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Aims and Scope

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

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

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Editorial

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Less is more: level IB–sparing radiation therapy in nasopharyngeal cancer

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Nasopharyngeal carcinoma (NPC) is a rare malignant tumor arising from the epithelium of the nasopharynx. There are three pathological subtypes of NPC: keratinizing squamous, non-keratinizing, and basal squamous. Overall, NPC accounts for approximately 0.7% of all cancers worldwide [1]. The incidence of NPC varies significantly with geographic location, with the highest incidence in Southeast Asia and North Africa. According to an annual report on cancer statistics in Korea, the incidence of NPC is approximately 0.2% of all cancer cases [2]. In 2019, 416 new cases of NPC were detected in Korea.

Radiotherapy (RT), either alone or in combination with chemotherapy, is the standard treatment for localized NPC. RT targets the gross tumor volume (GTV) of the primary tumor, metastatic lymph nodes (LN), and risk areas, considering the tumor spread patterns. Primary tumors of the nasopharynx tend to invade the surrounding soft tissues and bones, and spread along several foramina of the skull base. Cervical LN metastasis is widespread, with 60%–90% of patients present with LN metastasis at diagnosis [3]. The pattern of cervical LN metastasis in NPC is predictable and ordered. Skip metastasis is rare, with a risk of 0.5% to 2.7% [4,5]. Level II and lateral retropharyngeal LNs are the most commonly involved areas, followed by levels III, VA, and IV. As the nasopharynx is a midline structure, the efferents of lymphatics draining the central location often reach lymph nodes on both sides, resulting in bilateral lymph node metastases in the neck. This is particularly common in NPC, affecting up to 50% of patients.

Traditionally, radiation targets routinely included the primary tumor, retropharyngeal area, and whole neck bilaterally. The Radiation Therapy Oncology Group 0225 protocol [6] and an institution in Hong Kong [7] routinely include bilateral level I to V LNs. This was based on the pattern of LN metastases, the radiation field of the conventional two-dimensional RT technique, and the use of less accurate imaging. In contrast, with more advanced imaging methods available, such as magnetic resonance imaging (MRI) and positron emission tomography/computed tomography, LN metastases more easily and accurately detected [8]. Intensity-modulated RT (IMRT) is now the standard technique. IMRT delivers a more precise and conformed radiation dose, allowing irradiation of the selected target volume. In the era of precision medicine, the routine use of traditional RT for the treatment of NPC is currently being challenged due to advancements in diagnostic and therapeutic techniques.

As target volume delineation has become more sophisticated, evidence-based consensus guidelines for target volumes in NPC have been suggested [9]. In addition, the accumulated tumor control and failure pattern data, after selected target volume irradiation, have led to significant advances in

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personalized treatment for RT targeting in NPC [10-17]. As a result of these efforts, a recent randomized phase III trial involving that elective upper neck irradiation of the uninvolved neck has shown similar regional control with less toxicity compared with whole-neck irradiation in patients with N0-N1 NPC [18].

Kim et al. [19] provided further evidence for this trend. They retrospectively analyzed 236 patients with NPC who were treated with IMRT. Of these, 212 received level IB-sparing RT, and 24 received non-IB-sparing RT. There was no level IB recurrence despite the use of level IB-sparing RT. After propensity score matching analysis, they reported that level IB LN-sparing RT is sufficiently safe and feasible for treating patients with NPC without level IB LN metastasis. The inclusion of level IB LNs in the target volume during NPC treatment is controversial. Level IB involves lymphatic drainage from the hard and soft palates, oral cavity, anterior nasal cavity, gums, and cheeks. The incidence of level IB LN metastasis is very low, approximately 2%–4% in patients with NPC. Moreover, isolated metastasis to level IB LN is rare [5]. As such, level IB irradiation is not routinely recommended. However, it is used in selected cases, such as in patients with level II LN involvement. The rationale for using level IB irradiation for these patients is that nearly all patients with level IB LN metastasis simultaneously have level II LN. It is assumed that the involvement of level II LN can block the lymphatic flow and cause the aberrant flow to level IB. Some authors have suggested that level II LN with a large or extracapsular extension (ECE) is a high-risk factor for level IB LN metastasis. Hence, patients with these features may need to be irradiated in the level IB areas. Zhang et al. [15] suggested that the level IB sparing technique is safe and feasible for low-risk patients with NPC and in the absence of level IIA LNs ≥ 2 cm or level IIA LNs with ECE, bilateral neck involvement, or oropharynx involvement. No level IB recurrence (0/904) was observed in among those who were low-risk. Ou et al. [17] also confirmed that the percentage of level IB recurrence in those treated with level IB-sparing IMRT was only 0.46% (1/216). Interestingly, data from Kim et al. [19] showed that about 40% of patients treated with level IB LN-sparing RT have high-risk features including ≥ 2 cm level IIA LNs and/or with ECE. Bilateral LN involvement was observed in approximately 35% of patients. Despite these high-risk features, no recurrence of IB LN was observed after level IB LN-sparing RT. Our institution has similar experiences. Level IB was not electively irradiated in our practice, regardless of the level II LN status. There was only one (0.3%) recurrence among 293 patients with NPC [20]. A recent study by Wang et al. [11] also supported tthe use of level IB-sparing RT and suggested that it is safe and feasible in patients with NPC with high-risk features. After propensity matching, the level IB failures in the level IB-sparing and level IB irradiation groups were 3/169 (1.8 %) vs. 2/169 (1.2 %) in patients with ECE or level II LN ≥ 2 cm.

Level IB LN-sparing RT aims to decrease the submandibular gland (SMG) dose and volume, which may reduce xerostomia. However, previous results have not shown clinical improvement in patient-reported xerostomia [15]. They explained that RT planning was performed without a dose constraint on the irradiated SMGs. Despite level IB LN-sparing RT, the mean dose exceeded the threshold dose of 39 Gy. Contrary to these results, Kim et al. [19] showed a 23.4% absolute reduction in the incidence of grade 2 xerostomia in the bilateral IB-sparing RT group compared with the non-IB-sparing RT group in their study, even though the mean SMG doses of level IB LN-sparing RT on the ipsilateral and contralateral sides were 51.2 Gy and 45.2 Gy, respectively [19]. Wang et al. [11] also showed that grade ≥ 1 dry mouth incidence after 5 years was lower in the level IB-sparing group (27.5% vs. 16.5%, p = 0.029). It is now feasible to reduces the mean dose to SMGs by 39 Gy using sophisticated RT, which may increase the possibility of a clinically significant improvement in symptoms related to xerostomia [21]. Furthermore, some authors have reported the feasibility of reducing the elective RT dose to approximately 36–40 Gy [22-24]. The lower elective dose can further decrease the RT dose to the SMGs, which may reduce RT-induced xerostomia, and improve patient outcomes.

In summary, RT for NPC is becoming increasingly sophisticated as the evidence for the use of advanced techniques accumulates. Level IB-sparing RT may be feasible and safe for patients with NPC and negative IB LN. Using this technique, quality of life may be improved by reducing the RT dose to SMGs in patients with NPC.

Conflict of Interest

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

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Review Article

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A practical review of watch-and-wait approach in rectal cancer

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Rectal resection surgery after neoadjuvant treatment has been the mainstay treatment of locally advanced rectal cancer. However, functional outcomes and quality of life after radical resection of the rectum remain suboptimal. The excellent oncologic outcomes in patients who achieved pathologic complete response after neoadjuvant treatment questioned the need for radical surgery. The watch-and-wait approach is a noninvasive therapeutic alternative for organ preservation and avoiding operative morbidity. In the watch-and-wait approach, patients with locally advanced rectal cancer who achieve excellent clinical response after neoadjuvant treatment undergo active surveillance rather than rectal cancer surgery. In this practical review, we summarized the main results of studies on the watch-and-wait approach and provided a practical method for implementing the watch-and-wait approach.

Keywords: Rectal neoplasms, Watch and wait, Non-operative management

Introduction

Neoadjuvant therapy—such as long-course chemoradiotherapy and short-course radiotherapy, surgical resection, and adjuvant chemotherapy—are conventional treatments of locally advanced rectal cancer [1]. Total mesorectal excision has been the mainstay of treatment of locally advanced rectal cancer [2]. However, functional outcomes and quality of life after radical resection remain suboptimal. Rectal surgery is associated with significant morbidity, such as poor body image and gastrointestinal, micturition, and sexual problems. In addition, patients with very low tumors undergo abdominoperineal resection, which results in permanent colostomy [3,4]. The excellent oncologic outcomes in patients who achieved pathologic complete response (CR) after neoadjuvant treatment questioned the need for radical resection surgery [5]. Accordingly, there has been a demand for omitting surgical resection in these patients. The watch-and-wait (WW) approach is a noninvasive therapeutic alternative for organ preservation and avoiding operative morbidity. In the WW approach, patients with locally advanced rectal cancer who achieve excellent clinical response after neoadjuvant treatment undergo active surveillance rather than rectal surgery. Growing evidence has indicated that the WW approach was a safe and effective option in patients who achieved excellent tumor response after neoadjuvant treatment. In this article, we summarized the main clinical results of the WW approach. Clinicians willing to adopt the WW strategy in their routine practice should assimilate the detailed approach. We provided a step-by-step practical review of the WW approach.

Landmark Studies on the WW Approach

Table 1 summarizes the characteristics and outcomes of landmark

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Table 1. Studies on watch-and-wait approach

Study, year	Analysis	Patients	Neoadjuvant therapy		Timing of assessment after neoadjuvant treatment	Outcomes[a]				
			Radiotherapy	Chemotherapy		Local regrowth	Salvage treatment after local regrowth	Distant metastasis	OS	DFS
Habr-Gama et al. [6], 2004	Observational retrospective	71/265 (underwent WW)	50.4 Gy/28 fx	5-FU and leucovorin	8 weeks	2 (2.8%)	2/2 (100%) had transanal resection or brachytherapy	–	5-yr rate: 100%	5-yr rate: 92%
Appelt et al. [7], 2015	Observational prospective	40/51 (underwent WW)	60 Gy/30 fx to tumor, 50 Gy/30 fx to elective lymph node volumes, and 5 Gy endorectal brachytherapy boost	Oral tegafur-uracil	6 weeks	9 (22.5%) 2-yr rate: 25.9%	9/9 (100%) had salvage surgery	3 (7.5%)	2-yr rate: 100% (in full population)	–
Renehan et al. [8], 2016	Observational mixed prospective-retrospective	129 (underwent WW) 31/259 plus 98 from WW registry	45 Gy/25 fx	Fluoropyrimidine-based chemotherapy	8 weeks or more	44 (34%)	32/44 (72.7%) had salvage surgery	4 (3.1%)	3-yr rate: 96%	3-yr non-regrowth rate: 88%
Dossa et al. [9], 2017	Meta-analysis	867 from 23 studies (underwent WW)	Various	Various	Various	2-yr rate: 15.7%	The pooled proportion of patients who had salvage therapy was 95.4%.	–	–	–
van der Valk et al. [10], 2018	IWWD report Observational mixed prospective-retrospective	1,009 (underwent WW)	Various	Various	Various	213/880 2-yr rate: 25.2%	Of 148 patients with information, 46 (31%) had local excision and 115 (78%) had salvage TME.	71 (8%)	5-yr rate: 85%	5-yr rate: 94%
Garcia-Aguilar et al. [11], 2022	OPRA trial Randomized phase II trial prospective	158 (underwent INCT-CRT, of which 105 underwent WW) 166 (underwent CRT-CNCT, of which 120 underwent WW)	45 Gy/25 fx to pelvic nodes and 50–56 Gy to primary tumor and involved nodes	Concurrent capecitabine or 5-FU with 8 cycles of FOLFOX or 5 cycles of CAPEOX before or after chemoradiation	8 ± 4 weeks	42/105 (40%): INCT-CRT 33/120 (27.5%): CRT-CNCT	All patients were recommended for TME.	3-yr distant metastasis-free survival rate: 84% (in full INCT-CRT group) and 82% (in full CRT-CNCT group)	–	3-yr rate: 76% (in full INCT-CRT population) and 75% (in full CRT-CNCT population)

DFS, disease-free survival; OS, overall survival; WW, watch-and-wait; CRT-CNCT, chemoradiotherapy followed by consolidation chemotherapy; FOLFOX, 5-fluorouracil, leucovorin and oxaliplatin; CAPEOX, capecitabine and oxaliplatin; INCT-CRT, induction chemotherapy followed by chemoradiotherapy; TME, total mesorectal excision.

[a] It represents the contents represent the outcomes of patients who underwent WW unless otherwise indicated.

studies. The first report on the WW strategy was published in 2004 by Habr-Gama et al. [6]. In this retrospective study, 71 patients with distal rectal adenocarcinoma who achieved clinical CR after chemoradiation with 5-fluorouracil (5-FU), leucovorin, and 50.4 Gy underwent the WW approach. The survival outcome was excellent, with a 5-year overall survival rate of 100% and disease-free survival rate of 92%.

A prospective observational study including patients with rectal adenocarcinoma (T2-3, N0-1) within the lower third of the rectum (6 cm) was reported in 2015 [7]. The patients received chemoradiotherapy with a high dose of radiation—60 Gy in 30 fractions to tumor, 50 Gy in 30 fractions to elective lymph node volumes, 5 Gy as endorectal brachytherapy boost, and oral tegafur-uracil (300 mg/m^2). Of the 51 patients, 40 (78%) achieved clinical CR and were allocated to the WW approach group. The 1-year local recurrence rate in the observation group was 15.5%. All nine patients who had local recurrence underwent salvage surgery, which was curative with clear resection margins.

A mixed-methods prospective retrospective cohort study including 129 patients managed with the WW strategy was reported in 2016 [8]. Of the 129 patients, 34% had local regrowth, of which 88% having non-metastatic local regrowth were salvaged. The 3-year overall survival rate was 96%, and 3-year non-regrowth disease-free survival rate was 88%. Comparing the outcomes in patients managed with the WW approach with those who underwent surgery using propensity matching analysis, no differences in 3-year non-regrowth disease-free survival and overall survival rates were noted.

A systematic review and meta-analysis assessing the evidence of the WW approach in patients with clinical CR after neoadjuvant chemoradiation was published in 2017 [9]. A pooled analysis of 23 studies including 867 patients showed a 2-year local regrowth rate of 15.7%. Most patients (95.4%) with regrowth underwent salvage treatments. There was no significant difference in overall survival for patients managed with WW after achieving clinical CR compared to patients managed with surgery after achieving clinical CR or patients achieving postoperatively confirmed pathologic CR.

In 2018, an international multicenter registry study conducted by the International Watch & Wait Database (IWWD) reported the results of 1,009 patients managed with the WW approach in 47 institutes from 15 countries [10]. The 2-year cumulative incidence of local regrowth was 25%. Local regrowth was most frequently detected in the first 2 years of follow-up (88%) and located in the bowel wall in most cases (97%). Distant metastases were identified in 71 (8%) of the 880 patients. The 5-year overall and disease-specific survival rates were 85% and 94%, respectively.

The OPRA trial was a prospective, randomized, phase II trial published in 2022. Three hundred twenty-four patients with stage II or III rectal cancer were randomly assigned to either the induction chemotherapy (5-fluorouracil, leucovorin and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CAPEOX)) followed by chemoradiotherapy (50–56 Gy with either capecitabine or 5-FU) or vice versa (chemoradiotherapy followed by consolidation chemotherapy) groups [11]. After tumor restaging, patients with clinical or near-CR underwent the WW protocol, whereas those with incomplete response underwent total mesorectal excision. The 3-year disease-free survival rate was 76% in both groups. This finding was comparable to the historical data of patients treated with neoadjuvant therapy and total mesorectal excision, showing a 3-year disease-free survival rate of 75%. The 3-year total mesorectal excision-free survival rate was 41% in the induction chemotherapy followed by chemoradiotherapy groups, and 53% in the chemoradiotherapy followed by consolidation chemotherapy groups. Local recurrence-free survival, distant metastasis-free survival, and overall survival rates were similar between the groups. Thus, the order of chemoradiation and systemic chemotherapy did not change oncologic outcomes. However, chemoradiation followed by consolidation chemotherapy was associated with a higher probability of organ preservation. The OPRA trial suggested that the WW strategy could be safely applied to patients with complete or near-CR after total neoadjuvant treatment.

The WW approach resulted in disease-free survival comparable to that of the standard treatment and gave patients a chance for preserving the rectum. Although there was a chance of local regrowth, most patients who experienced local regrowth underwent successful salvage surgery. However, Smith et al. [12] reported a higher distant metastasis rate among patients who had local regrowth than that among those who did not have local regrowth (36% vs. 1%; $p < 0.001$). The WW approach may be safe in most patients. However, better risk stratification is needed for more precise patient selection.

1. Quality of life

Quality of life is an important aspect when considering the WW approach. In a retrospective case-control study, bowel function was assessed using a questionnaire in 21 patients who underwent the WW approach and 21 matched patients who underwent sphincter-preserving surgery [13]. Patients in the WW arm had better overall bowel function, with the greatest difference on the urgency/soilage subscale. A similar case-control study including 41 patients managed with the WW strategy and 41 matched patients after chemoradiation and surgery showed that patients managed with the WW approach had a better quality of life with fewer defecation and sexual and urinary tract function problems [14].

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2. Who will be the candidate for WW approach?

The inclusion criteria for the IWWD protocol (version 2.1) were as follows [15]. First, patients who achieved clinical CR after neoadjuvant therapy at assessment of tumor response or after local excision (ypT0Nx) following neoadjuvant therapy and underwent a surveillance program with no immediate surgery were included. Second, patients with local clinical CR and M1 disease registered under a separate category were included. Third, these inclusion criteria also comprised patients with a clinical near-CR to neoadjuvant therapy, in whom it was decided to defer surgery, prolong the observation period, and perform reassessment. Patients who subsequently achieved clinical CR within 24 weeks after the last radiotherapy fraction were considered to follow the WW strategy. Fourth, patients who have not achieved clinical CR after neoadjuvant treatment as a result of residual disease but nevertheless received organ-preserving treatment consisting of strict surveillance were also included. These patients may have been included in the registry under different categories. The OPRA study included patients with clinical stage II or III rectal adenocarcinomas. Patients with clinical or near-CR after neoadjuvant treatment participated in the WW protocol. Patients with recurrent rectal cancer, evidence of distant metastasis at diagnosis, or history of pelvic irradiation were excluded from the study. In summary, patients with locally advanced rectal cancer treated with CR or near-CR after neoadjuvant treatment were good candidates for the WW approach.

How to Perform the Neoadjuvant Treatment?

Chemoradiation is the mainstay of treatment before the WW approach. Many series studies including that by Habr-Gama et al. [16] used chemoradiation before the WW approach [16-19]. In the IWWD study, chemoradiation was most commonly used (804/880, 91%) and most patients (781/880, 88.8%) underwent a single therapy, while some (92/880, 10.5%) received a combination modality [10]. Most patients received capecitabine or 5-FU for concurrent chemotherapy. However, the pathologic CR rate was usually less than 15% after standard long-course chemoradiation [20,21]. Several therapeutic strategies have been considered to increase the chance of patients for undergoing the WW approach.

The first strategy was total neoadjuvant therapy. Total neoadjuvant treatment included chemoradiotherapy or short-course radiotherapy and chemotherapy, which were delivered before surgery (or as non-operative management). Total neoadjuvant treatment has been increasingly adopted for the treatment of locally advanced rectal cancers. Recent randomized phase 3 trials have shown the efficacy of total neoadjuvant treatment compared with standard chemoradiation. In the RAPIDO trial, the total neoadjuvant treatment group received short-course radiotherapy (5×5 Gy) followed by six cycles of CAPOX chemotherapy or nine cycles of FOLFOX4 followed by total mesorectal excision. Three years after randomization, the cumulative probability of disease-related treatment failure was 23.7% in the total neoadjuvant treatment group versus 30.4% in the standard care group ($p = 0.019$) [20]. The pathological CR rate doubled in the total neoadjuvant treatment group (28% vs. 14%). In the PRODIGE23 trial, the total neoadjuvant treatment group was administered neoadjuvant chemotherapy with six cycles of fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX), followed by chemoradiotherapy, total mesorectal excision, and adjuvant chemotherapy (six cycles of FOLFOX6 or four cycles of CAPEOX) [21]. The 3-year disease-free survival rates were 76% in the total neoadjuvant treatment group and 69% in the standard-of-care group ($p = 0.034$). Pathologic CR was more than doubled in the total neoadjuvant treatment group (28% vs. 12%). In the CAO/ARO/AIO-12 trial, patients were assigned to receive either three cycles of 5-FU, leucovorin, and oxaliplatin before 5-FU/oxaliplatin chemoradiation or chemoradiation before chemotherapy [22], the pathological CR rates were 17% or 25%, respectively. The 3-year disease-free survival rate was 73% in both groups. These high pathological CR rates in patients treated with total neoadjuvant treatment imply that the use of total neoadjuvant treatment may increase the possibility that patients could undergo the WW approach. In a prospective, randomized phase II OPRA trial, total neoadjuvant treatment and either the WW approach or total mesorectal excision based on tumor response were evaluated [11]. The total neoadjuvant treatment consisted of either induction chemotherapy followed by chemoradiotherapy or chemoradiotherapy followed by consolidation chemotherapy. Approximately half of those receiving chemoradiotherapy followed by consolidation chemotherapy achieved sustained clinical CR and preserved the rectum at 3 years. In a retrospective study, by Chin et al. [23], 90 patients received short-course radiotherapy (25 Gy in 5 fractions) to the pelvic area, followed by consolidation chemotherapy. An optional simultaneous integrated boost dose of 30 Gy was prescribed to the primary and extramesorectal lymph nodes at 35 Gy. Patients with clinical CR ($n = 43$; 47.8%) underwent the WW approach.

The second strategy to enhance tumor response is radiation dose escalation. Radiation dose escalation can be achieved using external-beam radiotherapy or brachytherapy. Habr-Gama et al. [24] conducted a retrospective study, in which patients undergoing standard chemoradiation (50.4 Gy and 2 cycles of 5-FU-based chemotherapy) were compared with those undergoing dose-escalated chemoradiation using external beam radiotherapy (54 Gy and 6 cycles of 5-FU-based chemotherapy). The clinical CR rate was higher

in the dose-escalated chemoradiation group (86% vs. 57%, respectively) compared with those who underwent standard chemoradiation. Patients undergoing dose-escalated chemoradiation were more likely to experience organ preservation and avoid definitive surgical resection at 5 years (67% vs. 30%). In the IWWD study, the standard dose was most frequently used (50 Gy in 354 patients and 45 Gy in 173 patients). However, dose-escalated radiotherapy was used in some patients (54 Gy in 102 patients and 60 Gy in 40 patients).

Brachytherapy is a type of internal radiotherapy. A small radioactive material is put into the body, inside or close to the cancer, or low-energy X-rays (contact X-ray brachytherapy) are used. In brachytherapy, energy is deposited mainly on the surface of tumor and penetrates only a few millimeters of tissue beneath tumor. This treatment delivers a higher dose of radiation directly to tumor than may be possible with external beam radiotherapy. In a prospective observational study conducted by Appelt et al. [7], both external beam radiotherapy and brachytherapy were used for dose escalation. Patients with T2 or T3, N0–N1 adenocarcinoma in the lower third of the rectum (6 cm) were administered chemoradiotherapy (60 Gy in 30 fractions to tumor, 50 Gy in 30 fractions to elective lymph node volumes, 5 Gy endorectal brachytherapy boost, and oral tegafur-uracil) every day for 6 weeks. High rates of clinical CR were achieved (78%). The local recurrence rate at 1 year was 15.5%. Sun Myint et al. [25] evaluated 83 patients who received a contact X-ray brachytherapy boost (mostly 90 Gy/3 fractions/4 weeks) following chemoradiotherapy or radiotherapy (45 Gy). Clinical CR was achieved in 53 patients (63.8%) after brachytherapy boosts. The local recurrence rate after clinical CR was 11.3% with a median follow-up of 2.5 years. In a French multicenter study, patients with rectal adenocarcinoma (T2-3; < 5 cm in diameter) were treated with contact X-ray brachytherapy delivering 90 Gy/3 fractions/4 weeks in combination with chemoradiation (50 Gy) for organ preservation [26]. Among the 74 patients, clinical or near-CR was noted in 71 (95%) at week 14. The 3-year local recurrence and cancer-specific survival rates were 10% and 88%, respectively. In a retrospective study by Garant et al. [27], patients received 40 Gy in 16 fractions of pelvic external beam radiation therapy followed by 3 weekly image-guided adaptive brachytherapy boosts of 10 Gy to the residual tumor for a total of 30 Gy in 3 fractions. With a median follow-up of 1.9 years, the proportion of clinical CR, tumor regrowth rate, and cumulative incidence of local relapse were 86.2%, 13.6%, and 16.8%, respectively, at 2 years. In these brachytherapy studies, rectal bleeding was found to be the main cause of toxicity. Although Sun Myint et al. [25] reported only grade 1 or 2 rectal bleeding, Appelt et al. [7] reported a rate of 7%, Gerard et al. [26] reported 12%, and Garant et al. [27] reported 13% of grade 3 rectal bleeding. In summary, standard long-course chemoradiation could be used for organ preservation. Therapeutic strategies for enhancing tumor response could also be used to increase the chance of undergoing the WW approach. These strategies include total neoadjuvant treatment and radiation dose escalation using either external beam radiotherapy or brachytherapy.

How to Assess Tumor Response after Neoadjuvant Treatment?

Careful reassessment should be performed after neoadjuvant treatment for proper selection of patients who could undergo the WW approach. In the OPRA trial, reassessment was performed using endoscopy, digital rectal examination, magnetic resonance imaging (MRI), and computed tomography (CT) of the chest, abdomen, and pelvis. According to the previously defined schema of endoscopy, digital rectal examination, and MRI in the protocol, tumor response was classified as CR, near-CR, and incomplete CR [28]. For example, CR is defined by endoscopic results of flat, white scar, telangiectasia with no ulcer or nodularity, normal findings on digital rectal examination, MRI results of only dark T2 signal and no visible lymph nodes on T2-weighted MRI, and no visible tumor on B800-B100 signal and/or lack of or low signal on the ADC map on diffusion-weighted MRI. In the IWWD study, reassessment consisted of endoscopy, digital rectal examination, and various imaging modalities, according to each institution's policy [10]. The diagnostic procedures at reassessment were endoscopy (89%), pelvic MRI (71%), pelvic CT (30%), endorectal ultrasound (8%), positron emission tomography scan (4%), carcinoembryonic antigen (CEA, 22%), and local excision (5%).

