Aims and Scope
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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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Has the growing evidence of radiotherapy for hepatocellular carcinoma increased the use of radiotherapy in elderly patients?

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Primary liver cancer, mostly hepatocellular carcinoma (HCC), is the sixth most common cancer and the third leading cause of cancer-related deaths worldwide [1]. HCC develops mostly in patients with chronic liver disease, such as cirrhosis from hepatitis B and C virus infection, alcoholic abuse, and nonalcoholic fatty liver disease, and the risk of developing HCC increases with age [2]. The selection of the treatment modality for HCC is generally determined by the tumor stage, underlying liver function, and performance status [3,4]. The clinical practice guidelines for HCC in Korea were first published in 2003 and have been revised four times since then in 2009, 2014, 2018, and 2022, respectively [4-6]. Over the past two decades, the role of radiotherapy (RT) in the treatment of HCC has changed significantly in the Korean clinical practice guidelines for HCC [4] due to growing evidence regarding its effectiveness and safety in treating HCC of various stages and clinical scenarios [7-15]. Furthermore, RT can be considered an alternative or complementary option for all stages of HCC that may be unsuitable for or ineffective to other locoregional treatments, including surgical resection, radiofrequency ablation, or transarterial chemoembolization, with or without systemic treatments.

In the last issue of the Radiation Oncology Journal, the paper titled “Radiotherapy trend in elderly hepatocellular carcinoma: retrospective analysis of patients diagnosed between 2005 and 2017” by Bae et al. [16] evaluated the trends of the use of RT in elderly patients with HCC. They found that the proportion of elderly patients (age ≥ 75 years) with HCC increased significantly from 3.1% in 2006 to 11.4% in 2017. The use of RT in elderly patients with HCC has also increased significantly from 6.1% between 2005 and 2009 to 15.3% between 2015 and 2017. Additionally, the proportion of elderly patients with HCC receiving RT with curative intent using advanced RT techniques, including stereotactic body radiotherapy and proton beam therapy, was significantly higher than that of younger patients (37.3% vs. 25.0%). The overall survival (OS) of elderly patients with HCC is worse than that of younger patients. This could be attributed to comorbidities, such as diabetes, hypertension, and poor performance status, which are more common in elderly patients than in younger patients. However, the OS of elderly patients with HCC who received RT as the initial treatment did not differ significantly from that of younger patients. Based on these findings, the authors concluded that RT could play an increasingly important role in the treatment of elderly patients with HCC in the future.
The treatment of elderly patients is often complicated. First, although defining elderly patients based on chronological age is a simple approach, the cutoff age for elderly patients has not yet been established (70, 75, or 80 years) [17-20]. Second, chronological age alone cannot fully explain the complex biological events and related conditions of the aging process, which include comorbidities, physical function, nutritional status, and mental function. These factors can affect treatment compliance, risk of adverse events, life expectancy, and other outcomes. Therefore, elderly patients are difficult to manage and likely to be undertreated in the real world. Only a few retrospective studies with small study populations are available on RT in elderly patients. However, available data suggest that RT in elderly patients is effective and safe, similar to that in younger patients. Similarly, Bae et al. [16] provide valuable insights regarding the changing trends in the use of RT in elderly patients with HCC and highlight its potential role as a curative treatment option in this population. The treatment of elderly patients with HCC, including RT, remains challenging, and prospective evidence in the literature and clinical practice guidelines is lacking. As life expectancy and the risk of developing HCC increase with age, the proportion of elderly patients with HCC also increases. Therefore, further investigations on the role of RT in elderly patients are warranted, as this has important implications in clinical practice.

Conflict of Interest

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

References


Introduction

Cancer is the first leading cause of death in Korea and lung cancer accounts for 22% of cancer deaths with approximately 30,000 new cases diagnosed in 2019 [1]. In terms of histological type, 80%–90% of lung cancers are classified as non-small cell lung cancer (NSCLC) [2]. Stage I NSCLC has recently increased, but more advanced stages are still 70%, which need multimodal therapy [2].

Among NSCLC patients with positive nodes, especially pathological N2 (pN2) disease, 35%–55% experience treatment failures even after complete resection followed by adjuvant chemotherapy and are associated with inferior overall survival (OS) [3,4]. According to the American Joint Committee on Cancer 8th edition, N2 is defined when metastasis is found in ipsilateral mediastinal and/or subcarinal lymph nodes [5]. With regard to the location and number of involved lymph nodes, N2 consists of a highly heterogeneous group. Besides, stage III pN2 possesses a wide variety of clinicopathologic features such as the size and characteristics of the primary tumor, making it more difficult to select patients who will benefit from postoperative treatments.

There has been a long debate regarding the appropriate use of postoperative radiotherapy (PORT) for patients with completely re-
sected NSCLC, although PORT is often employed for patients with pN2 NSCLC. Especially, the Lung ART trial presented in 2020 seemed to put an end to the controversy over PORT: no more PORT for stage IIIA pN2 after complete resection [6]. However, in 2021, the updated results of Lung ART reported that PORT significantly improved mediastinal relapse-free survival, despite no difference in metastasis-free survival [7]. Therefore, the authors concluded that a personalized prescription of PORT might be allowed based on prognostic factors.

In this review, we will not discuss PORT after incomplete resection (R1 or R2), which is a well-established PORT indication, and briefly summarize previous studies for PORT after R0 resection. We then highlight the major breakthroughs derived from recent randomized clinical trials (RCTs), updating current lung cancer treatment guidelines. Ultimately, we want to give answers about how to select and manage patients with completely resected pN2 NSCLC patients.

**Historical Perspective on PORT for N2 Stage NSCLC**

Given the assumption that high local recurrence in pN2 patients than pN0–1 was thought to be due to the challenges of achieving complete surgical removal of microscopic lymph node metastasis in the mediastinum, a retrospective analysis was conducted at Mayo Clinic on a cohort of 224 patients with pN2 status between 1987 and 1993 to evaluate the potential benefit of PORT in these patients [8]. The 4-year freedom from local recurrence (83% vs. 40%, p < 0.0001) and survival rate (43% vs. 22%, p = 0.0005) were higher in the PORT group. This study published in 1997 was the largest evaluating PORT in pN2 patients in that era, suggesting that PORT can enhance both local control and OS. Large-scale RCTs have been initiated since then.

The landmark PORT meta-analysis in 1998, which initially included nine old RCTs (PORT vs. observation), showed unfavorable survival outcomes after PORT–OS, hazard ratio (HR) = 1.21, p = 0.001; disease-free survival (DFS), HR = 1.13, p = 0.007; locoregional relapse-free survival (LRRFS), HR = 1.16, p = 0.005 [9]. In subgroup analysis, PORT was detrimental with stages I–II, whereas, for stage III, there was no clear evidence of a detriment. After the publication of this meta-analysis, there was a sustained decline in PORT use. Consequently, few papers were published in early 2000. However, considering patients were recruited in the mid to late 1900s, this meta-analysis had several criticized points, despite the importance of this analysis. Participants might have been evaluated with inadequate staging and they received no longer standard treatment including old radiotherapy (RT) techniques such as cobalt-60 equipment, large fraction size, and large treated volume with two-dimensional RT planning. In some trials included in the meta-analysis, the total dose was quite lower than the currently used, and adjuvant chemotherapy was not done.

Meanwhile, two studies published in 2006 made clinicians reconsider PORT for N2 NSCLC. The first one, the Surveillance, Epidemiology, and End Results (SEER) database analysis using 7,465 patients with resected NSCLC between 1998 and 2002 showed that although PORT was associated with a significant decrease in survival for patients with N0 and N1 disease, PORT was associated with more prolonged cancer-specific (5-year: 36% vs. 27%, p = 0.0298; HR = 0.850, p = 0.0133) and overall survival (5-year: 27% vs. 20%, p = 0.0036; HR = 0.855, p = 0.0077) for patients with N2 disease [10]. In addition, there was a post-hoc analysis of the Adjuvant Vinorelbine International Trialist Association (ANITA) trial, which was designed to compare the effect of adjuvant vinorelbine plus cisplatin with observation in completely resected NSCLC [11]. As PORT was not mandatory in this study, a non-randomized sub-analysis was conducted to compare OS in patients who did or did not receive PORT. The results showed that PORT led to longer OS, both in the chemotherapy arm (5-year: 47% vs. 34%) and in the observation arm in N2 disease (5-year: 21% vs. 17%).

Subsequent several retrospective studies have been published and they also suggested that a significant increase in DFS and 5%–15% of overall survival benefit was observed with PORT use in un-selected N2 [12–14]. China multicenter retrospective study showed that the 5-year OS was 30.5% in the postoperative chemoradiotherapy group and 22.2% in the postoperative chemotherapy group (p = 0.007) [12]. For 5-year DFS, the postoperative chemoradiotherapy and postoperative chemotherapy group had a rate of 14.4% and 9.3%, respectively (p = 0.003). Another single institutional retrospective study showed that PORT had a significantly longer OS time (p = 0.046), DFS interval (p = 0.009), as well as significantly higher LRRFS (p = 0.025), distant metastasis-free survival rate (p = 0.001) [13]. Based on this, they conducted a PORT-C trial which will be discussed in a later section. The largest retrospective one was the US National Cancer Data Base (NCDB) study published in 2015. It included 4,483 patients with pN2 NSCLC who underwent complete resection and adjuvant chemotherapy from 2006 to 2010. On multivariable analysis, it demonstrated a similar gain of additional PORT (HR = 0.886) compared to the previous results of the SEER database: use of PORT was associated with an increase in median and 5-year OS compared with no PORT (median: 45.2 vs. 40.7 months, 5-year: 39.3% vs. 34.8%, p = 0.014) [14].

The steady advancement of RT delivery methods has raised expectations that modern PORT will contribute to improved survival. In the updated meta-analysis of 11 trials, a total of 2,387 patients
were included for survival analysis, and previous RCTs were stratified according to the use or non-use of linear accelerators (LINAC) [15]. In terms of local tumor failure, local recurrence significantly decreased with PORT, and the most significant decrease was observed in the group treated with LINAC only, with a relative risk (RR) of 0.31. With regard to OS, for the whole group, there was no improvement with PORT use. However, an increase in OS was observed in the LINAC-only group, with a RR of 0.76. PORT with LINACs was estimated to reduce local recurrence rates from 30% to 10% and PORT was estimated to increase the absolute 5-year OS by 13% (approximately 20% × 2/3 by generating a hypothesis model). These results reinforced further investigations of PORT using modern LINAC.

