fractions. The dose constraints used for treatment planning are shown in Table 2. Toxicity was evaluated weekly during the treatment using Radiation Therapy Oncology Group (RTOG) criteria by treating radiation oncologists (ROs) with 3–15 years of clinical experience. The endpoint was the occurrence of severe OM (grade ≥ 3) at any time during the treatment. The RTOG grading criteria are as follows: grade 0, no findings; grade 1, painless ulcers, erythema, or mild soreness; grade 2, painful erythema, edema, or ulcers, but can eat; grade 3, painful erythema, edema, or ulcers and cannot eat; and grade 4, requires parenteral or enteral support [18].

The inclusion criteria were first-time histologically confirmed diagnosis of squamous cell carcinoma HNC, treatment with IMRT or VMAT with a curative aim, completion of the prescribed RT course, and availability of weekly toxicity evaluations. Exclusion criteria were patients having OM before RT initiation, treatment re-planning before severe OM occurred and dental CT metal artifacts.

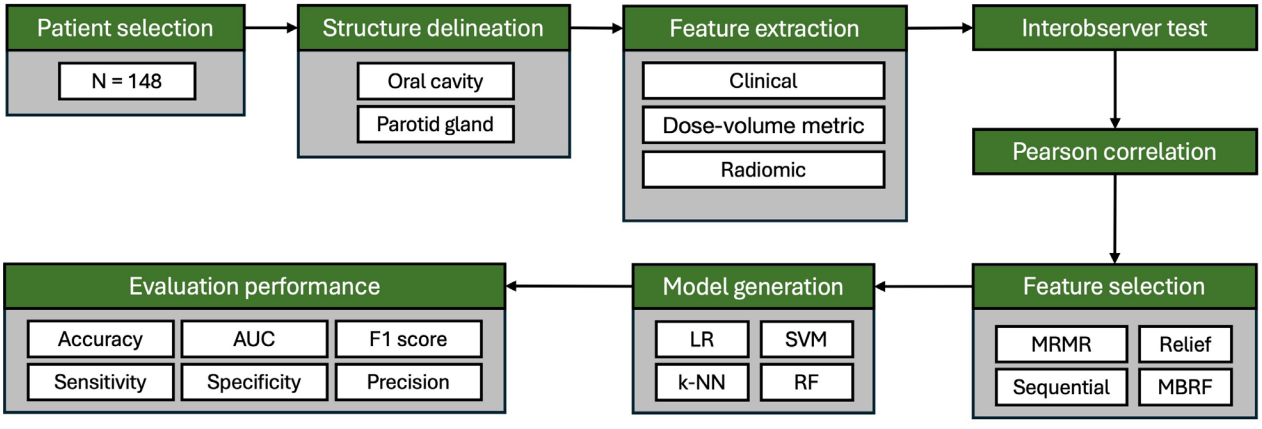

Fig. 1. The flow diagram of this work. LR, logistic regression; AUC, area under the curve; SVM, support vector machine; k-NN, k-nearest neighbors; RF, random forest; MRMR, minimum redundancy maximum relevance; MBRF, model-based permuted predictor importance for random forest.

https://doi.org/10.3857/roj.2025.00416

Table 1. Patient demographics and characteristics

Characteristic	All data (n = 148)	Training data (n = 119)	Test data (n = 29)
Oral mucositis			
Grade < 3	98 (66.2)	79 (66.4)	19 (65.5)
Grade ≥ 3	50 (33.8)	40 (33.6)	10 (34.5)
Sex			
Male	115 (77.7)	91 (76.5)	24 (82.8)
Female	33 (22.3)	28 (23.5)	5 (17.2)
Age (year)			
Range	19–89	29–89	19–81
Median	59	60	56
Subsite			
Oral cavity	56 (37.8)	42 (35.3)	14 (48.3)
Nasopharynx	33 (22.3)	26 (21.8)	7 (24.1)
Oropharynx	19 (12.9)	17 (14.3)	2 (6.9)
Hypopharynx	16 (10.8)	14 (11.8)	2 (6.9)
Larynx	17 (11.5)	16 (13.5)	1 (3.5)
Other	7 (4.7)	4 (3.4)	3 (10.3)
Treatment			
Postop RT	46 (31.1)	37 (31.1)	9 (31.0)
Definitive RT	102 (68.9)	82 (68.9)	20 (69.0)
Prescribed dose (Gy)			
Prescribed dose	60.00–74.24	60.00–74.24	60.00–74.24
Median	70.00	69.99	69.96
Chemotherapy			
Yes	110 (74.3)	91 (76.5)	19 (65.5)
No	38 (25.7)	28 (23.5)	10 (34.5)
Techniques			
IMRT	8 (5.4)	7 (5.9)	1 (3.5)
VMAT	140 (94.6)	112 (94.1)	28 (96.5)
BMI (kg/m^2)			
Underweight (< 18.5)	32 (21.6)	26 (21.9)	6 (20.7)
Normal (18.5–24.9)	68 (45.9)	56 (47.1)	12 (41.4)
Overweight (≥ 25.0)	47 (31.8)	36 (30.2)	11 (37.9)
No data	1 (0.7)	1 (0.8)	0 (0)
Retropharyngeal lymph node			
Bilateral	2 (1.4)	2 (1.7)	0 (0)
Unilateral	11 (7.4)	9 (7.5)	2 (6.9)
None	135 (91.2)	108 (90.8)	27 (93.1)

RT, radiation therapy; IMRT, intensity modulated radiation therapy; VMAT, volumetric modulated arc therapy; BMI, body mass index.

2. Imaging and structure delineation

The CT images were acquired pre-treatment for each patient. Three different CT machines were used, including Philips Brilliance Big Bore (n = 135), Siemens SOMATOM go.Open Pro (n = 11), and Siemens Biograph 64 (n = 2). For each CT scanner, the CT Hounsfield unit (HU) calibration was performed using Gammex 467 Tissue Characterization Phantom (Gammex Inc., Middleton, WI, USA) or Advanced Electron Density Phantom (Sun Nuclear Corp., Melbourne, FL, USA) to ensure correct electron densities to be used in dose calculation. The CT protocol included fixed parameters, namely, 512 × 512 pixels, 3 mm slice thickness, 1.2 mm pixel size and 120 kV, as well as variable parameters including the tube current-exposure time product of 245 ± 32 mAs and 50–70 cm^3 contrast agent. For Philips Brilliance Big Bore, most of the scans used a fixed 250 mAs, while for the other two scanners the mAs was automatically modulated across different areas of the body with varying thicknesses. The amount of contrast agent was adjusted based on patient weight for consistent image quality.

Parotid glands were manually delineated during the planning stage by the treating ROs. The oral cavity was originally not delineated. Therefore, in this work, an experienced RO with ≥ 15 years of experience manually delineated the oral cavity for all patients.

Table 2. Dose constraints used for IMRT and VMAT planning

Structure	Objective (major, Gy)	Variation (minor, Gy)
CTV 70	$D_{100\%} \geq 70$	$D_{100\%} \geq 68.6$
CTV 59.4	$D_{100\%} \geq 59.4$	$D_{100\%} \geq 58.2$
CTV 54	$D_{100\%} \geq 54$	$D_{100\%} \geq 52.9$
PTV 70	$D_{95\%} \geq 70$	$D_{95\%} \geq 66.5$
PTV 59.4	$D_{95\%} \geq 59.4$	$D_{95\%} \geq 56.43$
PTV 54	$D_{95\%} \geq 54$	$D_{95\%} \geq 51.3$
Brainstem	$D_{max} < 54$	$D_{1cc} < 59$
Spinal cord	$D_{max} < 45$	
Cochlea Lt and Rt	$D_{mean} < 45$	$D_{mean} < 50$
	$D_{max} \leq 55$	$D_{5\%} < 55$
Eyes	$D_{mean} < 35$	
	$D_{max} < 50$	
Internal acoustic canal Lt and Rt	$D_{mean} < 45$	
	$D_{max} \leq 54$	
Larynx	$D_{mean} < 44$	
Lips	$D_{mean} < 30$	$D_{mean} < 50$
Lens	$D_{max} < 10$	
Oral cavity	$D_{mean} < 40$	$D_{mean} < 45$
Optic nerve Lt and Rt	$D_{max} < 54$	
Optic chiasm	$D_{max} < 54$	
Parotid gland Lt and Rt	$D_{mean} < 26$	$D_{50\%} < 30$
Superficial parotid lobe Lt and Rt	$D_{mean} < 26$	$D_{50\%} < 30$
Temporal lobe Lt and Rt	$D_{max} < 70$	$D_{max} < 72$
		$D_{1cc} < 65$
Temporomandibular joint Lt and Rt	$D_{1cc} < 75$	

IMRT, intensity modulated radiation therapy; VMAT, volumetric modulated arc therapy; CTV, clinical target volume; PTV, planning target volume; Lt, left side; Rt, right side; $D_{x\%}$, dose received by x% of the volume; D_{1cc}, maximum dose received by 1 cm^3 of the volume.

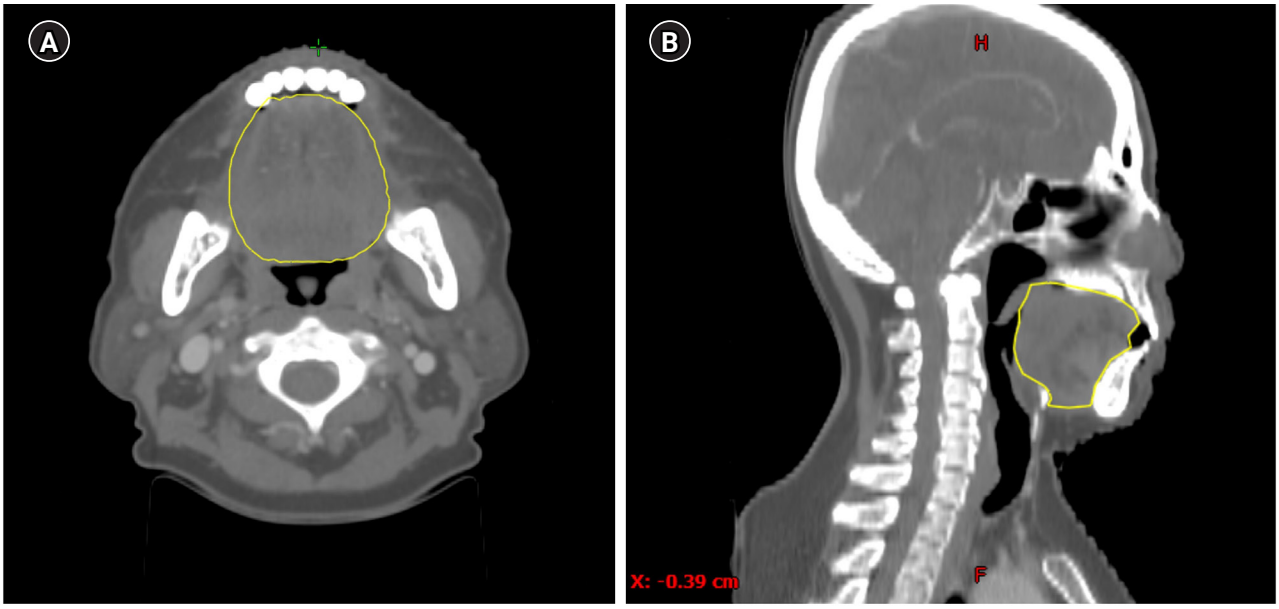

Fig. 2. Example of the delineation of oral cavity structures: (A) axial view and (B) sagittal view.

Fig. 2 shows an example of the delineation of oral cavity structures in CT images. The delineation of the extended oral cavity was partly based on Hoebers et al. [19]. For simplicity and consistency, the extended oral cavity was defined as the area posterior to the internal arches of the mandible and maxilla. This extended oral cavity could be subdivided into the oral tongue and the anterior oropharynx by drawing a vertical line from the posterior hard palate to the hyoid bone, known as the circumvallate line.

3. Feature extraction

The candidate predictors for severe OM were categorized into clinical, dose-volume metric, and radiomic feature types, in total 301 features, as given in the supplementary file. Clinical features included sex, age, tumor subsite, T category, N category, treatment type, concurrent chemotherapy, RT technique, number of fractions, BMI before RT, status of retropharyngeal lymph node metastasis, oral cavity volume, and parotid gland volume. Dose-volume metric features extracted from the treatment plans included the total dose to the target, dose per fraction, D_{max}, D_{min}, D_{mean}, $D_{5\%}$ – $D_{95\%}$ in 10% increments, and $V_{10\ Gy}$ – V_{75Gy} in 5 Gy increments for the oral cavity and parotid glands. The clinical features, toxicity scores, and dose-volume metric features were recorded from the Hospital Information System and Eclipse treatment planning system version 13.6 (Varian Medical Systems, Palo Alto, CA, USA).

Radiomic features for each organ were extracted from the CT images using AccuContour AI-assisted Auto-delineation Tool version 3.1 (Manteia Data Technologies Ltd, Milwaukee, WI, USA), including 14 shape, 18 first-order, and 75 texture-order features (a total of 107 features for each organ of interest). For patients who underwent re-planning after having severe OM, dose-volume metrics and radiomic features were extracted from the original treatment plan. No preprocessing of the CT images was performed. The radiomic plugin of AccuContour was PyRadiomics [20]. Most features extracted by PyRadiomics followed feature definitions as described by the Imaging Biomarker Standardization Initiative (IBSI) [21]. Some differences arose where several equally valid alternatives existed, for which PyRadiomics opted for the one alternative, while the IBSI standard recommended another [21].

It is to note that since parotid gland segmentation was performed by several treating ROs and radiomic features were directly related to organ contours, we have performed a robustness test of parotid gland radiomic features in terms of interobserver delineation variability in our previous study based on the intraclass correlation coefficient (ICC) [22]. In that study, parotid gland radiomic features derived from the contours made by three observers were compared as follows: (1) treating ROs vs. a selected RO; (2) treating ROs vs. AI-based autosegmentation using the AccuContour software; (3) a selected RO vs. autosegmentation; and (4) all three observers (treating ROs, a selected RO, and autosegmentation). Of 107 parotid gland radiomic features, the majority of the shape features were found to be robust but also mostly correlated, while most of the first-order and texture features tended to be susceptible to delineation variability. Based on that work, only 42 parotid gland radiomic features that passed the robustness test, i.e., having the ICC of at least 0.75, were included in this study.

https://doi.org/10.3857/roj.2025.00416

4. Model development

The entire dataset was randomly divided into 80% training and 20% test datasets. The random split was conducted until the proportions of severe and non-severe OM cases were similar across the entire, training, and test datasets, as shown in Table 1. For model training, five-fold cross-validation was performed on the training dataset, as explained later in this section. Four modeling approaches were carried out: the approaches A–C using either the clinical features, dose-volume metric features, or radiomic features, respectively, and the approach D pooling all types of features initially before the feature selection process. The latter approach demonstrated the full pool of variables typically done for modeling multivariate radiation-induced toxicity risks [23].

MATLAB version R2023a (MathWorks Inc., Natick, MA, USA) was used for modeling and statistical analysis throughout this study. The Pearson correlation analysis was used to assess the relationship between dose-volume metric and radiomic features. For a pair of features with strong correlation ($r \geq 0.80$), only one of the features was selected for the modeling to mitigate multicollinearity, redundancy, and model instability. Then, four feature selection algorithms were employed to reduce model overfitting, including (1) minimum redundancy maximum relevance (MRMR) (function "fscmrmr"), (2) Relief (function "relieff"), (3) sequential (function "sequentialfs"), and (4) model-based permuted predictor importance for random forest (MBRF) (function "oobPermutedPredictorImportance") [24].

Additionally, four ML classification algorithms were used for the modeling, namely, (1) logistic regression (LR) (function "fitglm"), (2) support vector machine (SVM) (function "fitcsvm"), (3) k-nearest neighbors (k-NN) (function "fitcknn"), and (4) random forest (RF) (function "fitcensemble") [24]. As a result, each classification algorithm was paired with four feature selection methods, resulting in 16 scenarios for each modeling approach, i.e., a total of 64 models for the investigation.