The timing of the reassessment varied according to the study. In the OPRA trial, reassessment was performed within 8 ± 4 weeks of neoadjuvant treatment. The IWWD protocol indicated that patients with CR after 12 weeks of neoadjuvant treatment would be able to participate. The IWWD protocol also stated that patients with near-CR and those who subsequently achieved clinical CR within 24 weeks could be considered to participate in the protocol. Although there was no consensus on the timing of reassessment, and the timing varied in a range of 4–20 weeks among studies [7,8,16,19,29-32], reassessment was usually performed after 8 weeks in many studies. An early assessment could be misinterpreted as an incomplete response. A sufficient time interval more than 8 weeks from neoadjuvant treatment and reassessment of tumor could allow for maximal tumor regression.

Although there was a good correlation between clinical CR after neoadjuvant treatment and pathologic CR after surgery, some patients still experienced local regrowth after achieving clinical CR

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Table 2. Suggested watch-and-wait protocol

Category	Description
Patients	Patients with locally advanced rectal cancer treated showing CR after neoadjuvant treatment or patients showing near-CR in whom it is decided to defer surgery and prolong the observation period and to perform reassessment
Neoadjuvant treatment	Standard long-course chemoradiation (45–50 Gy with capecitabine or 5-fluorouracil). To enhance tumor response, radiation dose escalation by external beam radiotherapy and/or brachytherapy boost or total neoadjuvant treatment can be used
Reassessment	Reassessment with endoscopy, digital rectal examination, and imaging modalities including pelvic MRI at least after 8 weeks post-treatment
Follow-up	Evaluation with endoscopy, digital rectal examination, and imaging modalities including pelvic MRI at least more than 3 times a year during the first 2 years and then once or twice a year thereafter

CR, complete response; MRI, magnetic resonance imaging.

during the WW duration [33]. Thus, it is important to accurately predict pathologic CR before surgery for the proper selection of patients who could undergo the WW strategy. Promising results have been achieved in studies using cutting-edge technologies. Shin et al. [34] and Bibault et al. [35] developed models to predict pathologic CR after neoadjuvant treatment using radiomics and deep learning technology, If a robust method for predicting pathologic CR is established in the future, the treatment outcome of the WW approach will be further improved.

How to Follow Up in the WW Approach?

A more intensive follow-up protocol was used in the WW approach than in the routine surveillance after standard treatment. The IWWD study emphasized the importance of endoscopic surveillance during the first 2 years because local regrowth occurred mostly in the first 2 years of follow-up (188/213, 88%), with regrowth nearly always located in the bowel wall (206/213, 97%). Heterogeneous surveillance schedules and modalities have been presented in various studies. For example, in the OPRA study, the WW protocol consisted of digital rectal examination and flexible sigmoidoscopy every 4 months for the first 2 years from the time of assessment of response and every 6 months for the following 3 years [11]. Rectal MRI was performed every 6 months for the first 2 years and annually for the following 3 years. In the protocol by Habr-Gama et al. [24], patients were followed up every 6 to 10 weeks during the first 2 years of follow-up, including repeat digital rectal examination, rigid proctoscopy, and CEA level determination. Visits were performed every 12 weeks (3 months) in the third year and every 24 weeks (6 months) thereafter. According to the protocol by Renehan et al. [8], the follow-up protocol consisted of digital rectal examination; MRI (every 4–6 months in the first 2 years); examination under anesthesia or endoscopy; CT scan of the chest, abdomen, and pelvis; and at least two CEA measurements in the first 2 years. In summary, digital rectal examination and endoscopy were the main tools used for follow-up evaluation. Pelvic MRI was another important imaging tool. CT scans of the chest, abdomen, and pelvis; positron emission tomography (PET)-CT scans; or CEA measurements could be used. Visits should be performed at least three times a year during the first 2 years. A summary of the proposed WW protocol is presented in Table 2.

Conclusion

The WW approach has proven its safety and effectiveness in many studies, including a prospective phase 2 randomized study and a large international database study in patients with rectal cancer with clinical or near-CR after neoadjuvant treatment. The WW approach can be a good therapeutic option in patients who do not hope for surgery. Since both surgery and the WW approach have their pros and cons, clinicians should carefully evaluate each patient's goals for treatment and patient's motivation to avoid surgery for maintaining their quality of life or pursue more definite treatment. The optimal intensity of neoadjuvant treatment to maximize tumor response must be determined. Randomized trials on intensive neoadjuvant treatment for undergoing the WW approach are being conducted (NCT02704520 and NCT04095299). A limitation is that no prospective phase 3 clinical study has directly compared between standard treatments and the WW approach. Further randomized controlled trials are required to validate this WW approach. Another limitation is that there was no international consensus regarding the WW protocol. An international consensus needs to be established based on optimal patient selection criteria, neoadjuvant treatment protocols, tumor response assessment criteria, and follow-up protocols.

Statement of Ethics

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

Conflict of Interest

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

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Author Contributions

Conceptualization, Byun HK, Koom WS. Funding acquisition, Byun HK, Koom WS. Investigation and methodology, Byun HK, Koom WS. Project administration, Byun HK, Koom WS. Resources, Byun HK, Koom WS. Supervision, Koom WS. Writing of the original draft, Byun HK Writing of the review and editing, Byun HK, Koom WS.

Data Availability Statement

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

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Safety and efficacy of salvage conventional re-irradiation following stereotactic radiosurgery for spine metastases

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Purpose: There has been limited work assessing the use of re-irradiation (re-RT) for local failure following stereotactic spinal radiosurgery (SSRS). We reviewed our institutional experience of conventionally-fractionated external beam radiation (cEBRT) for salvage therapy following SSRS local failure.
Materials and Methods: We performed a retrospective review of 54 patients that underwent salvage conventional re-RT at previously SSRS-treated sites. Local control following re-RT was defined as the absence of progression at the treated site as determined by magnetic resonance imaging.
Results: Competing risk analysis for local failure was performed using a Fine-Gray model. The median follow-up time was 25 months and median overall survival (OS) was 16 months (95% confidence interval [CI], 10.8–24.9 months) following cEBRT re-RT. Multivariable Cox proportional-hazards analysis revealed Karnofsky performance score prior to re-RT (hazard ratio [HR] = 0.95; 95% CI, 0.93– 0.98; p = 0.003) and time to local failure (HR = 0.97; 95% CI, 0.94–1.00; p = 0.04) were associated with longer OS, while male sex (HR = 3.92; 95% CI, 1.64–9.33; p = 0.002) was associated with shorter OS. Local control at 12 months was 81% (95% CI, 69.3–94.0). Competing risk multivariable regression revealed radioresistant tumors (subhazard ratio [subHR] = 0.36; 95% CI, 0.15–0.90; p = 0.028) and epidural disease (subHR = 0.31; 95% CI, 0.12–0.78; p =0.013) were associated with increased risk of local failure. At 12 months, 91% of patients maintained ambulatory function.
Conclusion: Our data suggest that cEBRT following SSRS local failure can be used safely and effectively. Further investigation is needed into optimal patient selection for cEBRT in the retreatment setting.

Keywords: Radiosurgery, Re-irradiation, Radiotherapy dosage, Local neoplasm recurrence, Neoplasm metastasis

Introduction

Estimated to occur in 40%–50% of advanced cancers [1], osseous spinal metastases are associated with substantial morbidity including pain, vertebral column fractures, and neurologic compromise manifesting as incontinence, radiculopathy, quadriparesis, respiratory arrest, and/or ambulatory dysfunction [2-4]. Patient ambulation is central to functional independence and has been shown to be a critical factor associated with health-related quality of life (HRQoL) and overall prognosis [5]. While treatment of spinal metastases alone is rarely curative, the use of local radiation therapy (RT) with or without surgery has shown to provide significant ben-

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efits including prolongation of survival, preservation of ambulation, maintenance of neurologic functions, and reduction of pain [6]. Spine stereotactic radiosurgery (SSRS) has been established as a safe and effective treatment for spinal metastatic disease by providing precise targeting of tumor volume with higher biological effective doses (BED) while sparing sensitive adjacent structures [3,6-9]. In recent years, advances in technology have allowed SSRS to be increasingly utilized for upfront treatment of spine metastases in place of conventionally-fractionated external beam radiation (cEBRT) [10,11].

Though SSRS is thought to confer more durable disease control when compared with conventionally-fractionated RT, particularly for radioresistant histologies [6,9,12], 10%–20% of patients nevertheless develop local failure within 12 months following treatment [13-15]. As such, there has been growing interest in better characterizing salvage therapy options for these patients. While there have been several studies defining the role of salvage re-irradiation (re-RT) after conventionally-fractionated RT [3,16-18], evidence regarding the safety and efficacy of cEBRT for local failure following SSRS is limited. While repeat SSRS has been reported to confer roughly 80% 1-year local control (LC) rate [15], the efficacy of cEBRT following failure after SSRS is unknown. When compared with repeat SSRS, cEBRT for re-RT has several potential advantages including more widespread access and lower resource utilization. Additionally, SSRS may not be universally accessible to patients across different races, insurances, or geographical regions [19]. cEBRT also covers the epidural space more completely, which is advantageous given that the most common pattern of failure following SSRS is an epidural location [13,15]. In some patients, SSRS may be contraindicated due to spine instability, cord compression, or the number of vertebrae involved. cEBRT may provide superior disease coverage as a salvage option following SSRS in patients with greater extent of disease.

The goal of this study was to review our institutional experience with the use of cEBRT for local spinal relapse following SSRS with a focus on safety and efficacy. We also sought to determine prognostic variables that may influence the overall survival (OS) and LC of using cEBRT re-RT for spine metastases previously treated with SSRS.

Materials and Methods

1. Patients

We performed a retrospective review of 54 patients that underwent conventional re-RT following image-confirmed local progression at a spinal metastatic site that was previously treated with SSRS at a single large, comprehensive cancer center between 2005 and 2020. Each patient was carefully chosen for SSRS following multidisciplinary discussions of patient eligibility. Patients were commonly selected for SSRS for having good performance status, minimal vertebral level involvement, and limited additional metastases. Chart review was performed after obtaining the Institutional Review Board approval by the University of Texas MD Anderson Cancer Center (No. PA13-0218). Written informed consent from subjects in this retrospective chart review was not required.

SSRS and re-RT dose constraints for organs-at-risk were in agreement with previously published recommendations [20,21]. A minimum interval of 6 months was preferred between RT courses. Individualized decisions to re-irradiate earlier than 6 months were determined on a case-by-case bases after multidisciplinary review and discussions of the risks and benefits of re-treatment with the patient.

Patient age at diagnosis, age at spinal metastasis, number of metastases at re-RT, sex, race, Karnofsky performance score (KPS), pain scores, local therapies, therapy-related toxicities, vertebral column fractures, epidural disease at re-RT, paraspinal disease at re-RT, date of last follow-up, ambulatory status, and date of local failure were collected from the medical record. Solitary bone disease was defined as disease with a single bone metastasis without visceral organ metastases at the time of re-RT. Limited LC has been reported with use of cEBRT for radioresistant spine tumors [12,22]. To assess whether tumor radiosensitivity impacted patient response to spinal re-RT, patients were classified as having either radioresistant or radiosensitive metastases based upon the histology of the primary lesion. Based on our institutional practice, histologies that were considered radioresistant included renal cell carcinoma (RCC), urothelial carcinoma, melanoma, sarcoma, hepatocellular carcinoma (HCC), cholangiocarcinoma, colorectal adenocarcinoma, and non-small cell lung cancer [9]. Radiosensitive histologies included thyroid, breast, anal, prostate, and esophagogastric adenocarcinomas.

2. Latency to initial SSRS, local control and overall survival

Latency to SSRS was calculated from the time of spinal metastasis diagnosis to SSRS treatment. Local failure following SSRS was defined as radiographic progression of disease at the previously treated site. LC following re-RT was defined as the absence of progression of disease at the treated site as assessed on magnetic resonance imaging (MRI). Radiographic progression following both SSRS and re-RT was defined as an increase in tumor size at the treated site. LC and OS were estimated using the Kaplan-Meier method. OS were also estimated for patients with radioresistant disease that were treated with either 40 Gy or 30 Gy in 10 fractions using the log-rank method. Median follow-up time was esti-

mated using the reverse Kaplan-Meier method. Predictors of LC and OS were determined using univariate and multivariable Cox proportional-hazards analysis. Univariate and multivariable competing risk regressions were also performed considering local progression and death as competing factors.

3. Evaluation of clinical characteristics and outcomes following SSRS and re-RT

Patient RT-related acute toxicities, radiation-induced myelopathy or neuropathy, and frequency of vertebral column fractures (VCF) were determined following both SSRS and re-RT. SSRS and re-RT dose, fractionation, and technique were also abstracted and compared between groups. KPS was abstracted from patient charts at 1-, 3-, 6-, and 12-month following re-RT. Median KPS was calculated at each time point and adjusted to account for patients that were lost to follow-up or deceased at each time point. All patients were ambulatory prior to re-RT. When it occurred, date of loss of ambulatory status following re-RT was noted.

4. Statistical considerations

Significance between patient and treatment characteristics was determined using a p-value threshold of ≤0.05. Normality and lognormality tests were performed to determine appropriate parametric and non-parametric tests for continuous variables. Categorical variables were assessed using χ^2 or Fisher exact tests. Comparisons of OS and LC between groups were performed using both the Gehan-Breslow-Wilcoxon and log-rank methods. Competing risk analysis for local failure was performed using the Fine-Gray model. Subhazard ratios (subHR) from the Fine-Gray competing risk analysis describe the effect of the variables on the event of interest while accounting for competing events [23]. Statistical calculations were performed with Prism 9.1.2 (GraphPad Software, Boston, MA, USA), RStudio (RStudio Inc., Boston, MA, USA), and Stata 16.1 SE (StataCorp LLC, College Station, TX, USA).

Results

1. Patients demographics, SSRS treatment, and disease characteristics

We analyzed data from 54 patients that underwent conventional re-RT following image-confirmed local progression at a spinal metastatic site that was previously treated with SSRS. Forty-one of patients (76%) had radioresistant metastases and 13 (24%) had radiosensitive histologies. Patient demographics and disease characteristics are detailed in Table 1. Baseline patient characteristics were balanced among both radiosensitivity groups. Most patients were non-Hispanic White (65%) and male (61%). Prior to SSRS, the proportion of patients with a KPS ≥80 was 92% for radiosensitive histologies and 91% for radioresistant histologies (Table 2). A higher proportion of patients with radioresistant disease were treated with higher BED_{10} ($p = 0.0001$). Radioresistant patients also had nominally higher rates of prior surgery at the SSRS site (29%) compared to the radiosensitive group (8%), though this value was not statistically significant ($p = 0.15$). At the time of re-RT, most patients had epidural disease (80%) and multiple visceral metastases (83%), whereas a minority had paraspinal disease (39%).

2. SSRS-local failure and re-irradiation characteristics

Despite differences in SSRS treatment doses, there was no difference in the median time to local failure between the radioresistant (11.9 months; 95% confidence interval [CI], 12.5–21.5) and radiosensitive cohorts (8.6 months; 95% CI, 6.0–26.2; $p = 0.54$) (Table 3). Following local failure, patients underwent fractionated re-RT to the site of spinal metastases. The median time between SSRS and re-RT was 13.1 months (95% CI, 9.5–17.9) and did not differ among radiosensitivity groups ($p = 0.982$). Patients were retreated due to either progression at treated site without pain (74%, 40/54) or progression with pain (26%, 14/54). Additionally, most patients received re-RT more than 6 months after initial SSRS (83%). The techniques used were 2D/3D (68%) and intensity-modulated radiation therapy (IMRT, 32%). KPS prior to re-RT, radiation technique, salvage surgery, and radiation dose were not significantly different between radioresistant and radiosensitive groups. Collectively, 33% of patients received salvage surgery prior to re-RT. Two patients received systemic therapies concurrent with re-RT; one with nivolumab/ipilimumab and one with gemcitabine. Most patients received 30 Gy in 10 fractions (78%) or 40 Gy in 10 fractions (15%). All patients receiving 40 Gy were treated with IMRT utilizing a simultaneous integrated boost (SIB) technique that restricted the dose to the spinal cord to a maximum of 34 Gy [24]. Patients with radioresistant histologies were preferentially chosen for treatment with 40 Gy in 10 fractions using a SIB. Other RT dose-fractionation schemes included 30 Gy in 20 fractions ($n = 1$), 20 Gy in 5 fractions ($n = 1$), 33 Gy in 14 fractions ($n = 1$), and 20 Gy in 10 fractions ($n = 1$). For cEBRT after SSRS, a high priority was given to keeping the 110% isodose line off the spinal cord. Examples of 3D treatment plans for cEBRT after SSRS versus cEBRT alone can be visualized in Fig. 1.

Across all patients, the most common acute toxicities included fatigue (37%), pain (33%), and esophagitis/dysphagia (24%). There were no acute toxicities of grade 3 or higher reported. Grade 2 toxicities accounted for 26% of the re-RT toxicities. There were five patients that experienced VCF at the spinal site following re-RT (9%) and were not different between radiosensitive and radioresis-

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Table 1. Patient demographics and characteristics

Characteristic	All patients	Radioresistant	Radiosensitive	p-value
Number of patients (%)	54 (100)	41 (75.9)	13 (24.1)	
Age at cancer diagnosis	53.4 ± 13.4	54.0 ± 13.0	51.2 ± 14.9	0.4738
Age at spinal metastasis	56.9 ± 12.5	56.4 ± 13.2	58.7 ± 10.1	0.5497
Race				0.9999
Non-Hispanic	48 (88.9)	36 (87.8)	12 (92.3)	
Hispanic	6 (11.1)	5 (12.2)	1 (7.7)	
Ethnicity				0.7237
White	35 (64.8)	26 (63.4)	9 (69.2)	
Black/African American	5 (9.3)	3 (7.3)	2 (15.4)	
Asian	4 (7.4)	3 (7.3)	1 (7.7)	
Middle Eastern	3 (5.6)	3 (7.3)	0 (0.0)	
Other	7 (13.0)	6 (14.6)	1 (7.7)	
Sex				0.7451
Male	33 (61.1)	26 (63.4)	7 (53.8)	
Female	21 (38.9)	15 (36.6)	6 (46.2)	
Histology				
Renal cell carcinoma	13 (25.9)	13 (34.1)	0 (0.0)	
Sarcoma	10 (18.5)	10 (24.4)	0 (0.0)	
Hepatocellular carcinoma	7 (11.1)	7 (14.6)	0 (0.0)	
Colorectal Adenocarcinoma	5 (9.3)	5 (12.2)	0 (0.0)	
NSCLC	4 (7.4)	4 (9.8)	0 (0.0)	
Melanoma	1 (1.9)	1 (2.4)	0 (0.0)	
Urothelial	1 (1.9)	1 (2.4)	0 (0.0)	
Thyroid (FTC)	2 (3.7)	0 (0.0)	2 (15.4)	
Thyroid (PTC)	2 (3.7)	0 (0.0)	2 (15.4)	
Breast	2 (3.7)	0 (0.0)	2 (15.4)	
Endometrial	1 (1.9)	0 (0.0)	1 (7.7)	
SCC	1 (1.9)	0 (0.0)	1 (7.7)	
Prostate	2 (3.7)	0 (0.0)	2 (15.4)	
Esophageal	1 (1.9)	0 (0.0)	1 (7.7)	
Stomach	1 (1.9)	0 (0.0)	1 (7.7)	
HNSCC	1 (1.9)	0 (0.0)	1 (7.7)	
Cancer extent				
Solitary bone disease				0.9999
Yes	9 (16.7)	7 (17.1)	2 (15.4)	
No	45 (83.3)	34 (82.9)	11 (84.6)	
Epidural disease				0.4920
Yes	43 (79.6)	34 (82.9)	9 (69.2)	
No	11 (20.4)	7 (17.1)	4 (30.8)	
Paraspinal disease				0.2056
Yes	21 (38.9)	25 (61.0)	5 (38.5)	
No	33 (61.1)	16 (39.0)	8 (61.5)	
Number of metastases				0.8593
1	9 (16.7)	7 (17.1)	2 (15.4)	
2	8 (14.8)	7 (17.1)	1 (7.7)	
3	12 (22.2)	8 (19.5)	4 (30.8)	
4–6	15 (27.8)	11 (26.8)	4 (30.8)	
> 7	10 (18.5)	8 (19.5)	2 (15.4)	

Values are presented as number of patients (%) or average ± standard deviation.
NSCLC, non-small cell lung cancer; FTC, follicular thyroid carcinoma; PTC, papillary thyroid cancer; SCC, squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma.
Statistical analysis was performed comparing radioresistant and radiosensitive histologies using appropriate tests.

Table 2. Baseline characteristics of patients at the time of initial course of stereotactic radiosurgery

Characteristic	All patients	Radioresistant	Radiosensitive	p-value
Latency to SSRS (day)	199.1 ± 59.6	170.7 ± 60.3	288.7 ± 161.6	0.5250
SSRS site location				0.3298
C spine	6 (11.1)	6 (14.6)	0 (0)	
T spine	31 (57.4)	23 (56.1)	8 (61.5)	
L/S spine	17 (31.5)	12 (29.3)	5 (38.5)	
SSRS dose (Gy/fx)				0.0001
16/1	1 (1.9)	0 (0)	1 (7.7)	
18/1	11 (20.4)	3 (7.3)	8 (61.5)	
24/1	29 (53.7)	28 (68.3)	1 (7.7)	
27/3	13 (24.1)	10 (24.4)	3 (23.1)	
Number of vertebrae				0.4596
1	37 (68.5)	27 (65.9)	10 (76.9)	
2	10 (18.5)	7 (17.1)	3 (23.1)	
3	6 (11.1)	6 (14.6)	0 (0)	
4	1 (1.9)	1 (2.4)	0 (0)	
BED_{10}				0.0001
42	1 (1.9)	0 (0)	1 (7.7)	
50	11 (20.4)	3 (5.6)	8 (61.5)	
51	13 (24.1)	10 (18.5)	3 (23.1)	
82	29 (53.7)	28 (51.9)	1 (7.7)	
Surgery				0.1513
RT alone	41 (75.9)	29 (70.7)	12 (92.3)	
Surgery + RT	13 (24.1)	12 (29.3)	1 (7.7)	
Number of non-contiguous SSRS-treated sites				0.4290
1	43 (79.6)	34 (82.9)	9 (69.2)	
> 1	11 (20.4)	7 (17.1)	4 (30.8)	
KPS prior to SSRS				0.7592
100	5 (9.3)	3 (7.3)	2 (15.4)	
90	27 (50.0)	20 (48.8)	7 (53.8)	
80	17 (31.5)	14 (34.1)	3 (23.1)	
< 70	5 (9.3)	4 (9.8)	1 (7.7)	

Values are presented as average ± standard error of the mean or number of patients (%).
SSRS, spine stereotactic radiosurgery; BED, biological effective dose; RT, radiotherapy; KPS, Karnofsky performance score.
Statistical analysis was performed comparing radioresistant and radiosensitive histologies using appropriate tests.

tant groups. Most VCF following salvage RT (4/5) were asymptomatic. Of patients that developed VCF, 60% (3/5) maintained local control for more than 15 months. All VCFs were believed to be attributable to disease progression. One patient with leiomyosarcoma developed grade 2 radiation-induced myelopathy. The patient was treated with 30 Gy in 10 fractions 17.9 months following SSRS, and developed myelopathy 4.7 months after re-RT. SSRS treatment provided a mean dose of 2,392 cGy and 788 cGy to the gross tumor volume (GTV) and spinal cord, respectively. Subsequent IMRT used a mean dose of 3,135 cGy and 791 cGy to GTV and spinal cord, respectively. This patient experienced weakness and pain bilaterally in the lower limbs, but did not severely impair ambulation. The patient was treated with steroids and did not develop local failure until 2 years following re-RT. There were no other cases of radiation-induced myelopathy or neuropathy in our cohort.

3. Survival and local control outcomes

Median follow-up time following cEBRT was 25 months (95% CI, 19.9–undefined) (Table 3). Rates of local failure were not significantly different among radioresistant and radiosensitive tumors ($p = 0.19$) or patients treated with 40 Gy versus 30 Gy ($p = 0.503$). LC for the entire cohort at 12 months was 81% (95% CI, 69.3–94.0) (Fig. 2A). Univariate analysis revealed age at diagnosis, age at spinal metastases, and KPS prior to SSRS were significantly associ-

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Table 3. Re-irradiation treatment characteristics and toxicities

Characteristic	All patients	Radioresistant	Radiosensitive	p-value
Time to SSRS LF (mo)	11.0 (5.3–26.9)	11.9 (12.5–21.5)	8.6 (6.0–26.2)	0.5450
Time from SSRS to re-RT (mo)	13.1 (9.5–17.9)	13.2 (9.3-19.5)	11.3 (6.5-37.3)	0.9818
Follow-up time (mo)	25.2 (19.9–undef)	34.7 (21.3–undef)	undef (17.2–undef)	0.8732
Time from SSRS to re-RT (mo)				
> 6	45 (83.3)	34 (82.9)	11 (84.6)	0.9999
> 12	30 (55.6)	24 (58.5)	6 (46.2)	0.5282
Conventional RT type				0.9999
2D/3D	37 (68.5)	28 (68.3)	9 (69.2)	
IMRT	17 (31.5)	13 (31.7)	4 (30.8)	
Salvage surgery				0.9645
Salvage surgery + PORT	14 (25.9)	11 (26.8)	3 (23.1)	
Salvage surgery	4 (7.4)	3 (7.3)	1 (7.7)	
No	36 (66.7)	27 (65.9)	9 (69.2)	
Systemic therapy				0.9999
Yes	2 (3.7)	2 (4.9)	0 (0)	
No	52 (96.3)	39 (95.1)	13 (100)	
RT dose				0.7078
30 Gy/10 fx	42 (77.8)	31 (75.6)	11 (84.6)	
40 Gy/10 fx	8 (14.8)	7 (17.1)	1 (7.7)	
Other	4 (7.4)	3 (7.3)	1 (7.7)	
KPS prior to re-RT				0.2977
90–100	22 (40.7)	17 (41.5)	5 (38.5)	
70–80	24 (44.4)	16 (39.0)	8 (61.5)	
50–60	7 (13.0)	7 (17.1)	0 (0)	
< 40	1 (1.9)	1 (2.4)	0 (0)	
Acute toxicities				0.1809
None	19 (35.2)	12 (29.3)	7 (53.8)	
Yes	35 (64.8)	29 (70.7)	6 (46.2)	
Fatigue	20 (37.0)	16 (39.0)	4 (30.8)	
Nausea/vomiting	7 (13.0)	6 (14.6)	1 (7.7)	
Diarrhea	1 (1.9)	0 (0)	1 (7.7)	
Esophagitis/dysphagia	13 (24.1)	9 (22.0)	4 (30.8)	
Pain	18 (33.3)	16 (39.0)	2 (15.4)	
Neurologic	2 (3.7)	2 (4.9)	0 (0)	
Other	6 (11.1)	5 (12.2)	1 (7.7)	
Acute toxicity grade				0.9999
1	26 (48.1)	21 (51.2)	5 (38.5)	
2	9 (16.7)	8 (19.5)	1 (7.7)	
VCF following conventional RT				0.9999
Yes	5 (9.3)	4 (9.8)	1 (7.7)	
Asymptomatic	4 (7.4)	3 (7.3)	1 (7.7)	0.9999
Symptomatic	1 (1.9)	1 (2.4)	0 (0)	
No	49 (90.7)	37 (90.2)	12 (92.3)	
Ambulatory dysfunction				0.0838
Yes	5 (9.3)	2 (4.9)	3 (23.1)	
Due to spinal disease progression	0 (0)	0 (0)	0 (0)	
Due to other disease sites	5 (9.3)	2 (4.9)	3 (23.1)	
Due to radiation myelopathy	0 (0)	0 (0)	0 (0)	
No	49 (90.7)	39 (95.1)	10 (76.9)	

Values are presented as median (95% confidence interval) or number of patients (%).
SSRS, spine stereotactic radiosurgery; LF, local failure; re-RT, re-irradiation; IMRT, intensity-modulated radiation therapy; PORT, post-operative radiation therapy; VCF, vertebral column fracture.
Statistical analysis was performed comparing radioresistant and radiosensitive histologies using appropriate tests.