Lastly, the Cochran database review was published in 2016, updating the above-mentioned meta-analysis in 1998 with two trials conducted in Italy and Korea [16]. In this analysis, patients with T3N0M0 were reclassified from stage IIIA to stage IIB according to the TNM system change, and treatment bias was evaluated using the Fisher test. The results of 2,343 patients from 11 trials demonstrated that PORT showed a detrimental effect on patients with completely resected NSCLC. Besides, in contrast to the above meta-analysis, LINAC only did not affect OS (HR = 1.02, 95% confidence interval [CI] = 0.80-1.31, p = 0.85).

The aforementioned studies are summarized in Table 1.

**Recent Results of Representative RCTs on PORT for N2 Stage NSCLC**

Several RCTs have been conducted on patients recruited in the recent 2000s, during which the advancement of imaging technology and treatment methods enabled more precise cancer staging, as well as, more sophisticated surgery and RT. In the following section, we will discuss four RCTs with a particular focus on the PORT-C and Lung ART trials, which were published in 2021 and 2022, respectively (Table 2).

The first RCT using modern PORT was conducted in China to compare adjuvant chemotherapy with adjuvant concurrent chemoradiotherapy (CCRT) in pN2 NSCLC [17]. Although this study has a

<table>
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<tr>
<th>Table 1. Overview of historical studies investigating postoperative radiotherapy for non-small cell lung cancer</th>
</tr>
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<tbody>
<tr>
<td><strong>Trial</strong></td>
</tr>
<tr>
<td>Sawyer et al. [8]</td>
</tr>
<tr>
<td>PORT Meta-analysis Tri-alists Group [9]</td>
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<tr>
<td>Lally et al. [10]</td>
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<tr>
<td>Douillard et al. [11]</td>
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<tr>
<td>Zou et al. [12]</td>
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<tr>
<td>Dai et al. [13]</td>
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<tr>
<td>Robinson et al. [14]</td>
</tr>
</tbody>
</table>

DFS, disease-free survival; OS, overall survival; pN2, pathological N2; PORT, postoperative radiotherapy; HR, hazard ratio; POCT, postoperative concurrent chemoradiotherapy; POCRT, postoperative concurrent chemoradiotherapy.
Table 2. Summary characteristics of recent randomized clinical trials for postoperative radiotherapy in completely resected N2 stage non-small cell lung cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study period</th>
<th>n</th>
<th>Stage</th>
<th>Randomization</th>
<th>DFS</th>
<th>OS</th>
<th>Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shen et al. [17]</td>
<td>2004–2009</td>
<td>135</td>
<td>IIIA-pN2</td>
<td>POCT vs. PCORT (50.4 Gy/28 Fx)</td>
<td>Median: 18 vs. 28 mo (p = 0.04)</td>
<td>Median: 28 vs. 40 mo (p = 0.07)</td>
<td>OS: Multiple pN2, PCORT favored</td>
</tr>
<tr>
<td>Sun et al. [18]</td>
<td>2009–2014</td>
<td>101</td>
<td>IIIA-pN2</td>
<td>POCT vs. PCORT (50 Gy/25 Fx)</td>
<td>Median: 21.9 vs. 24.7 mo (p = 0.40)</td>
<td>Median: 83.5 vs. 74.3 mo (p = 0.38)</td>
<td>OS: Never smoker, multiple pN2, PCORT favored</td>
</tr>
<tr>
<td>PORT-C [19]</td>
<td>2009–2017</td>
<td>364</td>
<td>IIIA-pN2</td>
<td>mITT</td>
<td>Median: 18.6 vs. 22.1 mo (p = 0.20)</td>
<td>Median: 81.5 mo not reached (p = 0.93)</td>
<td>DFS: Lymph nodes ≥ 4, PORT favored</td>
</tr>
<tr>
<td>Lung ART [20]</td>
<td>2007–2018</td>
<td>501</td>
<td>IIIA-pN2</td>
<td>(After adjuvant chemotherapy)</td>
<td>Median: 22.8 vs. 30.5 mo (p = 0.05)</td>
<td>Median: 83.1% vs. 82.6% (p = 0.41)</td>
<td>DFS: Preoperative chemotherapy alone, PORT favored</td>
</tr>
</tbody>
</table>

DFS, disease-free survival; OS, overall survival; pN2, pathological N2; POCT, postoperative chemotherapy; POCRT, postoperative concurrent chemoradiotherapy; PP, per-protocol; NS, not significant.

A small number of patients due to slow accrual, three-dimensional conformal radiotherapy (3D-CRT) with optimal RT dose of 50.4 Gy in 28 fractions and modern chemotherapy regimen—paclitaxel (175 mg/m²) and cisplatin (60 mg/m²)—was applied. As a result, the adjuvant CCRT group showed decreased local (18/66 vs. 34/69, p = 0.01) and distant failures (32/66 vs. 45/69, p = 0.05) and improved DFS rate (5-year: 30.3% vs. 18.8%, p = 0.04) of these patients, compared with adjuvant chemotherapy. Despite the marginal significance of the difference, a superior OS was observed in the adjuvant CCRT group (5-year: 37.9% vs. 27.5%, p = 0.07), and in subgroup analysis, adjuvant CCRT increased the OS rate of patients with multiple N2 (p = 0.02).

A similar randomized phase II trial for only unsuspected or minimal N2 NSCLC was conducted in South Korea, reporting no significant differences in DFS and OS between adjuvant CCRT and chemotherapy alone [18]. The exploratory analysis of subgroups demonstrated that OS might be improved when patients with non-adenocarcinoma (HR = 0.359, 95% CI = 0.093–1.390) or with fewer than 15 lymph nodes dissected (HR = 0.575, 95% CI = 0.135–2.446) were treated with adjuvant CCRT. A cautious interpretation of this result needs because of a very small number of patients. Compared to the study by Shen et al. [17], the Korean study showed a higher OS, and the authors attributed this to the thorough staging workup and invasive mediastinal staging procedures. This difference in study populations might reduce the role of adjuvant RT in the Korean trial. Furthermore, there was a contrast between the two groups that multistation pN2 patients favored chemotherapy alone in the Korean trial and CCRT in the Chinese study. Distant metastasis frequently occurred in multistation pN2 disease and the insufficient dose of chemotherapy in CCRT did not control distant metastasis properly, leading to decreased OS. Further validation is required. The number of patients experiencing locoregional failure only was 5 (9.8%) in CCRT and 7 (14.0%) in the chemotherapy alone.

The phase III PORT-C trial enrolled patients with completely resected N2 NSCLC and randomized 1:1 to PORT 50 Gy and observation after four cycles of adjuvant platinum-based chemotherapy [19]. Intensity-modulated radiotherapy (IMRT) was applied in 89% of patients. The primary endpoint was DFS. The clinical features were comparable between the two groups: 80% of patients had adenocarcinoma, and nearly 60% were not cN2 which underlies the importance of pretreatment mediastinal staging. The 3-year DFS rates in PORT and observation were 40.5% versus 32.7%, respectively, in the modified intent-to-treat analysis (HR = 0.84, 95% CI = 0.65–1.09, p = 0.20). In the per-protocol analysis, PORT significantly improved DFS (42.8% vs. 30.6%; HR = 0.75, 95% CI = 0.57–1.00, p = 0.05) but not OS (82.6% vs. 83.1%; HR = 0.83, 95% CI = 0.53–1.30, p = 0.41). The local recurrence—only was less observed in the PORT group compared to the non—PORT (3-year: 9.5% vs. 18.3%; Fine-Gray HR = 0.55, 95% CI = 0.31–0.97, Gray test p = 0.04). The authors described that no RT-related mortality was observed, and most deaths occurred due to cancer progression.

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The low toxicity rate can be attributed to the use of IMRT and the implementation of stricter dose constraints for organs at risk. We need to take a closer look at which 44 of 184 patients (23.9%) in the PORT arm refused PORT, and 10 of 180 patients (5.6%) in the observation arm actually received PORT. Besides, although all patients completed four cycles of postoperative chemotherapy, 61.9% of patients still experienced distant metastasis. This may have offset the benefits of locoregional control from PORT, resulting in no improvement in DFS and OS.

Another phase III trial, the Lung ART trial, also randomized 1:1 to PORT of 54 Gy (3D-CRT of 89% and IMRT of 11%) and observation [20]. This trial did not meet the primary accrual goal due to slow enrollment. Baseline patient characteristics were comparable between the two groups. Major tumor histology was adenocarcinoma over 70%. Although over 90% of patients were staged with positron emission tomography-computed tomography scan, of enrolled cases, 40% had microscopic, unforeseen N2. And about 34% of the patients had single N2 station involvement. Adjuvant chemotherapy was not mandatory at that time and unlike the previous three studies, neoadjuvant chemotherapy was allowed. Nevertheless, the majority of patients (96%) were treated with chemotherapy (preoperative, postoperative, or both). In primary endpoint analysis, non-significant improvement of DFS was shown: 3-year DFS rate of 43.8% in control, higher than expected, and 47.1% with PORT; median DFS of 8 months increased by PORT (30.5 vs. 22.8 months; HR = 0.86, 95% CI = 0.68–1.08, p = 0.18). PORT did not increase OS. The control arm was much more likely to suffer mediastinal relapse (46.1% vs. 25%), which indicated approximately 50% risk reduction of locoregional failure by PORT, but intercurrent death was more common in the PORT arm (14.6% vs. 5.3%). Notably, 11 patients among 21 deaths in the PORT group died with cardiopulmonary toxicity. This indicates the level of recommendation in the original guideline. Although the American Society for Radiation Oncology (ASTRO) does not publish very up-to-date official guidelines after the publication of recent RCTs, in the previous guidelines they described that PORT addition after R0 resection in N2 disease showed no definitive proof of a positive or negative impact on OS but showed better local control than observation strategies [22].