Regarding feature selection, MRMR, Relief, and MBRF used statistical measures to assign an importance score to each feature, while the sequential algorithm selected a subset of features that best predicted the outcome by sequentially forward selection of features until there was no improvement in prediction. For the algorithms that ranked feature importance scores (MRMR, Relief, and MBRF), only features with non-zero importance scores were considered. Then, all sets of most important features were used for training the ML model. For example, if there were *n* features with non-zero importance scores, *n* sets of most important features with the number of elements ranging from 1 to *n*, were used to train an ML model. The model hyperparameters were randomly searched for 30 times. For each set of features and hyperparameters, the model was trained using five-fold cross-validation. The set of features and hyperparameters that gave the highest accuracy and F1 score from the five-fold cross-validation was used in the final model of each modeling approach.

It is also to note that for filter-typed feature selection algorithms, i.e., MRMR and Relief, the same set of features was first selected by the algorithm regardless of which ML algorithm was used for training. However, since we implemented the sequential selection of the most important features in the model training, the final set of selected features may be different depending on the ML algorithm used, as shown in the supplementary file.

5. Model evaluation

To evaluate the model performance during model training with five-fold cross-validation and blind testing on the test dataset, we generated a confusion matrix containing the following elements. True positive (TP): The number of events in which the actual values and the predicted values are both positive; false positive (FP): The number of events in which the actual values are negative, but the predicted values are positive; false negative (FN): The number of events in which the actual values are positive, but the predicted values are negative; true negative (TN): The number of events in which the actual values and the predicted values are both negative.

The performance metrics considered in this study included:

·Accuracy, or the fraction of correct prediction, calculated from:

$$\text{Accuracy} = \frac{(\text{TP} + \text{TN})}{(\text{TP} + \text{TN} + \text{FP} + \text{FN})} \quad (1)$$

·Precision, or the ability of the classifier to correctly label positive values:

$$\text{Precision} = \frac{(\text{TP})}{(\text{TP} + \text{FP})} \quad (2)$$

·Sensitivity, which is the synonym of the recall and TP rate, showing the ability of the model to find all positive value, given by:

$$\text{Sensitivity} = \frac{(\text{TP})}{(\text{TP} + \text{FN})} \quad (3)$$

·Specificity, which is the synonym of the TN rate, demonstrating the ability of the model to correctly identify negative values out of all actual negative values, given by:

$$\text{Specificity} = \frac{(\text{TN})}{(\text{TN} + \text{FP})} \quad (4)$$

·F1 score, or a weighted average of the precision and sensitivity metrics, which can be written as:

$$\text{F1 score} = 2 \times \frac{(\text{Precision} \times \text{Sensitivity})}{(\text{Precision} + \text{Sensitivity})} \quad (5)$$

·Area under the receiver operating characteristic curve (AUROC), which is commonly used to visualize the performance of a binary classifier [25]. The receiver operating characteristic curve is the plot of the sensitivity versus the FP rate. The latter was calculated from:

$$\text{False positive rate} = \frac{(\text{FP})}{(\text{FP} + \text{TN})} \quad (6)$$

The closer the AUROC is to 1, the better the classification model is.

For model testing, the model with the highest AUROC and accuracy on the test dataset was considered the best model of each modeling approach. Confidence intervals (CI) of the model performance metrics were evaluated by conducting bootstrapping (n = 1,000) on the test dataset. The 95% CI provided a measure of the uncertainty associated with the model prediction.

Moreover, we investigated if there was statistically significant difference between the error rates produced by any pair of models using McNemar's test (α = 0.05) [26]. A p-value exceeding 0.05 suggested that there was no statistically significant difference between the error rates produced by both models.

Finally, to identify the feature importance that was comparable between models, the mean absolute Shapley values were calculated using the "shapley" function in MATLAB. The Shapley value of a feature at a chosen query point corresponds to the deviation of the prediction from the average prediction due to that feature [27]. A query point refers to a row of input features for the model. In this work, we used all data (training and test data) as query points and evaluated the mean absolute Shapley values. A feature with a larger contribution to the output of the model resulted in a higher mean absolute Shapley value.

Results

The selected features, hyperparameters, and model performance of all 64 final models are given in the supplementary file. Tables 3 and 4 show the performance metrics of the best model of each modeling approach obtained from the five-fold cross-validation and blind testing, respectively. Fig. 3 shows the mean absolute Shapley value to demonstrate the feature importance for the best-performing model of each modeling approach. The subsite was commonly found to contribute to the prediction of the models that included clinical features (models A and D). Similarly, $D_{45\%}$ of the oral cavity was commonly found to be one of the largest contributors to the

Table 3. Performance of the best-performing model of each modeling approach obtained from the five-fold cross-validation

Modeling approach	Included features	Best-performing model	Acc	AUROC	F1 score	TPR	TNR	Precis
A	Only clinical features	RF-MBRF	0.792	0.883	0.737	0.875	0.875	0.636
B	Only dose-volume metric features	RF-MRMR	0.833	0.840	0.778	0.875	0.813	0.700
C	Only radiomic features	RF-MBRF	0.792	0.766	0.706	0.750	1.000	1.000
D	All features (before feature selection process)	RF-MRMR	0.875	0.895	0.938	0.857	0.800	0.750

Acc, accuracy; AUROC, area under the receiver operating characteristic curve; TPR, true positive rate; TNR, true negative rate; Precis, precision; RF, random forest; MBRF, model-based permuted predictor importance of random forest classification; MRMR, minimum redundancy maximum relevance.

Table 4. Performance of the best-performing model of each modeling approach on the test dataset

Modeling approach	Included features	Best-performing model	Acc	AUROC	F1 score	TPR	TNR	Precis
A	Only clinical features	RF-MBRF	0.756 (0.751–0.761)	0.722 (0.716–0.727)	0.623 (0.615–0.631)	0.606 (0.595–0.615)	0.838 (0.833–0.843)	0.670 (0.659–0.681)
B	Only dose-volume metric features	RF-MRMR	0.825 (0.820–0.829)	0.798 (0.792–0.803)	0.729 (0.721–0.736)	0.703 (0.694–0.713)	0.892 (0.888–0.897)	0.780 (0.769–0.788)
C	Only radiomic features	RF-MBRF	0.791 (0.786–0.796)	0.747 (0.742–0.752)	0.656 (0.647–0.665)	0.598 (0.589–0.609)	0.896 (0.892–0.900)	0.758 (0.747–0.767)
D	All features (before feature selection process)	RF-MRMR	0.930 (0.926–0.933)	0.901 (0.897–0.905)	0.884 (0.879–0.889)	0.802 (0.795–0.810)	1.000 (1.000–1.000)	1.000 (1.000–1.000)

The values outside the parentheses are the averages and those in the parentheses are 95% confidence intervals.
Acc, accuracy; AUROC, area under the receiver operating characteristic curve; TPR, true positive rate; TNR, true negative rate; Precis, precision; RF, random forest; MBRF, model-based permuted predictor importance of random forest classification; MRMR, minimum redundancy maximum relevance.

https://doi.org/10.3857/roj.2025.00416

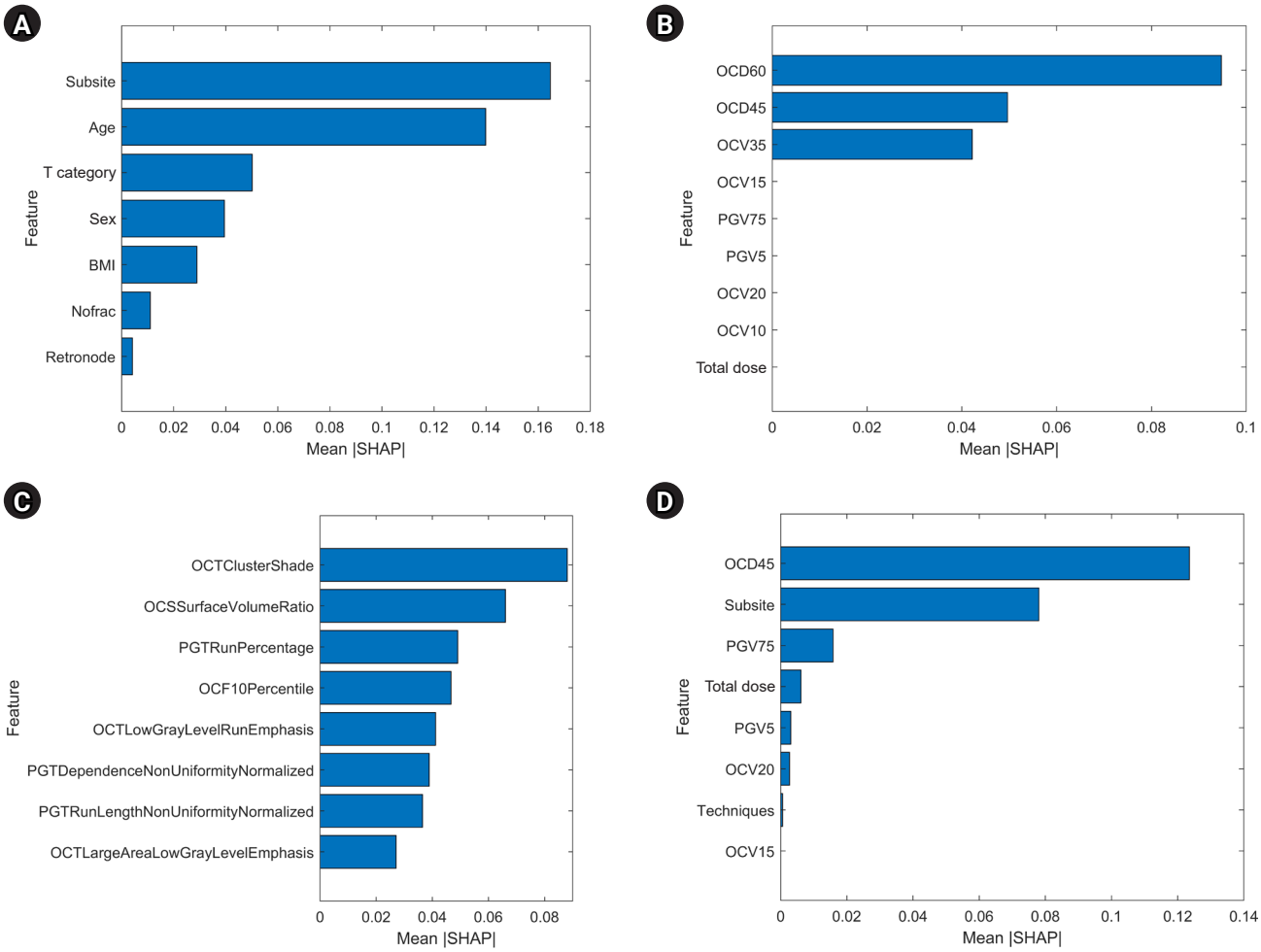

Fig. 3. Shapley values to demonstrate the feature importance for the modeling approaches A–D (panels A–D, respectively). In the feature names, "Nofrac" stands for the number of fractions, while "PG" and "OC" in the first two letters of the feature names denote the parotid gland and oral cavity, respectively. BMI, body mass index; OCD, oral cavity dose; OCV, oral cavity volume; PGV, parotid gland volume; OCT, oral cavity texture feature; OCS, oral cavity shape feature; PGT, parotid gland texture feature; OCF, oral cavity first-order feature.

prediction of the models that included dose-volumetric features (models B and D).

The overall best-performing model was the approach D with the RF classifier and the MRMR feature selection algorithm. This model achieved the highest accuracy and AUROC of 0.930 (95% CI, 0.926 to 0.933) and 0.901 (95% CI, 0.897 to 0.905), respectively. The most important features were $D_{45\%}$ of the oral cavity, the subsite, V_{75Gy} of the parotid glands, the total dose to the target, V_{5Gy} of the parotid glands, V_{20Gy} of the oral cavity, and the RT technique, respectively (Fig. 3).

As shown in Table 4, the best-performing model of each modeling approach was based on the RF classifier with either the MRMR or MBRF feature selection algorithm. All modeling approaches could achieve the AUROCs of at least 0.722 with the numbers of selected features ranging from 8 to 9.

Table 5. The p-values obtained from the comparison between the error rates produced by any pair of models using McNemar's test

Model	B	C	D
A	0.727	1.000	0.125
B		1.000	0.250
C			0.219

Table 5 shows the p-values obtained from the comparison between the error rates produced by any pair of models using McNemar's test. We found that the differences in the error rates between any pair of modeling approaches were not statistically significant ($p > 0.05$).

For the overall best-performing model (approach D), for which $D_{45\%}$ of the oral cavity (OCD45) was identified as the most important dose-volumetric feature (Fig. 3), we further explored a dose

constraint that could help to avoid severe OM. In this analysis, we investigated the threshold for OCD45, above which the prediction was likely to be positive (severe OM) (predicted positive rate ≥ 0.5) and the model was likely to classify correctly (AUROC ≥ 0.7).

Fig. 4 shows the plot of the predicted positive rate and AUROC against the threshold for OCD45. Based on this assumption, OCD45 ≥ ~54 Gy was likely to result in severe OM. Therefore, the recommended constraint for $D_{45\%}$ of the oral cavity could be 54 Gy.

Discussion and Conclusion

This study focused on developing ML-based prediction models for severe OM (grade ≥ 3) from HNC IMRT or VMAT using four modeling approaches based on different types of features (clinical, dose-volume metric, and radiomic). Model training was done using four different ML classifiers (LR, SVM, k-NN, and RF) coupled with four different feature selection algorithms (MRMR, relief, sequential, and MBRF).

The process of feature selection was crucial for minimizing the number of irrelevant and redundant features by selecting the most informative predictors, resulting in improvement of the model performance. In this work, we found that the RF classifier coupled with either the MRMR or MBRF feature selection algorithm showed the best performance for all modeling approaches, with the number of selected features in the range of 8–9.

Fig. 3 indicated that the subsite was an important clinical feature, as it was the only clinical feature consistently selected by all models that included clinical features. Although most of our data had oral cavity cancer (37.8%), the proportions of other subsites were not negligibly small, e.g., 22.3% had cancer in the nasopharynx and 12.8% in the oropharynx. Our findings that the subsite was the important feature aligned with that reported by Elting et al. [28] that the risk of developing OM was higher in those who had oral cavity or oropharynx primaries compared with those with larynx or hypopharynx primaries (99% vs. 64%; $p < 0.001$). Additionally, $D_{45\%}$ of the oral cavity was found to be the important dose-volume metric feature consistently selected by both the approaches B and D.

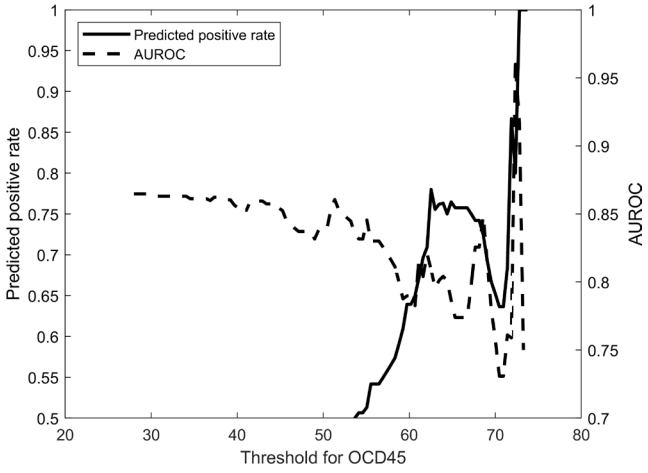

Fig. 4. Predicted positive rate and area under the receiver operating characteristic curve (AUROC) against the threshold for $D_{45\%}$ of the oral cavity (OCD45).

The modeling approach D, which performed best, demonstrated the full pool of variables similar to development of multivariate radiation-induced toxicity risk prediction models that usually included a pool of clinical and dose-volumetric features [23]. The addition of radiomic features may have offered the opportunity to improve the performance of the predictive model. However, due to our feature selection strategy and the random selection of the hyperparameters used for training the models, the final set of features of the overall best-performing model (approach D) did not contain any radiomic features.