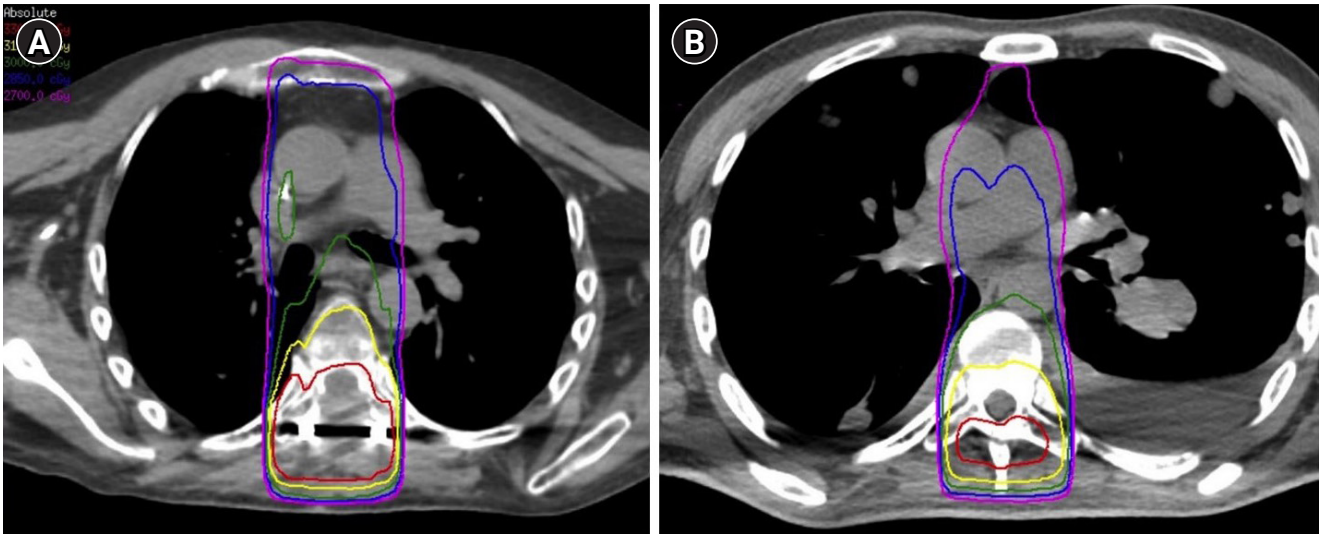

Fig. 1. Comparison of three-dimensional treatment plans for cEBRT in a radiation-naïve patient (left) and cEBRT after SSRS (right). cEBRT, conventionally-fractionated external beam radiation; SSRS, spine stereotactic radiosurgery.

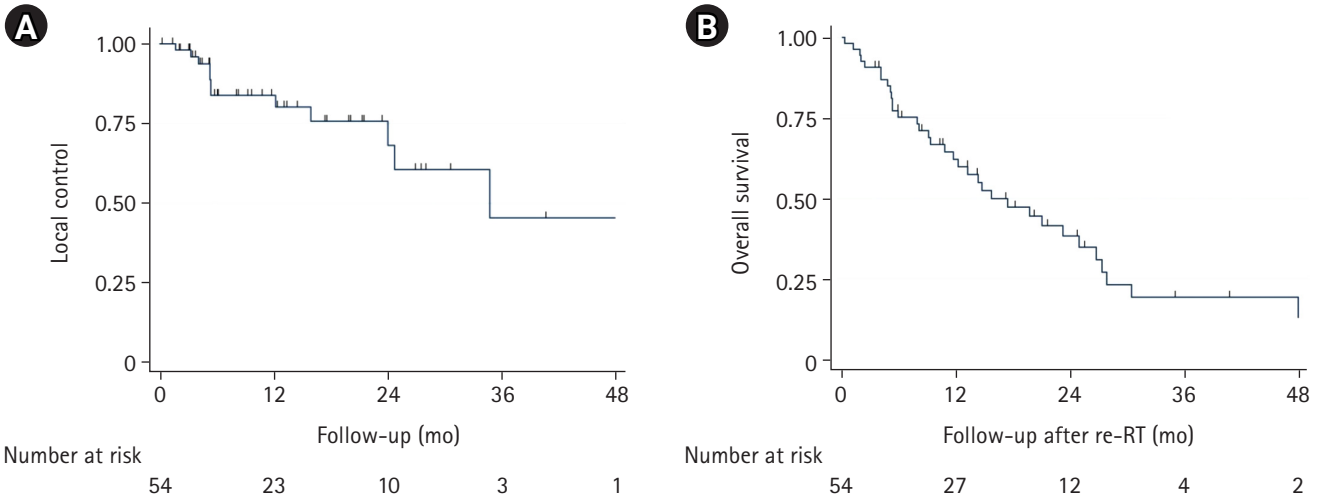

Fig. 2. (A) Local control and (B) overall survival Kaplan-Meir curves for included patients. re-RT, re-irradiation.

ated with LC (Table 4). However, after multivariable analysis, only age at spinal metastases and KPS prior to SSRS remained significant. Competing risk regression multivariable analysis between OS and LC revealed radioresistant histology (subHR = 0.36; 95% CI, 0.15–0.90; p = 0.03) and the presence of epidural disease (subHR = 0.31; 95% CI, 0.12–0.78; p = 0.01) were associated with increased risk of local failure (Table 5).

The median OS from re-RT was 15.8 months (95% CI, 11.7–26.7) for the entire cohort (Fig. 2B). Univariate analysis revealed that age at diagnosis, radiosensitivity, sex, race, number of metastases, presence of epidural disease, pre-SSRS surgery, pre-SSRS KPS, number of non-contiguous SSRS-treated sites, BED_{10}, or salvage surgery were not associated with OS (Table 4).

KPS prior to re-RT (HR = 0.96; 95% CI, 0.93–0.99; p = 0.003), time to SSRS local failure (HR = 0.97; 95% CI, 0.94–0.996; p = 0.003), and presence of solitary bone disease (HR = 0.30; 95% CI, 0.10–0.87; p = 0.027) were significantly associated with OS. Male sex (HR = 1.90; 95% CI, 0.91–3.80; p = 0.09) was also not significant. Multivariable Cox proportional hazards analysis revealed KPS pre-re-RT (HR = 0.95; 95% CI, 0.93–0.98; p = 0.003) and time to local failure following SSRS (HR = 0.97; 95% CI, 0.94–1.00; p = 0.04) to be significantly associated with improved OS, while male sex (HR = 3.41; 95% CI, 1.46–8.34; p = 0.004) was associated with worse OS. Using the log-rank test, no difference was observed in OS (p = 0.886) between patients receiving 30 Gy versus 40 Gy.

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Table 4. Mortality and local control hazard ratios

Attributes	Mortality HR				Local control HR			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age at diagnosis	1.00 (0.98–1.03)	0.7295	-		0.95 (0.91–0.99)	0.0125	1.08 (0.92–1.27)	0.3397
Radiosensitivity	0.94 (0.43–2.02)	0.8657	-		3.60 (0.47–28.0)	0.2179	-	
Male sex	1.93 (0.95–3.93)	0.0691	3.92 (1.64–9.33)	0.0021	0.63 (0.20–2.00)	0.4465	-	
Race (White vs. non-White)	1.21 (0.58–2.51)	0.6183	-		0.97 (0.29–3.20)	0.9542	-	
Solitary bone disease	0.30 (0.10–0.87)	0.0272	0.57 (0.11–1.07)	0.0653	0.26 (0.03–2.08)	0.2063	-	
Number of metastases	1.05 (0.94–1.17)	0.3640	-		1.10 (0.92–1.30)	0.2975	-	
Age at spinal metastases	1.00 (0.97–1.03)	0.9803	-		0.93 (0.89–0.97)	0.0009	0.84 (0.71–0.99)	0.0413
Epidural disease	0.65 (0.29–1.43)	0.2809	-		1.70 (0.50–5.50)	0.4066	-	
Pre-SSRS surgery	0.96 (0.44–2.08)	0.9158	-		2.40 (0.76–7.80)	0.1319	-	
Pre-SSRS KPS	0.97 (0.94–1.01)	0.1474	-		0.93 (0.89–0.98)	0.0091	0.91 (0.86–0.97)	0.0015
Number of non-contiguous SSRS-treated sites	1.21 (0.65–1.98)	0.6924	-		0.74 (0.22–2.50)	0.6278	-	
BED_{10}	1.00 (0.98–1.02)	0.8583	-		1.00 (0.98–1.10)	0.3464	-	
KPS pre-re-RT	0.96 (0.93–0.99)	0.0028	0.95 (0.93–0.98)	0.0026	0.97 (0.92–1.01)	0.1721	-	
Time to local failure following SSRS (mo)	0.97 (0.94–0.996)	0.0279	0.97 (0.94–1.00)	0.0379	1.00 (0.92–1.00)	0.1721	-	
Paraspinal disease	0.64 (0.32–1.27)	0.2046	-		1.00 (0.98–1.00)	0.4847	-	
VCF post-re-RT	0.73 (0.32–1.27)	0.6020	-		1.20 (0.37–3.60)	0.8050	-	
Salvage surgery	0.56 (0.27–1.88)	0.1319	-		2.10 (0.84–5.20)	0.1121	-	

SSRS, spine stereotactic radiosurgery; KPS, Karnofsky performance score; BED, biological effective dose; VCF, vertebral column fracture; re-RT, re-irradiation; HR, hazard ratio; CI, confidence interval.

Table 5. Competing risk regression analysis for local failure

Attributes	Univariate competing risk regression		Multivariable competing risk regression	
	subHR (95% CI)	p-value	subHR (95% CI)	p-value
Age at diagnosis	1.05 (1.01–1.09)	0.016	1.02 (0.97–1.06)	0.510
Radiosensitivity	0.55 (0.27–1.13)	0.100	0.36 (0.15–0.90)	0.028
Male sex	2.14 (1.02–4.49)	0.044	1.88 (0.72–4.86)	0.190
Race (White vs. non-White)	1.36 (0.64–2.89)	0.420	-	
Solitary bone disease	0.93 (0.42–2.06)	0.850	-	
Number of metastases	0.96 (0.86–1.08)	0.530	-	
Age at spinal metastases	1.06 (1.02–1.11)	0.004	1.06 (1.001–1.12)	0.062
Epidural disease	0.41 (0.21–0.82)	0.012	0.31 (0.12–0.78)	0.013
Pre-SSRS surgery	0.52 (0.19–1.41)	0.200	-	
BED_{10}	0.99 (0.97–1.01)	0.500	-	
KPS pre-re-RT	0.98 (0.95–1.01)	0.290	-	
Paraspinal disease	0.68 (0.33–1.39)	0.290	-	
VCF post-re-RT	0.21 (0.04–1.14)	0.070	0.18 (0.08–0.34)	< 0.001
Salvage surgery	1.28 (0.64–2.53)	0.480	-	

SSRS, spine stereotactic radiosurgery; KPS, Karnofsky performance score; BED, biological effective dose; VCF, vertebral column fracture; re-RT, re-irradiation; subHR, subhazard ratio; CI, confidence interval.

4. KPS and ambulatory status after salvage RT

Median KPS was maintained between 70–80 up to 12 months after salvage RT (Fig. 3). Five patients developed ambulatory dysfunction (9%), a rate which did not differ between the radiosensitivity groups (p = 0.084) (Table 3). Of the five patients that developed ambulatory dysfunction, two patients developed neurologic compromise due to other metastatic sites, while three patients were limited in their ability to walk secondary to pain and musculoskeletal deconditioning. Ambulatory dysfunction in all five patients was not attributable to sequelae of radiation or progression at the

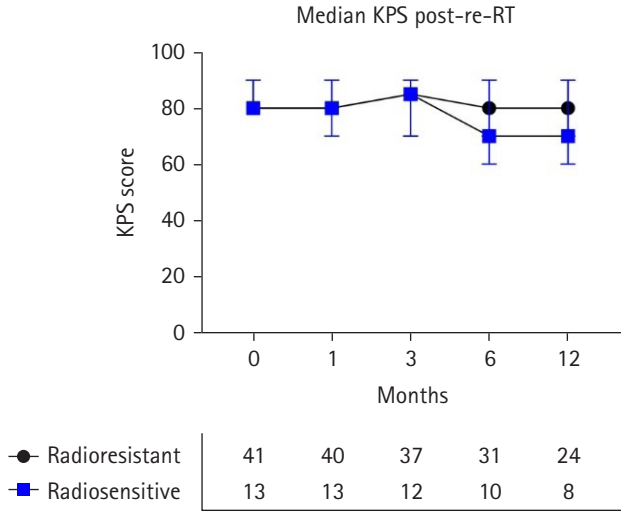

Fig. 3. Karnofsky performance status (KPS) at months following re-irradiation (re-RT) stratified by histology type.

treated site, but rather due to progression at other levels.

Discussion and Conclusion

The primary goal of re-RT is to improve patient QoL by controlling pain and preserving functional independence. The first application of SSRS was for the use of re-RT following cEBRT failure. Subsequent studies have assessed the outcomes and efficacy of SSRS following cEBRT failure and shown that SSRS re-RT can provide LC rates of 66%–93% with median OS of 10–21 months [3,16-18]. However, with the increasing use of SSRS as first-line RT for spine metastases, questions remain regarding how to manage local recurrence following SSRS. Several series have examined re-SSRS following local failure and have shown a 48% 1-year OS with minimal toxicity [15]. However, re-SSRS may not always be a preferred option for patients as SSRS may not be readily available at all centers, requires lengthy treatment planning with highly specialized dosimetry and physics teams, and additionally requires longer treatment times, which patients with painful spinal metastases may not be able to tolerate. Our experience with cEBRT following SSRS failure shows comparable efficacy to reports using re-SSRS following SSRS failure [15]. There were no grade 3–5 late toxicities reported, and despite one patient experiencing radiation-mediated myelopathy, this patient was able to maintain exceptional local control and was still alive at last follow up. Similarly, while 9% (n = 5) of patients developed VCF following re-RT, most durably maintained local control prior to progression.

One concern that treating physicians may have with using cEBRT following SSRS failure may be inadequate efficacy for radioresistant histologies [9,12]. In the current series, radiosensitivity grouping was not associated with either OS or LC in the multivariable model. However, the competing risk assessment between OS and local failure found radioresistant tumors to be associated with an increased risk of local failure. Despite this, there was no difference seen at in median KPS or in the rate of ambulatory dysfunction between the radiosensitive and radioresistant groups. We also assessed whether different cEBRT doses were associated with survival or LC. With 40 Gy in 10 fractions, concerns about high risks of toxicity may exist given that 30 Gy is typically delivered to the cord. While no such increased toxicity risk was observed, we also failed to observe differences in OS or LC between patients re-treated with 40 Gy and those treated with 30 Gy. A true dose-response relationship could not be robustly evaluated given the limited number of dose/fractionation schemes and subgroups sizes presented in the current study.

The only variables significantly associated with survival were KPS prior to re-RT, time to local failure following SSRS, and male sex. Performance status is a well-established predictor of OS in patients treated with RT bone metastases [25-27]. Furthermore, an accelerated rate of local failure is indicative of more aggressive disease and often worse prognosis. Male sex has been associated with decreased survival in a variety of cancers [28]. However, there have been mixed reports regarding the prognostic value of sex for OS in patients with spine metastases treated with radiation [26,27]. We assessed whether variability in sex as a prognostic marker could be confounded by tumor histology as men comprised most of the patients with RCC (10/13) and HCC (7/7) in the present study. However, in our univariate analysis, these tumor histologies did not associate with worse survival. It is possible that the prognostic significance of male sex could be confounded by other factors not explored in this study such as mutational burden and tumor size [15,18,29]. We observed a significant association of local failure with epidural disease, consistent with prior reports [13,15].

While we observed limited late toxicities and favorable outcomes, re-RT should be used in carefully selected patients with a full discussion of the potential risks and benefits in shared decision-making with the patient. The tolerance of organs-at-risk depends on various factors including age, treatment dose, fractionation pattern, organ type, tumor type, and time interval between re-RT [30]. It has been estimated that spinal cord recovery following RT after 6 months is 25%, and radiation earlier than 6 months can significantly increase the risk of myelopathy [20]. We generally recommend having a minimum interval of 6 months between radiation courses to mitigate the risk of toxicity. We do not recommend using re-RT if 3 months or less has lapsed since prior treatment and we generally exercise caution if the interval is between 3 and

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6 months.

To our knowledge, this is the first study to assess the efficacy and safety of cEBRT following SSRS failure. There are inherent limitations to this retrospective study including selection and information bias. Additionally, we are limited in our ability to determine the impact of cEBRT re-RT on pain management and other QoL measures as these are not routinely documented before and after therapy. Given that many patients with spinal metastatic disease ultimately succumb, it is possible that the true rate of late cord toxicities from re-RT is higher than reported. Assessment of subclinical myelopathy was not possible given that formal organ level assessments were not performed. Furthermore, a comparison group was not included in this study, limiting our ability to make conclusions about this technique relative to others. The patient population in this study was heterogenous with a wide variety of antecedent treatments and different tumor histologies, which may have introduced confounding factors. We were also limited in our ability to detect prognostic factors for OS and LC in the setting of a limited number of events observed. Inclusion of more granular information regarding treatment volumes and a greater diversity of tumor histologies could provide more robust evaluation of prognostic factors associated with the efficacy of re-RT with cEBRT. Still, the strengths of this study include long patient follow-up using serial MRI assessment in a relatively large patient population allowing us to more readily determine tumor response to RT. We further attempted to include a variety of variables and adjust for known confounders with the use of multivariable and competing risk modeling.

In conclusion, our data show that re-RT with cEBRT for SSRS-treated metastases is feasible and associated with favorable local control, and that re-RT with conventional fractionation following local failure after SSRS may be safe and effective for patients. cEBRT re-RT was associated with comparable median OS and LC with patients treated with re-SSRS from historical controls and conferred minimal toxicities. For maximal safety, we recommend a latency of at least 6 months following SSRS before re-treatment.

Statement of Ethics

All patient information was de-identified in this study. Written informed consent from subjects in this retrospective chart review was not required. The study was approved by our institutional review board on human research, and was specifically reviewed and approved by the Institutional Review Board of University of Texas MD Anderson Cancer Center (No. PA13-0218).

Conflict of Interest

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

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Author Contributions

Conceptualization, Florez MA, De B, Chapman BV, Prayongrat A, Thomas JG, Ghia AJ. Investigation, Florez MA, De B, Chapman BV, Prayongrat A, Thomas JG. Formal analysis, Florez MA, De B. Writing of the original draft, Florez MA, De B, Chapman BV, Prayongrat A, Thomas JG, Beckham TH, Wang C, Yeboa DN, Bishop AJ, Briere T, Amini B, Li J, Tatsui CE, Rhines LD, Ghia AJ. Writing of the review and editing, Florez MA, De B, Chapman BV, Prayongrat A, Thomas JG, Beckham TH, Wang C, Yeboa DN, Bishop AJ, Briere T, Amini B, Li J, Tatsui CE, Rhines LD, Ghia AJ.

Data Availability Statement

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

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Peripheral blood lymphocyte changes after stereotactic ablative body radiotherapy to lung or liver metastases in patients with oligometastatic cancers

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Purpose: To perform the analysis of the peripheral blood lymphocyte changes after stereotactic ablative radiotherapy (SABR) in patients with oligometastatic cancers.

Materials and Methods: The dynamics of the immune status in peripheral blood was prospectively evaluated in 46 patients with lung (17 cases) or liver (29 cases) metastases treated by SABR. Flow cytometry of peripheral blood lymphocyte subpopulations was performed before SABR, 3–4 weeks and 6–8 weeks after the end of SABR: 3 fractions of 15–20 Gy or 4 fractions of 13.5 Gy. The number of treated lesions varied from 1 (32 patients) to 2–3 (14 patients).

Results: SABR induced a significant increase of T-lymphocytes ($CD3^+CD19^-$) ($p = 0.001$), T-helper ($CD3^+CD4^+$) ($p = 0.004$), activated cytotoxic T-lymphocytes ($CD3^+CD8^+HLA\text{-}DR^+$) ($p = 0.001$), activated T-helpers ($CD3^+CD4^+HLA\text{-}DR^+$) ($p < 0.001$). A significant decrease of T-regulated immune suppressive lymphocytes ($CD4^+CD25^{bright}CD127^{low}$) ($p = 0.002$) and NKT-cells ($CD3^+CD16^+CD56^+$) ($p = 0.007$) was recorded after the SABR. The comparative analysis demonstrated that lower doses of SABR ($EQD_{2Gy(\alpha/\beta=10)}$ = 93.7–105.7 Gy) induced significant increase of T-lymphocytes, activated cytotoxic T-lymphocytes, and activated $CD4^+CD25^+$ T-helpers, while SABR with higher doses ($EQD_{2Gy(\alpha/\beta=10)}$ = 150 Gy) was not associated with these effects. A more efficient activations of T-lymphocytes ($p = 0.010$), activated T-helpers ($p < 0.001$), and cytotoxic T-lymphocytes ($p = 0.003$) were associated with SABR to a single lesion. A significant increase of T-lymphocytes ($p = 0.002$), T-helpers ($p = 0.003$), and activated cytotoxic T-lymphocytes ($p = 0.001$) was observed after SABR for hepatic metastases in contrast to SABR for lung lesions.

Conclusion: Changes in peripheral blood lymphocytes after SABR could be influenced by the location or the number of irradiated metastasis, and the dose of SABR.

Keywords: Stereotactic body radiotherapy, Immune response, Dose fractionation, Abscopal effect

Introduction

Radiotherapy is an important and obligatory component of treatment programs in 50%–70% patients with cancer [1]. It has been traditionally considered as a method that improved the locoregional control. Radiobiologically, the radiation exposure is perceived as a cytotoxic treatment causing DNA breaks with lethal events that manifested by cell death through necrosis, apoptosis, and autophagy [2]. During the last decades, there appeared numerous evidence that radiotherapy and especially stereotactic ablative radiotherapy

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(SABR) are also characterized by systemic effects mainly represented by antitumor immune response usually called an abscopal effect.

A certain number of hypotheses tried to explain systemic effects of radiotherapy. It was proposed that the radiation damage of various tumors is associated with the release of increased presentation of antigens and release of effector molecules (HMGB1) triggering molecular patterns associated with damage of tumor cells (DAMPs), activation of proteasomal pathways and major histocompatibility complex molecules (HLA) of the 1st class, NKG2D ligand expression, complement fixation, interferon 1st type production, and induction of cell immunogenic death [3-6]. Besides, it should be mentioned that irradiation affects vessel, tumor stoma and tumor stem cells. Tumor irradiation, as is pointed out, activates the antigen-presenting cells and cytotoxic T-lymphocytes that can finally induce tumor cell death both in the irradiation area and in unirradiated sites.

Unfortunately, until now the immunologic changes occurring during and after the SABR have not been sufficiently studied in clinical practice. In the presented prospective observation study, we have performed a complex analysis of the dynamics of immune status before and after SABR of various (in number and localization) metastatic lesions.

Materials and Methods

The dynamics of immune status in peripheral blood was prospectively evaluated in 46 patients (30 females and 16 males; mean age, 55.9 years; 95% CI, 52.4–59.4) with lung or liver metastases treated by SABR from September 2018 to July 2021.

This study was prospective observation single center study, and it was approved by the local ethics committee of N.N. Petrov National Cancer Center (Protocol No. 13, dated November 29, 2018). Voluntary informed consent for stereotactic radiotherapy and immunological studies was obtained in writing form from all patients.

Inclusion criteria were as follows: morphologically confirmed disease; oligometastatic disease (less than four lesions); the first SABR session; anatomical localization of metastases in liver or lungs, allowing for a radical SABR course; the size of liver or lung metastasis is less than 5 cm; no treatment by immune checkpoints inhibitors or/and chemotherapy at least 2 months before and after SABR.

Exclusion criteria were radiotherapy 6 or less months before SABR; immunotherapy before or during the treatment; age <18 years; Karnofsky performance status <70%; chemotherapy 2 months before or during SABR.

The immune status of patients was evaluated before irradiation, 3–4 and 6–8 weeks after the end of SABR. Distribution of the patients according to the localization of the primary lesion and irradiated metastatic sites is presented in Table 1.

SABR was performed according to the standard volumetric modulated arc therapy technique with respiratory gating and obligatory cone-beam CT guidance of every session. Lung metastases were irradiated as 3 fractions of 20 Gy (peripheral metastases) or 4 fractions of 13.5 Gy (lesions with proximity to ribs or central "fly zone"). Liver metastases were irradiated in 3 fractions of 15–20 Gy. The number of treated lesions varied from 1 (32 patients) to 2–3 (14 patients). The dynamics of immune status was analyzed in patients with liver (29 cases) and lung (17 cases) metastases separately after SABR within the equivalent dose—$EQD_{2Gy(\alpha/\beta=10)}$ of 93.75–105.75 Gy (group A, 23 patients) or $EQD_{2Gy(\alpha/\beta=10)}$ of 150 Gy (group B, 23 patients). All included patients underwent SABR treatment for all oligometastatic lesions.