**Current Guidelines and Recommendations on PORT for N2 Stage NSCLC**

As discussed in the previous parts, robust evidence to support the use of PORT in the treatment of N2 stage NSCLC is still lacking. Currently, most international guidelines mention the use of PORT as follows: in the case of R1 or R2 resection, there is generally no big difference in the use of PORT, but for pN2 disease after R0 resection, the recommendation level is not high or it is suggested to apply selectively [21–24] (Table 3).

In the National Comprehensive Cancer Network guidelines, postoperative chemotherapy can be administered followed by PORT or concurrently depending on the margin status [21]. PORT is recommended with a category 2A for N2 after R0 resection. Although the American Society for Radiation Oncology (ASTRO) does not publish very up-to-date official guidelines after the publication of recent RCTs, in the previous guidelines they described that PORT addition after R0 resection in N2 disease showed no definitive proof of a positive or negative impact on OS but showed better local control than observation strategies [22].

**Table 3.** The latest recommendation in various guidelines for postoperative radiotherapy in completely resected N2 stage non–small cell lung cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>Guideline</th>
<th>Recommendation level</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>2015</td>
<td>ASTRO</td>
<td>Strong</td>
<td>May improve local control</td>
</tr>
<tr>
<td>2017</td>
<td>ESMO</td>
<td>C (optional)</td>
<td>May be an option following individual risk assessment</td>
</tr>
<tr>
<td>2017</td>
<td>ASCO</td>
<td>Moderate</td>
<td>Recommend a postoperative multimodality evaluation</td>
</tr>
<tr>
<td>2022</td>
<td>ASCO</td>
<td>Weak</td>
<td>Not routine use for patients without ECE who received platinum-based chemotherapy</td>
</tr>
<tr>
<td>2023</td>
<td>NCCN</td>
<td>Category 2A</td>
<td>Consider RT</td>
</tr>
</tbody>
</table>

ASTRO, American Society for Radiation Oncology; ESMO, European Society for Medical Oncology; ASCO, American Society of Clinical Oncology; ECE, extracapsular extension; NCCN, National Comprehensive Cancer Network; RT, radiotherapy.

At present, there are no official recommendations from the European Society for Radiotherapy and Oncology.

This indicates the level of recommendation in the original guideline.

Category 1: chemotherapy followed by atezolizumab or pembrolizumab or osimertinib.
However, the guidelines of the medical society including the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) more conservatively state that PORT use in R0 resection can be considered “only in selected cases” following individual risk assessment [23,24]. The ESMO recommends no routine use of PORT in single N2 status and only permits PORT after careful evaluation of locoregional recurrence risks [23]. In multistation N2, definitive CCRT is preferred but multidisciplinary approaches are required. According to the ASCO guidelines published in 2017, postoperative multimodal assessment is recommended to determine the advantages and disadvantages of receiving PORT [24]. Recently updated ASCO guideline mentions that PORT should not be routinely offered for patients receiving platinum-based chemotherapy either before or after surgery and without extracapsular extension (ECE) [25]. But, the strength of its recommendation is weak. ASTRO has released an updated article agreeing with this ASCO guideline [26].

Conclusively, in the current status, PORT is not recommended routinely for all patients with completely resected pN2 NSCLC. The decision on whether to use PORT should be made on an individualized basis, taking into account the risk factors presented in the following section.

Factors Affecting the Choice of PORT for N2 Stage NSCLC: Implications for Patient Selection

There is still no robust answer in PORT patient selection, and various data exist for each study. Here are some of the most important factors to consider:

1. Multistation/extensive mediastinal involvement after mediastinal dissection

In the Lung ART trial, multiple mediastinal node stations were involved in about 30% of patients [20]. DFS was affected by ≥2 stations involved, compared with a single station (HR = 1.46, 95% CI = 1.1–1.9, p = 0.01). A previous study suggested a potential DFS benefit of PORT in patients with multiple station mediastinal lymph node metastases (5-year: 43.2% vs. 16.6%, p = 0.037) [27]. It also demonstrated in another retrospective study that PORT improved DFS in patients with multiple N2 stations metastases compared with single N2 station metastasis (5-year: 41.7% vs 5.9%, p = 0.0220) [28]. In regard to OS, patients with multiple pN2 favored postoperative CCRT over chemotherapy alone [17]. On the contrary, some investigators also claimed that single N2 station involvement was a predictor of benefit from PORT [29]. Although the number of patients was too small, the Korean trial reported that chemotherapy alone (n = 8) was more effective than CCRT (n = 5) for patients with N2 multistation (OS: HR = 5.572, 95% CI = 1.01–30.754) [18].

2. The number of metastatic lymph nodes or lymph node ratio

In the SEER data analysis including 3,373 patients from 2004 to 2013, multivariable analysis showed that the number of positive lymph nodes (≤3) was independently associated with better OS and lung cancer-specific survival, then the use of PORT demonstrated better OS compared to no-PORT for patients with positive lymph nodes (>3), but not for patients with less number of positive lymph nodes (≤3) [30]. In terms of DFS, it also showed consistent results in the PORT-C (HR = 0.75, 95% CI = 0.58–0.98, p = 0.04) [19]. Other studies using the SEER data or NCDB showed that PORT can be indicated in patients with a specific range of lymph node-positive ratios [31–34]. The proposed cutoff for lymph node ratio varied among studies, with some suggesting a threshold of >15% [34], ≥30% [33], ≥50% [31], or 60%–80% [32].

3. ECE

Importantly, ECE has reflected the aggressive biological behavior in several types of cancers, including head and neck, breast, and colorectal cancers [35–37]. In patients with completely resected stage IIA–IIIA NSCLC, ECE also represents a powerful prognostic factor [38]. PORT led to a significant improvement in OS among negative ECE patients (HR = 0.518, 95% CI = 0.276–0.971, p = 0.04) but did not have a similar effect on positive ECE patients [39]. Although recently conducted RCTs did not evaluate the association between ECE and PORT [17–20], the status of ECE can potentially aid in selecting pN2 patients who will benefit from PORT. On the other hand, some argue that in cases where there is ECE or lymph node capsular rupture, the resection should be considered incomplete [40], and this may necessitate the use of PORT.

4. Histology (squamous cell carcinoma vs. adenocarcinoma)

There is a discrepancy regarding the NSCLC histology that shows the benefits of PORT. Several studies proposed that PORT may confer a greater advantage in treatment outcomes for squamous cell carcinoma [27,41]. They reported increases in the 5-year OS (from 37.1% to 63.2%, p = 0.026) and DFS (from 23.3% to 70.1%, p = 0.011) by PORT. But others found that the presence of the papillary predominant adenocarcinoma subtype was a reliable indicator of the potential benefit from PORT [29].

5. ypN2 in case of receiving neoadjuvant chemotherapy

Neoadjuvant chemotherapy is an alternative treatment option for
resectable NSCLC [21]. Patients with ypN2 status may have a greater extent of regional tumor involvement and increased chemotherapy resistance when compared to those with pN2 status. Thus, the use of PORT can potentially enhance locoregional management and ultimately improve overall survival [42]. Large-scale retrospective studies using SEER or NCDB suggested that PORT benefited patients with persistent N2 disease after neoadjuvant chemotherapy [34,42,43]. In the Lung ART trial, subgroup analysis revealed that PORT significantly improved DFS in ypN2 patients (3-year: 49.4% vs. 20.8%; HR = 0.52, 95% CI = 0.28–0.98) [20].

Several risk factors above can predict the benefit of PORT and can be considered when selecting patients. Several nomograms or scoring systems have been developed to help physicians screen and counsel patients with resected N2 [44–46]. As a simplified model of them, one article insisted that patients who meet three or more of the following criteria are strongly advised to undergo PORT: smoking index (number of cigarettes smoked per day × number of cigarette-years) ≤ 400, C2N2, pT3, squamous cell carcinoma, and ≥ 4 positive nodes [44].

Although definite high-risk factors are still not consistently identified, PORT should not be completely disregarded in these patients as a potentially useful treatment option. Rather, it can be summarized that steady research efforts are needed in consideration of the future perspectives introduced in the next section.

**Ongoing Trials, Future Directions, and Conclusions**

As summarized above, it is thought that more clinical evidence is still needed for the application of the PORT for pN2 patients, but the protracted length of adjuvant trials for the resectable stage of NSCLC has resulted in slow progress and high expenses. It is highly likely that the high-level evidence for PORT we currently had will not be updated for years. Japan Clinical Oncology Group 1916 (J-PORT study, UMIN000042905) is in progress using a scheme similar to the PORT-C trial, but we still have to wait several years to get another prospective randomized evidence [47].

From a different perspective, the clinical trial using stereotactic body radiotherapy (SBRT) in the adjuvant setting was launched in 2019 for patients with close-involved surgical margins or pN2 (NCT04073745). Considering SBRT has an extremely short treatment duration and fewer side effects compared with conventional RT, the positive results of this trial would broaden the PORT indications in NSCLC.

Another big change to consider is the development and change of systemic chemotherapy for resectable stage NSCLC. More recently, the promising progress in the treatment of metastatic NSCLC has increased interest in using immune checkpoint blockades or targeted agents at resectable stages. IMpower010 made adjuvant atezolizumab maintenance one of the options after routine adjuvant chemotherapy [48]. Of course, the usual PORT that can be considered subsequently after adjuvant chemotherapy was not allowed under the IMpower010 research protocol. However, a considerable portion of enrolled patients subsequently required post-relapse mediastinal RT. These results suggest the possibility that there is still a role for PORT to further increase the therapeutic outcome.

In contrast, PORT may not be beneficial in patients with actionable mutations. The ADAURA trial found that the use of osimertinib after surgery significantly improved DFS in patients with epidermal growth factor receptor (EGFR) mutation-positive completely resected stage IB to III NSCLC (compared with placebo), therefore the additional benefit of PORT may be limited considering the high efficacy of osimertinib in EGFR mutation-positive stage III NSCLC [49].

Another important recent challenge to applying PORT is the increased use of the neoadjuvant approach led by the CheckMate 816 regimen [50]. Since many neoadjuvant trials did not include PORT in the protocol, there is very little evidence on how to apply PORT to patients who received these treatments. Hopefully, adopting perioperative immune checkpoint blockades can improve distant metastasis control and may re-consider the role of robust locoregional control by PORT.