Among all the classification algorithms investigated, the RF classifier yielded the best performance for all modeling approaches. RF selected and scored features after passing through the initial feature selection process, which may seem like a repetition of feature selection, resulting in the models choosing only the most crucial features for the prediction. This finding was consistent with the study of Dean et al. [12], who employed ML and spatial dose metrics to predict severe OM and demonstrated that RF emerged as the top-performing algorithm.

Overall, the models developed using dose-volume metric features (approaches B and D) achieved the accuracies and AUROCs in the ranges of 0.825–0.930 and 0.798–0.901, respectively, while those neglecting dose-volume metric features (approaches A and C) yielded the accuracies and AUROCs in the ranges of 0.756–0.791 and 0.722–0.747, respectively. This result indicated that in the absence of dose-volume metric features, the models showed slightly lower performance compared to the models that included dose-volume metric features. Nevertheless, from McNemar's test, the error rates between any pair of modeling approaches were not significantly different.

Comparing with the other similar studies, our best-performing model (approach D with RF and MRMR), which had the AUROC of 0.901, outperformed the previously reported conventional NTCP models with the AUROCs ranging from 0.62 to 0.84 [5,7,9-12,15]. Another similar study was that reported by Agheli et al. [14], who employed RF with MRMR feature selection and CT-based radiomic features combined with dose-volume metric and clinical features to predict severe OM during and 2 months after IMRT treatment. Their findings were similar to ours in terms of that using all feature

 https://doi.org/10.3857/roj.2025.00416

types with the RF classifier and MRMR feature selection algorithm yielded the best performance, with an AUROC of 0.92 and an accuracy of 0.90. In our study, we found that the models that used only dose-volume metric features were superior to those using only clinical or radiomic features. In contrast, in the study of Agheli et al. [14], the model that used only dose-volume metric features had the lowest performance. However, their model was trained only on 39 patients with 20 selected features, while our study used a larger cohort and the best model contained only eight features and yielded similar performance on the cross-validation and test datasets (0.67% difference in the AUROCs), as shown in Tables 3 and 4, respectively, which suggested that our model was not overfitted.

Considering the relatively high predictive performance of the final model (AUROC of 0.901), it may enable early prediction of severe OM during the treatment planning process. This can assist physicians in creating personalized and effective treatment plans, such as, adjusting the radiation dose to the oral cavity and parotid glands, providing supportive care in oral hygiene, administering medications like Difflam or Morphine to alleviate symptoms based on individual needs and risks, as well as selecting patients to a different treatment modality such as proton therapy. As exemplified in Fig. 4, a dose constraint of $D_{45\%}$ of the oral cavity of ~54 Gy could be recommended based on the high proportion of predicted positives together with the high AUROC values. A similar approach could be done with different thresholds of predicted positive rate and AUROC depending on the acceptance levels of each center.

Some limitations of this study should be mentioned. Firstly, it was a retrospective study, which lacked certain data that could contribute to the induction of OM, such as oral hygiene, comorbidities, smoking status, and salivary secretory function. This data was not typically recorded in our institution. In future studies, the development of a prospective study is essential to include additional data in the model development, which could potentially improve the predictive performance of the models.

Secondly, the radiomic features utilized in this study were limited to original features without any filtering techniques, such as, Laplace and Wavelet. Including filtering techniques may provide additional power in predicting outcomes, as they have the potential to capture specific anatomical characteristics that could contribute to the prediction process. Also, involving MR-based radiomic features in the modeling could improve the model performance, as has been shown by Sheikh et al. [29].

Another issue with radiomics was that different imaging protocols may affect radiomic feature values. Varghese et al. [30] reported that changes in slice thickness affected the reproducibility of radiomic features more intensely compared to other imaging variables, and changes in kVp and mAs affected mainly higher-order texture features, such as, image transformation. In this work, although three different CT scanners were used for the CT simulation, the CT HU calibration was performed for each CT scanner to ensure correct HUs. Moreover, most of other imaging variables were fixed except the tube current–exposure time product (mAs) and the amount of contrast agent. Regarding mAs, previous studies reported that variable mAs was unlikely to have a large effect on radiomic features extracted from CT images [31] and the most affected features were higher-order features [30] not included in this study. In addition, the effect of contrast agent on HNC IMRT planning has been reported to be tolerably small [32], reflecting the relatively similar HUs between CT images with and without contrast agent enhancement for this treatment site.

The imbalance between the proportions of negative and positive cases (66.2% vs. 33.8%) could hinder the developed models to effectively learn and predict positive results (severe OM) as accurately as negative results. Consequently, the true positive rate values of some of the modeling approaches were lower than the other metrics. Also, the data used in this study was from a single institution, thus, lacking external validation potentially introducing bias. Future work should address these limitations.

Lastly, there are several grading criteria for OM. The most used ones are those established by the World Health Organization (WHO) [33], the RTOG, and the US National Institutes of Health (Common Terminology Criteria for Adverse Events [CTCAE]) [34]. While the WHO scale was derived from functional and objective parameters, and the current version of the CTCAE criteria completely depend on the patient-reported outcome [18], the RTOG criteria require both patient and clinical input. The RTOG criteria were chosen in this work as they were applied in our clinic. Moreover, it has been reported that when severe OM was the primary outcome (grade $\geq$ 3 in the RTOG scale criteria), the three scales performed similarly, in contrast to when each score or the most severe form of OM (grade 4) were considered [18].

In summary, the best-performing model for predicting severe OM after IMRT or VMAT was based on the RF classifier and MRMR feature selection algorithm with the accuracy and AUROC of 0.930 and 0.901, respectively. For this model, $D_{45\%}$ of the oral cavity, subsite, V_{75Gy} of the parotid glands and the total dose to the target were identified as the most important features. The constraint for $D_{45\%}$ of the oral cavity at 54 Gy could be recommended from this study. Our results suggested that the inclusion of clinical and dose-volumetric features was most promising for ML-based prediction of severe OM, although information obtained prior to dose calculation (clinical or radiomic features) may also be used exclusively with insignificantly different error rates.

Statement of Ethics

The study protocol was reviewed and approved by the Human Research Ethics Committee, Chulabhorn Royal Academy (Project Code EC 026/2566). There is no informed consent as it was a retrospective study.

Conflict of Interest

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

Funding

KB acknowledges the Scholarship for Commemoration of the 60th Birthday of Her Royal Highness Princess Chulabhorn Krom Phra Srisavangavadhana for Development of Medical Physicists, Chulabhorn Royal Academy, Thailand (Contract No. 64/01). This work was supported by Chulabhorn Royal Academy, Thailand (Fundamental Fund: fiscal year 2023 by National Science Research and Innovation Fund) [Contract No. FRB660044/0240 Project code 180856].

Author Contributions

Conceptualization, KB, TL; Data curation, KB, SS, KC; Methodology (oral cavity delineation), SC; Methodology (radiomic feature extraction), KB, PJ; Data interpretation (demographics and toxicity grading), KB, TL, SC; Machine learning model development, KB; Formal analysis (ML model results), KB, TL, TF; Writing - original draft, KB, TL; Writing - review and editing, all authors; Approval of final manuscript, all authors.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material file. The MATLAB codes and the examples of input files for training and testing the models, as well as the trained models that support the findings of this study are openly available in GitHub at https://github.com/radsimbio/MINT_OM.

References

1. Yeh SA. Radiotherapy for head and neck cancer. Semin Plast Surg 2010;24:127–36.
2. Jham BC, da Silva Freire AR. Oral complications of radiotherapy in the head and neck. Braz J Otorhinolaryngol 2006;72:704–8.
3. Maria OM, Eliopoulos N, Muanza T. Radiation-induced oral mucositis. Front Oncol 2017;7:89.
4. Muanza TM, Cotrim AP, McAuliffe M, et al. Evaluation of radiation-induced oral mucositis by optical coherence tomography. Clin Cancer Res 2005;11:5121–7.
5. Bhide SA, Gulliford S, Schick U, et al. Dose-response analysis of acute oral mucositis and pharyngeal dysphagia in patients receiving induction chemotherapy followed by concomitant chemo-IMRT for head and neck cancer. Radiother Oncol 2012;103:88–91.
6. Otter S, Schick U, Gulliford S, et al. Evaluation of the risk of grade 3 oral and pharyngeal dysphagia using atlas-based method and multivariate analyses of individual patient dose distributions. Int J Radiat Oncol Biol Phys 2015;93:507–15.
7. Strigari L, Pedicini P, D'Andrea M, et al. A new model for predicting acute mucosal toxicity in head-and-neck cancer patients undergoing radiotherapy with altered schedules. Int J Radiat Oncol Biol Phys 2012;83:e697–702.
8. Kanehira T, van Kranen S, Jansen T, Hamming-Vrieze O, Al-Mamgani A, Sonke JJ. Comparisons of normal tissue complication probability models derived from planned and delivered dose for head and neck cancer patients. Radiother Oncol 2021;164:209–15.
9. Orlandi E, Iacovelli NA, Rancati T, et al. Multivariable model for predicting acute oral mucositis during combined imrt and chemotherapy for locally advanced nasopharyngeal cancer patients. Oral Oncol 2018;86:266–72.
10. Hansen CR, Bertelsen A, Zukauskaite R, et al. Prediction of radiation-induced mucositis of H&N cancer patients based on a large patient cohort. Radiother Oncol 2020;147:15–21.
11. Li PJ, Li KX, Jin T, et al. Predictive model and precaution for oral mucositis during chemo-radiotherapy in nasopharyngeal carcinoma patients. Front Oncol 2020;10:596822.
12. Dean JA, Wong KH, Welsh LC, et al. Normal tissue complication probability (NTCP) modelling using spatial dose metrics and machine learning methods for severe acute oral mucositis resulting from head and neck radiotherapy. Radiother Oncol 2016;120:21–7.
13. Dean JA, Welsh LC, Wong KH, et al. Normal tissue complication probability (NTCP) modelling of severe acute mucositis using a novel oral mucosal surface organ at risk. Clin Oncol (R Coll Radiol) 2017;29:263–73.
14. Agheli R, Siavashpour Z, Reiazi R, Azghandi S, Cheraghi S, Paydar R. Predicting severe radiation-induced oral mucositis in head and neck cancer patients using integrated baseline CT radiomic, dosimetry, and clinical features: a machine learning approach. Heliyon 2024;10:e24866.

 https://doi.org/10.3857/roj.2025.00416

15. Liu Z, Huang L, Wang H, et al. Predicting nomogram for severe oral mucositis in patients with nasopharyngeal carcinoma during intensity-modulated radiation therapy: a retrospective cohort study. Curr Oncol 2022;30:219–32.
16. Isaksson LJ, Pepa M, Zaffaroni M, et al. Machine learning-based models for prediction of toxicity outcomes in radiotherapy. Front Oncol 2020;10:790.
17. Gabrys HS, Buettner F, Sterzing F, Hauswald H, Bangert M. Design and selection of machine learning methods using radiomics and dosiomics for normal tissue complication probability modeling of xerostomia. Front Oncol 2018;8:35.
18. Villa A, Vollemans M, De Moraes A, Sonis S. Concordance of the WHO, RTOG, and CTCAE v4.0 grading scales for the evaluation of oral mucositis associated with chemoradiation therapy for the treatment of oral and oropharyngeal cancers. Support Care Cancer 2021;29:6061–8.
19. Hoebers F, Yu E, Eisbruch A, et al. A pragmatic contouring guideline for salivary gland structures in head and neck radiation oncology: the moist target. Am J Clin Oncol 2013;36:70–6.
20. van Griethuysen JJ, Fedorov A, Parmar C, et al. Computational radiomics system to decode the radiographic phenotype. Cancer Res 2017;77:e104–7.
21. Zwanenburg A, Vallieres M, Abdalah MA, et al. The image biomarker standardization initiative: standardized quantitative radiomics for high-throughput image-based phenotyping. Radiology 2020;295:328–38.
22. Buasawat K, Chamchod S, Fuangrod T, Suntiwong S, Liamsuwan T. Interobserver delineation variability of computed tomography-based radiomic features of the parotid gland. Radiat Oncol J 2024;42:63–73.
23. Stieb S, Lee A, van Dijk LV, Frank S, Fuller CD, Blanchard P. NTCP modeling of late effects for head and neck cancer: a systematic review. Int J Part Ther 2021;8:95–107.
24. The MathWorks Inc. Statistics and machine learning toolbox, version R2023a [Internet]. Natick, MA: The MathWorks Inc.; 2023 [cited 2025 Jul 1]. Available from: https://www.mathworks.com/help/stats/index.html.
25. Cabot JH, Ross EG. Evaluating prediction model performance. Surgery 2023;174:723–6.
26. McNemar Q. Note on the sampling error of the difference between correlated proportions or percentages. Psychometrika 1947;12:153–7.
27. Rodriguez-Perez R, Bajorath J. Interpretation of compound activity predictions from complex machine learning models using local approximations and shapley values. J Med Chem 2020;63:8761–77.
28. Elting LS, Cooksley CD, Chambers MS, Garden AS. Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. Int J Radiat Oncol Biol Phys 2007;68:1110–20.
29. Sheikh K, Lee SH, Cheng Z, et al. Predicting acute radiation induced xerostomia in head and neck cancer using MR and CT radiomics of parotid and submandibular glands. Radiat Oncol 2019;14:131.
30. Varghese BA, Hwang D, Cen SY, et al. Identification of robust and reproducible CT-texture metrics using a customized 3D-printed texture phantom. J Appl Clin Med Phys 2021;22:98–107.
31. Mackin D, Ger R, Dodge C, et al. Effect of tube current on computed tomography radiomic features. Sci Rep 2018;8:2354.
32. Choi Y, Kim JK, Lee HS, et al. Influence of intravenous contrast agent on dose calculations of intensity modulated radiation therapy plans for head and neck cancer. Radiother Oncol 2006;81:158–62.
33. World Health Organization. WHO handbook for reporting results of cancer treatment [Internet]. Geneva: World Health Organization; 1979 [cited 2025 Jul 1]. Available from: https://iris.who.int/handle/10665/37200.
34. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [Internet]. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health; 2010 [cited 2025 Jul 1]. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/.

ROJ Radiation Oncology Journal

Original Article

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2025;43(4):206-213
https://doi.org/10.3857/roj.2025.00612

Histopathological risk stratification for early-stage endometrial cancer patients receiving adjuvant vaginal brachytherapy

Hae Sol Lim[1], Won Park[1], Won Kyung Cho[1], Jeong-Won Lee[2], Chel Hun Choi[2], Tae-Joong Kim[2], Yoo-Young Lee[2]

[1]*Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*
[2]*Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*

Received: September 17, 2025
Revised: October 10, 2025
Accepted: October 16, 2025

Correspondence:
Won Park
Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea
Tel: +82-2-3410-2601
E-mail: wonro.park@samsung.com
ORCID:
https://orcid.org/0000-0003-4686-2071

Purpose: This study aims to figure out prognostic factors affecting treatment outcomes for early-stage endometrial cancer patients undergoing adjuvant vaginal brachytherapy (VBT) and to develop a histopathological risk stratification model.

Materials and Methods: We retrospectively reviewed International Federation of Gynecology and Obstetrics stage I endometrioid endometrial cancer patients who underwent primary surgery followed by VBT from January 2010 to December 2022. The high dose rate VBT was prescribed in either 30 Gy in 6 fractions or 21 Gy in 3 fractions. To identify significant factors influencing locoregional recurrence-free survival (LRRFS), disease-free survival (DFS), and overall survival (OS), Cox proportional hazards regression was applied. Patients were stratified into risk groups according to the identified prognostic factors.

Results: A total of 217 patients were reviewed with a median follow-up of 58.4 months. The recurrences were observed in 21 cases (9.7%). Distant metastasis accounted for most of the failure pattern (18/21 patients, 85.7%). The 5-year LRRFS, DFS, and OS rates were 94.5%, 91.2%, and 98.7%, respectively. Multivariate analysis revealed three statistically significant prognostic factors for DFS: high grade (hazard ratio [HR], 6.12; p = 0.010), tumor size ≥4 cm (HR, 6.48; p = 0.001), and depth of myometrial invasion ≥50% (HR, 4.97; p = 0.027). Risk stratification based on these factors demonstrated significant differences in DFS only between intermediate and high-risk groups (p = 0.002).