The assessment of immune status was made in three checkpoints: before the radiation (checkpoint 1), in 3–4 weeks (checkpoint 2), and in 6–8 weeks (checkpoint 3) after the end of SABR. The immune status was characterized by the count of several main

Table 1. Patient distribution according to the primary tumor and localization of the irradiated metastases

Primary	n	Localization of the irradiated metastases	
		Liver	Lung
Colorectal adenocarcinoma	20	17	3
Breast cancer			
Luminal B subtype	5	4	1
HER2-enriched subtype	1	0	1
Triple-negative subtype	1	1	0
Non-small cell lung cancer			
Adenocarcinoma	1	0	1
Squamous cell carcinoma	2	1	1
Adenosquamous carcinoma	1	1	0
Poorly differentiated	1	0	1
Soft tissue sarcoma			
Leiomyosarcoma	4	2	2
Extraskeletal myxoid chondrosarcoma	1	0	1
Parotid cancer			
Adenoid cystic carcinoma	1	0	1
Clear cell carcinoma	1	0	1
Low grade adenocarcinoma	1	0	1
Epithelioid malignant melanoma	2	2	0
Esophageal squamous cell carcinoma	1	1	0
Prostate acinar adenocarcinoma	1	0	1
Hepatocellular carcinoma	1	0	1
Clear cell renal cell carcinoma	1	0	1
Total	46	29	17

HER2, human epidermal growth factor receptor 2.

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peripheral blood lymphocyte subpopulations.

The calculations were performed with flow cytometry method. To process the data, we used BD FACSDiva software (version v8.0.1; BD Biosciences, San Jose, CA, USA). The subpopulation composition of peripheral blood immunocompetent cells was studied on a BD FACSCanto II flow cytometer. We evaluated the relative value of lymphocytes; T-lymphocytes ($CD3^+CD19^-$); B-lymphocytes ($CD3^-CD19^+$); T-helpers ($CD3^+CD4^+$); activated T-helpers with different phenotypes ($CD3^+CD4^+HLA\text{-}DR^+$ and $CD4^+CD25^+$); cytotoxic T-lymphocytes ($CD3^+CD8^+$); activated cytotoxic T-lymphocytes ($CD3^+CD8^+HLA\text{-}DR^+$); NK-cells ($CD3^-CD16^+CD56^+$); NKT-cells ($CD3^+CD16^+CD56^+$); T-regulatory lymphocytes ($CD4^+CD25^{bright}CD127^{low}$); double-positive T-lymphocytes ($CD3^+CD4^+CD8^+$); double-negative T-lymphocytes ($CD3^+CD4^-CD8^-$); and the immunoregulatory index ($CD4^+/CD8^+$).

The values of this immune status indicators (T-lymphocytes; B-lymphocytes; T-helpers; activated T-helpers with phenotype $CD3^+CD4^+HLA\text{-}DR^+$; cytotoxic T-lymphocytes; activated cytotoxic T-lymphocytes; NK-cells; NKT-cells; double-positive T-lymphocytes; double-negative T-lymphocytes and the immunoregulatory index) were calculated from the total count of lymphocytes. $CD4^+CD25^+$ activated T-helpers and T-regulatory lymphocytes were calculated as a percentage of the T-helper ($CD3^+CD4^+$) population.

For calculation of the absolute value of the immunocompetent cells, a two-platform analysis system was used; the calculation was made using the results of a hematological analyzer.

We used antibodies for a multicolor panel (BD FACSCanto2 HIV reagents kits, 6-color TBNK reagent) mouse anti-human HLA-DR monoclonal antibodies labeled with V450, CD25 antibodies labeled with FITC (BD Biosciences), CD4 monoclonal antibodies labeled with BD PerCP-Cy5.5 fluorochrome and CD127 antibodies labeled with Pe-Cy7.

The statistical analysis of the data was performed in R version 3.6.2 (https://www.r-project.org/). Friedman test was used to determine statistically significant differences in immune status dynamics [7]. Nemenyi's criterion was used as a post hoc test for multiple pair-wise comparisons [8]. A p-value less than 0.05 was considered statistically significant. The relative value (percentage) of the immunocompetent cells was used for the statistical analysis.

Results

The analysis of immune status parameters in patients with extensive irradiated solid tumors revealed a statistically significant increase of T-lymphocytes ($CD3^+CD19^-$) in 3–4 weeks after the irradiation compared to the analysis performed before the stereotactic radiotherapy (χ^2 Friedman = 13.781; omnibus p = 0.001; pairwise p = 0.001). Besides, a statistically significant increase of T-helper subpopulation ($CD3^+CD4^+$) (χ^2 Friedman = 11.01; omnibus p = 0.004; pairwise p = 0.003) was noted in 3–4 weeks after the irradiation compared to the analysis performed before the radiotherapy and to non-significant decrease by the period of 6–8 weeks after the irradiation.

A statistically significant increase of activated cytotoxic T-lymphocytes carrying the $HLA\text{-}DR^+$ antigen was noted in 3–4 weeks after SABR (pairwise p = 0.001) with a continuing rise of this subpopulation in 6–8 weeks after the irradiation (pairwise p = 0.004) (χ^2 Friedman = 15.4; omnibus p = 0.001) (Fig. 1A). A detailed calculation is presented in Supplementary Table S1).

An increase of activated T-helpers was noted 3–4 and 6–8 weeks after the SABR compared to the values obtained before the irradiation (χ^2 Friedman = 38.8; omnibus p < 0.001; pairwise p = 0.001 and 0.001, respectively) (Fig. 1B). A detailed calculation is presented in Supplementary Table S1.

A decrease of T-regulated immune suppressive lymphocytes ($CD4^+CD25^{bright}CD127^{low}$) was recorded in 3–4 and 6–8 weeks after the SABR (χ^2 Friedman = 12.96; omnibus p = 0.002, pairwise p = 0.004 and 0.010, respectively) compared to the values obtained before the irradiation (Fig. 1C). A detailed calculation is presented in Supplementary Table S1.

Besides, a decrease of B-lymphocytes ($CD3^-CD19^+$) was recorded in 3–4 and 6–8 weeks after the SABR compared to the values recorded before the irradiation (χ^2 Friedman = 35.4; omnibus p = 0.001; pairwise p = 0.001 and 0.002, respectively).

A decrease of NKT-cells ($CD3^+CD16^+CD56^+$) was noted in 6–8 weeks after the irradiation compared to the analysis performed before the SABR (χ^2 Friedman = 9.8; omnibus p = 0.007; pairwise p = 0.006).

Statistically significant differences in the dynamics of other immune cells in the peripheral blood (activated $CD4^+CD25^+$ T-helpers, NK-cells, double positive T-lymphocytes, double negative T-lymphocytes) were not revealed.

The comparative analysis demonstrates a significant correlation between changes in the peripheral blood immune cells and the $EQD_{2Gy(\alpha/\beta=10)}$ delivered to the metastatic lesions. While examining T-lymphocytes ($CD3^+CD19^-$) after the SABR, a statistically significant increase of T-lymphocytes was discovered in 3–4 weeks after the irradiation in both dose groups—group A: $EQD_{2Gy(\alpha/\beta=10)}$ = 93.75–105.75 Gy (χ^2 Friedman = 7.3; omnibus p = 0.030; pairwise p = 0.020); group B: $EQD_{2Gy(\alpha/\beta=10)}$ = 150 Gy (χ^2 Friedman = 7.1; omnibus p = 0.030; pairwise p = 0.030).

The dynamic pattern in activated cytotoxic T-lymphocytes ($CD3^+CD8^+HLA\text{-}DR^+$) is quite interesting. When administering $EQD_{2Gy(\alpha/\beta=10)}$ = 93.75–105.75 Gy, a statistically significant increase

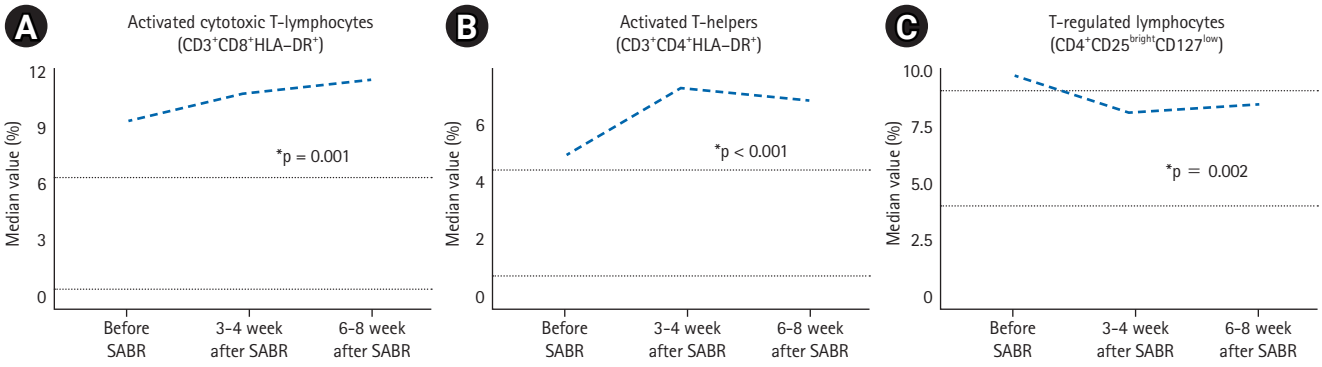

Fig. 1. Dynamics in the number of (A) activated cytotoxic lymphocytes, (B) activated T-helpers, and (C) T-regulatory lymphocytes. SABR, stereotactic ablative radiotherapy.

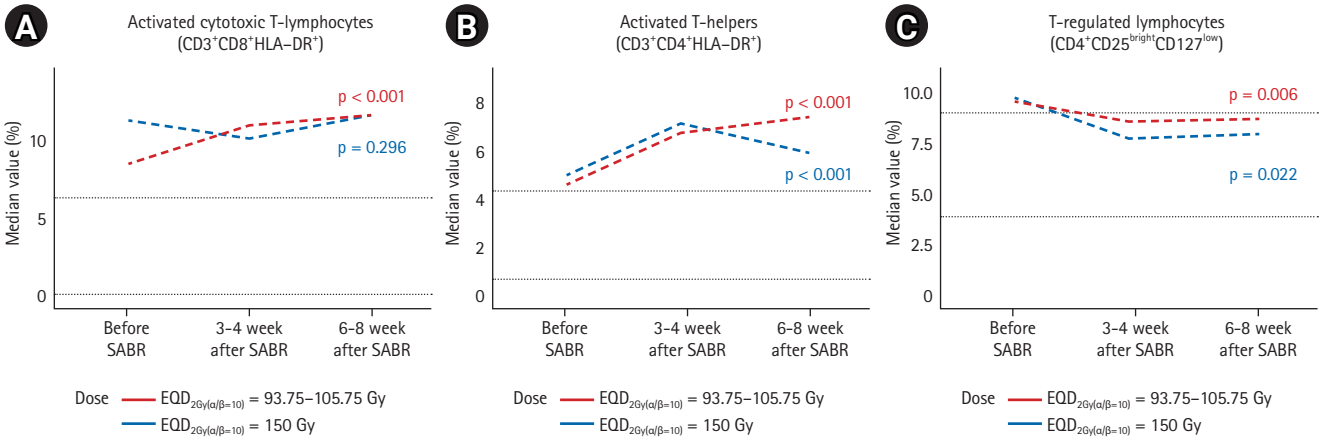

Fig. 2. Dynamics in the number of (A) activated cytotoxic lymphocytes, (B) activated T-helpers, and (C) T-regulatory lymphocytes depends on delivered EQD_{2Gy} ($\alpha/\beta = 10$). SABR, stereotactic ablative radiotherapy; EQD, equivalent dose.

of cells in the given population was noted both in 3–4 and 6–8 weeks after the irradiation (χ^2 Friedman = 16.1; omnibus p < 0.001; pairwise p = 0.001 and 0.003, respectively). At the same time, statistically significant differences in the number of activated cytotoxic T-lymphocytes after SABR with $EQD_{2Gy(\alpha/\beta=10)}$ = 150 Gy were not recorded (Fig. 2). A detailed calculation is presented in Supplementary Table S2.

A statistically significant increase of T-helpers was recorded in 3–4 weeks after irradiating the lesions with $EQD_{2Gy(\alpha/\beta=10)}$ = 93.75–105.75 Gy (χ^2 Friedman = 6.96; omnibus p = 0.030; pairwise p = 0.030). There were no differences in cells of the given subpopulation in dose group B ($EQD_{2Gy(\alpha/\beta=10)}$ = 150 Gy).

A statistically significant increase of activated T-helpers phenotype ($CD3^+CD4^+HLA\text{-}DR^+$) was noted in 3–4 and 6–8 weeks after the SABR when compared to the values obtained before SABR. These differences were significant in both groups: in group A ($EQD_{2Gy(\alpha/\beta=10)}$ = 93.75–105.75 Gy) (χ^2 Friedman = 26.2; omnibus p < 0.001; pairwise p = 0.001 and 0.001, respectively) and in group B ($EQD_{2Gy(\alpha/\beta=10)}$ = 150 Gy) (χ^2 Friedman = 14.2; omnibus p < 0.001; pairwise p = 0.001 and 0.003, respectively). Concurrently, in group B we mentioned a tendency for decrease in the number of activated T-helpers 6–8 weeks after the SABR when the values were compared to the data obtained 3–4 weeks after irradiation.

Moreover, the analysis of another subpopulation of the activated T-helpers ($CD4^+CD25^+$) demonstrated a statistically significant increase of activated T-helpers in 6–8 weeks after the SABR within the $EQD_{2Gy(\alpha/\beta=10)}$ = 93.75–105.75 Gy (group A) when compared to the values obtained before the SABR (χ^2 Friedman = 6.3; omnibus p = 0.040; pairwise p = 0.030, respectively). In group B ($EQD_{2Gy(\alpha/\beta=10)}$ = 150 Gy) we did not mention statistically significant differences in the number of activated T-helpers before and at various time points after SABR.

In the subgroup of T-regulatory (suppressors) lymphocytes we also found dose dependent effects. In particular, a significant reduction of T-regulatory lymphocytes (χ^2 Friedman = 7.7; omnibus p = 0.022; pairwise p = 0.040) was mentioned 3–4 weeks after

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SABR to metastatic lesions with $EQD_{2Gy(\alpha/\beta=10)}$ = 150 Gy. On the contrary, we did not reveal significant differences in the number of T-regulatory lymphocytes after SABR within $EQD_{2Gy(\alpha/\beta=10)}$ = 93.75–105.75 Gy.

In 46 consecutive patients, we compared the dynamics of immune status according to the number of the irradiated lesions. Group I consisted of 32 patients with one irradiated metastatic lesion and group II (14 patients) with 2–3 irradiated metastases. After SABR of a single lesion we mentioned numerous changes in immune profile. First of all, a statistically significant increase of T-lymphocytes ($CD3^+CD19^-$) was recorded in 3–4 weeks after the SABR (χ^2 Friedman = 9.2; omnibus p = 0.010; pairwise p = 0.008). In addition, an increase in the number of T-helper quantity (χ^2 Friedman = 9.1; omnibus p = 0.010; pairwise p = 0.008) was noted in the same timeframe (Fig. 3). On the contrary, we did not find any change in the number of the above-mentioned cells in the group with 2–3 irradiated lesions (group II). A detailed calculation is presented in Supplementary Table S3.

The increase of activated T-helpers ($CD3^+CD4^+HLA\text{-}DR^+$) was noted in group I in 3–4 weeks and 6–8 after the irradiation compared to the values obtained before the SABR (χ^2 Friedman = 33.2; omnibus p < 0.001; pairwise p = 0.001 and 0.001, respectively), and in group II, these changes were non-significant. However, an upward tendency was evident (χ^2 Friedman = 6.9; omnibus p = 0.033; pairwise p = 0.060 and 0.060, respectively).

A statistically significant increase of the cytotoxic T-lymphocytes was revealed in 3–4 and 6–8 weeks after the SABR of a single lesion (χ^2 Friedman = 11.6; omnibus p = 0.003; pairwise p = 0.005 and 0.020, respectively), and in group II, these changes were non-significant.

The analysis of T-regulatory lymphocytes in group with one irradiated lesion demonstrated a decrease of this subpopulation in 3–4 and 6–8 weeks after SABR compared to the values detected before the start of radiotherapy (χ^2 Friedman = 13.2; omnibus p = 0.001; pairwise p = 0.005 and 0.006, respectively). T-regulatory lymphocytes demonstrated a statistically insignificant downward tendency in the group having 2–3 irradiated lesions.

We also evaluated changes of the immune status in connection with the localization (lung vs. liver) of irradiated metastases. An increase of activated T-helpers was observed in both groups 3–4 and 6–8 weeks after SABR when compared to the values obtained before the irradiation: in group with SABR for hepatic lesions (χ^2 Friedman = 29.2; p = 0.001; pairwise p = 0.001 and 0.001, respectively) and for lung lesions (χ^2 Friedman = 8.9; omnibus p = 0.012; pairwise p = 0.020 and 0.040, respectively).

Significant changes in the number of T-lymphocytes (χ^2 Friedman = 12.8; omnibus p = 0.002; pairwise p = 0.002 and 0.020, respectively) and T-helpers (χ^2 Friedman = 10.6; omnibus p = 0.003; pairwise p = 0.006 and 0.051, respectively) were observed after SABR for hepatic metastases: both populations increased in 3–4 weeks after the irradiation followed by true decrease of T-lymphocytes in 6–8 weeks after the SABR. Statistically significant differences of the above parameters after SABR for lung metastases were not revealed (Fig. 4). A detailed calculation is presented in Supplementary Table S4.

A statistically significant increase of activated cytotoxic T-lymphocytes carrying antigen $HLA\text{-}DR^+$ was registered in 3–4 weeks (pairwise p = 0.004) and in 6–8 weeks (pairwise p = 0.010) (χ^2 Friedman = 12.2; omnibus p = 0.001) after the SABR for liver metastases. Similar differences were not revealed after irradiation of lung lesions.

Moreover, a statistically significant increase of the immunoregu-

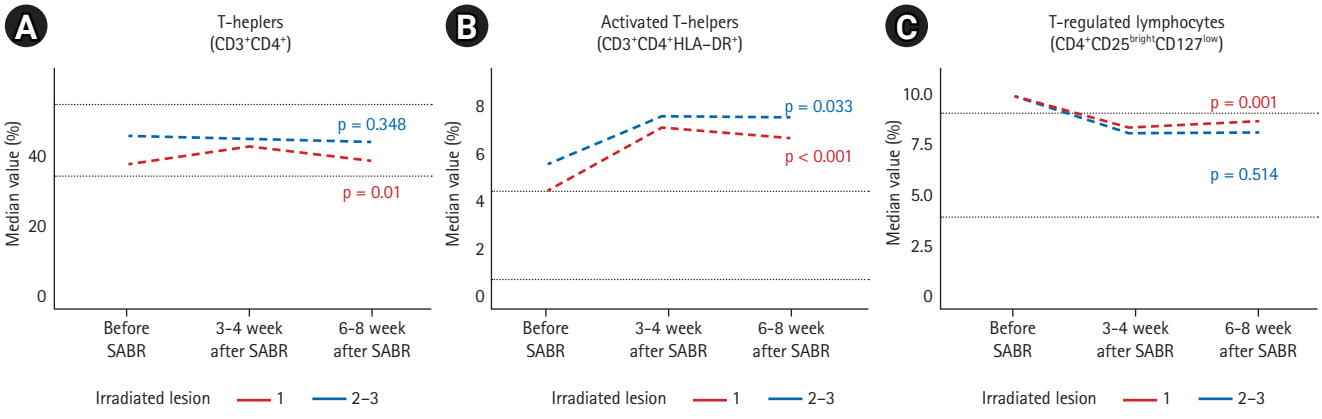

Fig. 3. Dynamics in the number of (A) T-helpers, (B) activated T-helpers, and (C) T-regulatory lymphocytes according to the number of the irradiated lesions. SABR, stereotactic ablative radiotherapy.

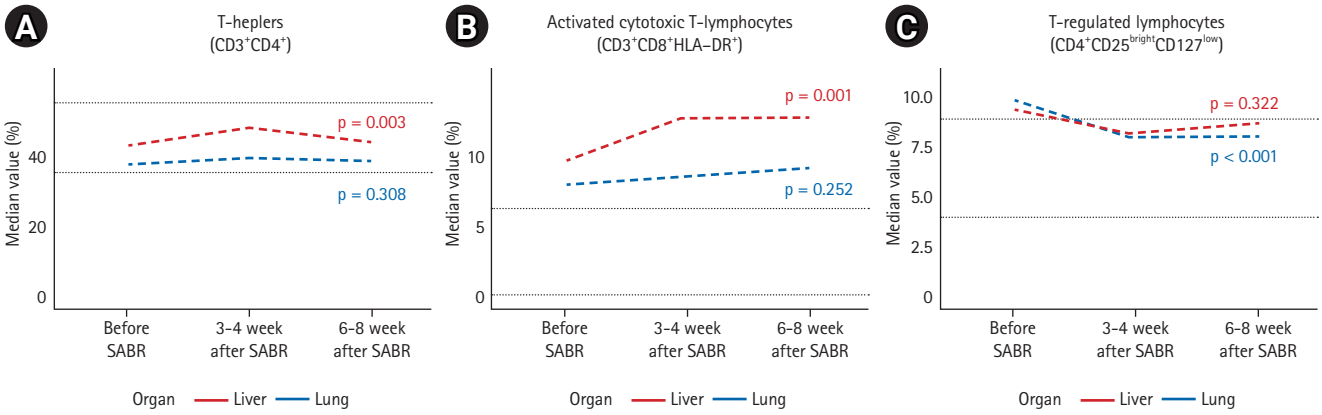

Fig. 4. Dynamics in the number of (A) T-helpers, (B) activated cytotoxic lymphocytes, and (C) T-regulatory lymphocytes according to localization of irradiated metastases. SABR, stereotactic ablative radiotherapy.

latory index was noted 3–4 weeks after SABR for liver metastases (pairwise p = 0.040) followed by a decrease in 6–8 weeks after the irradiation (χ^2 Friedman = 10.8; omnibus p = 0.004; pairwise p = 0.010).

On the contrary, a statistically significant decrease of T-regulatory lymphocytes (χ^2 Friedman = 15.6; omnibus p < 0.001) was registered only after SABR for lung metastases: 3–4 weeks (pairwise p = 0.001) and 6–8 weeks (pairwise p = 0.006) after irradiation.

Discussion and Conclusion

Different populations of immune cells characterizing SABR induced changes of the immune status were dynamically evaluated during this study. These parameters reflect differences in both T-cell and humoral component of the immune system. The obtained results identify the activation of T-cell immune response mainly by the increase of T-lymphocytes ($CD3^+CD19^-$); T-helpers ($CD3^+CD4^+$); activated T-helpers ($CD3^+CD4^+HLA\text{-}DR^+$) and activated cytotoxic T-lymphocytes ($CD3^+CD8^+HLA\text{-}DR^+$) against the decrease in activity of the antibody producer cells ($CD3^-CD19^+$).

Chua et al. [9] investigated the immune responses to radiotherapy in 10 consecutive patients using in-depth mass cytometric profiling of circulating lymphocytes. It is interesting that the authors demonstrated significant heterogeneity of the immune status among patients before the initiation of radiotherapy and in seven non-irradiated people of the control group. Nevertheless, they demonstrated immune stimulatory effect of radiotherapy that was characterized by significant increase in the frequency of CD8 positive T cells from baseline.

Other authors [10,11] also point out the significance of tumor infiltration by activated $CD8^+$ T-cell. In 2018, Zheng et al. [12] presented data confirming that a higher level of cytotoxic $CD8^+$ T-cells in peripheral blood after the irradiation predicts a better survival without progression in patients with stage I non-small-cell lung cancer treated with SABR. They concluded that the enhancement of the tumor antigen specific cell immunity by combining radiotherapy and immunotherapy might become a decisive strategy in improving survival of these patients. Other authors [13,14] underline the importance of activated T-helpers and the role of T-regulatory cells in realization of antitumor immune response.

Considering the above-mentioned issues, a special focus in interpretation of our research must be concentrated on the post-SABR activation of T-cell component: T-lymphocytes ($CD3^+CD19^-$), T-helpers ($CD3^+CD4^+$), activated T-helpers ($CD3^+CD4^+HLA\text{-}DR^+$), and activated cytotoxic T-lymphocytes ($CD3^+CD8^+HLA\text{-}DR^+$) with parallel reduction in the number of T-regulatory lymphocytes. These changes indicated that the state of T-cell inflammatory phenotype or "hot" tumor is likely to be reached after SABR. As is proved by Turajlic et al. [15], this condition is associated with a good response to immunotherapy by checkpoint inhibitors.

Most of the discussions about the possible additive or supra-additive effect of immune check point inhibitors with irradiation underline an important role of proper sequencing of these modalities. In particular, Buchwald et al. [16] demonstrated that a concurrent administration of both modalities was characterized by the effective immune response. On the other hand, in the PEMBRO-RT randomized trial therapy by check point inhibitors started 1 week after radiotherapy and was associated with the improvement in local control and disease-free survival [17]. Similar results were obtained in multicenter prospective randomized PACIFIC demonstrating that the start of therapy by PD-L1 inhibitors must be initiated during the first 2 weeks after the end of radiotherapy [18]. Results of our study indicated that the highest activation of T-cell immune response was recorded 3–4 weeks after the SABR and probably this

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timing can be optimal for combining radiotherapy with other immunotherapeutic interventions as, for instance, treatment with immune checkpoint inhibitors (PD-1/PD-L1; CTLA-4).

The effect of radiotherapy technique and the value of absorbed dose on the antitumor immune response intensity is still a matter for debates. Some authors reported that irradiation with large (> 10 Gy) dose per fraction and high absorbed radiation dose causes massive release of tumor antigens and increased frequency of abscopal effects [19,20]. Many other authors found out that the optimal immunomodulation effects of radiotherapy can be obtained with the help of less aggressive regimes, most often as 3 fractions of 8–10 Gy [16,19,21]. It was proposed that these SABR schemes are characterized by the optimal balance between accumulation of neoantigens and activation of immunosuppressive exonuclease Trex1 [21]. Our results suggest that SABR for hepatic and lung metastases with $EQD_{2Gy(\alpha/\beta=10)}$ = 93.75–105.75 Gy was associated with a more active immune response through the increase of T-lymphocytes ($CD3^+CD19^-$); activated T-helpers ($CD3^+CD4^+HLA\text{-}DR^+$ and $CD4^+CD25^+$); activated cytotoxic T-lymphocytes ($CD3^+CD8^+HLA\text{-}DR^+$). On the contrary, SABR with $EQD_{2Gy(\alpha/\beta=10)}$ = 150 Gy shows only a statistically significant decrease of T-regulatory lymphocytes.

Many authors [4,22] indicate the importance of SABR to all metastatic sites in order to decrease tumor burden, which is associated with an improved response, irradiates all manifested sites that are immunologically heterogeneous because this comprehensive radiotherapy program can maximize the probability of inducing compelling local immune effects [22]. Surprisingly, our data indicate that in patients with 2–3 irradiated metastatic lesions activation of immune cells in peripheral blood was significantly lower. We also demonstrated that the number of irradiated lesions influences the dynamic of immune response with early activation of T-cell subpopulations after SABR for one lesion and later activation of T-cells after SABR for 2–3 metastatic lesions.