Along with these, other ongoing trials of novel systemic therapy with targeted agents or immunotherapy may also change PORT indications. The contribution of improved locoregional control to survival depends on the effectiveness of systemic treatment. If better systemic control were achieved and patterns of failure were changed, the role of PORT may be revisited. So far, in surgically resected NSCLC, the efficacy of systemic treatment varies from patient to patient due to various factors, and it is not possible to accurately determine whether PORT can improve survival under certain levels of systemic control. Further evidence is needed in the midst of these recent changes and adequately powered trials to establish clinically meaningful benefits are awaited.

In conclusion, PORT for completely resected pN2 NSCLC has been an area of ongoing debate. The first choice for pN2 NSCLC patients after complete resection had been PORT since the late 1990s; however, the Lung ART and PORT-C trials have challenged this notion. Despite demonstrating a noteworthy decrease in the locoregional recurrence rate, PORT has yet to produce any survival advantage. Nevertheless, the potential benefits of PORT for patients with high-risk features remain uncertain. Nevertheless, we cautiously recommend the use of PORT for N2 stage NSCLC patients with high-risk features, such as high and/or persistent mediastinal...
tumor burdens. Future research should focus on identifying optimal candidates for PORT and determining its effectiveness in combination with novel systemic therapies. Ultimately, the goal is to establish clinically meaningful benefits for patients with completely resected pN2 NSCLC.

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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Data Availability Statement

Not applicable.

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17. Shen WY, Ji J, Zuo YS, et al. Comparison of efficacy for postope-


Comparison of sequential versus concurrent chemoradiation regimens in non-metastatic muscle-invasive bladder cancer

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Introduction

Bladder cancer is the sixth most common cancer in the United States, with a median presentation in the eighth decade of life [1,2]. The treatment approach for non-metastatic bladder cancer depends on whether there is an invasion of the muscular layer of the bladder wall [3]. For muscle-invasive, non-metastatic bladder cancer, neoadjuvant chemotherapy followed by radical cystectomy is a standard of care [3]. However, radical cystectomy is a complex procedure with a high risk of potential complications and morbidity. Further, not all patients are appropriate surgical candidates.

An alternative potentially curative modality to radical cystectomy in patients with muscle-invasive, non-metastatic disease is chemoradiation after transurethral resection of bladder tumor [3].
Several studies have supported the efficacy of chemoradiation in muscle-invasive bladder cancer, with cumulative 5-year overall survival data in trials ranging from 49%-73% [4-9]. The BC 2001 trial identified that a 5-fluorouracil/mitomycin C (5FU/MMC) regimen delivered concurrently with radiation significantly improved outcomes relative to radiation alone; 5FU/MMC is now a commonly used regimen for concurrent chemotherapy [10]. The chemoradiation approach has the advantage of being less invasive than surgery and offering the potential to spare the bladder. However, there is a lack of research defining the optimal sequencing of chemoradiation and therapy in this setting.

In past studies, patients frequently received chemotherapy concurrently with radiation [6,8-11] with some studies incorporating a neoadjuvant methotrexate-cisplatin-vinblastine (MCV) chemotherapy regimen prior to radiation [12,13]. Zapatero et al. [14] clinical trial was a small trial of 80 patients with muscle-invasive bladder cancer, in which 41 patients received the MCV regimen followed by 60 Gy radiation to the bladder, and 39 received concurrent cisplatin with 64.8 Gy radiation to the bladder. No significant difference in overall survival was found between the treatment arms; however, patients in the sequential arm did not receive radiation therapy unless they achieved complete response with chemotherapy, therefore the trial did not provide a direct comparison of sequential versus concurrent chemoradiation. Additionally, the trial had several limitations, most prominently the limited number of patients enrolled. There is a need to expand on these data to determine whether the choice to deliver chemotherapy sequential to or concurrent with radiation affects survival. The effect of patient demographic and disease-specific factors on outcomes in these two treatment arms also has not been widely examined.

To address these gaps in knowledge, we extracted patient data from the National Cancer Database (NCDB) to compare patients with non-metastatic bladder cancer who were not surgical candidates and treated with chemoradiation sequentially or concurrently. Our primary objective was to compare patient demographic factors and tumor stage between patients who received chemotherapy prior to or concurrent with radiation, to determine whether these factors were associated with the treatment regimen. Our secondary objective was to compare survival outcomes in patients treated with upfront chemotherapy prior to radiation treatment, or concurrent radiation with chemotherapy to help outline best practices for non-surgical candidates in this setting.

**Materials and Methods**

1. **Data source and population**
   Data for this study were extracted from the 2018 NCDB, a clinical oncology database sourced from hospital registry data that are collected at more than 1,500 Commission on Cancer accredited programs. Overall survival is defined as the number of months from the date of initial diagnosis to the date of last contact or death due to any cause. Two treatment strategies are defined based on the sequence of chemotherapy and radiation. Treatment 1 is defined as a sequential treatment in which chemotherapy start date is more than 14 days prior to radiation start date (180 days prior to radiation as maximum). Treatment 2 is defined as a concurrent treatment in which chemotherapeutic start date is started within 14 days of radiation start date (before or after). A total of 671,462 patients were enrolled for bladder cancer between 2004 and 2008. After the inclusion/exclusion criteria (Fig. 1), 3,064 patients remained. After definition of the treatments, another 837 patients did not fit into either treatment group, leaving 2,227 patients included in this analysis.

2. **Demographic and clinical staging information**
   Age at diagnosis, sex, race, Charlson-Deyo score, facility location, and facility type were considered as patient demographic information and facility information. Race was categorized as White, Black, and other/unknown. The Charlson-Deyo score is a weighted score derived from the sum of the scores for each of the comorbid conditions listed in the Charlson Comorbidity Score mapping table [15]. The American Joint Committee on Cancer (AJCC) clinical staging information from the AJCC 7th edition is compared between treatments and survival time. Staging information was divided into clinical T staging based on histology and clinical N staging based on lymph node involvement.

3. **Statistical analysis**
   Patient demographic and facility information were summarized by treatment strategies using medians and ranges for continuous variables and frequencies and percentages for categorical variables. Based on the Shapiro-Wilk test, continuous variables did not fit a normal distribution, so the Wilcoxon two-sample test was applied to compare the difference between the two treatment strategies. The chi-square test was used to compare categorical variables by treatment strategy. The Kaplan-Meier method and log-rank tests were used to estimate overall survival distributions among groups defined by: two treatments (sequential, concurrent); age (≥ 77, ≤ 77 years); clinical T stage (T1–2, T3–4); clinical N stage (N0, N1–3); clinical N stage (N0–1, N2–3); and Charlson-Deyo score (0, 1, 2, ≥ 3). Cox proportional hazard model was conducted to explain the relationship between the two treatments and overall survival, while adjusting for age, sex, race, clinical T stage, clinical N stage, and Charlson-Deyo score. The proportional hazard assumption was...
Fig. 1. Flowchart of selection of study patients from National Cancer Database (NCDB). NA, Not Applicable; IS, In situ; AJCC, American Joint Committee on Cancer; N0, No regional lymph node involvement; M0, No distant metastasis; NOS, Not otherwise specified.
tested to show the hazard function was proportional over time using a supremum test. If a p-value was larger than 0.05 for each variable, the model satisfied the proportional hazard assumption. If the proportional assumption was violated, stratification analysis would be conducted. Interactions between treatment strategy and covariates were considered in the Cox regression model. If the interaction was significant (p < 0.05), then it was kept in the model; and a backward model selection method will be used to select the best model.

Results are presented as estimates, hazard ratio (HR), 95% confidence interval, and p-values. p-values < 0.05 are considered statistically significant. All statistical analyses were undertaken using SAS Software version 9.4 (SAS Institute Inc., Cary, NC, USA).

For matching analysis, pairs between sequential and concurrent treatment patients were constructed using greedy nearest neighbor matching on the logit of the propensity score 1:1 without replacement. Covariates in Table 1 such as age, sex, race, Charlson-Deyo score, facility location, facility type, type of bladder cancer, and AJCC clinical T, N stage were included during the matching. After matching, a dataset with a sample size of 1,108 was created, with 554 patients in the sequential group and 554 patients in the concurrent group. Then, Kaplan-Meier estimate and a censored model, including treatment group, age, sex, race, clinical T/N stage, Charlson-Deyo score, type of cell, and interaction term between type of cell and treatment group was constructed based on the matched data.

Results

Table 1 shows the breakdown of demographic and staging characteristics between patients receiving concurrent chemoradiation or sequential chemotherapy followed by radiation. Patients in the sequential treatment group were found to be significantly younger than those in the concurrent group (Median age 74 years vs 78 years, p<0.001). Most patients in both groups had transitional cell carcinoma, however, the differences in the breakdown of distribution of cancer type between the two groups were significant. All the patients with adenocarcinoma (8/8) were in the concurrently treated group, and 81% (53/65) of the patients with squamous cell carcinoma were in the concurrently treated group. No significant differences were noted in sex, race, Charlson-Deyo score, treatment facility location, or facility type between the two groups. There was also no significant difference in the total dose of radiation or number of fractions received between the two groups. Mean and median times from the start of chemotherapy to the start of radiation therapy in the sequential group were 85.4 days and 84 days, respectively, with a range from 15–180 days.

Patients in the sequential group were significantly more likely to have greater clinical T stage than patients in the concurrent group (clinical stage T4: 10.65% of patients treated sequentially vs. 6.75% of patients treated concurrently, p = 0.001) (Table 1). Sequentially treated patients were also significantly more likely to have nodal metastases than patients treated concurrently (p = 0.004). There was no significant difference in overall survival between the two treatment groups (p = 0.533 (Fig. 2A); median time to death or last contact was 27.9 months in the sequential group and 25.2 months in the concurrent group. In an adjusted Cox proportional hazard regression model, the risk of death in the sequential treatment group was not significantly different than that in the concurrent group (HR = 1.336, p = 0.297) (Table 2). Age, sex, race, or histology were not significantly associated with overall survival (Table 2). The only factor significantly associated with overall survival was the Charlson-Deyo score; scores of 0–2 were associated with a significantly decreased risk of death relative to scores ≥3 (Table 2, Kaplan-Meier estimate for Charlson-Deyo score shown in Supplementary Fig. S1). To determine whether survival was equivalent when adjusting for differences in demographic and disease stage variables between groups, a matching analysis was performed to generate paired patients between groups matched by age, sex, race, Charson-Deyo score, facility location, facility type, type of bladder cancer, and AJCC clinical T and N stage. A Kaplan-Meier estimate (Fig. 2B) and Cox proportional hazard regression model (Table 3) were performed on the matched groups (Fig. 2B and Table 3, respectively). The results were consistent with the unmatched Kaplan-Meier and Cox model results; there was no significant difference in overall survival between the two treatment groups after matching analysis (p = 0.539).