Conclusion: Our histopathological risk stratification model could successfully differentiate the high-risk group from others in early-stage endometrial cancer patients. This model provides crucial prognostic information and could be helpful, especially in resource-limited settings where molecular classification might not be readily available.

Keywords: Endometrial neoplasms, Adjuvant radiotherapy, Brachytherapy

Introduction

Endometrial cancer is the sixth most common malignancy in women worldwide and the seventh most common female cancer in South Korea, where its incidence has been rising since 1999 [1-3]. Surgery is the primary treatment modality of endometrial cancer. Following the surgery, recent guidelines recommend either observation or postoperative vaginal brachytherapy (VBT), depending on individual risk factors. Known risk factors include age over 60 years, lymphovascular space invasion (LVSI), tumor size, depth of myometrial invasion (DoMI), and involvement of the lower uterine segment [4,5]. However, there remains an inconsistency across guidelines regarding the inclusion and weighting of these risk factors. For example, the European Society of Gynaecological Oncology (ESGO)/European Society for Radiotherapy and Oncology (ESTRO)/European Society of Pathology (ESP) guidelines define high-intermediate risk using age ≥ 60 years with any risk factor. In contrast, American Society for Radiation Oncology employs age thresholds

Copyright © 2025 The Korean Society for Radiation Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

of 50–69 years with two or more risk factors or ≥ 70 years with one or more risk factors [6,7]. Regarding tumor size, European guidelines do not formally incorporate tumor size as an independent risk factor despite emerging evidence that larger tumor size, particularly ≥ 4 cm or ≥ 2 cm, is associated with increased risk of lymph node metastasis, recurrence, and worse survival outcomes [6,8-10]. Furthermore, while the ESGO/ESTRO/ESP guidelines distinguish between focal and substantial LVSI in risk stratification, the National Comprehensive Cancer Network guidelines still consider LVSI as a binary factor (presence or absence) without further subdivision [6,11]. These variations reflect ongoing uncertainty in optimal risk stratification strategies and the need for further validation of prognostic factors.

In light of these considerations, we retrospectively analyzed the treatment outcomes in patients with early-stage endometrial cancer who received adjuvant VBT. The objective is to identify prognostic factors influencing treatment outcomes and to gather evidence that could support the optimization of adjuvant treatment for early-stage endometrial cancer.

Materials and Methods

1. Patients

This study included patients diagnosed with stage I endometrial cancer according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system who underwent primary surgery followed by adjuvant VBT at the authors' institution from January 2010 till December 2022. Patients who were excluded from the analysis were patients with a history of other gynecologic malignancies, those who underwent external beam radiotherapy (EBRT) along with VBT, as well as individuals with non-endometrioid histology, and those with a follow-up duration of less than 6 months (Fig. 1).

2. Treatments

Primary surgical procedures included radical hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection, and/or para-aortic lymph node sampling, depending on the clinical indication. Adjuvant VBT was recommended to initiate within 4 to 8 weeks after surgery. The indication for the treatment was for patients with pathological findings indicating stage IA with grade 2 or 3 tumors, or stage IB with grade 1 or 2 tumors, provided they had additional high-risk factors. We designated three high-risk factors, which included age over 60 years, tumor size ≥ 4 cm, or positive LVSI.

High-dose-rate VBT was delivered to the vaginal stump using ovoid applicators. Patients were positioned in the lithotomy position on a gynecological examination table. The applicator size (mini-ovoid or medium-sized ovoid) was selected based on individual vaginal diameter. Following applicator insertion, Vaseline gauze packing was placed anteriorly and posteriorly to optimize applicator positioning and displacement of adjacent organs at risk. Treatment planning was performed using two-dimensional orthogonal X-ray imaging. The prescription was set at a depth of 0.5 cm from the vaginal surface. There were two different dose schemes: either 30 Gy in six fractions delivered every other day or 21 Gy in three fractions delivered twice weekly, with treatment intervals of 2 to 3 days. Each treatment session lasted ten to twenty minutes per fraction, with treatment duration varying according to the decay of the iridium-192.

3. Follow-up protocol and recurrence definition

Post-treatment follow-up examinations were systematically performed to monitor for disease recurrence. During the first 2 years, patients had regular clinical evaluations, including physical examinations, carbohydrate antigen 125 tumor marker tests, and Pap smear tests, on a quarterly basis. Imaging studies, including abdominopelvic computed tomography (AP CT scans were examined every 6 months, while chest computed tomography scans were performed annually for five years. During follow-up, the presence and severity of gastrointestinal (GI) and genitourinary (GU) toxicities were also evaluated. Acute (within ≤ 90 days after VBT initiation) and late (> 90 days after VBT initiation) toxicities were graded

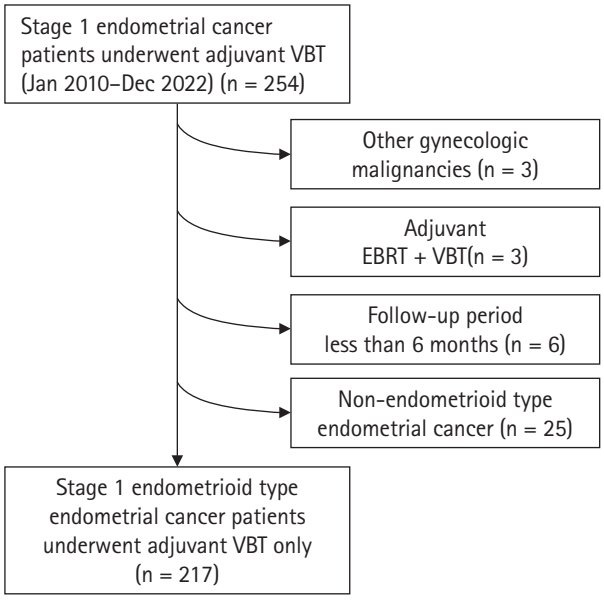

Fig. 1. Flowchart of study population. EBRT, external beam radiotherapy; VBT, vaginal brachytherapy.

https://doi.org/10.3857/roj.2025.00612

according to the Common Terminology Criteria for Adverse Events version 5.0 [12].

Recurrence was defined and categorized based on location. Local recurrence (LR) referred to recurrence confined to the vaginal stump. Regional recurrence (RR) was defined as recurrence within the pelvic lymph node(s) or pelvic side wall, without involving any visceral organs. Distant metastasis (DM) was defined as involvement of extra-pelvic lymph node(s) or visceral organs. Locoregional recurrence (LRR) included both LR and RR. Survival time was calculated from the date of primary surgery to the first recurrence or death. Recurrence was confirmed using imaging modalities, including AP CT, pelvis magnetic resonance imaging, and F-18 fluorodeoxyglucose positron emission tomography–computed tomography. When clinically feasible, further histological confirmation via biopsy was recommended.

For statistical analyses, both univariate and multivariate analyses were performed with the Cox proportional hazards regression model to identify significant prognostic factors. Based on the number of these factors, patients were stratified into distinct risk groups. The rates of locoregional recurrence–free survival (LRRFS), progression-free survival (PFS), and overall survival (OS) were estimated with the Kaplan-Meier method. To distinguish differences among the risk groups, multiple group comparisons were conducted using Bonferroni-corrected pairwise tests as post-hoc analysis. A p-value <0.05 was considered statistically significant. SPSS software version 24.0 (IBM Corp., Armonk, NY, USA) and R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria) were used for the statistical analyses.

Results

1. Patient characteristics

A total of 217 patients with stage I endometrial cancer underwent adjuvant VBT. Table 1 summarizes patient characteristics. The median follow-up period was 58.4 months (range, 13.6 to 172.9 months). According to FIGO staging, 103 patients (47.7%) had stage IA disease, and 113 patients (52.3%) had stage IB disease. Tumors were grade 1 in 21.7% of cases, grade 2 in 47.9%, and grade 3 in 30.4%. For further analysis, we classified grades 1 and 2 as low-grade and grade 3 as high-grade for analytical convenience. The mean tumor size was 3.52 cm, with 129 patients (59.4%) having tumors smaller than 4 cm and 88 patients (40.6%) having tumors 4 cm or larger. LVSI was absent in 145 patients (67.8%) and present in 69 patients (32.2%). The DoMI of 50% or greater was observed in 113 patients (52.3%), while 103 patients (47.7%) had invasion of less than 50%. Regarding radiotherapy dose schemes, 119 patients (54.8%) received 30 Gy in 6 fractions, and 98 patients (45.2%) received 21 Gy in 3 fractions.

2. Patterns of failure

Among the 217 patients, a total of 21 recurrences were observed (9.7%), and Fig. 2 illustrates the detailed failure patterns. LR occurred in six patients (2.8%), with one patient having isolated LR and five patients experiencing combined LR and DM. RR was identified in five patients (2.3%), with two patients having isolated RR and three patients presenting with combined RR and DM. DM was the most common failure pattern, occurring in 18 patients (8.3%), with 10 patients having isolated DM. Among the sites of DM, the lung was the most frequent location, seen in eight patients. Six of these had isolated lung metastasis. Para-aortic lymph nodes were the second most common site, affected in three patients, of whom two had isolated para-aortic lymph node metastasis. Bone metastasis was observed in three patients. Other sites included mediasti-

Table 1. Patients' characteristics

	No. (%)
Age (year)[a]	58.0 (30.0–81.0)
≤ 60	121 (55.8)
> 60	96 (44.2)
FIGO stage	
Stage IA	103 (47.7)
Stage IB	113 (52.3)
Grade	
1	47 (21.7)
2	104 (47.9)
3	66 (30.4)
Tumor size (cm)[a]	3.52 ± 1.68
< 4 cm	129 (59.4)
≥ 4 cm	88 (40.6)
LVSI	
Negative	145 (67.8)
Positive	69 (32.2)
DoMI	
< 50%	103 (47.7)
≥ 50%	113 (52.3)
Washing cytology	
Negative	183 (95.3)
Positive	9 (4.7)
RT regimen	
30 Gy/6 fxs	119 (54.8)
21 Gy/3 fxs	98 (45.2)

FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; DoMI, the depth of myometrial invasion; RT, radiotherapy.
[a]Normal distribution variables are described as mean ± standard deviation, and non-normal distribution variables are described as median (range).

nal lymph nodes in two patients, supraclavicular lymph nodes in one patient, and various visceral organs, including sigmoid colon, rectum, ureter, liver, and spleen, were observed in five patients. No patients experienced the concurrent recurrence of all three patterns of recurrence simultaneously.

3. Survival outcomes and prognostic factors

The survival outcomes are shown in Fig. 3. The 5-year LRRFS, disease-free survival (DFS), and OS rates were 94.5%, 91.2%, and 98.7%, respectively.

The univariate and multivariate analyses for LRRFS, PFS, and OS are summarized in Table 2. Firstly, univariate analysis of LRRFS identified tumor size ≥4 cm as a significant prognostic factor (hazard ratio [HR], 4.20; 95% confidence interval [CI], 1.08 to 16.30; p = 0.038). In multivariate analysis of LRRFS, the factor still remained statistically significant (HR, 6.69; 95% CI, 1.35 to 33.05; p = 0.020). Secondly, univariate analysis of DFS also revealed tumor size ≥4 cm as a significant prognostic factor (HR, 4.21; 95% CI, 1.57 to 11.34; p = 0.004). However, in multivariate analysis, three factors emerged as statistically significant prognostic factors: high grade (HR, 6.12; 95% CI, 1.55 to 24.24; p = 0.010), tumor size ≥4 cm (HR, 6.48; 95% CI, 2.14 to 19.66; p = 0.001), and DoMI ≥50% (HR, 4.97; 95% CI, 1.20 to 20.52; p = 0.027). Lastly, univariate analysis of OS showed that high grade was a significant prognostic factor (HR, 7.45; 95% CI, 1.46 to 37.95; p = 0.016), which maintained statistical significance in multivariate analysis (HR, 10.33; 95% CI, 1.19 to 89.28; p = 0.034).

4. Prognostic stratification

Based on the univariate and multivariate analyses of DFS results, three adverse prognostic factors were identified: high grade, tumor size ≥4 cm, and DoMI ≥50%. Patients were stratified into risk

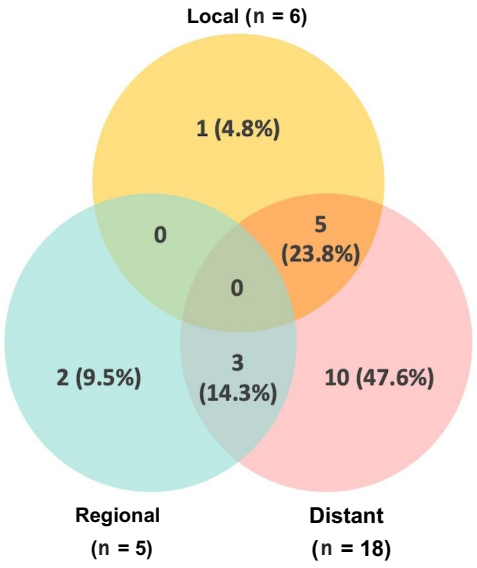

Fig. 2. Venn diagram of local and/or regional and/or distant recurrences after adjuvant vaginal brachytherapy.

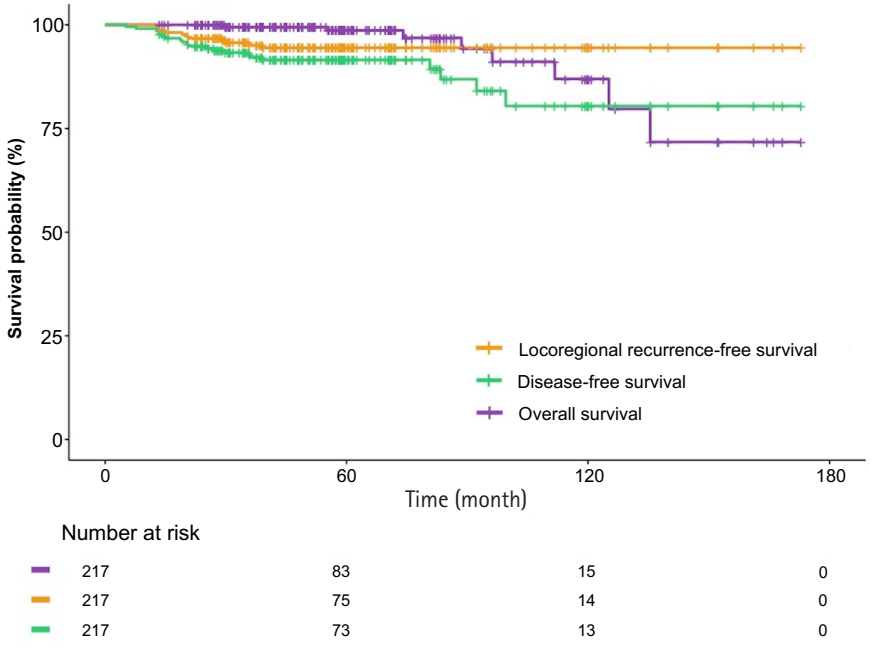

Fig. 3. Locoregional recurrence-free survival, disease-free survival, and overall survival of all patients.

https://doi.org/10.3857/roj.2025.00612

https://doi.org/10.3857/roj.2025.00612

Table 2. Univariate and multivariate logistic regression for locoregional failure-free survival, disease-free survival, and overall survival

	Locoregional recurrence-free survival				Disease-free survival				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (year)												
< 60	-				-		-		-		-	
≥ 60	0.71 (0.20–2.49)	0.591	1.01 (0.24–4.18)	0.994	1.78 (0.72–4.41)	0.215	2.25 (0.76–6.64)	0.142	2.16 (0.50–9.28)	0.300	3.32 (0.56–19.77)	0.187
Grade												
Low	-		-		-		-		-		-	
High	1.98 (0.58–6.74)	0.274	3.63 (0.71–18.52)	0.121	1.83 (0.73–4.58)	0.197	6.12 (1.55–24.24)	0.010	7.45 (1.46–37.95)	0.016	10.33 (1.19–89.28)	0.034
Tumor size (cm)												
< 4	-		-		-		-		-			
≥ 4	4.20 (1.08–16.30)	0.038	6.69 (1.35–33.05)	0.020	4.21 (1.57–11.34)	0.004	6.48 (2.14–19.66)	0.001	0.88 (0.20–3.76)	0.858	1.48 (0.30–7.31)	0.632
DoMI (%)												
< 50	-		-		-		-		-		-	
≥ 50	1.39 (0.38–5.06)	0.620	2.45 (0.48–12.60)	0.283	2.29 (0.84–6.19)	0.104	4.97 (1.20–20.52)	0.027	0.68 (0.15–3.09)	0.613	2.04 (0.25–16.36)	0.504
LVSI												
Negative	-		-		-		-		-		-	
Positive	1.81 (0.53–6.15)	0.342	2.36 (0.60–9.30)	0.219	1.33 (0.52–3.38)	0.547	1.90 (0.65–5.52)	0.238	0.29 (0.03–2.40)	0.251	0.62 (0.07–5.88)	0.679

HR, hazard ratio; CI, confidence interval; DoMI, depth of myometrial invasion; LVSI, lymphovascular space invasion.