These conflicting results can be partly explained by the fact that in preclinical and clinical studies, response to immunotherapy has been shown to be strongly associated with tumor burden, with higher response in lower burden [23,24]. However, the restricted number of analyzed patients and an observational design of the study makes the conclusion about the association between SABR-induced immunologic changes and the number of irradiated metastases to be very preliminary and speculative.

Currently, there is no clear understanding of what kinds of immune system changes occur in metastatic patients after SABR administered to lesions of various localizations. Tang et al. [25] reported that in patients with non-small-cell lung cancer the antitumor immunologic response is more active after the SABR for hepatic metastases than after irradiation of lung lesions. Our data obtained in mixed population of oncologic patients indicated the same trend: a more pronounced activation of T-cell immune component was mentioned in patients with SABR for liver lesions compared to the group with irradiated lung metastases. Probably this phenomenon can be explained by significant differences in immunogenic potential of lung and liver tissues with high concentration of macrophages and other lymphatic elements in liver. Additionally, it is well-known that macrophages play an important role in the functioning of immune system: first, as the cells that presented tumor antigens to $CD8^+$ T-cells; second, as the activated macrophages that damage neighboring cells by various signaling factors [26,27].

Our study has a number of meaningful limitations. First, it is a relatively small number of evaluated patients that might have underpowered some changes in the immune landscape (as in irradiating lung lesions or in SABR to multiple lesions). Moreover, the obtained data might have been critically impacted by the group heterogeny with regard to the localization and histological variant of the primary tumors. In order to overcome these limitations we tried to perform multivariate analysis, but this has not been successful due to a very small sample size of the subgroups.

However, it seems possible to make several preliminary conclusions: (1) SABR is associated with the activation of T-cell component of the immune system ($p \leq 0.01$) which is manifested by the increase of T-lymphocytes ($CD3^+CD19^-$), T-helpers ($CD3^+CD4^+$), activated T-helpers ($CD3^+CD4^+HLA\text{-}DR^+$), and activated cytotoxic T-lymphocytes ($CD3^+CD8^+HLA\text{-}DR^+$) affected by the decrease of regulatory T-lymphocytes ($CD4^+CD25^{bright}CD127^{low}$) and antibody producer cells ($CD3^-CD19^+$). The activation is most evident in 3–4 weeks after the SABR. (2) Lower doses of SABR ($EQD_{2Gy(\alpha/\beta=10)}$ = 93.7–105.7 Gy) are associated with the most significant activation of T-cell immune response ($p \leq 0.04$) than SABR with higher total dose ($EQD_{2Gy(\alpha/\beta=10)}$ = 150 Gy). (3) SABR for a single metastatic lesion induces a more pronounced activation of T-cell immune response than irradiation of two or three lesions ($p \leq 0.03$). (4) SABR for a hepatic lesion result in a more pronounced activation of T-cell immune response than SABR for lung metastases ($p \leq 0.04$).

Immunogenic effects of radiation therapy are complex, controversial and not perfectly understood. It becomes clear that many factors (localization and number of irradiated lesions, the dose and fractionation scheme, irradiated volume, etc.) can significantly influence the immunomodulating activity of radiation therapy, and further research in this field is of paramount clinical importance.

Statement of Ethics

This study was approved by the local ethics committee of N.N.

Petrov National Cancer Center (Protocol No. 13 dated November 29, 2018). Voluntary informed consent for stereotactic radiotherapy and immunological studies was obtained in writing form from all patients.

Conflict of Interest

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

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Author Contributions

Conceptualization, Novikov SN, Aleksandrovna BI, Vasilevich KS. Formal analysis, Novikov SN, Aleksandrovna BI, Yurievich ZA. Data curation, Viktorovich GD, Viktorovich GD, Ivanovna TE, Evgenevich AF, Ivanovich AA, Markovich GM. Investigation and methodology, Viktorovna EN. Writing–original draft, Novikov SN, Yurievich ZA. Writing–review and editing, Novikov SN, Aleksandrovna BI, Yurievich ZA, Viktorovna EN, Viktorovich GD, Alexandrovna FE, Ivanovna TE, Evgenevich AF, Ivanovich AA, Markovich GM, Vasilevich KS.

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.2022.00521.

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Liquid biopsy using cfDNA to predict radiation therapy response in solid tumors

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Purpose: This study explored the potential feasibility of cell-free DNA (cfDNA) in monitoring treatment response through the measurement of chromosomal instabilities using I-scores in the context of radiation therapy (RT) for other solid tumors.
Materials and Methods: This study enrolled 23 patients treated with RT for lung, esophageal, and head and neck cancer. Serial cfDNA monitoring was performed before RT, 1 week after RT, and 1 month after RT. Low-depth whole-genome sequencing was done using Nano kit and NextSeq 500 (Illumina Inc.). To measure the extent of genome-wide copy number instability, I-score was calculated.
Results: Pretreatment I-score was elevated to more than 5.09 in 17 patients (73.9%). There was a significant positive correlation between the gross tumor volume and the baseline I-score (Spearman rho = 0.419, p = 0.047). The median I-scores at baseline, post-RT 1 week (P1W), and post-RT 1 month (P1M) were 5.27, 5.13, and 4.79, respectively. The I-score at P1M was significantly lower than that at baseline (p = 0.002), while the difference between baseline and P1W was not significant (p = 0.244).
Conclusion: We have shown the feasibility of cfDNA I-score to detect minimal residual disease after RT in patients with lung cancer, esophageal cancer, and head and neck cancer. Additional studies are ongoing to optimize the measurement and analysis of I-scores to predict the radiation response in cancer patients.

Keywords: Cell-free DNA, Liquid biopsy, Radiotherapy

Introduction

The role of radiation therapy (RT) has evolved, with approximately 50% of cancer patients undergoing RT during treatment [1,2]. Advances in RT techniques, such as intensity-modulated radiotherapy and image-guided radiotherapy enabled conformal dose distribution and precise treatment delivery. However, individualized dose prescription based on radiation sensitivity remains challenging for

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radiation oncologists. A lack of biomarkers that can easily and reliably predict RT response is one of the reasons that impair precision medicine in the field of radiation oncology. Imaging biomarkers have been widely explored in the field of RT. However, in clinical practice, taking images frequently to monitor response is discouraged due to high medical costs, the risk of excessive radiation exposure, and patient inconvenience.

In this context, liquid biopsy has gained attention as a promising method for predicting response or detecting minimal disease during cancer treatment [3,4]. Circulating tumor DNA (ctDNA) refers to DNA fragments released from tumor cells and it comprises 0.1%–10% of cell-free DNA (cfDNA) [5]. In cancer patients, increased cell turnover and apoptosis by tumors lead to the release of DNA fragments into the bloodstream, and more cfDNA is detected compared to the healthy population [6,7]. The previous studies suggested that the fragmentation patterns of cfDNA across the whole genome could be used for screening or monitoring treatment response in cancer patients [8]. Emerging evidence suggests the potential of ctDNA or cfDNA in monitoring treatment response or detecting minimal residual disease in cancer treatment [9,10]. However, few studies have addressed the role of cfDNA before and after RT [11].

There are various methods to analyze cfDNA as a biomarker in cancer treatment, from targeting specific mutations to profiling chromosome instabilities. Low-coverage whole genome sequencing (LC-WGS) is a rapid and practical approach for estimating chromosomal instabilities (CINs) by detecting overall chromosomal alterations across the genome. CINs are observed more frequently and affect a large scale of the genome in cancers compared to healthy controls. The potential role of CINs in predicting treatment response and tumor burden in cancer patients has been recently suggested [12-15]. As a tool for calculating genomic instabilities, the I-score, which represents CINs of cfDNA from LC-WGS data, was developed and its feasibility as a predictive biomarker for locally advanced esophageal cancer was previously described [16].

This preliminary study explored the potential feasibility of cfDNA in monitoring treatment response through the measurement of CIN using I-scores in the context of RT for other solid tumors, including esophageal cancer.

Materials and Methods

1. Study population, sample extraction, and response evaluation

This prospective pilot study enrolled 23 patients treated with RT for lung, esophageal, and head and neck cancer after approval of the

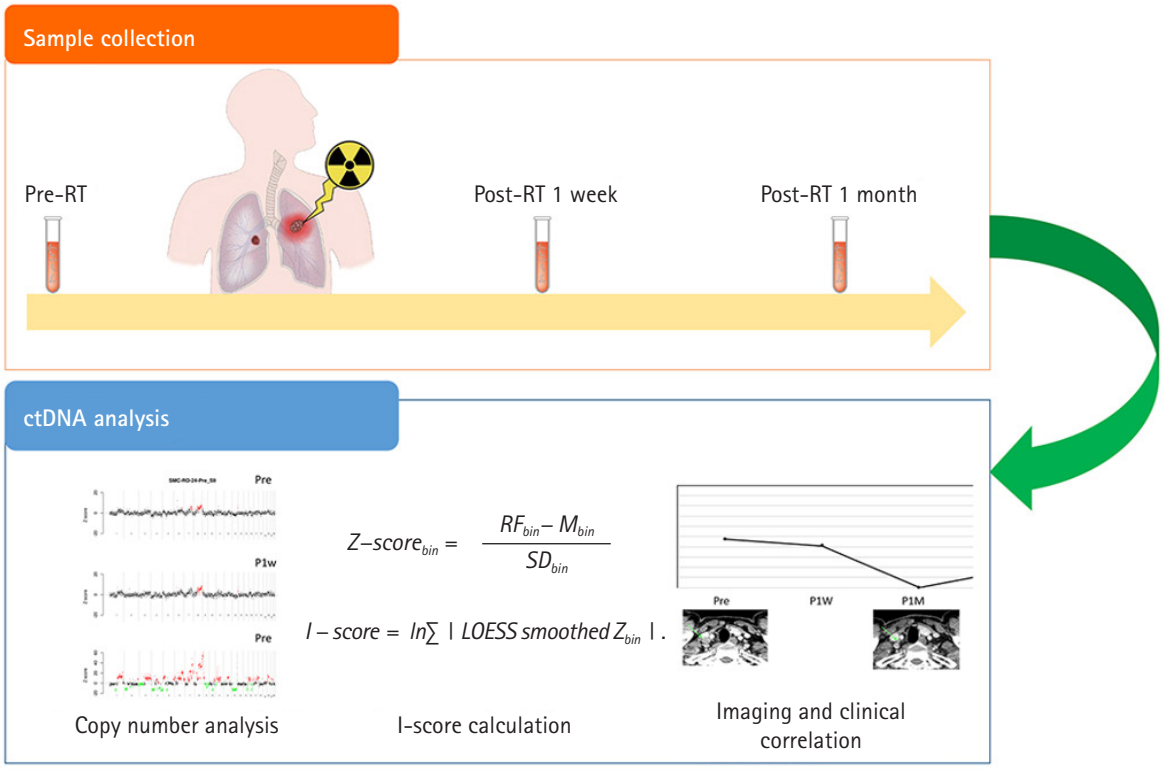

Fig. 1. Illustration of study schemes. RT, radiation therapy; RF_{bin}, relative frequency of a bin in a patient; M_{bin}, mean of the relative frequencies of a bin in normal healthy subjects; SD_{bin}, standard deviation of relative frequencies of a bin in normal healthy subjects.

Institutional Review Board at Samsung Medical Center (No. 2019-01-104). All participants provided written informed consent prior to enrollment. Of all patients, the aim of RT was curative in 20 (87.0%) and palliative in 3 (13.0%). For serial monitoring of cfDNA, blood sampling was performed before RT, 1 week after RT, and 1 month after completion of RT (Fig. 1). One month after RT completion, treatment response was evaluated by computed tomography (CT) in 19 patients or positron emission tomography-CT scans in four patients according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [17]. Plasma samples from 358 healthy volunteers were used as negative controls and the use of this healthy control was approved by the Institutional Review Board of Green Cross Laboratories, Yongin, Korea (No. GCL-2021-1048-01).

2. cfDNA extraction and preparation

Peripheral blood samples (10 mL) from patients were collected in EDTA tubes and centrifuged within 4 hours at room temperature to isolate the plasma, and then stored at −80°C. DNA was extracted from plasma samples using the Chemagic cfDNA 2k kit (Perkin Elmer Inc., Waltham, MA, USA). This cfDNA was used for library preparation using the Truseq Nano kit (Illumina Inc., San Diego, CA, USA) for low-depth whole-genome sequencing. The pooled libraries of 24 samples per run were analyzed using the NextSeq 500 (Illumina Inc.) in a 75-base single-read mode. An average of 11.1 M mapped read pairs were analyzed per sample after the mapping quality filter.

3. Calculation of genome instability

Sequenced reads were aligned to the hg19 reference genome using the BWA-MEM algorithm (0.7.5.a) with default parameters. Polymerase chain reaction (PCR) duplicates were removed, and reads with mapping quality below 60 were excluded from further analysis. After splitting the whole genome into 1 Mb bins, bins located in low-mapping regions were not used for the genomic instability calculation. The relative frequency of sequencing reads mapped to each bin was calculated and corrected for GC-content bias using the LOESS algorithm [18]. To measure the patient's local instability, the Z-score was calculated by comparing the relative frequency for each bin to those of healthy control subjects. The Z-score for each bin was calculated using the following formula:

$$Z\text{–}score_{bin} = \frac{RF_{bin} - M_{bin}}{SD_{bin}}$$

where, RF_{bin} is the relative frequency of a bin in a patient, M_{bin} is the mean of the relative frequencies of a bin in normal healthy subjects, and SD_{bin} is the standard deviation of relative frequencies of a bin in normal healthy subjects. To measure the extent of genome-wide copy number instability, we developed an I-score. A high I-score indicates a high level of genomic instability. The LOESS algorithm was applied to smooth the Z-scores of the adjacent bins. The I-score was calculated as follows:

$$I - score = ln\sum \mid LOESS\ smoothed\ Z_{bin} \mid .$$

4. I-score cutoff values

The distribution of the I-score from healthy controls is shown in Supplementary Fig. S1. The mean I-score was 4.467, and the maximum value was 6.516. The cutoff value of 5.09 was used, which is the 95th percentile value of the I-score from healthy controls.

5. Statistical analysis

Differences in I-scores at different time points were calculated using the paired Wilcoxon signed-rank test, and differences in I-scores by treatment response were assessed using the Mann–Whitney U test and Kruskal–Wallis test. The relationship between the I-scores and gross tumor volumes was calculated using Spearman rank correlation coefficient test. All tests were two-sided and p-values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

Results

1. Patient characteristics

A total of 23 patients were enrolled, and their characteristics are described in Table 1. The median age was 63 years (range, 46 to 74 years). The most common primary site was the lung (n = 12), followed by the esophagus (n = 5), oropharynx (n = 4), and parotid gland (n = 2). The median equivalent dose in the 2 Gy fraction was 65.0 Gy (range, 20 to 70.68 Gy) and the median gross tumor volume (GTV) was 31.3 mL (range, 0.9 to 158.1 mL). The detailed characteristics of the patients, serial values of the I-scores, and treatment responses are summarized in Supplementary Table S1.

2. Pretreatment and post-treatment values of the I-scores

The cutoff value of 5.09 was identified from the data of the non-cancer population, and the pretreatment I-score was elevated to more than 5.09 in 17 patients (73.9%). The relationship between tumor burden and I-score was evaluated using Spearman rank correlation coefficients between the GTV and baseline I-scores (Fig. 2A). There was a significant positive correlation between the GTV and the baseline I-score (Spearman rho = 0.419, p = 0.047). The median I-scores at baseline, post-RT 1 week (P1W), and post-RT 1

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Table 1. Characteristics of patients (n = 23)

Characteristic	Value
Sex	
Male	21 (91.3)
Female	2 (8.7)
Age (yr)	63 (46–74)
Primary site	
Lung	12 (52.2)
Esophagus	5 (21.7)
Parotid gland	2 (8.7)
Oropharynx	4 (17.4)
Histologic type	
Squamous cell carcinoma	15 (65.2)
Adenocarcinoma	5 (21.7)
Adenoid cystic carcinoma	2 (8.7)
Neuroendocrine carcinoma	1 (4.3)
Total radiation dose range (Gy)	20.0–68.4
Daily radiation dose range (Gy)	2.15–6.0
BED_{10} (Gy)	78.0 (24–84.82)
EQD_2 (Gy)	65.0 (20.0–70.68)
Treatment aim	
Salvage	10 (43.5)
Neoadjuvant	6 (26.1)
Definitive	4 (17.4)
Palliative	3 (13.0)
GTV volume (mL)	31.3 (0.9–158.1)

Values are presented as number (%) or median (range).
BED_{10}, biologically effective dose with α/β = 10 Gy; EQD_2, equivalent dose in 2 Gy fraction; GTV, gross tumor volume.

month (P1M) were 5.27, 5.13, and 4.79, respectively (Fig. 2B). The I-score at P1M was significantly lower than that at baseline (p = 0.002), while the difference between baseline and P1W was not significant (p = 0.244).

Dynamic changes in the I-score at different time points in each patient are shown in Fig. 2C. At 1 week after RT, I-score was available in 21 patients (91.3%), among whom, the score decreased in 13 patients (56.5%), while it increased in eight patients (34.8%). At 1 month after RT, the I-score decreased in 16 patients (50%), while seven patients (21.9%) showed higher P1M I-scores than the baseline I-scores.

3. Relationship between the I-score and treatment response

In all patients, at 1 month after RT, complete response (CR) and partial response (PR) occurred in 2 (8.7%) and 13 (56.5%) patients, respectively. Five patients (21.7%) showed stable disease (SD), and three (13.0%) experienced progressive disease (PD), all of whom experienced outfield progression.

The association between the I-scores and treatment response at 1 month after RT is shown in Fig. 3A. The median I-scores of the patients with CR, PR, SD, and PD were 5.32, 4.77, 4.89, and 5.91, respectively (p = 0.222). Even among those patients who were given curative RT, there was no statistically significant difference in median I-scores based on treatment response (Supplementary Fig. S2). Fig. 3B and Supplementary Fig. 3 show a waterfall plot of I-score changes and percentage changes from baseline at 1 month after RT.

Fig. 4 shows the clinical course of a patient (P4), the only case with long-term cfDNA I-score assessment from baseline to 10 months after RT. He had been treated with salvage RT with concurrent chemotherapy for recurrent lung cancer located in the mediastinal lymph nodes and supraclavicular lymph nodes. After RT completion, a decreased size of treated LNs was observed on CT scans at 1 month and 4 months after RT. The I-score at 1 month also decreased from 5.30 at baseline to 4.52 and 4 months after RT, and further decreased to 4.44. At 7 months, the I-score increased to 5.21; however, the CT scan at 7 months did not show any evidence of disease progression. However, at 10 months, the I-score further increased to 5.27 and a slightly increased size of treated LN was detected on CT scan, and multiple disease progression developed at 12 months after RT.

Discussion and Conclusion

In this study, we evaluated the feasibility of cfDNA monitoring to predict treatment response and detect minimal residual disease after RT using the I-score calculated from LC-WGS. Emerging studies have applied different methodologies to analyze cfDNA, including next-generation sequencing cancer panels, methylation detection, whole-genome sequencing, and whole-exome sequencing [19-21]. LC-WGS is a non-targeted approach to identifying genomic instabilities and is a time-and cost-effective method. The prognostic effect of the I-score in patients with cancer has been reported previously in various solid tumors [16,22,23]. Oh et al. [22] measured I-scores in 151 patients with advanced hepatocellular carcinoma and reported that the pretreatment I-score was a significant prognostic factor for survival. Kim et al. [16] included 61 patients with esophageal cancer and showed that a higher I-score at pretreatment was associated with a poor prognosis. Woo et al. [23] also showed that the stage-adjusted I-score of cfDNA was associated with progression-free survival in patients with pancreatic adenocarcinoma.

We also measured I-scores serially to evaluate their potential role as predictors of radiation response. Of the 23 patients in this

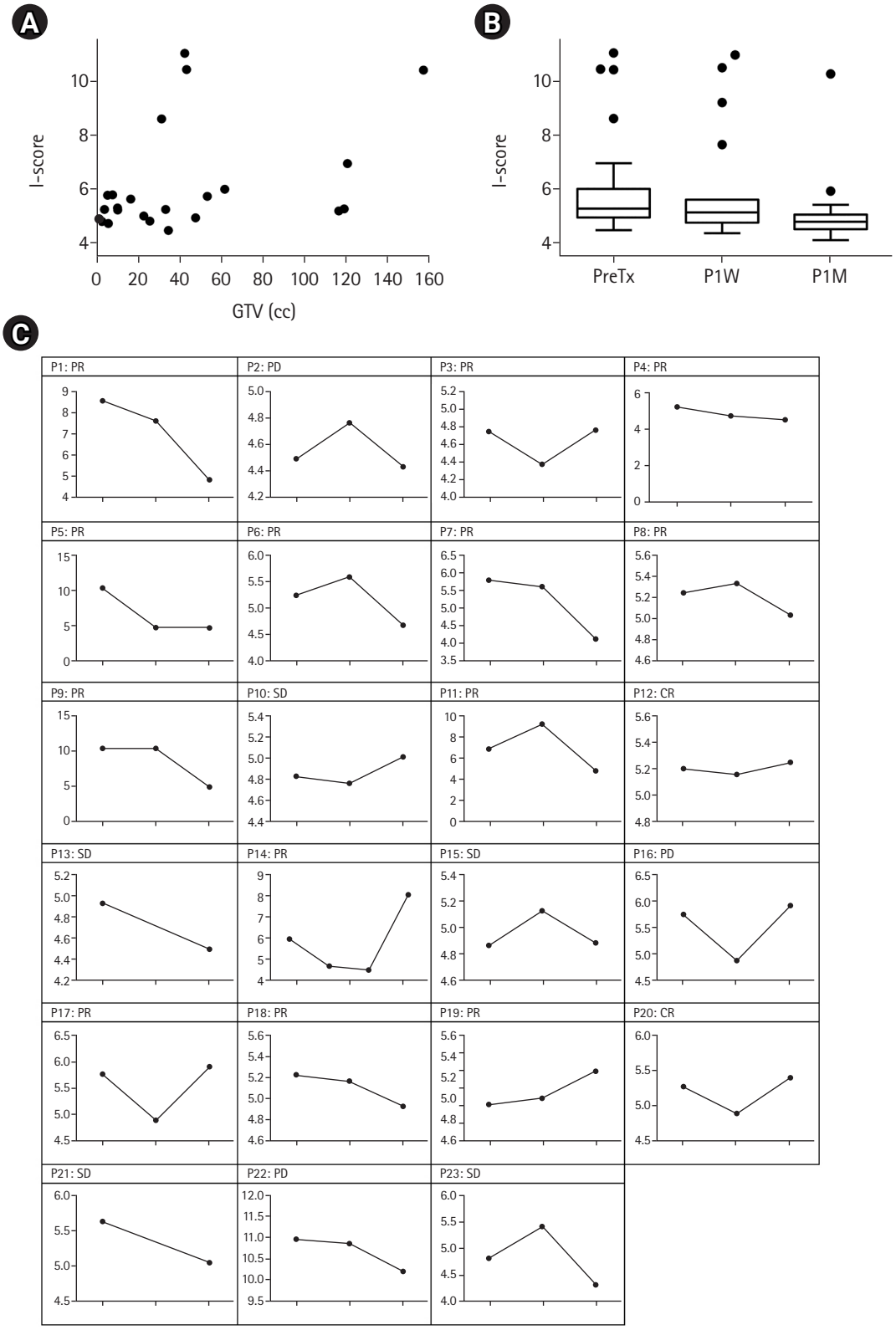

Fig. 2. Dynamics of the I-scores before and after radiation therapy. (A) Relationship between I-scores and GTVs. (B) Box and whisker plots of the I-scores at different time points. The box indicates the 75% (upper) and 25% (lower) quantiles and the horizontal line inside the box represents the median. The whiskers above and below the box represent the maximum and minimum values. Statistical difference between the groups was calculated by non-parametric Wilcoxon test (*$p < 0.05$). (C) Dynamic changes in the I-scores before and after radiation therapy in each case. CR, complete response; PD, progressive disease; PR, partial response; GTV, gross tumor volume; SD, stable disease; PreTx. pre-treatment; P1W, post-treatment 1 week; P1M, post-treatment 1 month.