Discussion and Conclusion

Our analysis found no difference in overall survival between patients who received chemotherapy prior to radiation and those who received concurrent chemoradiation only. While we were unable to exclude patients in the sequential group who continued to receive chemotherapy during radiation, our data still allow for a comparison of the effect of neoadjuvant chemotherapy on survival in this setting. Our data demonstrate that chemotherapy administered prior to radiation does not decrease survival outcomes relative to patients receiving only concurrent chemoradiation.

Our study represents the first retrospective review of patient data comparing concurrent versus sequential chemoradiation in bladder cancer and involved an analysis of a database containing over 670,000 bladder cancer patients. Findings from our study are concordant with the earlier clinical trial [14]; both studies showed
Table 1. Comparison of demographic and AJCC clinical staging information between patients who received sequential or concurrent chemoradiation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sequential treatment (n = 554)</th>
<th>Concurrent treatment (n = 1,673)</th>
<th>p-value</th>
</tr>
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<td>Age (yr)</td>
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<td>78 (35–90)</td>
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<tr>
<td>1</td>
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</tr>
<tr>
<td>2</td>
<td>50 (9.03)</td>
<td>142 (8.49)</td>
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<tr>
<td>≥3</td>
<td>32 (5.78)</td>
<td>87 (5.20)</td>
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<td>Facility location</td>
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<tr>
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<tr>
<td>Other</td>
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<tr>
<td>AJCC clinical T</td>
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</tr>
<tr>
<td>cT1</td>
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<td>118 (7.05)</td>
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<tr>
<td>cT2</td>
<td>385 (69.49)</td>
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<tr>
<td>cT3</td>
<td>56 (10.11)</td>
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<td>cT4</td>
<td>59 (10.65)</td>
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</tbody>
</table>

Values are presented as median (range) or number (%).
AJCC, American Joint Committee on Cancer.
*p < 0.05, group differences were tested using chi-square test for categorical variables, Wilcoxon two-sample test for continuous variables (age, number of fractions, and total dose) that are not normally distributed.
Chemoradiation for bladder cancer

Fig. 2. (A) Kaplan-Meier curve of overall survival time in patients with non-metastatic bladder cancer treated with either sequential chemotherapy followed by radiation therapy (Upfront Chemo then RT, blue line, n = 554) or concurrent chemotherapy and radiation therapy (Concurrent Chemo then RT, red line, n = 1,673). (B) Kaplan-Meier curve of overall survival time after matching (Upfront Chemo then RT, blue line, n=554; Concurrent Chemo then RT, red line, n = 554).

Table 2. Cox model of overall survival and treatment, adjusted for age, sex, race, clinical stage and Charlson-Deyo, histology and the interaction between treatment and histology

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter estimate</th>
<th>p-value</th>
<th>HR (95% CI)</th>
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<td>Sequential treatment</td>
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<td>0.297</td>
<td>1.336 (0.776–2.299)</td>
</tr>
<tr>
<td>Age (continuous)</td>
<td>0.002</td>
<td>0.624</td>
<td>1.002 (0.995–1.009)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>-0.051</td>
<td>0.555</td>
<td>0.950 (0.801–1.126)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
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<td>0.702</td>
<td>1.067 (0.764–1.491)</td>
</tr>
<tr>
<td>Black</td>
<td>0.261</td>
<td>0.231</td>
<td>1.299 (0.847–1.992)</td>
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<tr>
<td>Clinical T stage, cT1-2</td>
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<td>0.154</td>
<td>1.173 (0.942–1.461)</td>
</tr>
<tr>
<td>Clinical N stage, cN0</td>
<td>0.125</td>
<td>0.441</td>
<td>1.134 (0.824–1.559)</td>
</tr>
<tr>
<td>Charlson-Deyo score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>-0.543</td>
<td>0.001*</td>
<td>0.581 (0.423–0.798)</td>
</tr>
<tr>
<td>1</td>
<td>-0.717</td>
<td>&lt; 0.001*</td>
<td>0.488 (0.348–0.685)</td>
</tr>
<tr>
<td>2</td>
<td>-0.607</td>
<td>0.004*</td>
<td>0.545 (0.362–0.852)</td>
</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transitional cell carcinoma</td>
<td>0.025</td>
<td>0.910</td>
<td>1.026 (0.664–1.584)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>-0.353</td>
<td>0.324</td>
<td>0.703 (0.440–2.509)</td>
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<tr>
<td>Adenocarcinoma</td>
<td>0.433</td>
<td>0.560</td>
<td>1.542 (0.293–3.974)</td>
</tr>
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<td>Sequential treatment (vs. concurrent)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Transitional cell carcinoma</td>
<td>-0.267</td>
<td>0.357</td>
<td>1.023 (0.867–1.206)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>0.187</td>
<td>0.790</td>
<td>1.610 (0.455–5.696)</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval.
* p < 0.05.

Table 2. Cox model of overall survival and treatment, adjusted for age, sex, race, clinical stage and Charlson-Deyo, histology and the interaction between treatment and histology.

A no difference in overall survival outcome. The Zapatero study [14] was limited by small patient numbers and by unequal treatments between groups but was prospective in nature. While our study was limited by its retrospective nature, it involved large numbers of patients and therefore provides a comprehensive analysis. The sequential group was more likely to have positive lymph
nodes and had a more advanced disease stage. Since systemic therapies administered neoadjuvant to local ablative therapy are used in patients with a greater likelihood of distant metastases, upfront chemotherapy prior to radiation could have been given in this group with the intent of ablating possible micrometastatic disease. Our data demonstrate equivalent survival in these patients despite more advanced disease relative to the concurrent chemoradiation-only group. This finding supports the efficacy of neoadjuvant chemotherapy prior to radiation in this patient cohort. However, even when matching patients between groups to adjust for differences in demographic and disease stage variables, there remained no difference in overall survival between the sequential and concurrent groups. To better determine whether more advanced tumor and lymph node stages preferentially benefit from sequential chemoradiation, further study is needed, including a multi-institutional, prospective trial in which patients are stratified by tumor and lymph node stage.

Notably, a proportion of the advanced disease patients in the sequential group may have received both neoadjuvant downstaging chemotherapy and concurrent chemoradiation as per National Comprehensive Cancer Network guidelines, which was not assessable through the NCDB database. There remains a need for further study to determine the efficacy of concurrent chemoradiation in the setting of patients having received neoadjuvant chemotherapy.

The previous BC 2001 trial demonstrated a clear advantage of concurrent chemoradiation vs radiation alone, with or without neoadjuvant chemotherapy [10]. This trial demonstrated a survival advantage of chemotherapy concurrent with radiation, with a HR of 0.62 with both neoadjuvant and concurrent chemoradiation relative to radiation alone, and a HR of 0.71 with concurrent chemoradiation relative to radiation alone [10]. Importantly, the HR was decreased regardless of whether neoadjuvant chemotherapy was given, suggesting concurrent chemotherapy to be efficacious regardless of whether the patient received neoadjuvant chemothera- py. The lower HR with neoadjuvant suggests there could be a greater benefit to giving both neoadjuvant and concurrent chemotherapy with radiation.

In addition to the difference in disease stage between groups in our analysis, the sequential group was also significantly younger. Neoadjuvant platinum-based chemotherapy is standard-of-care for the surgical approach [16], and younger patients are more likely to be considered surgical candidates. Therefore, it could be that a proportion of sequentially treated patients were initially intended as surgical candidates, and received neoadjuvant chemotherapy in preparation for surgery, but later opted for radiation treatment as a bladder-sparing approach. A future study using a database with information on the intent of treatment could provide more information on clinical decision-making related to patient demographic

| Table 3. Cox model of overall survival and treatment after matching, adjusted for age, sex, race, clinical stage and Charlson-Deyo, histology and the interaction between treatment and histology |
| Variable | Parameter estimate | p-value | HR (95% CI) |
| Sequential treatment | 0.218 | 0.437 | 1.243 (0.717–2.155) |
| Age (continuous) | 0.004 | 0.404 | 1.004 (0.995–1.013) |
| Sex, male | -0.154 | 0.214 | 0.857 (0.672–1.093) |
| Race | | | |
| White | 0.116 | 0.630 | 1.123 (0.700–1.802) |
| Black | 0.117 | 0.711 | 1.124 (0.606–2.084) |
| Clinical T stage, cT1-2 | -0.008 | 0.958 | 0.992 (0.747–1.318) |
| Clinical N stage, cN0 | 0.187 | 0.320 | 1.206 (0.834–1.743) |
| Charlson-Deyo score | | | |
| 0 | -0.746 | 0.001* | 0.474 (0.312–0.722) |
| 1 | -0.739 | 0.001* | 0.477 (0.303–0.752) |
| 2 | -0.847 | 0.002* | 0.429 (0.249–0.739) |
| Type | | | |
| Transitional cell carcinoma | -0.043 | 0.852 | 0.958 (0.609–1.506) |
| Squamous cell carcinoma | 0.122 | 0.845 | 1.130 (0.334–3.826) |
| Sequential treatment (vs. concurrent) | | | |
| Transitional cell carcinoma | -0.185 | 0.537 | 0.831 (0.461–1.496) |
| Squamous cell carcinoma | -0.340 | 0.694 | 0.711 (0.130–3.885) |

HR, hazard ratio; CI, confidence interval. *p < 0.05.
and disease factors, and their effect on patient outcomes.