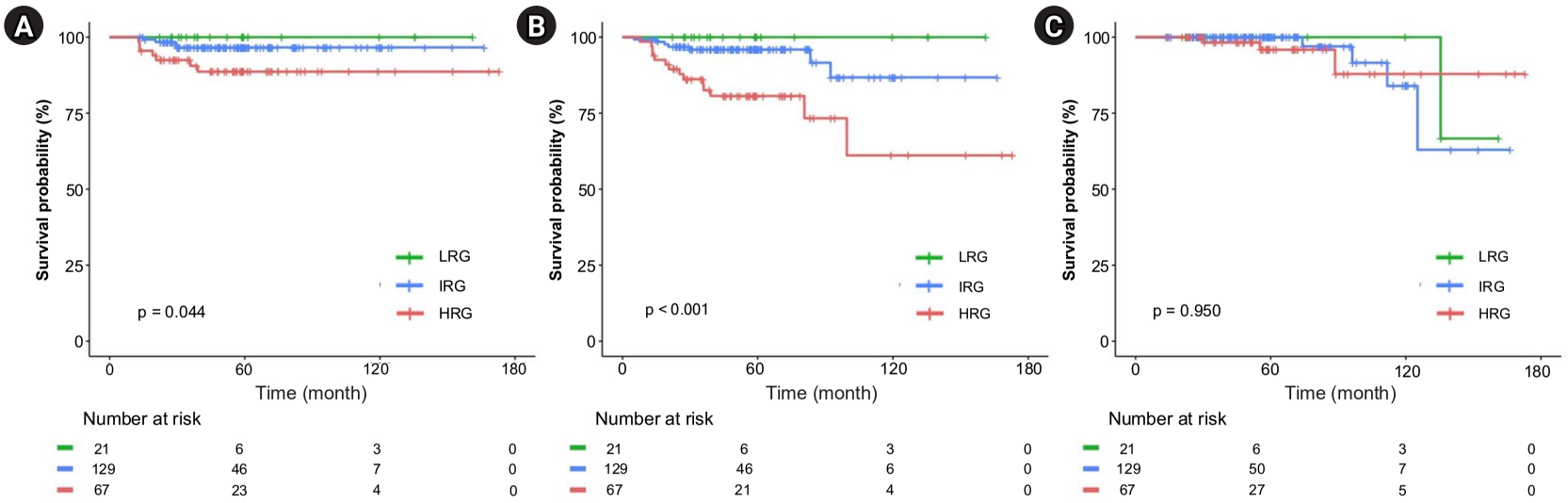

Fig. 4. Locoregional recurrence-free survival (A), disease-free survival (B), and overall survival (C) in low-risk group (LRG), intermediate-risk group (IRG), and high-risk group (HRG). Risk group is stratified by the number of positive prognostic factors including high grade, tumor size ≥ 4 cm, and depth of myometrial invasion ≥ 50%.

groups according to the number of adverse prognostic factors they had: low-risk group (0 factors, n = 21), intermediate-risk group (1 factor, n = 129), and high-risk group (≥ 2 factors, n = 67).

Fig. 4 demonstrated the survival outcomes based on risk stratification. For LRRFS (Fig. 4A), there were statistically significant differences between risk groups (p = 0.044). However, the post-hoc analysis, using the Bonferroni correction, did not reveal any statistically significant differences between individual risk groups. The p-values for each comparison were as follows: low-risk vs. intermediate-risk: p > 0.99, low-risk vs. high-risk: p = 0.415, intermediate-risk vs. high-risk: p = 0.096. When looking at DFS as shown in Fig. 4B, statistically significant differences were demonstrated between risk groups (p < 0.001). After applying Bonferroni correction for the post-hoc analysis, however, the pairwise comparisons resulted only in intermediate-risk vs. high-risk being statistically significant (p = 0.002). The comparison between low-risk and high-risk was borderline significant (p = 0.077), whereas the comparison between low-risk and intermediate-risk was not significant (p = 0.803). For OS (Fig. 4C), there was no statistically significant difference between risk groups (p = 0.950).

Since the high-risk group showed significantly lower DFS rates compared to the low or intermediate-risk group, failure patterns within this subgroup were further analyzed. Out of 67 high-risk patients, 14 (20.9%) experienced recurrence—more than twice the overall recurrence rate of 9.7%. Additionally, the high-risk group accounted for 14 of the 21 total recurrences (66.7%). DM was the most common failure pattern, seen in 12 patients (12 out of 67, 17.9%), with seven experiencing isolated DM. LR and RR were observed in five (7.5%) and two patients (3.0%), respectively. Isolated LR and RR each occurred in one patient. LR combined with DM was observed in four patients, while RR combined with DM occurred in one.

5. Toxicities

Treatment-related toxicities are summarized in Table 3. Among 217 patients, acute GI toxicities occurred in 12 patients (5.5%) as grade 1, with no grade 2 or higher toxicities observed. Acute GU toxicities were reported in 20 patients (9.2%) as grade 1 and two patients (< 1%) as grade 2, with no grade 3 or higher acute GU toxicities. Late GI toxicities occurred in three patients (1.4%) as grade 1, with no grade 2 or higher late GI complications. Late GU toxicities were observed in six patients (2.8%) as grade 1 and six patients (2.8%) as grade 2.

Table 3. Acute and late gastrointestinal and genitourinary toxicities

	Grade 1	Grade 2	≥ Grade 3
Acute (n = 217)			
Gastrointestinal	12 (5.5)	0 (0)	0 (0)
Genitourinary	20 (9.2)	2 (< 1.0)	0 (0)
Late (n = 217)			
Gastrointestinal	3 (1.4)	0 (0)	0 (0)
Genitourinary	6 (2.8)	6 (2.8)	0 (0)

Values are presented as number (%).

Discussion and Conclusion

The management of early-stage endometrial cancer has evolved significantly, with the PORTEC-1, -2, and -3 trials demonstrating that VBT provides equivalent oncological outcomes to pelvic EBRT with superior quality of life and fewer GI complications [13-15]. These trials established prognostic traditional clinicopathological factors, such as FIGO stage, histological grade, tumor size, DoMI, and LVSI [6,13-15]. However, molecular profiling-based risk stratification has fundamentally changed the treatment strategies by providing more precise prognostic information than clinicopathological factors alone, with the PORTEC-4a trial demonstrating that molecular profiling enables safe treatment de-escalation for a substantial part of patients while identifying high-risk patients who benefit from intensified therapy [16]. The 2025 ESGO-ESTRO-ESP guidelines have formally integrated molecular classification system (POLEmut, dMMR, p53abn, and NSMP) into clinical decision-making, representing a major paradigm shift toward personalized medicine [17]. Our study contributes to this evolving landscape by examining treatment outcomes in 217 patients with stage I endometrioid endometrial cancer who received adjuvant VBT. Notably, patterns of failure showed that isolated LRR were uncommon, with DM occurring in 18 patients (86.2% of all recurrences). Nearly half of all failures involved isolated DM, indicating that some patients may have occult systemic disease despite presenting with early-stage disease.

Regarding survival patterns, the 5-year LRRFS rate of 94.5% remained steady at 10 years, suggesting most LRR occurs within the first five years. On the other hand, the DFS rate decreased more noticeably, going from 91.2% at 5 years to 80.4% at 10 years. This decline suggests there may be a continued risk of DM between 5 and 10 years post-treatment. This pattern strongly suggests that DM, particularly in the lung as seen in our cohort, is more likely to develop during the extended follow-up rather than immediately after treatment.

Our risk stratification model, based on three histopathological factors, showed overall statistical significance for both LRRFS and DFS. However, post-hoc analysis revealed that the prognostic discrimination was primarily driven by the differences between the

https://doi.org/10.3857/roj.2025.00612

intermediate-risk and high-risk groups in DFS, with limited differentiation among the other risk group comparisons. In additional analysis, we found that the high-risk group—defined as patients meeting two or more of the following criteria: tumor size ≥ 4 cm, high grade, or DoMI ≥ 50%—accounted for more than half of all recurrences in the entire cohort, with most recurrences in this group including DM. While these findings confirm established prognostic factors rather than novel discoveries, the critical observation is the predominance of DM over LRR. However, the lack of OS difference between risk groups and the low absolute recurrence rate highlights a fundamental challenge: conventional histopathological factors alone have limited precision to justify treatment intensification, risking overtreatment of majority who remain disease-free. This emphasizes the need for integrating molecular profiling with conventional risk factors. Further investigations are warranted to determine whether such a combined approach can accurately identify patients at genuine risk for DM who might benefit from systemic therapy while avoiding overtreatment of those with excellent prognosis from local therapy alone.

Regarding treatment tolerability, adjuvant VBT demonstrated a rather favorable safety profile in our study, with no grade 3 or higher GI or GU toxicities observed in either the acute or late phases. This acceptable toxicity profile supports VBT as a well-tolerated adjuvant modality for early-stage endometrial cancer patients.

Our study has several limitations that should be noted. Its retrospective nature may introduce selection bias, and data from a single institution might restrict how broadly the results apply. Although our median follow-up of 58.4 months is considerable, it might not detect very late recurrences. Additionally, our cohort includes patients treated before molecular classification was adopted, which limits direct comparison with current molecular-based treatment approaches. The relatively small number of recurrence events (21 cases) could reduce the statistical power to identify additional prognostic factors with modest clinical impact.

Despite these limitations, our study findings could suggest the importance of histopathological risk factors, even as the clinical focus is increasingly shifting to molecular classification. While molecular profiling provides superior prognostic precision, its implementation remains challenging in many institutions due to cost and technical barriers, particularly in resource-limited settings [18-20]. Traditional histopathological factors remain valuable as accessible screening tools in such contexts. However, future clinical trials should target patients with combined high-risk histopathological and molecular features to evaluate whether systemic therapy can address the DM risk that local therapy alone cannot prevent. Our results demonstrate that careful evaluation of conventional pathological features can effectively identify high-risk patients, confirming that traditional histopathological factors still hold significant clinical value in endometrial cancer management.

Our histopathological risk stratification model successfully detects high-risk patients with early-stage endometrial cancer who might need more aggressive treatment. This approach provides important prognostic insights and stays clinically useful, especially in environments where molecular classification isn't readily available.

Statement of Ethics

The study protocol was approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2022-06-012) and the informed consent was waived due to its retrospective nature.

Conflict of Interest

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

Funding

None.

Author Contributions

Conceptualization: WP. Methodology: HSL, WP. Investigation: HSL, WP. Data curation: HSL, WP, WKC, JWL, CHC, TJK, YYL. Formal analysis: HSL, WKC. Validation: WKC, JWL, CHC, TJK, YYL. Writing of the original draft: HSL, WP. Writing of the review and editing: WP. Project administration: WP.

Data Availability Statement

All data generated or analyzed during this study are included in this article and/or its supplementary material files. Further enquiries can be directed to the corresponding author.

References

1. Shim SH, Lim J, Kim JH, et al. Trends in the incidence and survival outcomes of endometrial cancer in Korea: a nationwide population-based cohort study. J Gynecol Oncol 2024;35:e32.
2. Amant F, Mirza MR, Koskas M, Creutzberg CL. Cancer of the corpus uteri. Int J Gynaecol Obstet 2015;131 Suppl 2:S96–104.
3. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for

36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.
4. Benedetti Panici P, Basile S, Salerno MG, et al. Secondary analyses from a randomized clinical trial: age as the key prognostic factor in endometrial carcinoma. Am J Obstet Gynecol 2014;210:363.
5. Doll KM, Tseng J, Denslow SA, Fader AN, Gehrig PA. High-grade endometrial cancer: revisiting the impact of tumor size and location on outcomes. Gynecol Oncol 2014;132:44–9.
6. Concin N, Matias-Guiu X, Vergote I, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Radiother Oncol 2021;154:327–53.
7. Klopp A, Smith BD, Alektiar K, et al. The role of postoperative radiation therapy for endometrial cancer: executive summary of an American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol 2014;4:137–44.
8. Sozzi G, Uccella S, Berretta R, et al. Tumor size, an additional risk factor of local recurrence in low-risk endometrial cancer: a large multicentric retrospective study. Int J Gynecol Cancer 2018;28:684–91.
9. Jiao S, Wei L, Zou L, et al. Prognostic values of tumor size and location in early stage endometrial cancer patients who received radiotherapy. J Gynecol Oncol 2024;35:e84.
10. Pavlakis K, Rodolakis A, Vagios S, et al. Identifiable risk factors for lymph node metastases in grade 1 endometrial carcinoma. Int J Gynecol Cancer 2017;27:1694–700.
11. National Comprehensive Cancer Network. NCCN guideline: uterine neoplasms [Internet]. Plymouth Meeting, PA: National Comprehensive Cancer Network; 2024 [cited 2024 Jun 17]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf.
12. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Bethesda, MD: National Cancer Institute; 2017.
13. Creutzberg CL, Nout RA, Lybeert ML, et al. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. Int J Radiat Oncol Biol Phys 2011;81:e631–8.
14. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet 2010;375:816–23.
15. de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol 2018;19:295–309.
16. van den Heerik A, Horeweg N, Nout RA, et al. PORTEC-4a: international randomized trial of molecular profile-based adjuvant treatment for women with high-intermediate risk endometrial cancer. Int J Gynecol Cancer 2020;30:2002–7.
17. Concin N, Matias-Guiu X, Cibula D, et al. ESGO-ESTRO-ESP guidelines for the management of patients with endometrial carcinoma: update 2025. Lancet Oncol 2025;26:e423–35.
18. Orellana TJ, Kim H, Beriwal S, et al. Cost-effectiveness analysis of tumor molecular classification in high-risk early-stage endometrial cancer. Gynecol Oncol 2022;164:129–35.
19. Dheur A, Bours V, De Cuypere M, et al. 2022-RA-193-ESGO Cost-effectiveness of molecular profiling for endometrial neoplasia: a single institution experience. Int J Gynecol Cancer 2022;32(Suppl 2):A91.
20. Plotkin A, Olkhov-Mitsel E, Nofech-Mozes S, et al. Budget impact analysis of molecular subtype profiling in endometrial cancer. Gynecol Oncol 2023;178:54–9.

https://doi.org/10.3857/roj.2025.00612

ROJ Radiation Oncology Journal

Case Report

pISSN 2234-1900 · eISSN 2234-3156
Radiat Oncol J 2025;43(4):214-219
https://doi.org/10.3857/roj.2025.00423

Radiation therapy in a ductal carcinoma in situ patient with ornithine transcarbamylase deficiency: a case report

Iris Kang[1], Justin Park[2,3], Christine Yang[2,3], Aster Kim[4], Mary Tang[5], Kaye Lu[6,7], Azadeh Carr[6,7], Stephen F. Sener[6,7], Rachel McGowan[8], Shoji Yano[9], Stella K. Yoo[2]

[1]*Keck School of Medicine of USC, University of Southern California, Los Angeles, CA, USA*
[2]*Department of Radiation Oncology, Los Angeles General Medical Center, Los Angeles, CA, USA*
[3]*Department of Radiation Oncology, Keck School of Medicine of USC, University of Southern California, Los Angeles, CA, USA*
[4]*University of California, Los Angeles, Los Angeles, CA, USA*
[5]*Pepperdine University, Pepperdine, CA, USA*
[6]*Department of Surgery, Los Angeles General Medical Center, Los Angeles, CA, USA*
[7]*Department of Surgery, Keck School of Medicine of USC, University of Southern California, Los Angeles, CA, USA*
[8]*Genetics Division, Department of Pediatrics, Los Angeles General Medical Center, Los Angeles, CA, USA*
[9]*Genetics Division, Department of Internal Medicine, Keck School of Medicine of USC, University of Southern California, Los Angeles, CA, USA*

Received: July 17, 2025
Revised: August 27, 2025
Accepted: September 16, 2025

Correspondence:
Stella K. Yoo
Department of Radiation Oncology, Los Angeles General Medical Center, 1100 North State Street, Clinic Tower A1B129, Los Angeles, CA 90033, USA
Tel: +1-323-409-1382
E-mail: syoo3@dhs.lacounty.gov
ORCID: https://orcid.org/0000-0001-8614-7254

Ornithine transcarbamylase (OTC) deficiency is a rare urea cycle disorder that impairs ammonia detoxification, increasing the risk of hyperammonemic crises under metabolic stress. While chemotherapy-related risks have been reported, data on the safety of ionizing radiation therapy (RT) in this population are limited. This case describes a 30-year-old woman with late-onset OTC deficiency diagnosed with right-sided ductal carcinoma in situ. She underwent segmental mastectomy followed by adjuvant 3D conformal RT (40 Gy in 15 fractions with a concomitant boost to 48 Gy). Her multidisciplinary care involved preoperative hydration, close nutritional monitoring, and serial ammonia measurements. She completed RT without treatment interruptions or signs of hyperammonemia. This case illustrates that breast RT can be delivered safely in patients with OTC deficiency with a multidisciplinary, preventative approach. To our knowledge, this is the first report describing RT planning and metabolic surveillance in this population.