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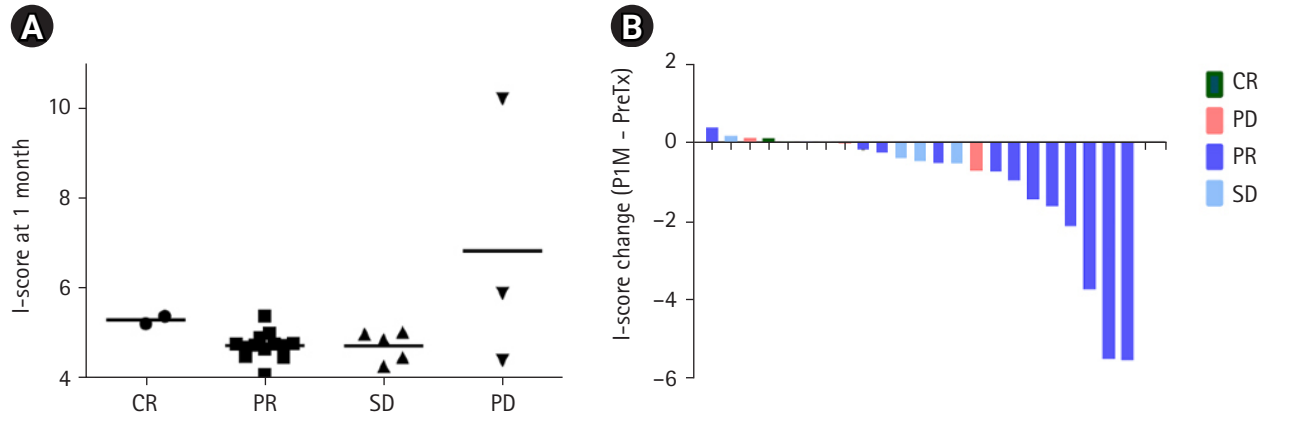

Fig. 3. Association between I-scores and treatment response. (A) I-score at 1 month after radiation therapy according to the treatment response. (B) Changes in the I-score according to the treatment response. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

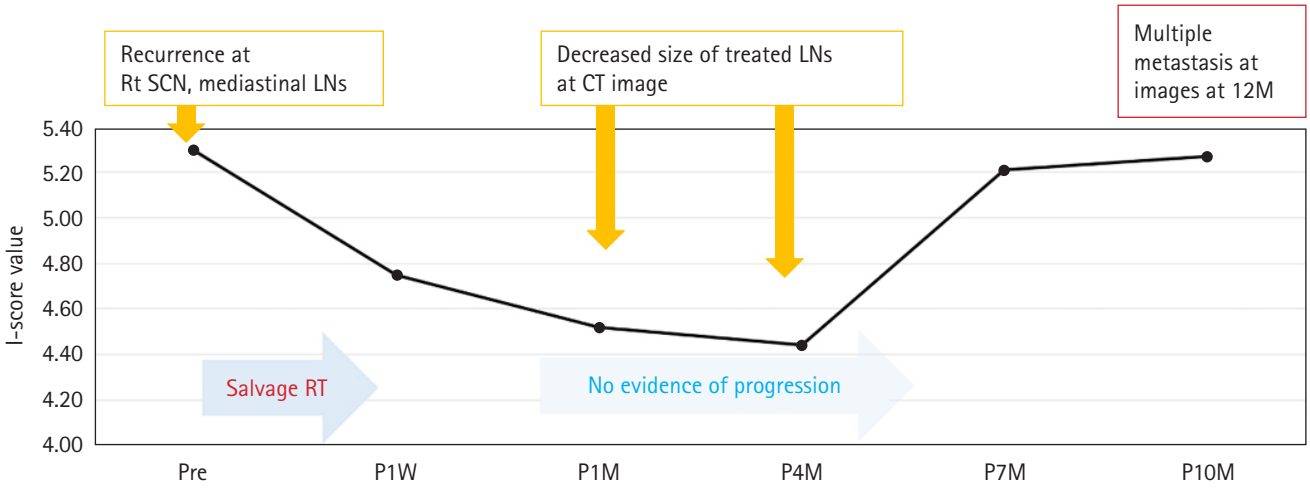

Fig. 4. Clinical courses and serial change in I-score values in example cases of patients who received salvage radiotherapy due to recurrent lung cancer. SCN, supraclavicular node; LN, lymph node; CT, computed tomography; RT, radiation therapy; Pre, pre-treatment; P1W, post-treatment 1 week; P1M, post-treatment 1 month; P4M, post-treatment 4 months; P7M, post-treatment 7 months; P10M, post-treatment 10 months.

study, the pretreatment I-score was elevated by more than 5.09 in 17 patients (73.9%). Among the 17 patients, I-scores decreased in 12 patients (70.6%) at 1 week after RT and in 14 patients (82.4%) after 1 month. At 1 month, PD was observed in three patients and two of them showed elevated I-scores at 1 month. However, as shown in Fig. 3, there was no clear difference in the I-scores between the CR, PR, and SD groups. Since RT is a local modality, the response evaluation of CR, PR, and SD was performed for irradiated tumors. However, PD includes progression in non-irradiated tumors. In the cohorts of this study, disease progression was most frequently observed in unirradiated areas, and the I-score seems to be more sensitive in detecting distant recurrence. A study that analyzed patients who underwent surgery for colorectal cancer also reported that minimal residual disease using cfDNA is more useful in predicting distant recurrence than locoregional recurrence [24]. To predict the local tumor response, additional methods such as identifying radiation signatures should be explored.

We found that pretreatment I-scores tended to be higher in larger tumors, which suggests that the I-score might be a surrogate marker for tumor burden (Fig. 2). The association between larger tumor burdens and higher levels of cfDNA has also been reported in previous studies [20,25]. Another interesting finding is that minimal residual disease following RT was detected earlier by cfDNA than by imaging studies. The benefit of cfDNA analysis in identifying recurrence earlier than radiologic imaging has been well-reported in previous studies [26,27]. Similarly, in this study, the serial monitoring of the I-score in P4 case demonstrated that the change in I-score was noticed before the progression of the

disease was detectable through imaging studies (Fig. 4). However, additional research with a larger population is required to fully understand the potential benefit of serial cfDNA I-score monitoring for the non-invasive detection of recurrence.

This study has several limitations. First, this study included a small number of patients with various solid tumors. The characteristics of cfDNA after RT might differ between individuals and tumor subtypes, and further studies with larger populations are needed. Second, limited sampling was performed in this study. Because of our limited financial resources, we were unable to perform serial blood samples in all patients. Serial monitoring of cfDNA at different times and a long follow-up period may be needed in future studies to find the optimal timing. Third, in 26.1% of the patients, the baseline I-score was not elevated. Lastly, the method we used does not specifically detect tumor DNA. More specific techniques to distinguish ctDNA from cfDNA might be needed to compensate for this method's limitation and improve the accuracy of liquid biopsy. Despite these drawbacks, this study investigated the feasibility of monitoring the I-score of cfDNA using LC-WGS, which is a relatively quick and simple method, and discovered several advantages and disadvantages of I-scores in predicting RT response.

In conclusion, this exploratory study has shown the feasibility of cfDNA I-score to detect minimal residual disease after RT in patients with lung cancer, esophageal cancer, and head and neck cancer. Additional studies are ongoing to optimize the measurement and analysis of cfDNA or ctDNA to predict the radiation response in cancer patients.

Statement of Ethics

This study was approval of the Institutional Review Board at Samsung Medical Center (No. 2019-01-104) and the Institutional Review Board of Green Cross Laboratories, Yongin, Korea (No. GCL-2021-1048-01).

Conflict of Interest

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

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Author Contributions

Conceptualization, Noh JM, Lim DH. Funding acquisition, Noh JM. Investigation and methodology, Cho WK, Lee J, Youn SM. Project administration, Oh D, Noh JM, Lim DH. Resources, Oh D, Cho EH, Noh JM, Yoon HG. Supervision, Lim DH, Cho EH. Writing of the original draft, Cho WK. Writing of the review and editing, Lee J, Youn SM, Yoon HG, Oh D, Lim DH, Cho EH, Noh JM. Software, Lee J, Youn SM. Formal analysis, Cho WK. Visualization, Cho WK.

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.2022.00444.

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Low body mass index is associated with poor treatment outcome following radiotherapy in esophageal squamous cell carcinoma

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Purpose: We aimed to determine whether patients with esophageal cancer with a low baseline body mass index (BMI) have a poor prognosis following radiotherapy (RT).
Materials and Methods: We retrospectively analyzed data from 50 patients with esophageal cancer to determine whether a low starting BMI (before RT) was associated with a poor outcome. All study participants were diagnosed with non-metastatic esophageal squamous cell carcinoma (SCC).
Results: The number of patients at each T stage were as follows: 7 (14%) patients at T1, 18 (36%) at T2, 19 (38%) at T3, and 6 (12%) at T4. Based on BMI, 7 (14%) patients were defined as underweight. A low BMI was common in patients with T3/T4 stage esophageal cancer (7/43, p = 0.01). Overall, the 3-year progression-free survival (PFS) and overall survival (OS) rates were 26.3% and 69.2%, respectively. In univariate analysis, clinical factors associated with poor PFS included being underweight (BMI <18.5 kg/m^2; p = 0.011) and a positive N status (p = 0.017). Univariate analysis also revealed that being underweight was associated with a decrease in OS (p = 0.003). However, being underweight was not an independent prognostic factor for PFS and OS.
Conclusion: Patients with esophageal SCC with a low starting BMI (BMI <18.5 kg/m^2) are more prone to have a negative survival outcome following RT than patients who are considered to be normal weight or overweight. For this reason, it is important that clinicians pay more attention to BMI when treating patients with esophageal SCC.

Keywords: Esophageal neoplasms, Radiotherapy, Body mass index, Underweight

Introduction

Weight loss has been extensively studied as a prognosis for treatment outcome in patients with cancer [1,2]. Pretreatment-associated weight loss has been shown to be detrimental for patients with cancer, and the prognosis is poor for cancers in specific gastrointestinal sites, including the stomach, pancreas, and esophagus [2]. Moreover, several reports have shown an association of body mass index (BMI) with both the incidence and prognosis of esophageal cancer [3,4]. Furthermore, a low BMI (i.e., < 18.5 kg/m^2) is a risk factor for mortality in patients with esophageal squamous cell carcinoma (SCC). For example, in 2007, Smith et al. [5] reported that patients with a high BMI had a lower mortality rate than patients with a normal or low BMI. A recent study by Gu et al. [6] also reported that patients with higher BMI exhibited longer survival. According to a recent study by Liu et al. [7], weight loss and high TNM stage were adverse prognostic factors for patients with esophageal SCC. In addition, based on a recent large-scale study in China by Ren et al. [4], underweight patients tended not to receive adjuvant chemotherapy, and high BMI was associated with better

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disease-specific survival. Finally, case control study in Australia by Lahmann et al. [8] also showed that high BMI was associated with a low risk of esophageal SCC regardless of smoking status. In contrast, Loehrer et al. [9] found that obese patients with adenocarcinoma had a worse prognosis compared to patients with normal BMI. Furthermore, Blom et al. [10] reported that the effect of BMI on prognosis was no longer apparent in patients with esophageal cancer who underwent esophagectomy. However, Chen et al. [11] reported that disease-free survival was shorter in patients with a high BMI who underwent surgery than in patients with a low to normal BMI.

In this study, we sought to evaluate whether baseline BMI is associated with treatment outcome in patients with esophageal SCC receiving curative RT. We also assessed the relationship between BMI and other clinical factors, such as T stage, N stage, and underlying type 2 diabetes. In addition, we analyzed the relationship between RT interruption and BMI. In 2013, 96% of reported esophageal cancers in Korea were SCC [12]. Therefore, study results reflect outcomes of radiotherapy (RT) in Korean patients with esophageal cancer.

Materials and Methods

1. Patient population

We retrospectively analyzed data from 50 patients with esophageal cancer who underwent curative RT as a first-line treatment. The study was conducted at Inje University Busan Paik Hospital, from December 2009 to January 2022. All patients were pathologically diagnosed with esophageal SCC before RT was initiated. None of the patients included in this study had stent insertion or feeding gastrostomy before RT. This study was approved by the Institutional Review Board in Busan Paik Hospital (IRB No. 2022-03-035). The informed consent was waived.

BMI was calculated according to the patient's medical records by dividing their weight in kilograms by their height in meters squared. Patients were defined as underweight, normal weight, and overweight based on a BMI of < 18.5 kg/m^2, 18.5–24.9 kg/m^2, and > 25 kg/m^2, respectively.

Patients were grouped as ever or never smokers. Alcohol abuse was categorized by obtaining a social history for each patient. Data on patient medical history about metabolic syndrome, such as diabetes and hyperlipidemia, was collected.

Tumor location was defined as occurring at three levels: upper thoracic esophagus (20–25 cm from the upper incisors), middle thoracic esophagus (25–30 cm from the upper incisors), and lower thoracic esophagus (30–50 cm from the upper incisors).

Our hypothesis in this study was that a lower body weight would be associated with poor treatment outcome following RT in patients with esophageal SCC. A relationship between BMI and the prognosis of patients with esophageal SCC has been previously shown in a study by Skipworth et al. [13] in 2009. According to a recent study by Liu et al. [7], weight loss and high TNM stage were adverse prognostic factors in patients with esophageal SCC. In addition, according to a recent large scale study in China by Ren et al. [4], underweight patients tended not to receive adjuvant chemotherapy, and high BMI was associated with better disease-specific survival. Therefore, in this study, we evaluated the prognostic effects of BMI in patients with esophageal SCC.

Arc intensity-modulated RT was planned for treatment. For radiation fields, the target volume was established as a 3–5 cm margin superiorly and inferiorly and as a 1-cm margin laterally in each direction relative to the primary tumor. Positron emission tomography with integrated computed tomography was used for contouring the tumor volume. RT was usually administered at a total dose of 50.4 Gy. A daily dose of 1.8–2 Gy per fraction was administered. RapidArc and VitalBeam (Varian Medical System, Palo Alto, CA, USA) were used for external beam RT.

Most patients received concurrent chemoradiotherapy. The common chemotherapy regimen during RT was several cycles of 5-fluorouracil and cisplatin (FP).

The primary outcome was progression-free survival (PFS), which was defined as the length of time between the initial diagnosis and either recurrence or the last follow-up (death was not included). The secondary outcome was overall survival (OS). PFS and OS were calculated from the date of pathologic diagnosis to the date of each event.

2. Inclusion and exclusion criteria

Patients included in this study were all older than 18 years of age. Patients diagnosed with distant metastases during their initial treatment were excluded from the study. Patients treated with less than 40 Gy for the cumulative dose for RT were also excluded, as this was considered as an insufficient radiation dose for curative therapy.

3. Statistical methods

The chi-squared test was used to determine clinical factors associated with disease progression. Significance was set at $p < 0.05$. Fisher exact test was used in this study. The Kaplan–Meier test was used to estimate PFS and OS, and the log-rank test was used to find factors related survival. In addition, the Cox regression proportional hazards model was used to define independent prognostic factors that were related to survival. MedCalc statistical software (MedCalc Software, Mariakerke, Belgium) and SPSS version 24 (IBM, Armonk, NY, USA) was used for statistical evaluation.

Results

1. Patients characteristics and treatment

The median follow-up period of the study was 9 months. Patient characteristics are outlined in Table 1.

Table 1. Patient characteristics

Characteristic	Value
Age (yr)	68 (46–83)
Sex	
Male	50 (100)
Female	0 (0)
Diabetes	
Yes	6 (12)
No	44 (88)
Hyperlipidemia	
Yes	2 (4)
No	48 (96)
Smoking	
Yes	25 (50)
No	25 (50)
Alcohol abuse	
Yes	15 (30)
No	35 (70)
Body mass index (kg/m^2)	
< 18.5	7 (14)
18.5–23	27 (54)
> 23	16 (32)
Location	
Upper	8 (16)
Middle	26 (52)
Lower	16 (32)
Histology	
Squamous cell carcinoma	50 (100)
Others	0 (0)
T stage	
T1	7 (14)
T2	18 (36)
T3	19 (38)
T4	6 (12)
N stage	
N0	20 (40)
N1	16 (32)
N2	12 (24)
N3	2 (4)
Radiotherapy dose (Gy)	50.4 (45–70)
< 50	4 (8)
≥ 50	46 (92)
Chemotherapy	
Yes	48 (96)
No	2 (4)

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

The patients enrolled this study were all older than 40 years of age (median, 68 years; range, 46 to 83 years). All patients had SCC. The number of patients at each T stage were as follows: 7 (14%) patients at T1, 18 (36%) at T2, 19 (38%) at T3, and 6 (12%) at T4. In addition, 30 (60%) patients had nodal metastases at diagnosis. Based on BMI, 7 (14%), 27 (54%), and 16 (32%) patients were defined as underweight, normal weight, and overweight, respectively. A total of six patients (12%) had type 2 diabetes. In addition, two patients (4%) had hyperlipidemia. Half of patients (n = 25; 50%) were smoker, and 15 patients (30%) were categorized as alcohol abuse.

Most patients (96%) received chemotherapy concurrently with RT. The most common chemotherapy regimen (n = 40; 80%) during RT was two or three cycles of FP every 3 weeks. Cisplatin chemotherapy alone every 3 weeks was used in 8 (16%) patients. The remaining two patients only received RT. Regarding the total radiation dose, the majority of patients (n = 46; 92%) received ≥ 50 Gy.

2. Progression pattern

During the median 9-month follow-up period (range, 1.5 to 85.7 months), 29 patients experienced disease progression. The disease progression rate did not differ based on prognostic factors (Table 2). Underweight did not significantly increase the incidence of failure (p = 0.635) (Table 2). More specifically, 21 (42%) patients experienced locoregional failure, and 11 (22%) patients showed distant failure. Among the patients with distant failure, three also experienced locoregional failure. Moreover, 19.0% (4/21) of patients who experienced locoregional failure were underweight.

Table 2. Failure pattern

Variable	No progression (n = 21)	Progression (n = 29)	p-value
T stage			0.500
T1-2	11	14	
T3-4	10	15	
N stage			0.260
N0	10	10	
N+	11	19	
Body mass index (kg/m^2)			0.635
< 18.5	3	4	
≥ 18.5	18	25	
Hyperlipidemia			0.331
Yes	0	2	
No	21	27	
Diabetes			0.499
Yes	3	3	
No	18	26	

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3. Survival analysis

Overall, the 3-year PFS and OS rates were 26.3% and 69.2%, respectively (Fig. 1A, 1B). The 3-year locoregional PFS rate (LRPFS) was 36.6%.

Table 2 shows the prognostic factors related OS and PFS. Univariate analysis revealed that both N stage and being underweight were associated with a lower PFS (p = 0.017 and p = 0.011, respectively) (Fig. 2A). Advanced T stage (T3/T4) tended to be negatively associated with PFS (p = 0.073) (Table 3). However, smoking and alcohol abuse did not reduce the PFS and OS (Table 3). Being underweight (p = 0.004) (Fig. 2B) and receiving a total radiation dose < 50 Gy (p = 0.001) (Table 2) was associated with a low OS.

We also found that being underweight was associated with impaired locoregional progression and significantly associated with a low LRPFS (p = 0.004) (Fig. 3). Except for underweight, there were no other prognostic factors associated with LRPFS in the univariate analysis.

Multivariate analysis showed that N stage was an independent prognostic factor for PFS and that total radiation dose was an independent prognostic factor for OS (Table 3). However, being underweight was not an independent prognostic factor for PFS or OS.

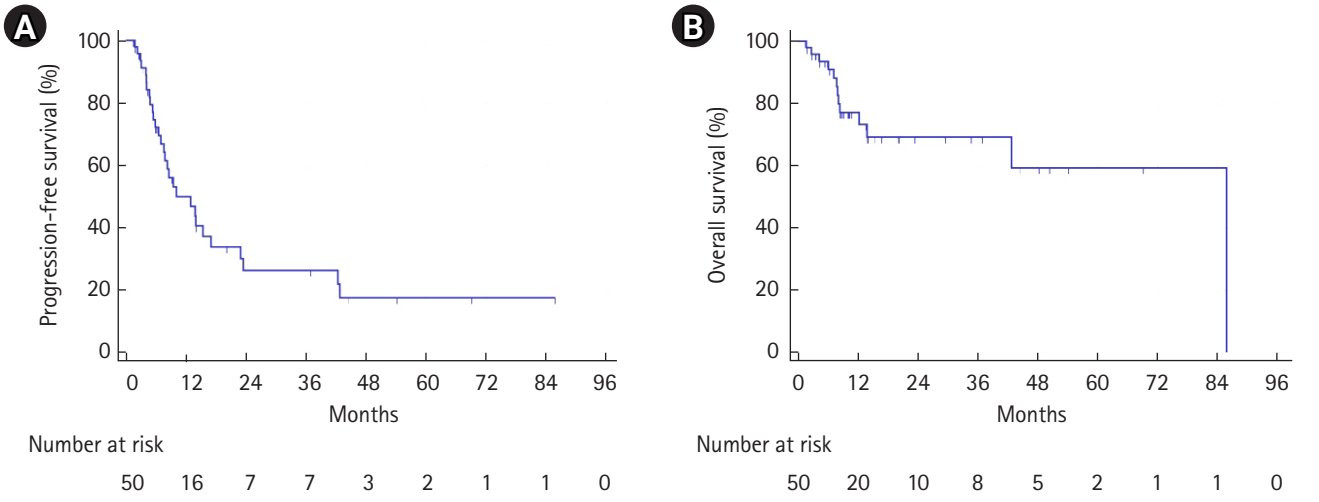

Fig. 1. (A) Progression-free survival rate. (B) Overall survival rate.

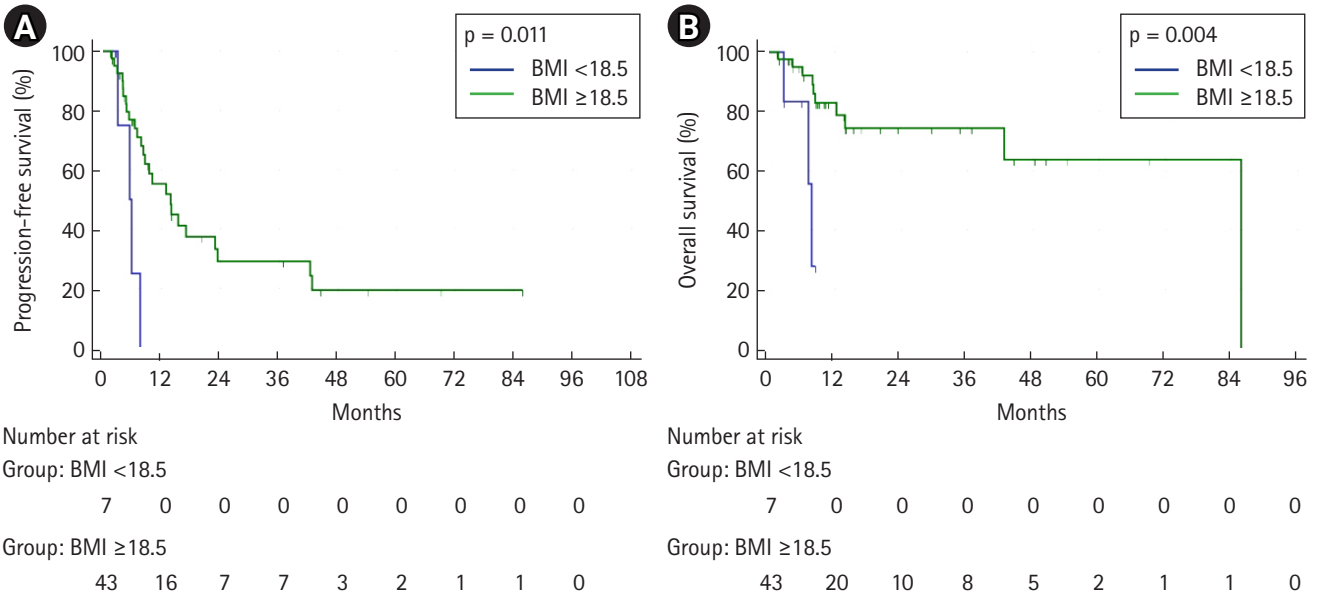

Fig. 2. (A) Progression-free survival and (B) overall survival according to body mass index (BMI, kg/m^2).

Table 3. Univariate and multivariate analyses for survival

Variable	PFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	3-yr (%)	p-value	95% CI	p-value	3-yr (%)	p-value	95% CI	p-value
T stage		0.073				0.003	10.219 (1.216–85.893)	0.032
T1-2	36.2				95.8			
T3-4	19.2				42.9			
N stage		0.017	2.368 (1.035–5.417)	0.041		0.415		
N0	45.3				77.5			
N+	10.3				66.5			
Diabetes		0.308				0.660		
Yes	55.6				75.0			
No	23.0				70.0			
Hyperlipidemia		0.762				0.768		
Yes	50.0				50.0			
No	24.4				73.6			
Smoking		0.695				0.460		
Yes	34.4				72.2			
No	21.4				71.8			
Alcohol abuse		0.273				0.181		
Yes	19.2				60.2			
No	29.5				76.2			
Body mass index (kg/m^2)		0.011	0.318 (0.098–1.030)	0.056		0.004	0.241 (0.048–1.226)	0.086
< 18.5	0				0			
≥ 18.5	29.1				76.8			
Radiotherapy dose (Gy)		0.370				0.001	0.088 (0.018–0.424)	0.002
< 50	0				30.0			
≥ 50	27.8				76.2			

PFS, progression-free survival; OS, overall survival; CI, confidence interval.

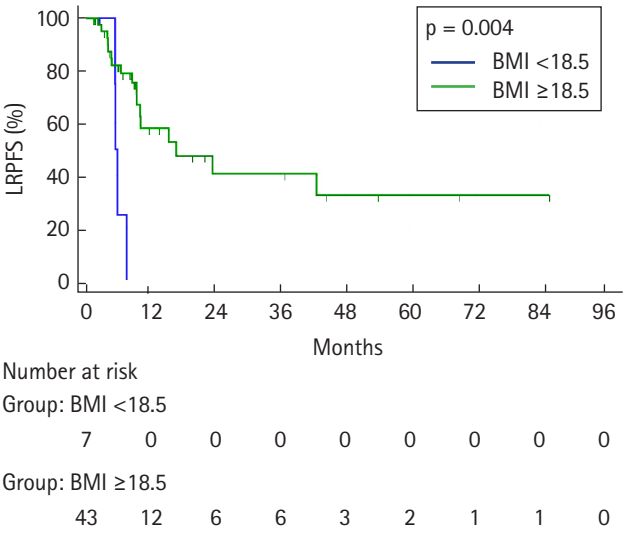

Fig. 3. Locoregional progression-free survival (LRPFS) according to body mass index (BMI, kg/m^2).

4. Correlation between body mass index and clinical factors

Table 4 shows the correlation between advanced T stage (T3/T4) disease and being underweight. A low BMI was common in patients with T3/4 stage esophageal cancer (7/43, p = 0.010) (Table 4). Neither positive N stage nor diabetes was associated with low BMI.

5. Treatment interruption

Treatment interruption during RT (total RT period > 50 days) occurred in 11 patients, and it occurred more frequently in underweight patients compared to that in normal or overweight patients (4/7 vs. 7/43, p = 0.034). However, treatment interruption during RT was not statistically related with increased disease progression rates (p = 0.741).

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Table 4. Relationship between BMI and clinical factors

Variable	BMI (kg/m^2)		p-value
	< 18.5	≥ 18.5	
T stage			0.010
T1-2	0	25	
T3-4	7	18	
N stage			0.687
N0	2	18	
N+	5	25	
Hyperlipidemia			0.737
Yes	0	2	
No	7	41	
Diabetes			0.576
Yes	7	37	
No	0	6	

BMI, body mass index.

Discussion and Conclusion

The present results suggest that a patient's pre-treatment weight greatly influences treatment outcome following RT in esophageal SCC. Furthermore, advanced T stage (T3/T4) was correlated with pre-treatment low body weight in esophageal SCC. This study provides useful clinical information for the management of patients with esophageal cancer.

These results confirm that a low body weight is a poor prognosis for patients with esophageal SCC. Zhang et al. [14] reported similar findings that pre-treatment low body weight was associated with poor treatment outcome in patients with esophageal cancer. However, the authors [14] recognized that other factors besides weight loss, such as stage, may have indirectly affected these poor treatment outcomes. Moreover, a case control study in Australia by Lahmann et al. [8] also showed that high BMI was associated with a low risk of esophageal SCC regardless of smoking status. Furthermore, according to a study by Button et al. [15], SCC usually has a longer lesion length compared to that of adenocarcinoma and frequently exhibits esophageal wall narrowing [8], which is more correlated with weight loss. Severe weight loss weakens the immune system and can easily exacerbate esophageal cancer. The current results also demonstrate that advanced T stage was associated with a low body weight before RT. Moreover, RT interruption occurred more frequently in patients with low BMI, i.e., underweight patients who did not receive a full dose of RT were more likely to suffer complications related to lowered immunity, such as leukopenia.