The only factor in our analysis found to significantly affect survival was Charlson-Deyo comorbidity index. A Charlson-Deyo score of 3 or greater was associated with decreased survival, relative to a score of 2 or less. This is consistent with literature reports; comorbidities, as determined by the Charlson index or by other measures of comorbidity level, have been found to independently predict survival in bladder cancer patients with the non-invasive or invasive disease [17,18]. While the Charlson-Deyo score is adjusted for age, age itself was not found to affect overall survival in either treatment group in our analysis. This highlights the morbidity and mortality of bladder cancer. With cancers in which patients are likely to die of their cancer rather than with their cancer, there is less skewing of overall survival data by patients who die of other age-related causes. Additionally, bladder cancer is known to be associated with patients with poor general health and significant smoking history which directly affect patient survival regardless of their bladder cancer diagnosis. Measures of cancer-specific survival, while not possible in our analysis should be performed in future studies to exclude non-cancer causes of mortality from survival calculations.

A further limitation of our study is the inability to evaluate disease-free survival or response rate since these data were not available in the database. We recommend a future multi-institutional clinical trial enrolling a larger patient number, designed as a non-inferiority study, and using a chemotherapy regimen that is standardized between treatment arms to guide clinical decision-making. Future clinical trials should include an evaluation of overall survival and various parameters of disease-free survival and disease progression.

In conclusion, evidence from our study and previous studies supports no difference in overall survival between patients with non-metastatic bladder cancer who received chemotherapy prior to radiation and those who received concurrent chemoradiation only. That no survival difference was found despite overall poorer prognostic features in the sequential patient group suggests downstaging chemotherapy prior to radiation may be advantageous for higher stage patients. However, further studies using more detailed database analysis and large clinical trials are needed to outline best practices for these patients.

**Statement of Ethics**

This study was conducted using national registry data, therefore written informed consent was not required.

**Conflict of Interest**

Benjamin A. Teply reports funding for clinical research from Bristol-Myers-Squibb, and Advisory Board Consultancy for Seagen and Astra Zeneca. Raymond C. Bergan is on the Scientific advisory Committee for the National Cancer Institute, Northwestern University, and University of Arizona. All other authors have no conflicts of interest to declare.

**Funding**

None.

**Author Contributions**


**Data Availability Statement**

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

**Supplementary Materials**

Supplementary materials can be found via https://doi.org/10.3857/roj.2023.00262.

**References**


Clinical outcomes of radical radiotherapy for pulmonary sarcomatoid carcinoma

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Introduction

Pulmonary sarcomatoid carcinoma (PSC) is a rare and aggressive subtype of non-small cell lung cancer (NSCLC), encompassing five pathologic types: carcinosarcoma, spindle cell carcinoma, pleomorphic carcinoma, giant cell carcinoma, and pulmonary blastoma [1]. With an incidence rate representing less than 1% of all lung cancers, PSC predominantly affects males and smokers [2]. The heterogeneous nature of this NSCLC subtype often leads to its detection at advanced stages due to its aggressive behavior and local invasiveness. Because of the rarity of PSC, there is a paucity of prospective clinical trials aimed at identifying the most effective treatment for this condition. Currently, radical surgery is recommended as the primary curative approach for early-stage patients, but the overall prognosis remains poor, with 5-year overall survival rates ranging between 12.3% and 25.1% [3,4]. Various approaches have been investigated for unresectable PSC but have failed to show significant survival gains. Notably, savolitinib, a selective MET tyrosine-kinase inhibitor, showed a response rate of 49.2% in a recent phase 2 study, which, although promising, is still not high enough [5].

Purpose: Pulmonary sarcomatoid carcinoma (PSC) is recognized for its aggressiveness and poor prognosis. The role of radical radiotherapy in PSC remains uncertain due to its scarcity and limited data. In the absence of an effective systemic agent, this study aims to explore the possibility of cure and to investigate potential prognostic factors and treatment outcomes.

Materials and Methods: From January 2005 to December 2021, 149 PSC patients were identified. Among 62 patients who received radiotherapy for lung lesions, 25 who underwent palliative radiotherapy and 16 who underwent surgery were excluded.

Results: The median patient age was 71 years. The majority were male, and 17 patients (81.0%) were diagnosed at an advanced stage. After radical radiotherapy, distant metastasis (47.6%) was the most common site of failure, while the local recurrence rate was quite low (9.5%). Eventually, five patients (26.3%) demonstrated either a partial response or complete remission, including three complete remissions with durable responses. The median progression-free survival (PFS) and overall survival were 4.6 months and 7.9 months, respectively. Univariate and multivariate analyses revealed that a tumor size >5 cm was associated with a worse prognosis (p = 0.045), while a radiation dose >58 GyEQD2 was significantly associated with better PFS (p = 0.038).

Conclusion: This study demonstrates clinical outcomes after radical radiotherapy in managing PSC, suggesting tumor size and radiation dose could be a predictor of a systemic response. Given the known bad prognosis but complete remission could be achieved in certain subgroups, future research should explore the potential strategies using radical radiotherapy for this challenging patient population.

Keywords: Lung neoplasms, Sarcoma, Radiotherapy
sequently, there is a demand for local treatment modalities with higher control rates other than surgery.

Radiotherapy (RT) plays a critical role in treating NSCLC, not only in early stages but also in inoperable or advanced stages. A retrospective study analyzing PSC using the Surveillance, Epidemiology, and End Results (SEER) database (n = 1,039) suggested better survival outcomes for patients who received RT—hazard ratio (HR) = 0.801, p = 0.041. However, due to limitations in database research, not only is it impossible to discern the purpose and timing of RT, but it also does not contain information about RT dose or local responses [3]. Until now, clinical data specifically investigating the therapeutic efficacy and response of PSC to radical RT is currently lacking. In the absence of an effective systemic agent, this study aims to explore the possibility of cure, and to elucidate the prognostic factors, tumor response, and survival outcomes following radical RT.

Materials and Methods

1. Patient population
The study design and protocol were reviewed and approved by the Institutional Review Board of Seoul National University Hospital (IRB No. H-2301-043-1393) and Seoul Metropolitan Government Seoul National University Boramae Medical Center (IRB No. 10-2023-34). Patients diagnosed with carcinosarcoma, spindle cell carcinoma, pleomorphic carcinoma, pulmonary blastoma, or those exhibiting focal sarcomatoid features in tissue biopsy results were identified from two institutions between January 2005 and December 2021. Inclusion criteria is patients receiving radical aim of RT for PSC. The exclusion criteria included patients who underwent salvage surgery on the pulmonary mass after radiotherapy and those diagnosed with distant metastasis or another carcinoma at the time of diagnosis. Out of 149 identified PSC patients, 62 had received radiotherapy targeted at lung lesions. Patients who underwent radiotherapy with palliative intent (n = 25) or those who had surgery either before or after radiotherapy (n = 16) were excluded. Consequently, 21 patients who received radical radiotherapy were selected for further analysis. The median follow-up duration was 7.4 months (range, 1.5 to 148.0 months).

2. Diagnostic work up and details of treatment
Chest computed tomography (CT) scans were performed to assess the extent of the tumor, while fluorodeoxyglucose–positron emission tomography (FDG-PET) scan was used to evaluate the presence of distant metastases. Tumor pathology was confirmed through tissue biopsy. Pulmonary function tests (PFT) were conducted before treatment initiation. RT doses ranged from 42 Gy to 66 Gy, administered in various fractionation schedules from 4 to 33 fractions. The gross tumor volume (GTV) was delineated for the primary lung tumor and the involved mediastinal lymph nodes. The internal target volume (ITV) was delineated using four-dimensional CT (4D-CT) for patients with tumors in the lower lobe with significant horizontal movement, as well as for those with small tumors for stereotactic ablative radiation therapy. The clinical target volume (CTV) was delineated with an expansion of 3–7 mm from the GTV, and adjustments were made as needed. The planning target volume was delineated from the CTV/ITV with a 5–7 mm margin. Concurrent chemoradiotherapy (CCRT) was considered for patients with nodal invasion who had an acceptable performance status. For patients who underwent CCRT, taxane/carboplatin or taxane/cisplatin were mainly applied, and one patient received etoposide/cisplatin due to focal neuroendocrine feature. Programmed death ligand-1 (PD-L1) inhibitor was applied sequentially in selected two PD-L1 positive patients.

3. Follow-up and definition of tumor response and toxicity
Follow-up chest CT scans were performed every three months. Tumor response was evaluated by measuring changes in the long axis of the primary lung lesion. A complete response was defined as the disappearance of the lesion on imaging, while a partial response was defined as a decrease of at least 30% in the initial tumor size. The eventual response is defined as the response evaluated at the time of the data analysis. Grade ≥ 3 toxicities, including respiratory, dermatological, and hematological events, were classified according to the Common Terminology Criteria for Adverse Events (version 5.0). Events occurring within 6 months were defined as acute toxicities, while those occurring after 6 months were classified as late toxicities.

4. Statistical analysis
Progression-free survival (PFS) was defined as the time interval from the initiation of curative radiotherapy to the time of tumor progression or death from any cause, with censoring applied to patients at their last follow-up. Survival rates were estimated using the Kaplan-Meier method. Overall survival (OS) was defined as the time interval from the initiation of curative RT to death from any cause. Univariate and multivariate analyses were conducted to identify prognostic factors for PFS using the Cox proportional hazards regression model. Backward stepwise selection was adopted for multivariate analyses. The prescribed radiation dose was calculated as the equivalent dose in 2-Gy fractions (EQD2), calculated by the Linear-Quadratic model, \(\alpha/\beta = 10 \text{ Gy}\). A swimmer plot was adopted to visualize the longitudinal duration of individual overall
systemic responses, excluding two patients who were lost to follow-up (n = 19). Each bar represents one patient, with annotation of the initiation of disease progression, partial response, and complete remission along the bar. A bar without any other annotation indicates stable disease. When there was no evidence of systemic progression at the last follow-up, the patient was regarded as having an ongoing response. Durable responses, defined as responses lasting more than 6 months, are annotated separately. A waterfall plot was adopted for visualizing the size change of the primary tumor after treatment, but five patients who were unable to measure the extent of disease due to radiation fibrosis were excluded when evaluating eventual response. All statistical analyses were performed using Stata 16.0 (StataCorp LLC, College Station, TX, USA).