Keywords: Ornithine carbamoyltransferase deficiency disease, Radiotherapy, Breast neoplasms, Hyperammonemia, Urea cycle disorders, Case reports

Introduction

Ornithine transcarbamylase (OTC) deficiency is an X-linked genetic disorder of the urea cycle caused by mutations in the OTC gene. The OTC enzyme is responsible for converting ornithine and carbamoyl phosphate into citrulline and phosphate, a crucial step in ammonia detoxification in the liver. The clinical severity of mutations in the OTC gene is determined by the type and position of the mutation, which can result in either complete or partial loss of enzyme function [1].

Hyperammonemic crises caused by the complete loss of enzyme function in neonatal-onset OTC deficiency can result in neurologic damage, coma, or death without timely treatment [1-3]. With partial loss late-onset OTC deficiency, the clinical presentation is often milder, with common symptoms including vomiting, lethargy, and confusion. Due to the often nonspecific and intermittent nature of such symptoms, diagnosis can be delayed or missed [4].

Metabolic disorders such as OTC deficiency can pose increased risk to side effects in cancer treatment, as chemotherapy, immunotherapy, and radiation therapy (RT) can induce significant changes

Copyright © 2025 The Korean Society for Radiation Oncology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

in the body's metabolic pathways. The metabolic stress caused by cancer treatment with disruptions in amino acid metabolism and nitrogen handling can potentially result in metabolic complications such as hyperammonemia, and underlying metabolic disorders can increase that risk [5].

Breast cancer remains the most commonly diagnosed cancer among women worldwide, accounting for 11.7% of all new cancer cases in 2020, and RT plays an integral role in treatment [6]. Adjuvant RT reduces local recurrence rate in both invasive and non-invasive breast cancer patients and is associated with improved overall survival in advanced cases [7]. Modern RT techniques enable personalized plans that optimize tumor control while minimizing exposure to adjacent healthy normal tissue.

While we found one case report on chemotherapy's impact on patients with OTC deficiency, there is a paucity of data regarding the effects of ionizing RT in this population [8]. As RT remains integral in breast cancer treatment, it is essential for physicians to recognize potential risks of RT in patients with urea cycle metabolic disorders such as OTC deficiency.

Case Report

We present the case of a 30-year-old pre-menopausal female with a known history of late-onset OTC deficiency who was diagnosed with stage 0 (pTisN0) estrogen receptor–positive progesterone receptor–positive ductal carcinoma in situ (DCIS) of the right breast. The tumor was found following a 1-week history of sharp breast pain. Diagnostic mammogram and ultrasound revealed 5 mm grouped calcifications in the right upper outer quadrant of the breast (Breast Imaging Reporting and Data System 4A). Core needle biopsy confirmed DCIS. She subsequently underwent Savi Scout-guided segmental mastectomy with final pathologic diagnosis demonstrating grade 2, cribriform-pattern DCIS with focal necrosis. No lymphovascular invasion was identified.

This patient had a family history of OTC deficiency. Two of her elder brothers died at 5 days and 14 days of age. She was initially diagnosed with OTC deficiency at age 9 after a two-year history of nausea that was exacerbated by infections. Gene sequencing identified a heterozygous pathogenic variant in the OTC gene (c.274G>A, p.Arg92Gln). During childhood, the patient experienced one to two hyperammonemia events per year, with symptoms of hand tremors, dizziness, and nausea. The patient's current symptom management includes a modified-protein diet, glycerol phenylbutyrate, and oral supplementation with arginine, carnitine, and multivitamins. During acute hyperammonemia events, she self-manages them with oral electrolyte drinks as needed.

To minimize the patient's risk of hyperammonemia during breast surgery, multiple perioperative precautions were undertaken. Her fasting time was minimized by scheduling her to be the first operative case that morning at 8:00 AM and having her consume a clear Ensure at 4:00 AM. She was also administered Dextrose 5% in Lactated Ringer IV hydration, before and during her surgery, to suppress catabolism.

The patient's ammonia level prior to surgery was 25 μmol/L, and her ammonia level was monitored every 4 hours after surgery (Table 1, Fig. 1). At 8:00 PM on the day of her surgery, her ammonia levels increased to 63 μmol/L. However, the patient was asymptomatic, and the subsequent level decreased to 45 μmol/L. She was discharged the following day without any complications or signs of hyperammonemia.

At the radiation oncology consultation, approximately three weeks after surgery, the patient was recovering well with no reported concerns. Final pathology confirmed grade 2 DCIS, 9 mm in greatest dimension, without necrosis or extensive intraductal component. Surgical margins were negative with closest margin being 5 mm at the anterior margin.

The patient underwent computed tomography (CT) simulation scan without contrast with arms overhead on a breast board in the supine position. Prophylactic IV hydration with 10% dextrose with electrolytes was considered; however, ultimately deferred given her prior tolerance of diagnostic CT imaging and relatively low dose of RT exposure during simulation. The patient tolerated the CT simulation well without issue.

A three-dimensional conformal radiation therapy (3D-CRT) plan was generated to a dose of 40 Gy in 15 fractions to the right whole breast, with a concomitant boost to 48 Gy to the tumor bed in the right upper outer quadrant, in accordance with the protocol from clinical trial Radiation Therapy Oncology Group 1005. The beam arrangement included three fields in oblique angles: left and right medial oblique tangents with an additional left anterior oblique beam for the concomitant boost. Field-in-field technique was employed to minimize dose inhomogeneity. Table 2 contains dosimet-

Table 1. Serum ammonia levels recorded over time

Date and time	Ammonia level (μmol/L)
Jan 7, 2025 10:37	25
Jan 7, 2025 17:07	23
Jan 7, 2025 20:25	63
Jan 8, 2025 00:06	45
Jan 8, 2025 06:16	55
Feb 18, 2025 11:32	27
Feb 19, 2025 10:58	15
Feb 25, 2025 12:09	14
Mar 4, 2025 10:54	14

https://doi.org/10.3857/roj.2025.00423

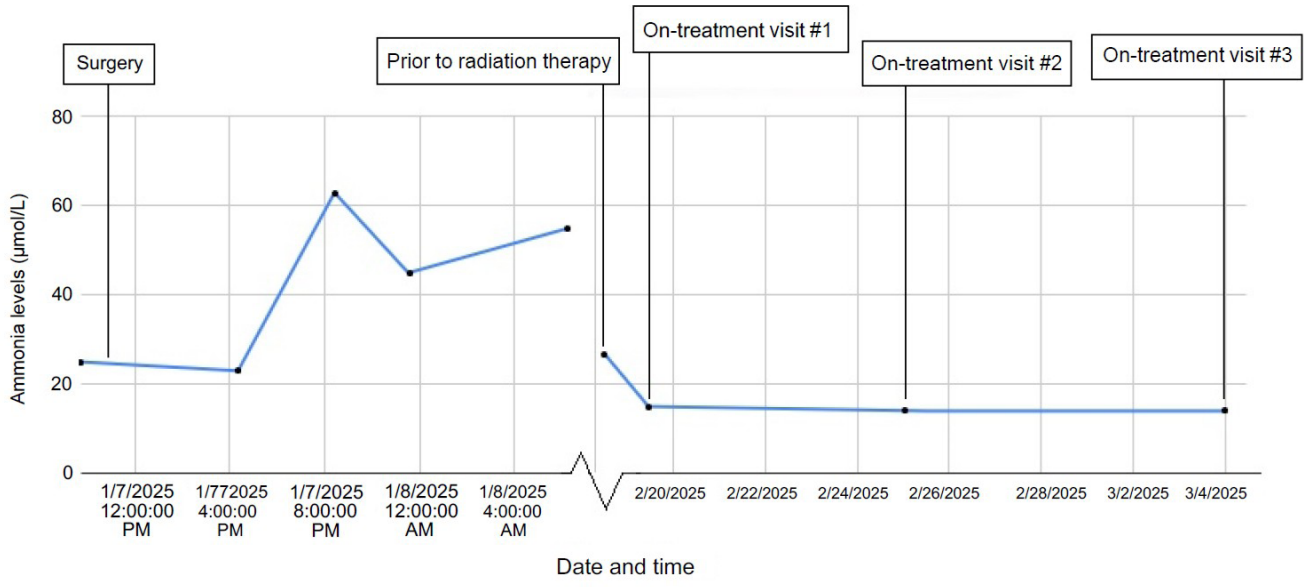

Fig. 1. Serum ammonia levels with respect to surgery date and radiation oncology clinic visits.

Table 2. Dosimetric parameters for 3D-CRT plan

Structure	Value
Right breast CTV	
V95%	99.6
V48Gy	30.2
V44Gy	47.8
Tumor bed	
V95%	95.5
V110%	0
Maximum dose (Gy)	51.3
Heart	
Mean dose (cGy)	24.2
Left lung	
V4Gy	0
Right lung	
V16Gy	4.2
V8Gy	7.5
V4Gy	16.8
Contralateral breast	
Maximum dose (cGy)	74.4
V144cGy	0

V95%: volume fraction of the clinical target volume (CTV) receiving at least 95% of the prescribed dose, indicating adequacy of target coverage; V48Gy and V44Gy: fractional volume of the target receiving ≥48 Gy or ≥44 Gy, respectively, representing dose uniformity within the target; V110%: fraction of the target volume receiving ≥110% of the prescribed dose, indicating potential areas of overdosage; V16Gy, V8Gy, V4Gy: fractional volume of the organ at risk (e.g., lung) receiving ≥16 Gy, ≥8 Gy, or ≥4 Gy, respectively, assessing radiation exposure to normal tissues and risk of toxicity.
3D-CRT, three-dimensional conformal radiation therapy; CTV, clinical target volume.

ric parameters and Fig. 2 shows representative images from the plan. In this patient's 3D-CRT plan, excellent target coverage was achieved, while doses to organs at risk were kept low (heart mean dose 24.2 cGy, left lung V4Gy = 0%, right lung V16Gy = 4.2%). The contralateral breast dose was also minimal (maximum 74.4 cGy). These low heart and lung doses reduced systemic stress and may have contributed to the prevention of hyperammonemic crisis in the setting of OTC deficiency.

The patient received weekly image-guided RT with weekly MV imaging. The patient completed the prescribed treatment without any treatment breaks or interruptions. During the duration of her RT course, the patient was closely followed by the medical genetics clinic. The patient increased her oral nutrition supplementation from two to three times per week to at least daily. The increase in calories and protein intake likely helped prevent catabolism.

Throughout RT, the patient's ammonia level was closely monitored due to the risk of possible metabolic complications (Table 1, Fig. 1). The patient's baseline ammonia level prior to RT initiation was 27 μmol/L. Serial lab levels remained stable throughout RT treatment including 15 μmol/L after the first fraction, 14 μmol/L after the fifth fraction, and 14 μmol/L after the tenth fraction. During RT, she reported mild discomfort and firmness of the right lateral aspect of her breast, and on the last week of treatment experienced burning and redness of the skin of the right breast, consistent with grade 1 dermatitis. Her grade 1 dermatitis was well controlled with over-the-counter topical lotion use administered twice a day. Overall, she tolerated the radiation treatment well with minimal radiation side effects and no hyperammonemic

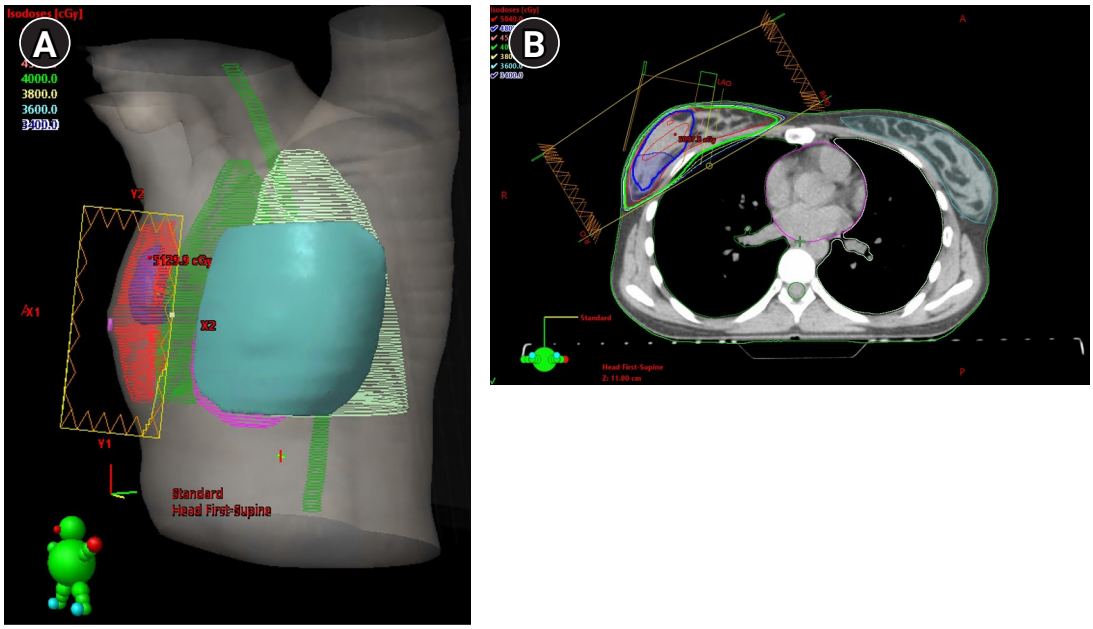

Fig. 2. (A) Beam's eye view of medial tangent. (B) Axial representation of three-dimensional conformal radiation therapy plan.

events. She started adjuvant endocrine therapy with 20 mg tamoxifen daily.

Discussion

In this case, the patient had an established diagnosis of OTC deficiency and had an effective treatment regimen for symptom control prior to her diagnosis of stage 0 breast cancer. Through close multidisciplinary collaboration with nutrition and medical genetics, a combination of perioperative precautions, dietary interventions, and close monitoring reduced her risk of hyperammonemic crisis during her cancer treatment.

Cancer treatments such as chemotherapy and immunotherapy are associated with direct toxicity to metabolic pathways, endocrine function disruption, and systemic inflammation. These disruptions can cause metabolic toxicities such as endocrine disorders, dyslipidemia, and electrolyte abnormalities [8]. There are documented cases of cancer treatment unmasking underlying OTC deficiency or inducing metabolic toxicities that emulate hyperammonemic crises of OTC deficiency [9-12]. A single case report described a case of a heterozygous carrier of OTC deficiency undergoing treatment for breast cancer who tolerated chemotherapy well with nausea, no vomiting, and no hyperammonemic events. Her protocol included increased caloric intake, protein restriction, infusion of dextrose 10% solution to deliver 3 mg/kg/min of glucose until oral intake resumed, and filgrastim administration after each doxorubicin and cyclophosphamide dose [8]. This case report did not discuss the effects or safety of RT. To our knowledge, there remains a gap in current literature on RT and its potential metabolic implications in patients with metabolic disorders such as OTC deficiency.