Similarly, sarcopenia seems to influence the survival outcomes for esophageal cancer patients treated with neoadjuvant chemoradiotherapy. According to a recent study by Yoon et al. [16], excessive muscle loss (skeletal muscle index <-10.0% in 50 days) was significantly associated with OS. Furthermore, Reisinger et al. [17] also argued that muscle mass loss during neoadjuvant chemoradiotherapy was related to postoperative mortality in patients with advanced stage esophageal cancer.

To avoid detrimental treatment outcomes because of weight loss or low pre-treatment weight, nutritional support should be provided to patients with esophageal cancer. Indeed, a study by Davies et al. [18] reported that early nutritional support and intervention may be helpful in improving the overall condition of patients with esophageal cancer, as an increase in mortality has been noted in patients with severe weight loss (i.e., > 10% of starting weight).

Stent insertion or feeding gastrostomy [19] may aid in improving a patients' nutritional condition. Whether stent insertion improves the overall health of patients remains debatable, but it would appear that providing patients with supplemental nutrition is a good option [20,21]. Additionally, post-RT stenting may aid in condition recovery in patients with esophageal cancer. Iwagami et al. [20] reported that esophageal metal stent insertion before RT contributed to a reduction in severe adverse events. Ogino and Akiho [19] also noted that percutaneous feeding gastrostomy could be useful for nutritional support in esophageal cancer. Considering the above, further studies are required to determine whether alleviation of dysphagia by medical devices, such as stent insertion or feeding gastrostomy, improves the patient's overall medical condition and nutritional status [18].

We acknowledge several limitations in our study. Firstly, the number of enrolled patients was limited due to the single, retrospective study design. Secondly, the weight of the patients was not continuously monitored throughout the study, and body weight was only recorded before the commencement of RT. Thirdly, BMI was not an independent prognostic factor of survival in multivariate analysis, even though low BMI was significantly clinical factor for PFS and OS in univariate analysis. BMI may be not independent factor because of small sample size. Further analysis revealed that advanced T stage disease influenced BMI.

In conclusion, a low starting BMI tends to be an adverse clinical factor for survival outcome in patients with esophageal SCC undergoing curative RT, even though it is not independent factor. Patients that were underweight at diagnosis commonly manifested advanced T stage disease. These results suggest that clinicians should pay special attention to underweight patients with esophageal cancer. Further studies investigating the effect of active nutritional support in underweight patients with esophageal SCC during and after RT are required to improve treatment outcome in these patients.

Statement of Ethics

This study was approved by the Institutional Review Board in Busan Paik Hospital (IRB No. 2022-03-035).

Conflict of Interest

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

Funding

None.

Author Contributions

Conceptualization, YC, JL. Investigation and methodology, YC, JL. Writing of the original draft, YC. Writing of the review and editing, JL, YC. Formal analysis, YC.

Data Availability Statement

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

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Excluding prepontine cistern from whole ventricle radiotherapy target volume in localized germinoma

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Purpose: The target delineation of whole ventricle radiotherapy (WVRT) in germinoma varies among radiation oncologists, especially regarding the inclusion of the prepontine cistern (PC). We evaluated the outcome of PC-sparing WVRT in localized germinoma.

Materials and Methods: We identified 87 localized intracranial germinoma patients who received radiotherapy (RT) following chemotherapy between 1999 and 2020. By institutional policy, RT for localized germinoma excluded PC from the target volume. WVRT was delivered to 65 patients (74.7%) and involved field radiotherapy (IFRT) to 22 patients (25.3%). The median dose was 45.0 Gy (range, 23.4 to 55.8 Gy) for the primary tumor and 19.8 Gy (range, 14.4 to 36.0 Gy) for the whole ventricle. We analyzed the dosimetric differences of the organs at risk between the PC-excluding plans and the PC-including ones.

Results: The median follow-up duration was 7.8 years (range, 1.0 to 22.5 years). The 10-year recurrence-free survival and overall survival rates were 86.3% and 90.9%, respectively. The recurrences occurred in eight patients (8.7%), including five patients after IFRT and three after WVRT. Five of them showed recurrences at lateral ventricles and only one patient experienced spinal cord relapse. However, no relapse in the PC occurred. Endoscopic third ventriculostomy was not a significant prognostic factor. The dosimetric comparisons showed significantly lower mean doses to the brainstem and the cochleae when the PC was excluded.

Conclusion: WVRT for localized germinoma can safely exclude the PC in the target volume, reducing radiation dose to the brain stem. The target protocol needs to reach a consensus regarding the PC in prospective trials.

Keywords: Radiotherapy, Cerebral ventricle, Germinoma

Introduction

Intracranial germinoma is an uncommon brain tumor in midline structures, mainly affecting children and young adults. It has a favorable prognosis with a 10-year overall survival around 95% [1,2]. Intracranial germinoma is characterized by a propensity for cerebrospinal fluid (CSF) spread and high radiosensitivity. The main principle of the treatment strategy has been de-intensification to minimize long-term toxicity by reducing radiation volume or dose. For localized intracranial germinoma, whole ventricle radiotherapy (WVRT) became a well-established standard treatment, replacing craniospinal irradiation (CSI) and whole brain radiotherapy (WBRT) [3,4].

Despite a consensus on treatment strategy, the definition of whole ventricle (WV) volume has not reached a robust consensus among clinicians or in guidelines, especially regarding the prepontine cistern (PC), a CSF subarachnoid space ventral to the pons and dorsal to the clivus. The survey of Mailhot et al. [5] revealed the most significant discrepancy in the inclusion of the PC among pediatric radiation oncologists. Over half of the responders (53.5%)

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stated that the PC would not be included, while 32.6% said that they would include it only after the third ventriculostomy. Consequently, the Children's Oncology Group (COG) generated a WVRT atlas for clinical trials in which, the inclusion of the PC was optional for according to clinician's preference [6]. However, this can lead to a significant deviation in clinical practice and prospective protocols, which can affect the resulting analysis.

In accordance with our institutional policy, radiotherapy for localized germinoma excludes the PC from the target volume, on the assumption that there is a low risk of recurrence related to the PC. In this study, we evaluated the oncological safety and outcome of WVRT excluding the PC in localized germinoma.

Materials and Methods

1. Patients

The Seoul National University Hospital Institutional Review Board approved this study and waived the requirement for patient informed consent (IRB No. H-2204-141-1319). Since the introduction of chemotherapy in the management of germinoma in 1999, chemotherapy followed by radiotherapy, has become our treatment protocol. Therefore, we reviewed the medical records of localized germinoma patients who received upfront chemotherapy followed by WVRT or involved field radiotherapy (IFRT) from January 1999 to December 2020. We excluded patients with CSF seeding (positive craniospinal fluid cytology or positive imaging) or multifocal lesions (more than two lesions) at the time of diagnosis. The patients with serum alpha-fetoprotein (AFP) above 10 ng/mL or serum beta-human chorionic gonadotropin (B-HCG) above 50 mIU/mL were also excluded. A total of 87 patients were eligible for the analysis.

Table 1 summarizes the baseline characteristics of the patients. The median age was 15 years (range, 4 to 44 years), and 72 patients (82.8%) were male. The Eastern Cooperative Oncology Group (ECOG) performance status in 79 patients (90.8%) was between 0 and 1. The solitary disease was found in 72 patients, and thereof, the most common solitary lesion was the pineal gland (n = 39) followed by the suprasellar (n = 16). We defined bifocal tumor as a non-solitary disease originating from two different intracranial sites. Of 15 patients with bifocal germinomas, three patients had tumors occurring other than in the suprasellar or pineal glands; these were in the thalamus and brain stem, both basal ganglia, and quadrigeminal cistern and tectal midbrain, respectively. Histologic confirmation was undertaken by stereotactic biopsy in 26 patients, endoscopic biopsy in 44, open biopsy in nine, and tumor removal in eight (subtotal removal in five, near total removal in two, and gross total removal in one). Endoscopic third ventriculostomy (ETV) was performed on 31 patients (35.6%). Information on the initial tumor markers was available for all but three patients. Eleven patients had serum B-HCG levels ranging from 6 to 28 mIU/mL, and three patients had serum AFP levels ranging from 9 to 10 ng/mL.

2. Treatment

Since 1992, our institution has had a combined treatment policy of chemotherapy followed by radiotherapy. Accordingly, the patients in our study were treated with the following chemotherapy regimens: two cycles (range, 1 to 4 cycles) of bleomycin, etoposide,

Table 1. Baseline characteristics of 87 localized intracranial germinoma patients

Characteristic	Value
Age (yr)	15 (4–44)
Sex	
Male	72 (82.8)
Female	15 (17.2)
ECOG performance status	
0–1	79 (90.8)
2	7 (8.0)
3–4	1 (1.1)
Tumor site	
Solitary	
Suprasellar	16 (18.4)
Pineal	39 (44.8)
Basal ganglia/thalamus	14 (16.1)
Others[a]	3 (3.4)
Bifocal	
Suprasellar and pineal	2 (2.3)
Suprasellar and other	7 (8.0)
Pineal and other	3 (3.4)
Others[b]	3 (3.4)
Diagnosis	
Stereotactic biopsy	26 (29.9)
Endoscopic biopsy	44 (50.6)
Open biopsy	9 (10.3)
Surgery[c]	8 (9.2)
Endoscopic third ventriculostomy	
Yes	31 (35.6)
No	56 (64.4)
Chemotherapy response	
Complete response	53 (60.9)
Partial response	29 (33.3)
Stable response	5 (5.7)

Values are presented as median (range) or number (%).
ECOG, Eastern Cooperative Oncology Group.
[a]Left temporal lobe, 3rd ventricle, corpus callosum.
[b]Thalamus and brain stem, both basal ganglia, quadrigeminal cistern and midbrain.
[c]Includes 5 subtotal removal, 2 near total removal, and 1 gross total removal.

and cisplatin or etoposide and carboplatin for 36 patients; four cycles of etoposide, carboplatin, and cyclophosphamide for 30 patients; four cycles of bleomycin, etoposide, cisplatin, cyclophosphamide for two patients; two cycles of cisplatin, etoposide, ifosfamide (VIP) for six patients; five cycles (range, 4 to 5 cycles) of cisplatin, etoposide, cyclophosphamide, and vincristine (CCG 9921A or 9931A) for seven patients; and "8-in-1" (solumedrol, vincristine, lomustine, procarbazine, hydroxyurea, cisplatin, cytosine arabinoside, and cyclophosphamide) for four patients. After upfront chemotherapy, 53 patients achieved a complete response (CR), 29 patients achieved a partial response, and five remained stable based on an MRI study before radiotherapy (Table 1).

Previously, as our main treatment, IFRT was delivered to the tumor bed with a 2-cm margin mainly using a 2D technique. For WVRT, contrast-enhanced T1/T2-weighted magnetic resonance imaging (MRI) was fused with simulation CT images. Gross tumor volume (GTV) was pre- or post-chemotherapy tumor bed or operative bed based on T1-enhanced and T2 high FLAIR MRI images. Clinical target volume (CTV) was expanded 5–10 mm from GTV. In the case of disease arising from the basal ganglia or thalamus, a 15-mm margin was added to the tumor bed, including T2 high signal intensity. Based on the T2-weighted MRI, the WV treatment volume encompassed the lateral, third, fourth ventricles, the suprasellar cistern, and the pineal cistern according to the COG guideline [6]. The PC was excluded from the WV volume in all patients (Fig. 1A). The large field included the primary tumor bed as well as the WV. Additional doses to the tumor bed were delivered sequentially.

Table 2 presents the radiation treatment characteristics. WVRT was delivered to 65 patients (74.7%) and IFRT to 22 patients (25.3%). The median total dose to the primary tumor bed was 45

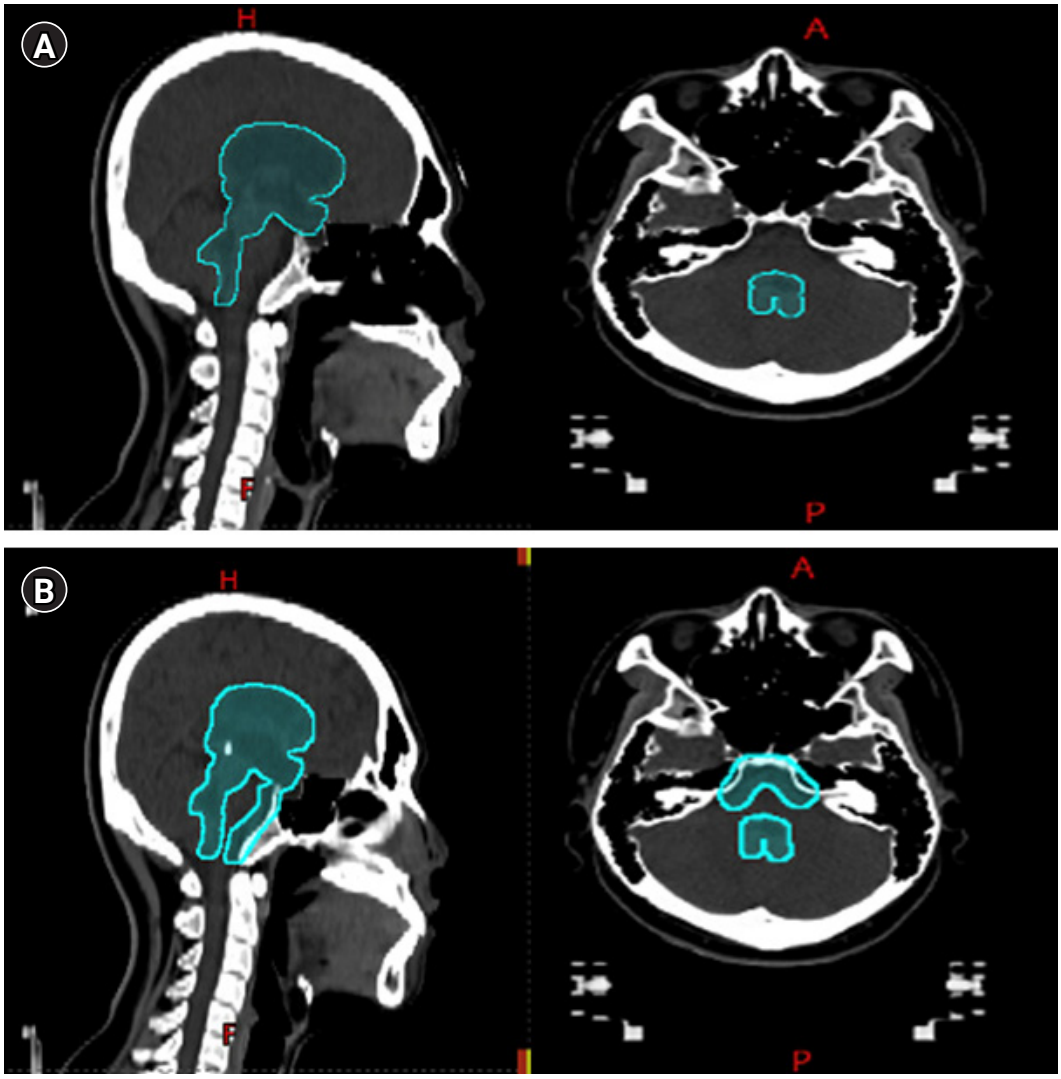

Fig. 1. Whole ventricular radiotherapy target delineation that shows (A) excluding prepontine cistern and (B) including prepontine cistern.

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Gy (range, 36 to 54 Gy) for IFRT and 45 Gy (range, 23.4 to 55.8 Gy) for WVRT. Patients who showed a CR to initial chemotherapy received the median dose of 45 Gy (range, 23.4 to 55.8 Gy) to the primary tumor bed, while those who did not show a CR were given the median dose of 50.4 Gy (range, 36.0 to 55.8 Gy). The WV was irradiated with the median dose of 19 Gy (range, 14.4 to 36.0 Gy).

3. Dosimteric analysis

Of 65 WVRT patients, the radiation therapy plans for 33 patients were retrievable. The intensity-modulated radiotherapy (IMRT) technique was used in 30 cases, while three cases were planned using three-dimensional conformal radiotherapy (3D-CRT). To evaluate the dosimetric effect of excluding the PC, we additionally generated the new plans that included the PC of 33 patients (Fig. 1B). The corresponding treatment modality (IMRT or 3D-CRT) to the one utilized in the original plan was used. The brainstem and each cochlea were manually contoured according to the guideline [7]. We collected the dosimetric information from the original plans and the newly constructed ones.

Table 2. Radiation treatment characteristics 87 localized intracranial germinoma patients

Treatment	Value
RT field	
IFRT	22 (25.3)
WVRT	65 (74.7)
RT dose (Gy)	
Primary tumor dose	
IFRT	45.0 (36.0–54.0)
WVRT[a]	45.0 (23.4–55.8)
Whole ventricle	19.8 (14.4–36.0)
RT technique	
IMRT (2005–2020)	33 (37.9)
3D-CRT (2003–2005)	33 (37.9)
2D (1999–2003)	21 (24.2)

Values are presented as number (%) or median (range).
RT, radiotherapy; IFRT, involved field radiotherapy; WVRT, whole ventricular radiotherapy; IMRT, intensity-modulated radiotherapy; 3D-CRT: three-dimensional conformal radiotherapy.
[a]Indicates the total dose to the primary tumor bed in WVRT.

4. Statistical analysis

We conducted statistical analysis by using Stata/SE 17 (StataCorp LLC, College Station, TX, USA). Overall survival (OS) was the duration from the date of initial histologic diagnosis to the date of the last visit or death from any cause. Similarly, recurrence-free survival (RFS) was calculated as the duration between the initial confirmation and any recurrence or death. We used the Kaplan-Meier method for survival analysis and a log-rank test to identify prognostic factors. Paired t-test was applied to compare the dose-volume metrics of the normal organ structures between the PC excluding plans and the PC including plans. The prescribed dose to 95% of the large field consisting of the WV and tumor bed was used as the reference.

Results

1. Failure pattern

During the median follow-up of 7.8 years (range, 0.49 to 22.5 years), eight patients experienced recurrences, including five in IFRT

Table 3. Summary of the treatment outcomes for 8 patients with relapses

Patient No.	RT field	Primary sites	RT dose (Gy)[a]	ETV	Time to relapse (yr)	Relapse site	Recur pattern	Salvage treatment	Status
1	WVRT	Suprasellar	36	No	8.30	Brainstem	In-field	CTx-CSRT	Stable
2	WVRT	Lt BG	45	No	10.60	Subependymal seeding (lateral ventricles), Lt BG, Lt frontal, Lt parietal	In-field, out-field	Surgery-CTx-CSRT	NED
3	WVRT	Pineal	45	Yes	1.20	Spinal cord (L1-4)	Out-field	CTx-CSRT- PBSCT	NED
4	IFRT	Rt BG	39.6	No	3.10	Rt frontal, Rt temporal	Out-field	CTx-CSRT-PBSCT	NED
5	IFRT	Rt BG	39.6	No	1.10	Lateral ventricle	Out-field	CTx	Dead
6	IFRT	Suprasellar, pineal	45	Yes	2.86	Suprasellar, lateral ventricle, optic nerve	In-field, out-field	CTx	Dead
7	IFRT	Pineal	36	Yes	2.26	Subependymal seeding (lateral ventricles)	Out-field	CTx-CSRT	NED
8	IFRT	Lt BG	54	No	2.32	Lateral ventricle, both temporal, Rt parietal	Out-field	SRS-CTx	Dead

RT, radiotherapy; ETV, endoscopic third ventriculostomy; WVRT, whole ventricular radiotherapy; CTx, chemotherapy; CSRT, craniospinal radiotherapy; BG, basal ganglia; NED, no evidence of disease; IFRT, involved field radiotherapy; PBSCT, peripheral blood stem cell transplantation; SRS, stereotactic radiosurgery.
[a]RT dose to the primary tumor bed only.

and three in WVRT (Table 3). The median time to recurrence after radiotherapy was 2.3 years. Four of five recurrent patients after IFRT experienced relapses at the ventricular area. All of the recurrences in IFRT were out-field, except one case of in-field relapse at the pineal gland. For WVRT, there was one patient who demonstrated spinal cord relapse at L1–L4. Other two WVRT patients developed very late infield-relapses. After 10.6 years, relapses in one patient with WVRT occurred at the bilateral lateral ventricular walls as well as the primary tumor bed at the basal ganglia, extending to the ipsilateral frontal lobe and parietal lobe. Another patient with WVRT developed a new lesion near the fourth ventricle after 8.3 years. However, no recurrence in the PC was observed among the patients with recurrences.

2. Treatment outcomes

After completion of radiotherapy, 32 of 34 non-CR patients eventually reached CR. Except them, there was one patient whose residual disease remained stable until the last follow-up. Another non-CR patient eventually experienced the disease relapse (patient #8 in Table 3). Overall, the 10-year RFS rate reached 86.3% (Fig. 2A) and the 10-year OS rate was 90.9% (Fig. 2B). When stratified by ETV, there was no significant difference in the 10-year RFS (85.8% vs. 87.2%; p = 0.818) (Fig. 3A) and the 10-year OS rate (89.8% vs 93.2%; p = 0.674) (Fig. 3B). Table 4 presents the results of the univariate and multivariate analysis, and none of the factors, including ETV, was significantly associated with RFS or OS.

All of the recurred patients received salvage treatment. Chemotherapy was given to all patients, while salvage radiotherapy was delivered as CSI to five patients and stereotactic radiosurgery (SRS) to one patient. One patient underwent total resection as initial treatment. Peripheral blood stem cell transplantation was also performed in two patients. Four patients (50.0%) were rescued after salvage treatment and remained alive until the last follow-up.

Of the eight deaths, two were attributed to the progression of recurrent disease. Bleomycin-induced pneumonitis and chemotherapy-induced neutropenic sepsis accounted for a further two; one patient with WVRT died of secondary malignancy; and the cause of death for the remaining three was either unrelated to the disease or unknown.

3. Dosimetric analysis

Table 5 presents the dosimetric comparison of the organs at risk between the PC-excluding plans and the PC-including plans among 33 WVRT patients. The dose parameters were measured for three normal structures: the brainstem, the left cochlea, and the right cochlea. Their original plans were compared with the newly generated plans which included the PC. Excluding the PC significantly reduced the D_{mean} (Gy) and the D_{mean} (%) for the brainstem (16.9 Gy vs. 20.3 Gy, $p < 0.001$ and 81.5% vs. 97.5%, $p < 0.001$, respectively). Similarly, the mean dose for the left and the right cochlea was significantly lower in the PC-excluding plans (8.3 Gy vs. 15.6 Gy, $p < 0.001$ and 9.7 Gy vs. 15.8 Gy, $p < 0.001$, respectively).

4. Secondary malignancy

During the follow-up period, three patients developed secondary malignancy one in WVRT and two in IFRT. The median time to the

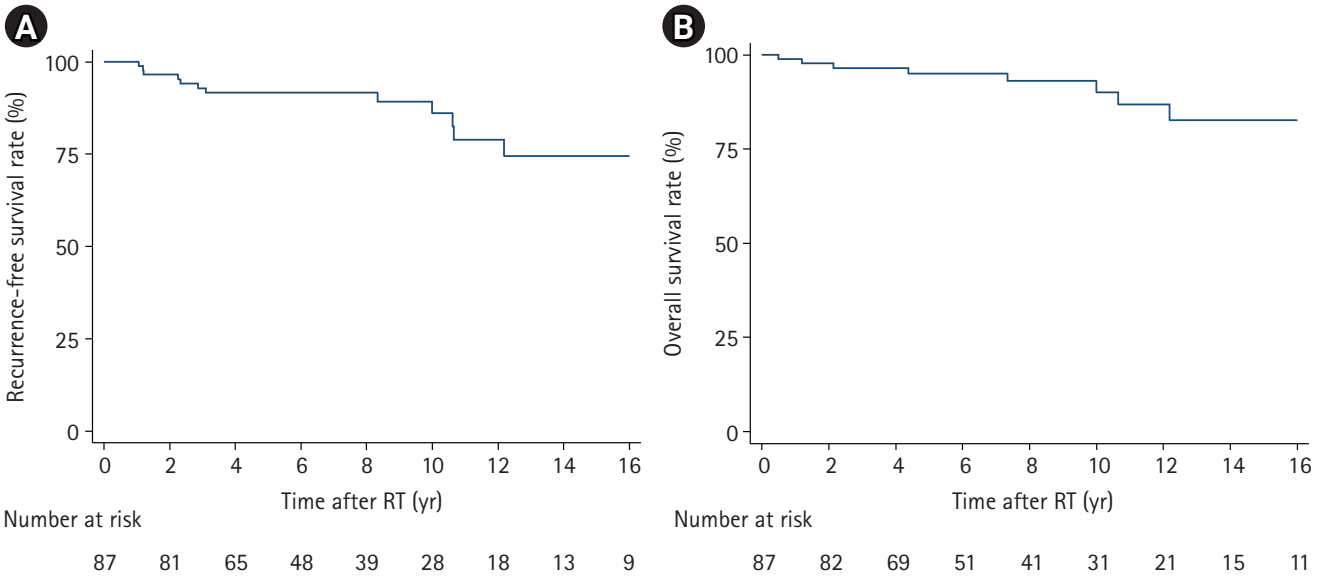

Fig. 2. Kaplan-Meier curves for recurrence-free survival (A) and overall survival (B) of patients with radiotherapy (RT).

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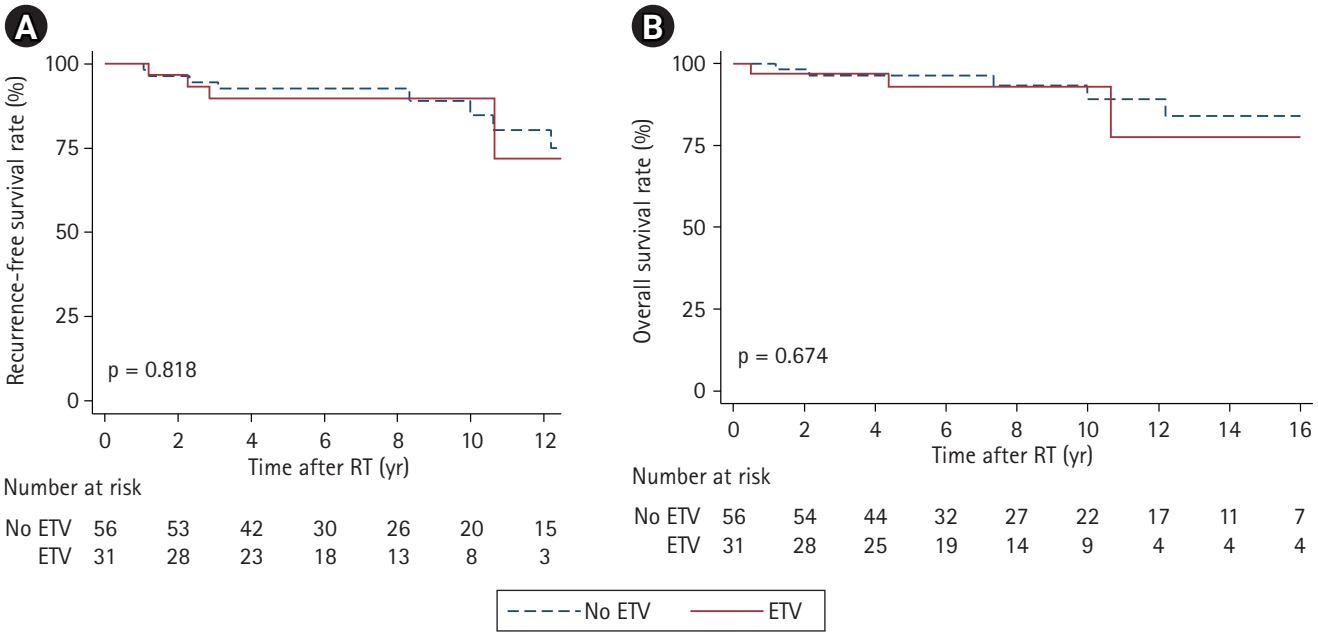

Fig. 3. Kaplan-Meier curves for recurrence-free survival (A) and overall survival (B) of patients with radiotherapy (RT) stratified by endoscopic third ventriculostomy (ETV).