**Results**

1. **Patient characteristics**

From January 2008 to December 2021, a total of 21 patients with pathologically confirmed sarcomatoid carcinoma who received radical RT were included in this study. The majority of these patients were male (n = 18; 85.7%), with a median age of 71 years and generally tolerable performance status. Baseline PFT revealed median values of forced expiratory volume in 1 second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO) to be 89% and 92.5%, respectively. More than half of the patients (n = 12; 57.1%) had a history of smoking. As per the American Joint Committee on Cancer 8th edition staging system NSCLC, 17 patients (81.0%) were classified into stage III or IV. Four patients diagnosed with stage IV were treated with a radical aim after 2020, when the concept of oligometastasis is accepted. Among them, two patients had contralateral lung nodules, one patient had suspected malignant pleural effusion without pathological confirmation and one patient had oligometastasis in the brain. Approximately half of the patients (n = 11; 52.4%) were diagnosed with pure sarcomatoid carcinoma, while the rest (n = 10; 47.6%) presented focal sarcomatoid features in their pathology reports. PD-L1 expression was positive in nine patients (42.9%), with the status unknown for 10 patients (47.6%). CCRT was administered to nine patients (42.9%), while 12 patients (57.1%) underwent radiotherapy alone. The median prescribed radiation dose was 60 Gy

Among the 19 patients available for response evaluation, five demonstrated a durable response to radical radiotherapy, which response lasted longer than 6 months. In the responder group, defined as those showing complete remission or partial response, all had a primary tumor size of less than 5 cm. The majority of responders had pure PCS (n = 4; 80.0%) as per their pathology reports, and no patient in this group showed negative PD-L1 expression status (range, 40% to 90%). Detailed patient characteristics are summarized in Table 1.

2. **Treatment response, survival outcomes, pattern of failure, and prognostic factors**

The median PFS and overall survival for the entire cohort (n = 21) were 4.6 months and 7.9 months, respectively (Fig. 1A). Among the 19 patients with follow-up data, 11 had experienced a good response to radiotherapy in the form of partial response or complete remission in their primary tumors. However, disease progression was observed in six of these patients after confirming their response. Durable response, defined as a response lasting more than 6 months, was observed in five patients, including three with complete tumor remission (Fig. 2). Three patients who achieved complete remissions had PFS of 148.0 months, 19.6 months, and 66.4 months, respectively. Patient #1, a 71-year-old male with stage III disease, had a 3.5-cm tumor and underwent CCRT, receiving a radiation dose of 66 Gy in 33 fractions with docetaxel and cisplatin. Patient #2, a 72-year-old male with stage II disease, presented with a 4.8-cm tumor and underwent radiotherapy alone, receiving 48 Gy in 4 fractions. Patient #3, a 51-year-old female with stage III disease, had a 3.3-cm tumor and underwent CCRT with docetaxel and cyclophosphamide. Ten patients exhibited a response within 1 month of RT, but this response subsided in six of them. The swimmer plot and the waterfall plot of the response is depicted in Figs. 2 and 3, respectively. At 1 month after treatment, follow-up chest CT imaging was available for 19 patients and none of them showed tumor growth after radiotherapy (Fig. 3A). One patient showed no change in the primary tumor while 11 patients (57.9%) displayed a 30% or greater reduction of their tumors. However, two patients experienced progression in distant metastasis without local progression; one patient had progression in both lungs and another in the retrocaval, cardiophrenic lymph node, and adrenal gland. In five patients, post-treatment tumor size became unmeasurable due to RT-induced fibrosis. Among the remaining 14 patients, five (35.7%) eventually showed a response (Fig. 3B).

Distant metastasis (n = 10; 47.6%) was the most common site of failure, often accompanied by regional recurrence (n = 5; 23.8%) and local recurrence (n = 1; 4.8%). Simultaneous regional recurrence and local recurrence occurred in one patient (4.8%), while only regional recurrence was observed in another patient (4.8%). The detailed pattern of failure is presented in Supplementary Table S1.

Univariate analysis of prognostic factors for PFS revealed that tumor size greater than 5 cm was associated with a significantly higher HR of 3.584 (95% confidence interval [CI], 1.030–12.468;
p = 0.045). Smoking history, PD-L1 expression status, distant metastasis, pure PCS, and treatment modalities did not show statistical significance. In the multivariate analysis, administering a higher radiation dose of > 58 Gy\textsubscript{EQD2} was significantly associated with a high PFS (HR = 0.204; 95% CI, 0.046–0.915; p = 0.038), suggesting a potential benefit of high-dose radiation in treating PCS (Table 2).

### 3. Adverse events after radical RT

Overall, the incidence of acute adverse events was 38.1%, and the incidence of late adverse events was 23.8%. Table 3 presents the adverse events, with a focus on respiratory toxicity. Among the acute adverse events, grade 1–2 respiratory toxicity was reported in eight patients (38.1%). Late respiratory toxicity of grade 1–2 was reported in five patients, and one patient (4.8%) experienced grade 3 respiratory toxicity well managed with supportive care.

### Discussion and Conclusion

Due to the rarity of PCS, limited research has been conducted, resulting in insufficient evidence for treatment implementation, es-
especially concerning radical RT. In this retrospective study, the entire cohort demonstrated dismal survival, with a median PFS of 4.6 months and a median OS of 7.9 months. However, better PFS was observed in patients with smaller tumors (≤ 5 cm). Furthermore, multivariate analyses suggested a potential beneficial effect of higher radiotherapy doses > 58 Gy\(_{EQD2}\). Long-term survivors with durable responses were found, providing a clue for achieving cure through radical RT with or without systemic chemotherapy.

PSC is historically known for its aggressive nature and consequent poor outcomes. According to recent SEER database studies, particularly concerning radical RT. In this retrospective study, the entire cohort demonstrated dismal survival, with a median PFS of 4.6 months and a median OS of 7.9 months. However, better PFS was observed in patients with smaller tumors (≤ 5 cm). Furthermore, multivariate analyses suggested a potential beneficial effect of higher radiotherapy doses > 58 Gy\(_{EQD2}\). Long-term survivors with durable responses were found, providing a clue for achieving cure through radical RT with or without systemic chemotherapy.

PSC is historically known for its aggressive nature and consequent poor outcomes. According to recent SEER database studies,
the median OS for the entire PSC patient group was reported as 9 months. However, this increased to 34 months when the disease was localized, with no regional or distant metastases [2,4]. In our cohort, survival outcomes were comparable to those reported in the literature. Notably, stage I-II patients accounted for four patients (19.1%) of our entire cohort (Table 1). Because patients who were suitable candidates for surgery were excluded, resulting in a higher proportion of patients with advanced stage disease. Given that advanced T, N, and M stages are often present at diagnosis in PSC, earlier disease stages (I-II) have been reported in 25.2%–

Table 2. Univariate and multivariate analysis of prognostic factor for progression-free survival

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>Multivariate analysis(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age, ≤ 70 yr (vs. &gt; 70 yr)</td>
<td>0.502 (0.172–1.467)</td>
<td>0.208</td>
</tr>
<tr>
<td>Sex, male (vs. female)</td>
<td>1.467 (0.325–6.624)</td>
<td>0.618</td>
</tr>
<tr>
<td>Smoking history, yes (vs. no)</td>
<td>2.083 (0.709–6.121)</td>
<td>0.182</td>
</tr>
<tr>
<td>Tumor size, &gt; 5 cm (vs. ≤ 5 cm)</td>
<td>3.584 (1.030–12.468)</td>
<td>0.045</td>
</tr>
<tr>
<td>PD-L1 expression status no (vs. yes)</td>
<td>1.863 (0.349–9.932)</td>
<td>0.466</td>
</tr>
<tr>
<td>Distant metastasis, yes (vs. no)</td>
<td>2.254 (0.676–7.516)</td>
<td>0.186</td>
</tr>
<tr>
<td>Pure pulmonary sarcomatoid carcinoma (vs. focal sarcomatoid feature)</td>
<td>0.777 (0.267–2.256)</td>
<td>0.642</td>
</tr>
<tr>
<td>Radiotherapy alone (vs. concurrent chemoradiotherapy)</td>
<td>0.988 (0.331–2.950)</td>
<td>0.983</td>
</tr>
<tr>
<td>Radiation dose(^b), &gt; 58 Gy(<em>{EQD2}) (vs. ≤ 58 Gy(</em>{EQD2}))</td>
<td>0.242 (0.057–1.030)</td>
<td>0.055</td>
</tr>
</tbody>
</table>

PD-L1, programmed death-ligand; HR, hazard ratio; CI, confidence interval.
\(^a\)Multivariate analysis done with backward stepwise selection.
\(^b\)Equivalent radiation dose in 2-Gy fractions (Gy\(_{EQD2}\), calculated by Linear-Quadratic model, α/β = 10 Gy).

Table 3. Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-2 respiratory toxicity</td>
<td>8 (38.1)</td>
<td>4 (19.0)</td>
</tr>
<tr>
<td>Grade 3 respiratory toxicity</td>
<td>0 (0.0)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Total</td>
<td>8 (38.1)</td>
<td>5 (23.8)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).
32.8% of cases in previous studies [1–4,6,7].

To date, the role of radiotherapy in PSC treatment has been consistently reported, but results have been somewhat controversial. Steuer et al. [8], for instance, reported a vague significance of both chemotherapy and radiotherapy compared to surgery in their National Cancer Database-based analysis. However, in a recent retrospective analysis using propensity score matching, patients who underwent RT showed longer OS compared to patients who received only the best supportive care (p < 0.001). The survival benefit was maximized in patients with stage I–III disease, with no survival benefit identified in stage IV patients [9].

In a retrospective study, Ung et al. [6] reported a median OS of 16.4 months for patients who underwent surgery, compared to an extremely dismal prognosis of 3.0 months for those who did not have surgery. Among the patients who did not undergo surgery, 75% were diagnosed with stage IV disease. A total of 28 patients received first-line chemotherapy, and a mere five patients underwent RT in conjunction with chemotherapy [6]. In PCS, resistance to chemotherapy is well documented, with poor response having progression rates reaching up to 85% [6,10]. When compared to the response rate of chemotherapy, a relatively better response was observed following RT. Out of a total of 21 patients, five were responders and 14 were non-responders, excluding two patients who were lost to follow-up. Despite the fact that more than half of the patients had RT alone (57.1%), 10 patients (52.6%) exhibited a decrease of 30% or more in primary tumor size eventually, and 11 patients (57.9%) showed such a decrease 1 month following radical RT (Fig. 3). Notably, given the favorable responses observed in stage IV oligometastatic cases, the use of aggressive RT could potentially improve patient outcomes compared to conventional chemotherapy, depending on the disease presentation and performance status.