RT can cause metabolic stress by inducing DNA damage and disrupting cellular processes. Ionizing radiation creates reactive oxygen species, causing cellular destruction and inducing systemic inflammation [13]. Metabolic pathways such as the pentose phosphate pathway and glutamine metabolism have been shown to have a direct relationship with RT in cancer treatment, as cells increase nucleotide synthesis to repair radiation-induced DNA damage [14].

Although a direct association with hyperammonemia and RT in cancer treatment has not been established, the theoretical risk of RT induced hyperammonemia has been studied in an in vitro study. Arginase is an enzyme that completes the final step of the urea cycle, and its sensitivity to RT was found to be related to induced hyperammonemia. The cells in this study were subject to RT ranging from 0 Gy to 8 Gy, and the results indicated that RT led to a dose-dependent increase in levels of ornithine, citrulline, and ammonia [15]. In addition, a randomized control study on mice revealed that RT increases polyamine synthesis in the brain, liver, and kidneys, consistent with radiation-induced activation of ornithine decarboxylase and increased release of free ammonia into the bloodstream [16]. These findings raise concern that RT may increase systemic ammonia levels, more so in patients with underlying OTC deficiency.

In contrast to the experimental data, our patient maintained

 https://doi.org/10.3857/roj.2025.00423

stable ammonia levels throughout RT. Several factors may have contributed to this outcome. Given the theoretical clinical risk for a hyperammonemic event in our patient with OTC deficiency, proactive nutritional support with avoidance of prolonged fasting, protein restriction, and glucose supplementation helped minimized catabolic stress. Careful RT planning also helped limit radiation exposure to organs at risk, reducing systemic stress. The use of a 15 fraction regimen also contributed to avoiding larger single fraction doses that may have caused more profound metabolic stress. Serial ammonia monitoring also allowed for early detection of abnormalities, though none developed. The patient's pre-existing diagnosis of OTC deficiency along with a multidisciplinary approach involving her surgeons, dietitian, geneticist, and radiation oncologist, allowed for successful and safe completion of her treatment course without a hyperammonemic event or treatment interruptions. The details and positive outcome in this case fill a gap in the current existing literature on the interaction between RT and OTC deficiency.

Given the metabolic stress that RT creates and the theoretical risk of hyperammonemia, heightened vigilance is crucial when providing RT to patients with metabolic disorders such as OTC deficiency. Despite theoretical concerns and limited data on the interaction between OTC deficiency and radiation exposure, this patient demonstrated that RT can be delivered safely with multidisciplinary proactive measures. This case report underscores the importance of close monitoring and multidisciplinary care and adds to the current literature on providing cancer treatment, specifically RT, safely to the population of patients with OTC deficiency.

Statement of Ethics

This case report was conducted in accordance with the ethical standards of our institution and with the 1964 Helsinki Declaration and its later amendments. Institutional Review Board (IRB) approval was not required for publication of this case report per institutional policy, as it describes a single patient observation without research intent. Informed consent was obtained from the patient for publication of the details of their medical case and accompanying images. All identifying information has been removed to protect patient privacy.

Conflict of Interest

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

Funding

None.

Author Contributions

Conceptualization, IK, SKY; Data curation, all authors; Formal analysis, IK, JP, CY; Investigation, IK, JP, CY, AK, MT; Project administration, SKY; Supervision, SKY; Visualization, JP, CY; Writing of the original draft, IK, JP, CY, AK, MT; Writing of the review and editing, all authors. Approval of final manuscript: all authors.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

References

1. Lee T, Misaki M, Shimomura H, et al. Late-onset ornithine transcarbamylase deficiency caused by a somatic mosaic mutation. Hum Genome Var 2018;5:22.
2. Gordon N. Ornithine transcarbamylase deficiency: a urea cycle defect. Eur J Paediatr Neurol 2003;7:115–21.
3. Lichter-Konecki U, Caldovic L, Morizono H, Simpson K, Mew NA, MacLeod E. Ornithine transcarbamylase deficiency. In: GeneReviews [Internet]. Seattle, WA: University of Washington, Seattle; 1993 [cited 2025 Mar 29]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK154378/.
4. Cavicchi C, Donati M, Parini R, et al. Sudden unexpected fatal encephalopathy in adults with otc gene mutations-clues for early diagnosis and timely treatment. Orphanet J Rare Dis 2014;9:105.
5. Luo Z, Eichinger KM, Zhang A, Li S. Targeting cancer metabolic pathways for improving chemotherapy and immunotherapy. Cancer Lett 2023;575:216396.
6. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.
7. Yang TJ, Ho AY. Radiation therapy in the management of breast cancer. Surg Clin North Am 2013;93:455–71.
8. Palka-Kotlowska M, Cabezon-Gutierrez L, Custodio-Cabello S, Quijada-Fraile P, Chumillas-Calzada S. Chemotherapy in a breast cancer patient heterozygous carrier of ornithine transcarbamylase deficiency. Cureus 2020;12:e8301.
9. Kotecki N, Penel N, Awada A. Metabolic disorders associated with the use of targeted cancer therapies. Curr Opin Oncol 2015;27:258–66.
10. Chapuy CI, Sahai I, Sharma R, Zhu AX, Kozyreva ON. Hyperammonemic encephalopathy associated with fibrolamellar hepatocellular carcinoma: case report, literature review, and proposed

treatment algorithm. Oncologist 2016;21:514–20.
11. Chan JS, Harding CO, Blanke CD. Postchemotherapy hyperammonemic encephalopathy emulating ornithine transcarbamoylase (otc) deficiency. South Med J 2008;101:543–5.
12. Laemmle A, Hahn D, Hu L, et al. Fatal hyperammonemia and carbamoyl phosphate synthetase 1 (cps1) deficiency following high-dose chemotherapy and autologous hematopoietic stem cell transplantation. Mol Genet Metab 2015;114:438–44.
13. Tapio S, Little MP, Kaiser JC, et al. Ionizing radiation-induced circulatory and metabolic diseases. Environ Int 2021;146:106235.
14. Read GH, Bailleul J, Vlashi E, Kesarwala AH. Metabolic response to radiation therapy in cancer. Mol Carcinog 2022;61:200–24.
15. van Rijn J, van den Berg J, Teerlink T, et al. Changes in the ornithine cycle following ionising radiation cause a cytotoxic conditioning of the culture medium of h35 hepatoma cells. Br J Cancer 2003;88:447–54.
16. Kalani Roy M, La Carpia F, Cendali F, et al. Irradiation causes alterations of polyamine, purine, and sulfur metabolism in red blood cells and multiple organs. J Proteome Res 2022;21:519–34.

 https://doi.org/10.3857/roj.2025.00423

Instructions for Authors

ROJ Radiation Oncology Journal

The Radiation Oncology Journal (ROJ) is a peer-reviewed publication of the Korean Society for Radiation Oncology. 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.

Manuscripts for submission to ROJ should be prepared according to the following instructions. ROJ follows the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (http://www.icmje.org/urm_main.html), commonly known as "the Vancouver style," if not otherwise described below.

1. RESEARCH AND PUBLICATION ETHICS

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

(1) Journal policies on authorship and contributorship

1) Authorship

Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreeing to be accountable for all aspects of the work in ensuring that the questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet these four conditions. For any persons who do not meet the above four criteria, they may be placed as contributors in the Acknowledgments section. Description of co-first authors or co-corresponding authors is also accepted if the corresponding author believes that their roles are equally contributed. After the initial submission of a manuscript, any changes in authorship must be explained by a letter to the Editor-in-Chief from the authors concerned. This letter must be signed by all authors of the paper. Copyright transfer and conflict of interest disclosure forms must be completed by every author. ROJ does not correct authorship after publication unless a mistake has been made by the editorial staff.

2) Originality and Duplicate Publication

All submitted manuscripts should be original and should not be considered by other scientific journals for publication at the same time. Any part of the accepted manuscript should not be duplicated in any other scientific journal without the permission of the editorial board. Submitted manuscripts are screened for possible duplicate publication by Similarity Check upon arrival. If duplicate publication related to the papers of this journal is detected, the authors will be announced in the journal, and their institutes will be informed, and there will also be penalties for the authors.

3) Secondary Publication

It is possible to republish manuscripts if the manuscripts satisfy the conditions of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. ROJ maintains a zero-tolerance policy when addressing allegations of plagiarism, duplicate publication (self-publication), data falsification, and scientific misconduct. Articles will be retracted if ethics violations are substantiated. Plagiarism is defined by the World Association for Medical Editors (WAME) as the "use of others' published and unpublished ideas or words (or other intellectual property) without attribution or permission and presenting them as new and original rather than derived from an existing source." ROJ participates in the Crosscheck/iThenticate program to investigate incidents of possible plagiarism. Manipulating data through fabrication, omission, or intentional distortion is unacceptable. Authors should be prepared to provide original data to editors if there is a question of authenticity. Claims of scientific misconduct are investigated and addressed, guided by the Committee of Publication Ethics (COPE) Code of Conduct.

(2) Statement of Informed Consent and Institutional Review Board Approval

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

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

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

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

(3) Statement of Human and Animal Rights

All studies on human subjects must be conducted according to the principles expressed in the World Medical Association Declaration of Helsinki. Clinical studies that do not meet the Helsinki Declaration will not be considered for publication. The name or initials of the patient should not be displayed, and the patient's identity should not be known when submitting photographs related to the patient. If there is a possibility that the patient's identity may be exposed, it should be stated that the patient has given written consent.

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

All studies dealing with clinical trials should be registered on the primary national clinical trial registration site, such as Korea Clinical Research Information Service (CRiS, http://cris.nih.go.kr), other primary national registry sites accredited by World Health Organization or ClinicalTrials.gov (http://clinicaltrials.gov), a service of the US National Institutes of Health.

(4) How the journal will handle complaints and appeals

When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board of ROJ will discuss the suspected cases and reach a decision. ROJ will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

(5) Journal policies on conflicts of interest/competing interests

Conflict of interest exists when an author or the author's institution, reviewer, or editor has financial or personal relationships that inappropriately influence or bias their actions. Such relationships are also known as dual commitments, competing interests, or competing loyalties. These relationships vary from being negligible to having great potential to influence judgment. Not all relationships represent true conflict of interest. On the other hand, the potential for conflict of interest can exist regardless of whether an individual believes that the relationship affects their scientific judgment. Financial relationships such as employment, consultancies, stock ownership, honoraria, and paid expert testimony are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, or the science itself. Conflicts can occur for other reasons as well, such as personal relationships, academic competition, and intellectual passion (http://www.icmje.org/conflicts-of-interest/). If there are any conflicts of interest, the authors should disclose them in the manuscript. The conflicts of interest may occur during the research process as well; however, it is important to provide disclosure. If there is a disclosure, editors, reviewers, and reader can approach the manuscript after understanding the situation and background for the completed research. The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors' interpretation of the data.

(6) Journal policies on data sharing and reproducibility

1) Open data policy

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

2) Clinical data sharing policy

This journal follows the data sharing policy described in "Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors" (https://doi.org/10.3346/jkms.2017.32.7.1051). As of July 1, 2018, manuscripts submitted to ICMJE journals that report the results of interventional clinical trials must contain a data sharing statement as described below. Clinical trials that begin enrolling participants on or after January 1, 2019, must include a data sharing plan in the trial's registration. The ICMJE's policy regarding trial registration is explained at http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. If the data sharing plan changes after registration,

this should be reflected in the statement submitted and published with the manuscript and updated in the registry record. All the authors of research articles that deal with interventional clinical trials must submit data sharing plan. Based on the degree of sharing plan, authors should deposit their data after deidentification and report the DOI of the data and the registered site.

(7) Journal's policy on ethical oversight

When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board will discuss the suspected cases and reach a decision. We will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

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

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

(8) Journal's policy on intellectual property

All published papers become the permanent property of the Korean Society for Radiation Oncology. Copyrights of all published materials are owned by the Korean Society for Radiation Oncology.

(9) Journal's options for post-publication discussions and corrections

The post-publication discussion is available through a letter to the editor. If any readers have a concern on any articles published, they can submit a letter to the editor on the articles. If there founds any errors or mistakes in the article, it can be corrected through errata, corrigenda, or retraction.

(10) Journal's policy on preprint

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

2. ELECTRONIC SUBMISSION OF MANUSCRIPT

Manuscript submission is only available through the online submission site at https://submit.e-roj.org. Submission instructions are available on the website. All articles submitted to the ROJ must comply with these instructions. Failure to do so will result in the return of the manuscript and a possible delay in publication. For assistance, please contact us via E-mail (rojeditor@gmail.com, roj@kosro.or.kr), telephone (+82-2-3410-3617).

3. PEER REVIEW PROCESS

The acceptance criteria for all papers are based on the quality and originality of the research and its clinical and scientific significance. Original Articles are generally reviewed at least by two peer reviewers. The Editor-in-Chief is responsible for final decisions regarding the acceptance of a peer-reviewed paper. An initial decision will normally be made within four weeks of receiving a manuscript, and the reviewers' comments are sent to the corresponding authors by E-mail. Revised manuscripts must be submitted online by the corresponding author. The corresponding author must indicate the alterations that

have been made in response to the referees' comments item by item. Failure to resubmit the revised manuscript within 12 weeks of the editorial decision is regarded as a withdrawal.

4. MANUSCRIPT PREPARATION

(1) General Guideline

Authors are required to submit their manuscripts after reading the following instructions. Any manuscript that does not conform to the following requirements will be considered inappropriate and may be returned. When a manuscript is received for consideration, the editors assume that no similar paper has been or will be submitted for publication elsewhere. The main document with manuscript text and tables should be prepared with an MS-word program

- The manuscript should be written in 11-point font with double-line spacing on A4-sized (21.0×29.7 cm) paper with 25 mm margins on the top, bottom, right and left.
- All manuscript pages are to be numbered at the middle of the bottom consecutively.

(2) Language

Manuscripts must be written succinctly in clear, grammatical English. All manuscripts originating from non-English speaking countries must be revised by a professional linguistic reviewer. Medical terminology should be written based on the most recent edition of Dorland's Illustrated Medical Dictionary or the most recent edition of English-Korean Korean-English Medical Terminology, published by the Korean Medical Association. The use of acronyms and abbreviations is discouraged and should be kept to a minimum. When used, they are to be defined where first used, followed by the acronym or abbreviation in parentheses. Drug and chemical names should be stated in standard chemical or generic nomenclature. Units of measure should be presented according to the SI units (e.g., Gy, Sv, Bq, m, kg, L).

(3) Reporting Guidelines for Specific Study Designs

For the specific study design, such as randomized control studies, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, it is recommended that the authors follow the reporting guidelines listed in the following table.

ORIGINAL ARTICLES

Original articles are reports of basic or clinical investigations. The manuscript for an original article should be organized on a separate page in the following sequence: title page, abstract and keywords, text (introduction, materials and methods, results, discussion, and conclusion), statements, references, tables, and figure legends.

1) Title page

The title Page should carry the following information.

- The title should be short, informative, and contain the major keywords (no more than 15 words). It is not necessary to lead with expressions like "clinical research on -" or "the study on -."
- Each author's name (first name, middle name, and surname) followed by the highest academic degree (e.g., Gil Dong Hong, MD).
- The name of the department (s) and institution (s) where the work was conducted. If the authors' affiliation is different, indicate individual departments and institutions by inserting a superscript letter immediately after the author's name, and the same letter in front of the appropriate institution.
- Running title of fewer than 60 characters.
- Source(s) of support in the form of grants, equipment, drugs, or all of these.
- Complete mailing address, telephone, and E-mail for correspondence and reprints.

2) Abstract and Keywords

The abstract should be no more than 250 words, and described concisely, in a paragraph, Purpose, Materials and Methods, Results, and Conclusion. Up to six keywords should be listed below the abstract. For selecting keywords, refer to the Medical Subject Headings; if suitable MeSH terms are not yet available for recently introduced terms, present terms may be used.