Table 4. Univariate analysis of prognostic factors associated with RFS and OS[a)]

Factor	10-yr RFS rate (%)	p-value	10-yr OS rate (%)	p-value
Age (≥ 15 yr vs. < 15 yr)	86.1 vs. 84.0	0.458	90.3 vs. 89.0	0.721
Sex (male vs. female)	83.6 vs. 100	0.112	88.4 vs. 100	0.215
ECOG performance status (0–1 vs. 2–4)	87.5 vs. 85.9	0.384	87.5 vs. 90.3	0.127
Tumor site				
Bifocal vs. solitary	85.1 vs. 86.9	0.612	82.5 vs. 91.9	0.184
BG/thalamus vs. others	85.3 vs. 86.6	0.136	85.7 vs. 91.3	0.387
Endoscopic third ventriculostomy (yes vs. no)	89.8 vs. 84.8	0.818	92.9 vs. 89.1	0.674
Complete chemotherapy response (yes vs. no)	93.2 vs. 86.1	0.701	87.7 vs. 85.9	0.524
RT field (IFRT vs. WVRT)	75.6 vs. 87.4	0.572	81.3 vs. 93.0	0.467
RT dose (≥ 45 Gy vs. < 45 Gy)	90.6 vs. 87.7	0.878	90.8 vs. 89.3	0.959

RFS, recurrence-free survival; OS, overall survival; ECOG, Eastern Cooperative Oncology Group; BG, basal ganglia; RT, radiotherapy; IFRT, involved field radiotherapy; WVRT, whole ventricular radiotherapy.
[a)]Log-rank test was used.

onset of secondary cancer was 20.1 years, ranging between 9.0 and 21.0 years after radiotherapy. One patient developed medulloblastoma within the prior radiotherapy field 9 years after WVRT and eventually died of disease progression. Two other patients were diagnosed with meningioma located outside the previous treatment fields 20.1 and 20.0 years after IFRT, respectively. They underwent surgical resection, and one of them received adjuvant radiotherapy due to histologic grade 2 with brain invasion.

Discussion and Conclusion

To the best of our knowledge, this is the first study to report the outcome of excluding the PC from WVRT in localized germinoma after upfront chemotherapy. Since we adopted WVRT at our institution, the PC has been excluded from the WVRT volume. However, we did not observe any failure near the PC and achieved comparable disease control and OS corresponding with previous reports [1,8-12]. Besides, we confirmed significant dose reduction in the normal organ structures such as the brainstem. As the primary interest has shifted on the deintensification of the treatment to re-

Table 5. Dosimetric comparison of the organs-at-risk between PC-excluding plans and PC-including plans among 33 patients[a]

Normal structure	PC-excluding plans (n = 33)	PC-including plans (n = 33)	p-value
Brainstem			
D_{mean} (%)[b]	81.5 ± 7.9	98.7 ± 6.3	< 0.001
D_{mean} (Gy)	16.9 ± 2.3	20.3 ± 3.3	< 0.001
Left cochlea			
D_{mean} (%)	41.8 ± 15.0	75.5 ± 13.4	< 0.001
D_{mean} (Gy)	8.3 ± 3.4	15.6 ± 3.8	< 0.001
Right cochlea			
D_{mean} (%)	46.2 ± 15.3	76.8 ± 15.0	< 0.001
D_{mean} (Gy)	9.7 ± 3.4	15.8 ± 4.3	< 0.001

Values are presented as mean ± standard deviation.
PC, prepontine cistern.
[a]Dosimetry analysis was available in 33 whole ventricle radiotherapy patients. The intensity-modulated radiotherapy technique was used in 30 cases, and the 3D technique was used in 3 cases.
[b]D_{mean} (%) was compared to the prescribed dose to the whole ventricle and tumor bed (large field).

duce long-term toxicity, reduced WVRT volume can be a reasonable and viable strategy.

The clinical outcomes of localized germinoma in our study were similar to the previous studies, but there were some differences regarding the treatment field. The 10-year RFS and OS were 86.3% and 90.9%. The 5-year OS rates for localized germinoma after chemoradiotherapy ranged from 88% to 97% and the 5-year DFS ranged between 95%–98.8%. In the SIOP CNS GCT 96 trial which showed the feasibility of replacing CSI alone by focal irradiation with chemotherapy, the rates of 5-year progression-free survival and OS were 88% and 96%, respectively [10]. Koh et al.'s multi-institutional Asian study [2] reported 97.4% of OS and 92.6% of RFS for non-metastatic germinoma with 19.8 Gy WVRT. One major difference between our study and others was the treatment field determined by tumor location, tumor multiplicity, and chemotherapy response. The SMC-G13 trial by Lee et al. [11] resulted in 5-year PFS of 96.7% and OS of 96.2% in localized germinoma patients. In their study, whole brain radiotherapy was given in case of basal ganglia germinoma, while all patients in our study received IFRT or WVRT regardless of tumor location. Byun et al.'s single institutional retrospective study [1] included 19 patients with solitary tumor treated by CSI after chemotherapy. In a Korean prospective multicenter cohort study by Lee at al. [9], the treatment field for solitary tumor was extended to CSI in case of non-CR after upfront chemotherapy. In our study, the boost dose was modified in response to chemotherapy, and patients received either IFRT or WVRT if the tumor was solitary or bifocal without evidence of metastasis.

Despite limited data regarding the incidence of recurrence in the PC, the risk of failure in the PC does not seem high based on the treatment outcomes after IFRT. The SFOP study revealed that most failures occurred near brain parenchyma such as the frontal lobe, temporal lobe, occipital lobe and third ventricles after IFRT [13]. In the SIOP GCT trial by Calaminus et al. [10], localized germinoma patients with IFRT experienced ventricular relapses outside the radiation field. All the four ventricular relapses after IFRT were located within lateral ventricles in the study by Nakumara et al. [14]. Furthermore, no recurrence in the PC was observed even when radiotherapy was replaced by intensive chemotherapy in da Sailva et al.'s international CNS germ cell tumor study [15]. Consistent with other reports, ventricular relapse sites were mainly located near lateral ventricles in our study.

One of the considerations as to include the PC in treatment volume is the receipt of ETV which is usually recommended for pineal germinoma causing hydrocephalus [4]. It fenestrates the floor of the third ventricle, creating CSF flow from the third ventricle to the PC. This flow may also raise a concern for tumor cell spread to the PC. In our study, only one patient with ETV experienced isolated spinal cord relapse after WVRT. ETV was neither significantly associated with the risk of recurrence nor survival. Similarly, the COG ACNS1124 trial, a prospective study of WVRT dose reduction, also showed ETV did not carry an increased risk of recurrence in localized germinoma patients treated with a reduced dose after chemotherapy [16,17]. Among a total of eight relapses, two patients (25%) experienced parenchymal recurrences within the ETV surgical tract rather than ventricular area. Although including the surgical tract in the target volume will be an area for investigation, our finding and the ACNS1124 trial at least seem to suggest that excluding the PC area from the treatment field is not necessarily associated with disease control.

Excluding the PC from the treatment volume reduced radiation dose to the brainstem, potentially minimizing neurocognitive sequelae. Several previous studies reported the radiological evidence

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and clinical outcome of radiotherapy-induced brain damage. For example, the longitudinal imaging study of medulloblastoma patients found decline in fractional anisotropy within the brainstem after radiotherapy, suggesting axonal damage and demyelination [18]. Furthermore, dose-dependent white matter damage was detected by diffusion tensor imaging (DTI) and even at the low dose of 10–20 Gy, the DTI metrics which implied extracellular changes became significantly different at 9–11 months [19]. Such radiologic changes were also correlated with impaired cognitive and motor function in pediatric posterior fossa tumor survivals [20]. As these findings demonstrate the importance of minimizing radiation exposure as much as possible, we expect that reducing volume in WVRT would contribute to lowering the risk of radiation toxicity related to the brainstem such as cognition and motor function.

In addition to sparing the brainstem, excluding the PC also significantly spared the cochlea. In young and adolescent germinoma patients, the crude risk of radiotherapy-related ototoxicity is approximately 10%, with the risk of ototoxicity increasing particularly in those who received cisplatin, reaching a 10-year cumulative incidence of 39.2% [21]. The correlation between cochlear radiation dose and toxicity has been observed in pediatric brain tumor patients who underwent cranial radiation [22]. Although it was feasible to meet the recommended constraint for the cochlea (D_{mean} < 35–45 Gy) in both the original plans and the PC including plans, it is still important to minimize the dose exposure as much as possible [7]. In a dosimetry analysis of the French Childhood Cancer Survivors Study (FCCSS), a correlation was found between inner ear dose and ototoxicity after cisplatin and radiation. Cohen-Cutler et al. [23] demonstrated that the minimal cochlear dose predicted hearing loss with an odds ratio of 1.64 per 10 Gy ($p = 0.043$). Although we did not have a detailed toxicity profile relevant to ototoxicity, excluding the PC in WVRT may not seem significant. However, given that cisplatin is one of the primary chemotherapy regimens for the treatment of germinoma, it is crucial to minimize the risk of developing ototoxicity by reducing radiation exposure to the cochlea, which is located very close to the PC.

Secondary cancer is a long-term complication of cancer survivors including germinoma. The incidence of secondary malignancy in germinoma patients ranges approximately between 5%–6% [24,25]. Previously, 5.3% of intracranial germinoma patients treated at our institution developed secondary malignancy with 20-year latent period (range, 4 to 26 years), which is consistent with the SEER database analysis of intracranial germ cell tumor patients [24,25]. One of the risk factors for secondary cancer development is the radiation field size [26]. Accordingly, we found a significantly higher risk of developing secondary malignancy after extended field radiotherapy such as WBRT or CSI compared to WVRT or IFRT [25]. Therefore, we expect that reducing the volume in WVRT would contribute to lowering the risk of radiation-related complications.

In an effort to reduce treatment volume, Yan et al. [27] from Princess Margaret Hospital explored the feasibility of excluding temporal ventricular horns from WVRT volume. Sparing temporal ventricular horns resulted in excellent disease control as well as a significantly reduced dose to the hippocampus and temporal lobes. Considering the correlation between hippocampus mean dose and hippocampal volume change in pediatric and young adult brain tumor patients, a reduced WVRT for these patients seems worthy of further exploration [28]. The study supported the safety of temporal horn sparing WVRT as they did not observe ventricular failure near the temporal horns among 29 patients with IFRT [1,29]. Although preserving the hippocampus is critical to neurocognitive outcomes, this approach may not always be viable. In our cohort, one patient experienced relapse at the temporal horn of the lateral ventricle, and further studies need to identify an eligible subset of germinoma patients.

Besides reducing WVRT volume, other strategies such as dose reduction and modern radiation techniques could help reduce treatment-related toxicity. The COG reported the favorable outcome of a reduced WVRT dose of 18 Gy in those who achieved a CR after chemotherapy. Despite a lack of statistical significance for non-inferiority, the 18 Gy WVRT regimen showed similar disease control with improved cognitive functioning compared with 24 Gy WVRT [17]. In addition, a study from the Hospital for Sick Children demonstrated the feasibility of omitting a boost dose to the tumor bed [30]. Advanced radiation techniques such as proton technique can be utilized as proton therapy offered dosimetric advantages for conformality and normal organ sparing compared to IMRT and volumetric modulated arc therapy for WVRT [31,32]. Proton beam radiotherapy was associated with a lower risk of secondary tumor development compared to IMRT (adjusted odds ratio = 0.31; 95% confidence interval, 0.26–0.36; $p < 0.001$) [33].

Our study, nevertheless, has some limitations. Firstly, we were unable to evaluate the functional consequences directly relevant to the brainstem and cochlea. This could be explained by the subclinical effect of radiation exposure or underestimation. Despite a long follow-up period, comprehensive neurological exams were not routinely performed, with primary emphasis being put on imaging studies and laboratory exams. Therefore, thorough neurological assessments related to specific structures will be valuable in understanding the toxicity profile after de-escalated WVRT. We nonetheless believe that it is still of paramount importance to minimize unnecessary radiation exposure, adhering to the principle of "As Low As Reasonably Achievable." The overall risk of late toxicity

would be less likely to occur than before with the use of modern radiotherapy techniques such as IMRT. Furthermore, chemotherapy regimens and radiation treatments were not consistent over the course of our study as the standard treatment for localized germinoma evolved over the period. However, the principle of radiation treatment was consistent as most of the patients were treated by one pediatric radiation oncologist.

In conclusion, our study showed the outcome of excluding the PC from WVRT in localized germinoma patients after chemotherapy, and our finding suggests that this can be one of the optimal strategies by reducing radiation treatment volume. However, future trials with long-term follow-up are required to reach a consensus on WVRT target volume.

Statement of Ethics

The Institutional Review Board of Seoul National University Hospital approved this study and waived the requirement for patient informed consent (IRB No. H-2204-141-1319).

Conflict of Interest

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

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None.

Author Contributions

Conceptualization: Lee JH. Investigation and methodology: Lee JH. Writing of the original draft: Ryu H. Writing of the review and editing: Ryu H, Lee JH. Formal analysis: Ryu H, Lee JH. Data curation: Ryu H, Lee JH.

Data Availability Statement

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

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Instructions for Authors

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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), telephone (+82-2-743-6574).

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.

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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.

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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."

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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.

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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

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6. ADDITIONAL INFORMATION

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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.

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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.

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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.

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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

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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.

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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.

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ROJ Radiation Oncology Journal

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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.

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Injection for Intravenous Use 50 mg/mL

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THE STANDARD OF CARE[1] FOR STAGE III UNRESECTABLE NSCLC

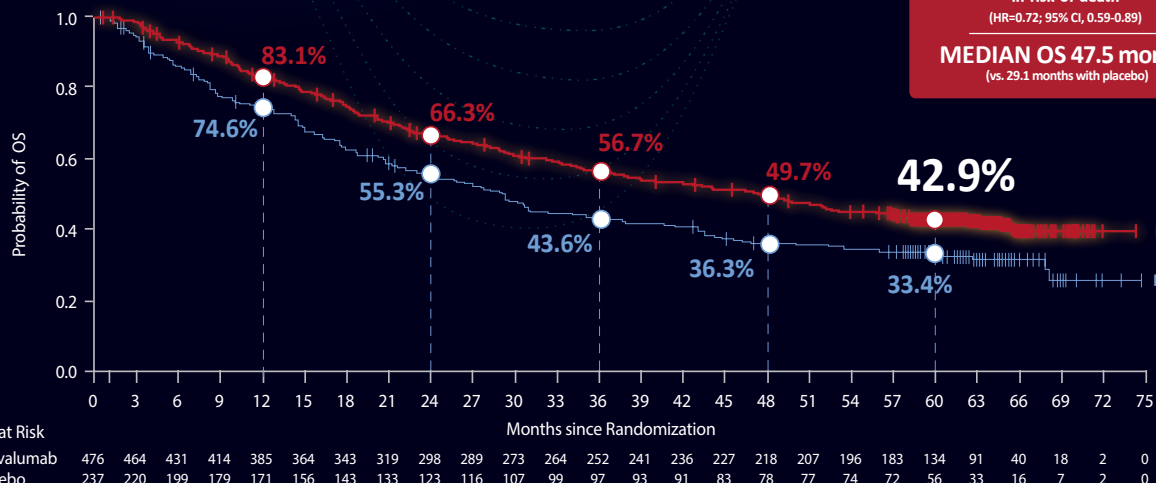
Following cCRT

임핀지™는 PACIFIC 연구에서 5년 전체생존율(OS rate) 42.9%로, 장기적인 생존개선 이점을 나타냈습니다.[2]

28% REDUCTION
in risk of death
(HR=0.72; 95% CI, 0.59-0.89)

MEDIAN OS 47.5 months
(vs. 29.1 months with placebo)

UPDATED 5-YEARS OVERALL SURVIVAL IN THE ITT POPULATION



No. at Risk

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

임핀지(durvalumab) 보험 적용 적응증[3,4]

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

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

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

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

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

PRESCRIBING INFORMATION

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

이상사례	중증도 (CTCAE v4.03)	용량 조절	코르티코스테로이드 요법 및 기타
면역 매개 폐렴증/간질성 폐질환	2등급	투여 보류•	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	3 또는 4등급	투여 중단	
면역 매개 간염	2등급이고, 알라닌 아미노기전이효소 (ALT) 또는 아스파르테이트 아미노기전이효소 (AST)가 정상상한치의 3-5배를 초과하거나 총 빌리루빈이 정상상한치의 1.5-3배를 초과	투여 보류•	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	3등급이고, ALT 또는 AST가 정상상한치의 5배 초과, 8배 이하 또는 총 빌리루빈이 정상상한치의 3배 초과, 5배 이하		
	4등급이고, ALT 또는 AST가 정상상한치의 8배를 초과 또는 총 빌리루빈이 정상상한치의 5배를 초과	투여 중단	
	다른 원인로 알려지지 않은 중증 (3등급) 면역 매개 이상사례의 경우 이 약의 투여를 중단한다. 면역 매개 이상사례가 다음 표에 요약되어 있다. (이 약의 용량 조정 및 관리 권장 사항)		
면역 매개 대장염 또는 설사	2 또는 3등급	투여 보류•	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	4등급	투여 중단	
면역 매개 내분비병: 간뇌하수체염	2-4등급	임상상으로 안정될 때까지 투여 보류	대증적 관리
면역 매개 내분비병: 갑상선 기능 저하증	2-4등급	안정될 때까지 투여 보류	갑상 지시호르몬 대체 개시
면역 매개 내분비병: 부신 기능 부전, 뇌하수체염/시상하부염	2-4등급	임상상으로 안정될 때까지 투여 보류	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량 및 임상 지시대로 호르몬 대체 개시
면역 매개 내분비병: 제1형 당뇨병	2-4등급	변경하지 않음	임상 지시대로 인슐린 치료 개시
면역 매개 신장염	2등급이고, 혈청 크레아티닌이 정상상한치 또는 기저치의 1.5-3배를 초과	투여 보류•	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	3등급이고 혈청 크레아티닌이 기저치의 3배를 초과 또는 정상상한치의 3-6배를 초과하거나, 4등급이고 혈청 크레아티닌이 정상상한치의 6배를 초과	투여 중단	
	혈뇨/요단백 1건을 초과 및 그 이상	투여 보류•	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
면역 매개 발진 또는 피부염 (약사 천포창 포함)	3등급	투여 중단	
	4등급	투여 중단	
면역 매개 심근염	2-4등급	투여 중단	2-4 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
면역 매개 근육염/ 다발근육염	2 또는 3등급	투여 보류••	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	4등급	투여 중단	
주입 관련 반응	1 또는 2등급	주입을 중단하거나 느리게 주입	주속 주입 반응의 예방을 위해 사전 약물 치료를 고려할 수 있음
	3 또는 4등급	투여 중단	
중증 근육 무력증	2등급	투여 보류•	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	3 또는 4등급, 또는 호흡 부전이나 기관 신경 삽조증의 징후가 있는 모든 등급	투여 중단	
기타 면역 매개 이상사례*	3등급	투여 보류•	1-2 mg/kg/일의 프레드니손 또는 등가량의 투여를 시작한 후 용량 감량
	4등급	투여 중단	

* 이상사례 표준 용어기준 (Common Terminology Criteria for Adverse Events; CTCAE), 버전 4.03 • 1등급 이하로 개선되면, 코르티코스테로이드의 감량을 시작하여 최소 1개월 간 지속하여야 한다. 약화되거나 개선이 없다면, 코르티코스테로이드의 용량 증가 및/또는 다른 적절 면역 억제제 사용을 고려한다. • 투여 날로 후, 1등급 이하로 개선되고 코르티코스테로이드 용량이 일일 ≤10mg 프레드니손 또는 등가량 이하로 감소되었을 경우, 12주 이내에서 이 약의 투여를 다시 시작할 수 있다. 3등급 이상사례 재발의 경우 이 약을 중단한다. • 코르티코스테로이드 투여에도 불구하고 2-3일 이내에 개선이 없다면, 신속히 추가적인 면역억제 치료를 시작한다. 희복(0등급)되면, 코르티코스테로이드의 감량을 시작하고 최소 1개월 간 지속한다. * 이상사례가 30일 이내에 1등급 이하로 회복되지 않거나 호중구 기능부전의 징후가 있는 경우에는 이 약 투여를 중단한다. ' 면역 혈소판 감소증, 뇌염 포함 의심되는 면역 매개 이상사례에 대해, 병인 확인 또는 대체 병인을 배제하기 위한 적절한 평가가 수행되어야 한다. 비- 면역 매개 이상사례에 대해, 2등급과 3등급 이상사례의 경우 1등급 이하가 될 때까지 이 약의 투여를 보류한다. 4등급 이상사례의 경우 이 약 투여를 중단한다 (예외적으로 4등급 림팡구 감소증 이상의 경우, 수반된 임상 징후 및 임상적 판단에 근거하여 투여 중단을 결정한다). 이 약은 경증도 간염에 환자에서는 용량 조절의 권장되지 않으며, 중등도 또는 중증 간장애 환자에서는 연구되지 않았다. 투여방법: 투여 전 이 약액병의 형식에 대한 지시 사항은 사용상의 주의사항). *13. 최대상의 주의사항' 을 참고한다. 혈관외 과 단백질 결합 0.2 또는 0.22 마이크로미터 인라인 혈터(in-line filter)를 포함하는 정맥 주사 라인을 통해 1시간에 걸쳐 주사액을 정맥 내 투여한다. 같은 주입 라인으로 다른 약물을 동시 투여하지 않는다. 사용하고 남은 약물이나 물품은 관련 규정에 따라 폐기되어야 한다. [사용상의 주의사항] 1.다음 환자에는 투여하지 말 것 이 약의 주성분 또는 첨가제에 과민증 병력이 있는 환자, 2.다음 환자에는 신중히 투여할 것 자가면역질환 또는 자가면역질환 병력이 있는 환자 3 악물이상반응 1) 임상시험에서 보고된 이상사례 이상사례는 MedDRA의 기준계 분류에 따라 기재되었다. 각 기준계 분류에서, 이상사례는 빈도가 높은 순으로 표기되었다. 각 빈도 군에서, 이상사례는 중증도가 높은 순으로 표기되었다. 또한, 각 이상사례의 해당 빈도 분류는 CIOMS III 희망에 따라 다음과 같이 정의된다: 매우 흔하게 (≥1/10), 흔하게 (≥1/100 ~ <1/10), 흔하지 않게 (≥1/1,000 ~ <1/100), 드물게 (≥1/10,000 ~ <1/1,000), 매우 드물게 (<1/10,000), 빈도 불명, 즉 이용 가능한 자료로부터 추정할 수 없음. 국소 진행성 비소세포폐암 - PACIFIC 연구 PACIFIC 연구 (475명에서 국소 진행성 절제 불가능한 비소세포폐암 환자로 이 연구 시작 전 1-42일 내에 2주기 이상의 항암화학방사선요법을 완료한 환자들을 대상으로 이 약(10 mg/kg)의 안전성이 평가되었다. 이 환자 집단에서 가장 흔한 이상사례는 기침 (40.2%, 위약군 30.3%), 상부 호흡기 감염 (26.1%, 위약군 11.5%) 및 발진 (21.7%, 위약군 12.0%)이었다. 3 또는 4등급 이상사례의 발생률은 이 약 투여군에서 12.8%, 위약군에서 9.8%이었다. 가장 흔한 3 또는 4등급 이상사례는 폐렴 (6.5%, 위약군 5.6%)이었다. 이 약 투여군의 8.2% 및 위약군의 5.6%에서 이상사례로 인해 투약을 중단하였다. 이 약의 투약 중단으로 이어진 가장 흔한 이상사례는 폐렴증 (4.8%)이었다. 중대한 이상사례는 이 약 투여군 12.8% 및 위약군 11.1%의 환자에서 발생하였다. 가장 흔한 중대한 약물이상반응은 2% 미만의 환자에서 보고된 폐렴증과 폐렴이었다. 치명적인 폐렴증과 치명적인 폐렴은 이 약 투여군과 위약군 간에 유사하게 1% 미만의 환자에서 보고되었다. 확장 병기 소세포폐암 - CASPIAN 연구 CASPIAN 연구에서 이전에 치료받지 않은 확장 병기 소세포폐암 환자에게 이 약과 에토포시드 및 카보플라틴 또는 시스플라틴을 병용투여 했을 때의 안전성이 평가되었다 (265명). 이 약과 화학요법을 병용 시의 안전성 프로파일은 이 약 단독요법 및 화학요법의 알려진 프로파일과 일관되게 나타났다. 이 임상연구에서 보고되지 않았더라도, 이 약 또는 화학요법 단독으로 발생한다고 알려진 이상사례는 병용요법 중에도 발생할 수 있다. [저장방법] 밀봉용기, 2-8℃에서 차광하여 보관 [포장단위] 2.4 mL × 1 바이알 / 박스, 10 mL × 1 바이알 / 박스 ※ 판약 구입시 사용기한이 경과되었거나 변질, 변품 또는 오손된 제품인 경우에는 구입처를 통하여 교환하여 드리며, 공정거래위원회 고시 " 소비자분쟁해결기준" 에 의거 소비자의 정당한 피해는 보상하여 드립니다. 이외를 무작위 발생 시 한국임약물안전관리원에 피해구제를 신청하실 수 있습니다. 문의 제약업체명: 2022년 03월 04일 수입(수입)자: 한국아스트라제네카 서울시 강남구 영동대로517 아셈타워 21층, 전화 02-2188-0800 • 보다 자세한 사항은 제품설명서 전문을 참고하시기 바랍니다. aiFZ2022031O

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