3) Text

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

Initiative	Type of study	Source
CONSORT	Randomized controlled trials	http://www.consort-statement.org
STARD	Studies of diagnostic accuracy	http://www.stard-statement.org
PRISMA	Preferred reporting items of systematic reviews and meta-analyses	http://www.prisma-statement.org
STROBE	Observational studies inepidemiology	http://www.strobe-statement.org

Introduction

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.

Materials and Methods

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.

Results

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.

Discussion and Conclusion

Emphasize the advances in knowledge provided by the study and the conclusions that follow from them. Do not repeat in detail the data given in the Results section. Include in the Discussion the implications of the findings and their limitations. Relate the observations to other relevant studies. Link the conclusions with the goals of the study, but avoid unqualified statements and conclusions not supported by the data.

4) Statements

All manuscripts must contain the following statements after the main text and before the reference list.

Statement of Ethics

In the manuscript, the authors should state that subjects have given their written informed consent and that the study protocol was approved by the institute's committee on human research.

(1) Study approval statement: Provide name and affiliation of the committee who approved the study and the decision reference number like as "This study protocol was reviewed and approved by [committee name, affiliation, and approval number]." If ethics approval was not required, or if the study has been granted an exemption from requiring ethics approval, this should also be stated, including the name of the ethics committee who made that decision.

(2) Consent to participate statement: For studies using human subjects, state whether written informed consent was obtained from participants to participate in the study. If written informed consent was not required, or if the study has been granted an exemption from requiring written informed consent, this should also be stated, including the name of the ethics committee who made that decision.

Conflicts of Interest Statement

All potential conflicts of interest must be stated within the text of the manuscript, under this heading. This pertains to relationships with pharmaceutical companies, biomedical device manufacturers, or other corporations whose products or services are related to the subject matter of the article. Such relationships include, but are not limited to, employment by an industrial concern, ownership of stock, membership on a standing advisory council or committee, being on the board of directors, or being publicly associated with the company or its products. Other areas of real or perceived conflict of interest could include receiving honoraria or consulting fees or receiving grants or funds from such corporations or individuals representing such corporations. Also, the nonfinancial relationships (personal, political, or professional) that may potentially influence the writing of the manuscript should be declared. Please state "The authors have no conflicts of interest to declare" if no conflicts exist.

Acknowledgement (optional)

If necessary, persons who have made substantial contributions, but who have not met the criteria for authorship, are acknowledged here. An exception is where funding was provided, which should be included in Financial Support.

Financial Support

Authors must give full details about the funding of any research relevant to the study, including the name of the funding agency, country

and the number of the grant provided by the funding agency.

Author Contributions

In the Author Contributions section, a short statement detailing the contributions of each person named as an author should be included. Contributors to the paper who do not fulfil the ICMJE criteria for authorship should be credited in the Acknowledgement section.

Data Availability Statement

Authors are required to provide a Data Availability Statement in their article that details whether data are available and where they can be found. The journal's data sharing policy strongly encourages authors to make all datasets on which the conclusions of the paper rely available to editors, reviewers, and readers without unnecessary restriction wherever possible. In cases where research data are not publicly available on legal or ethical grounds, this should be clearly stated in the Data Availability Statement along with any conditions for accessing the data.

Examples of Data Availability Statements:

- The data that support the findings of this study are openly available in [repository name e.g "figshare"] at http://doi.org/[doi], reference number [reference number]
- Publicly available datasets were used in this study. These can be found in [repository name e.g "figshare"] at http://doi.org/[doi], reference number [reference number]
- All data generated or analyzed during this study are included in this article [and/or] its supplementary material files. Further enquiries can be directed to the corresponding author.
- The data that support the findings of this study are not publicly available due to [REASON WHY DATA ARE NOT PUBLIC e.g., their containing information that could compromise the privacy of research participants] but are available from [e.g., the corresponding author [author initials] OR Data sharing committee [PROVIDE CONTACT DETAILS including email address] upon reasonable request]
- The data in this study was obtained from [third party source] where [RESTRICTIONS/LICENCE] may apply. Such a dataset may be requested from [source contact information].

5) References

In the text, references should be cited with Arabic numerals in brackets, numbered in the order cited. In the references section, the references should be numbered in order of appearance in the text and listed in English. List all authors if there are less than or equal to six authors. List the first three authors followed by "et al." if there are more than three authors. If an article has been published online, but has not yet been given an issue or pages, the digital object identifier (DOI) should be supplied. Journal titles should be abbreviated in the style used in Medline. Other types of references not described below should follow Citing Medicine: The NLM Style Guide for Authors, Editors, and Publishers.

Journal articles:

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

Book:

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

Conference paper:

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

Online sources:

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

6) Tables

Each table should be typed in the separate sheet. The title of the table should be on top-placed, and the first letter of all words (except articles, conjunctions, prepositions) should be capitalized. Tables are numbered in order of citation in the text. Lower case letters in superscripts [a], [b], [c] ... should be used for special remarks. Within a table, if a non-standard abbreviation is used or description may be necessary,

then list them under annotation below. The statistical significance of observed differences in the data should be indicated by the appropriate statistical analysis.

7) Figures

Upload each figure as a separate image file. The figure images should be provided in PowerPoint file, TIFF, JPEG, GIF, or EPS format with high resolution (preferably 300 dpi for figures and 600 dpi for line art and graph). The figures should be sized to column width (8.5 cm or 17.5 cm). If figures are not original, the author must contact each publisher to request permission, and this should be remarked on the footnote of the figure. Figures should be numbered, using Arabic numerals, in the order in which they are cited. All figures should be cited in the text (e.g., Fig. 1, Fig. 1A-C, Figs. 1 and 2). In the case of multiple prints bearing the same number, use capital letters after the numerals to indicate the correct order (e.g., Fig. 1A, Fig. 1B). A figure legend should be in English and a one-sentence description rather than a phrase or a paragraph. Capitalize the first letter of the first word. A legend for each light microscopic photograph should include the name of stain and magnification. Electron microscopic photographs should have an internal scale marker.

REVIEWS

Reviews should be comprehensive analyses of specific topics. They are organized as follows: title page, abstract and keywords, introduction, body text, conclusion, conflicts of interest, acknowledgments (if necessary), references, tables, and figure legends. Upload each figure as a separate image file. There should be an unstructured abstract equal to or less than 200 words. References should be obviously related to documents and should not exceed 50.

CASE REPORTS

Case reports will be published only in exceptional circumstances, when they illustrate a rare occurrence of clinical importance. The manuscript for a case report should be organized in the following sequence: title page, abstract and keywords, introduction, case report(s), discussion, conflicts of interest, acknowledgments (if necessary), references, tables, and figure legends. Upload each figure as a separate image file. The abstract should be unstructured, and its length should not exceed 150 words. References should be obviously related to documents and should not exceed 20. It is not necessary to use the word "introduction."

EDITORIAL

Editorials should be commentaries on articles published recently in the journal. Editorial topics could include active areas of research, fresh insights, and debates. Editorials should be no more than four to five pages in length, including references, tables, and figures.

LETTERS TO THE EDITOR

Letters to the Editor should include brief constructive comments that concern previously published papers. Letters to the Editor should be no more than two pages. It should have maximum five references, 1 table, and 1 figure. Letters could be edited by the Editorial Board. Responses by the author of the subject paper may be provided in the same issue or next issue of the Journal

5. COMMUNICATIONS TO THE PUBLISHER

We invite inquiries to the editorial office at any time during the editorial process. For all matters concerning presubmission, editorial policies, procedures, business inquiries, subscription information, orders, or changes of address, please contact the editorial office.

Editorial Committee Office
Department of Radiation Oncology, Samsung Medical Center, Proton Therapy Center, B2, 81, Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea
Tel: +82-2-3410-3617
E-mail: rojeditor@gmail.com ,roj@kosro.or.kr

6. ADDITIONAL INFORMATION

(1) Copyright

All published papers become the permanent property of The Korean Society for Radiation Oncology. Upon acceptance of the manuscript, the authors will be required to sign a statement confirming that the manuscript contains no material the publication of which violates any copyright or other personal or proprietary right of any person or entity.

(2) Page Proofs

Corresponding authors are provided with page proofs and are asked to carefully review them for data and typesetting errors. When proofs are available, the corresponding author will receive a notification. Corrections to proofs must be returned via e-mail within 48 hours. Publication may be delayed if proofs are not returned by the publisher's deadline.

(3) Charges

There are no charges for submission and publication.

***NOTICE*:** These recently revised instructions for authors will be applied beginning with the June 2022 issue.

Research and Publication Ethics

ROJ Radiation Oncology Journal

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

1. Journal policies on authorship and contributorship

1) Authorship

Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreeing to be accountable for all aspects of the work in ensuring that the questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet these four conditions.

For any persons who do not meet the above four criteria, they may be placed as contributors in the Acknowledgments section. Description of co-first authors or co-corresponding authors is also accepted if the corresponding author believes that their roles are equally contributed.

After the initial submission of a manuscript, any changes in authorship must be explained by a letter to the Editor-in-Chief from the authors concerned. This letter must be signed by all authors of the paper. Copyright transfer and conflict of interest disclosure forms must be completed by every author. ROJ does not correct authorship after publication unless a mistake has been made by the editorial staff.

2) Originality and Duplicate Publication

All submitted manuscripts should be original and should not be considered by other scientific journals for publication at the same time. Any part of the accepted manuscript should not be duplicated in any other scientific journal without the permission of the editorial board. Submitted manuscripts are screened for possible duplicate publication by Similarity Check upon arrival. If duplicate publication related to the papers of this journal is detected, the authors will be announced in the journal, and their institutes will be informed, and there will also be penalties for the authors.

3) Secondary Publication

It is possible to republish manuscripts if the manuscripts satisfy the conditions of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. ROJ maintains a zero-tolerance policy when addressing allegations of plagiarism, duplicate publication (self-publication), data falsification, and scientific misconduct. Articles will be retracted if ethics violations are substantiated. Plagiarism is defined by the World Association for Medical Editors (WAME) as the "use of others' published and unpublished ideas or words (or other intellectual property) without attribution or permission and presenting them as new and original rather than derived from an existing source." ROJ participates in the Crosscheck/iThenticate program to investigate incidents of possible plagiarism. Manipulating data through fabrication, omission, or intentional distortion is unacceptable. Authors should be prepared to provide original data to editors if there is a question of authenticity. Claims of scientific misconduct are investigated and addressed, guided by the Committee of Publication Ethics (COPE) Code of Conduct.

2. Statement of Informed Consent

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

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

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

3. Statement of Human and Animal Rights

All studies on human subjects must be conducted according to the principles expressed in the World Medical Association Declaration of Helsinki. Clinical studies that do not meet the Helsinki Declaration will not be considered for publication. The name or initials of the patient should not be displayed, and the patient's identity should not be known when submitting photographs related to the patient. If there is a possibility that the patient's identity may be exposed, it should be stated that the patient has given written consent.

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

All studies dealing with clinical trials should be registered on the primary national clinical trial registration site, such as Korea Clinical Research Information Service (CRiS, http://cris.nih.go.kr), other primary national registry sites accredited by World Health Organization or ClinicalTrials.gov (http://clinicaltrials.gov), a service of the US National Institutes of Health.

4. How the journal will handle complaints and appeals

When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board of ROJ will discuss the suspected cases and reach a decision. ROJ will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

5. Journal policies on conflicts of interest/competing interests

Conflict of interest exists when an author or the author's institution, reviewer, or editor has financial or personal relationships that inappropriately influence or bias his or her actions. Such relationships are also known as dual commitments, competing interests, or competing loyalties. These relationships vary from being negligible to having great a potential for influencing judgment. Not all relationships represent true conflict of interest. On the other hand, the potential for conflict of interest can exist regardless of whether an individual believes that the relationship affects his or her scientific judgment. Financial relationships such as employment, consultancies, stock ownership, honoraria, and paid expert testimony are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, or of the science itself. Conflicts can occur for other reasons as well, such as personal relationships, academic competition, and intellectual passion (http://www.icmje.org/conflicts-of-interest/). If there are any conflicts of interest, authors should disclose them in the manuscript. The conflicts of interest may occur during the research process as well; however, it is important to provide disclosure. If there is a disclosure, editors, reviewers, and reader can approach the manuscript after understanding the situation and background for the completed research. The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors' interpretation of the data.

6. Journal policies on data sharing and reproducibility

1) Open data policy

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

2) Clinical data sharing policy

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

7. Journal's policy on ethical oversight

When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board will discuss the suspected cases and reach a decision. We will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

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

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

8. Journal's policy on intellectual property

All published papers become the permanent property of the Korean Society for Radiation Oncology. Copyrights of all published materials are owned by the Korean Society for Radiation Oncology.

9. Journal's options for post-publication discussions and corrections

The post-publication discussion is available through a letter to the editor. If any readers have a concern on any articles published, they can submit a letter to the editor on the articles. If there founds any errors or mistakes in the article, it can be corrected through errata, corrigenda, or retraction.

10. Journal's policy on preprint

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

Checklist

ROJ Radiation Oncology Journal

1. Copyright transfer form has been signed by all authors.

2. Ethics disclosure form has been signed by corresponding author.

3. The manuscript shall be written by Microsoft Office Word or HWP processing programs.

4. A title page including author details and a manuscript without author details of the original file of the article should be submitted separately.

5. The original file of the article should not include the affiliations and names of the authors.

6. Standard abbreviations are defined in a key at their first appearance in the manuscript, and are consistent throughout the text.

7. Generic names are used for all drugs. Trade names are avoided.

8. Normal laboratory values are provided in parentheses when first used.

9. Research or project support/funding is noted in cover letter.

10. Internal review board approval of study is indicated in cover letter.

11. References are accurate, complete and in numerical order as they appear in the text, only the first 3 authors are listed.

12. No more than 50 references are cited in review article.

13. No more than 55 references are cited in original article.

14. No more than 20 references are cited in case report.

15. A corresponding author and complete address, telephone number and e-mail address are provided in cover letter.

16. Written permission from publishers to reproduce or adapt previously published illustrations or tables is included.

17. Informed consent forms for identifiable patient descriptions, photographs and pedigrees are included.

Copyright Transfer Form

ROJ Radiation Oncology Journal

This form applies to manuscripts submitted for the possible publication

Manuscript Title: _____

Date (MM/DD/YYYY): _____

Manuscripts will not be processed until the Radiation Oncology Journal Editorial Office has received this signed form. Please upload the completed form when you submit a manuscript on the E-Submission website (submit.e-roj.org).

The copyright to this article is transferred to the Radiation Oncology Journal (ROJ) effective if and when the article titled above is accepted for publication. If the article has more than two authors, each author must individually transfer his or her right in the article to the ROJ by signing this form. If the article is not published in the ROJ, this form is void and will not take effect. If it is signed and the article is published, the copyright transfer covers the exclusive right to reproduce and distribute the article, including reprints, translation, photographic reproduction, microfilm, electronic form (offline, online) or any other reproductions of similar feature.An author or authors may store it in his or her archive an author-made version of his/her article on his/her own website and his/her affiliated institution's depository library, including his/her final version; however he/she may not use the ROJ's PDF version which is posted on its own website. Provided permission is given to the author/authors by ROJ, he/she may only post his/her version of the article and a link to the original source of publication is inserted to the published article on the ROJ's website.Please use the exact and correct DOI for the article to ensure appropriate linking between sites. Articles listed on the ROJ's website are indexed, abstracted, and referenced by many indexing services and consortia such as SCIE, EMBASE, Google Scholar and KMCI.Each author guarantees that this contribution is original and that he/she has full responsibility to make this grant. The author signs for and accepts full responsibility for releasing this content. The author should declare that, to the best of his/her knowledge and belief, this manuscript does not infringe on the copyright or other proprietary rights of any third party. The author should understand that his/her submission of this manuscript does not guarantee publication in the ROJ. If there are multiple authors, names will appear in the ROJ in the order in which you listed them during the online submission and on this sheet. Therefore, please be sure to list names according the order you want to see in the final version. Each author should sign on the following, as appropriate.

Name (Print)	Signature