Our results demonstrated a significant association between tumor size and treatment response. All the patients who responded to the treatment had a tumor size of ≤ 5 cm. In contrast, 50% of the non-responder had a tumor size of ≤ 5 cm (n = 7). In our univariate analysis, a tumor size > 5 cm was associated with poorer PFS (HR = 3.584; 95% CI, 1.030–12.468; p = 0.045). However, this finding did not reach statistical significance in the multivariate analysis, similar to other variables such as age, gender, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status, FEV1, DLCO, disease stage, histology and PD-L1 expression status, which were not significantly associated with treatment response. Distant metastasis demonstrated a trend towards poorer PFS (HR = 2.652; 95% CI, 0.764–9.202; p = 0.125). The role of distant metastasis as a prognostic factor in PCS has also been reported in previous research [11]. Additionally, in our cohort, one patient received a radiation dose of 42 Gy in 21 fractions due to poor performance status and showed stable disease after RT. The other three patients, who were treated with less than 58 Gy(≤50), experienced distant metastases, with or without regional recurrence (Supplementary Table S1). Our multivariate analysis further revealed that receiving a radiation dose > 58 Gy(≤50) (HR = 0.242; 95% CI, 0.057–1.030; p = 0.055) was associated with better PFS. Hypofractionation could be considered for some patients who are unable to undergo long-term RT, as observed in our cohort. This information could serve as preliminary evidence suggesting a minimal radiation dose for radical treatment of PSC. Furthermore, in our cohort, the pre-treatment PFT was relatively tolerable, and less than 5% of patients experienced acute or late respiratory toxicity following radical treatment.

The necessity of adjuvant treatment continues to be under investigation, although our study excluded patients who had undergone surgery, the impact of perioperative RT was not analyzed. With a modest benefit in OS with RT over no treatment, Liang et al. [9] reported a trend of a detrimental effect of adjuvant RT after propensity score matching. Furthermore, there is very limited evidence on neoadjuvant radiation. A SEER database-based retrospective study reported that an extremely small portion of patients (n = 76; 1.6%) had undergone neoadjuvant RT, but this was associated with superior OS (p = 0.018) [7]. In our study, less than half (42.9%) of the cohort had undergone concurrent chemotherapy with radiotherapy, which had no clinical significance (HR = 0.988; 95% CI, 0.331–2.950; p = 0.983). The role of CCRT in locally advanced PSC was also unknown. Conflicting results have also been reported for perioperative chemotherapy in PCS. While researchers at Memorial Sloan Kettering found no difference in survival among recipients of neoadjuvant chemotherapy, a recent meta-analysis showed longer OS with adjuvant chemotherapy (HR = 0.566; 95% CI, 0.439–0.729; p = 0.021) [12,13]. Investigators at Mayo Clinic suggested potential benefits of perioperative chemotherapy in a univariate analysis [11].

Until now, the appropriate treatment for advanced, inoperable PCS has not been established. The clinical significance of immunotherapy is emerging. Even though prognostic value of PD-L1 expression status have not identified in PSC, previous studies reported the prognostic significance of PD-L1 expression and the presence of metastatic disease in patients with NSCLC [14,15]. Future research should further investigate these factors in the context of PCS and the potential utility of novel treatment approaches, such as immunotherapy, in combination with radiation therapy. Recently, prospective clinical studies of cytotoxicity, targeted therapy, and immunotherapy in PCS have been initiated (NCT03022500,
Limitations of our study include the retrospective design and small sample size, as we excluded patients who had palliative RT or who have not undergone RT. Despite these limitations, our study provides real-world clinical data on the response from radical RT, suggesting the feasibility of active RT for PSC including oligometastasis. Further prospective efforts are needed to confirm these results and to establish the optimal treatment approach for patients with PSC.

In conclusion, our study supports the feasibility of radical RT in managing PCS, demonstrating the potential significance of a high biologically effective radiation dose > 58 GyEQD2. In the absence of an effective systemic agent, durable response was observed in 26.3% of the patients and long-term survivors were found. However, given the limited sample size, larger prospective studies are warranted to validate these findings and to identify optimal treatment strategies for this challenging patient population.

Statement of Ethics

The Institutional Review Board of Seoul National University Hospital (No. H-2301-043-1393) and Seoul Metropolitan Government Seoul National University Boramae Medical Center (No. 10-2023-34) approved this study and waived the requirement for patient informed consent.

Conflict of Interest

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

Funding

None.

Author Contributions

Conceptualization: Kim BH. Investigation and methodology: Kim BH. Writing of the original draft: Lee CW. Writing of the review and editing: Lee CW, Kim HJ, Kim BH. Formal analysis: Lee CW, Kim BH. Data curation: Lee CW, Kim BH.

Data Availability Statement

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

 Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2023.00437.

References


Application of surface-guided radiation therapy in prostate cancer: comparative analysis of differences with skin-marking-guided patient setup

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Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Introduction

The precision of radiation therapy administration has been enhanced by technological progress, and the growing adoption of hypofractionation has underscored the significance of ensuring accurate patient setup [1-3]. The most commonly used method for patient posture setup in clinics is the laser guide with skin marking, which involves drawing lines on the body of the patient or applying a tattooed reference point during the simulation and then aligning it with a laser in the treatment room. However, skin markings can be erased during conventional fraction treatment, causing inconvenience to patients who cannot wash their bodies. In case the skin markings are gone, the simulation and treatment plan must be re-evaluated, which can be time- and cost-inefficient. Additionally,
tattoos are invasive and can cause physical or psychological discomfort if they are permanent [4]. Moreover, due to the elasticity of the skin, even when the laser is aligned with the skin marking, there remains a possibility that the setup may not be entirely accurate.

Surface-guided radiotherapy (SGRT) utilizes three light projectors and an optical camera to generate a 3D map of the body contour of the patient, which is compared to a reference surface image. The software analyzes the differences in real-time and displays them as translational and rotational delta values. Since the beam is non-ionizing, it allows for real-time adjustment of the positional setup during treatment, improving accuracy and efficiency [5]. In addition, studies on the application of the surface guide to patient identification, patient safety [6], and motion management are ongoing [2,7], and gating radiotherapy as well as set up in head and neck cancer [8-10], stereotactic radiosurgery, and breast cancer [7,11-15]. This study aims to measure and compare the accuracy of the surface-guided setup. We aim to confirm that surface guide setup is a comfortable and accurate method for patients, which does not require additional effort.

Materials and Methods

We analyzed 2,735 external radiation treatments administered to 125 patients who underwent external beam radiotherapy (EBRT) for prostate cancer at Asan Medical Center between August 2021 and February 2022. Patient data for this study were collected through an Institutional Review Board (IRB)-approved retrospective chart review (IRB No. S2023-0461-0001). After the range of treatment was confirmed by the physician, the patients lay down on their backs with pillows under their heads and ankles and arms raised above their chests. The balloon catheter was then inserted into the rectum, adjusted to fit the patient, inflated with 80 mL of air, and secured. The scanning range was set to the proximal femur from T11. Administration of contrast required the scan to use a 2.5-mm slice after a delay of approximately 180–210 seconds. Skin marking was performed after computed tomography (CT) simulation (Discovery RT; GE HealthCare, Waukesha, WI, USA) for all treated patients, with a horizontal line connecting both femur heads, mid-pelvis lines on both lateral sides, and a midline based on the patient’s pubic symphysis. Skin markings were applied to four locations, and a CT simulation was performed. All patients were treated with Halcyon equipped with the AlignRT (Vision RT Inc., London, UK) surface guide system.

The patient was initially positioned and aligned during each treatment using the skin marking method drawn during CT simulation. After turning off the laser, the patient was gently aided to stand up, and then the surface guide was setup using the AlignRT system. Then, based on the surface guide couch value, cone-beam computed tomography (CBCT) image guide was performed. The couch values are labeled as “M” during the skin marking setup, “S” during the SGRT setup, and “C” after CBCT and couch shift. Gap (M-C) represents the difference between “M” and “C,” Gap (S-C) represents the difference between “S” and “C,” and Gap (M-S) represents the difference between “M” and “S” (Fig. 1). AlignRT comprises three light projectors and one optical camera installed on the ceiling of the treatment room. The optical camera analyzes the light beams emitted from the projectors to create a 3D map of the body contour, then compares it with the reference image’s body contour (Fig. 2A). A reference surface image was created from the external surface of the CT simulation scan and imported through the DICOM file. The AlignRT software compares real-time surfaces and displays any differences as three translational (ventral, lateral, longitudinal) and three rotational (yaw, roll, pitch) delta values. During daily treatment, the translational delta values were kept within 3 mm, and the rotational delta values were setup within 1°. The translational shift was accomplished via couch movement for patient setup, while the rotational shift was performed manually (Fig. 2B). Both lateral thighs were set as region-of-interest (Fig. 2C). The setup time was measured from the start of surface guide setup to the final shift using CBCT, just before beam irradiation, and was compared with the time taken in other treatment rooms where prostate cancer was treated with TomoTherapy (Accuray Inc., Sunnyvale, CA, USA).

Statistical analysis was performed using R statistics version 4.1.3 and Microsoft Excel 2020. The vertical, longitudinal, and lateral couch values of the skin-marking and surface-guide setups were analyzed based on surface-guide couch values. The couch values of the skin-marking setup and the surface-guide setup were indirectly
compared by analyzing the couch value obtained after performing CBCT with image guidance. A t-test was used to compare the difference in the final shift value between the skin-marking and surface-guide methods and the setup time for each method.

In this study, we examine the translation vector by calculating its magnitude using the square root of the sum of the squares in each direction. This can be expressed mathematically as follows:

\[
\text{Magnitude of translation vector} = \sqrt{(Δ_{\text{vertical}})^2 + (Δ_{\text{longitudinal}})^2 + (Δ_{\text{lateral}})^2}
\]

By analyzing the three directions collectively, we obtain a single numerical value that represents the magnitude of the translation vector [9,16]. Then a multiple linear regression analysis was conducted to determine if there was an association with patient characteristics.

Results

The median age of the patients was 71.3 years (range, 45 to 88 years), with a median height of 165.5 cm (range, 152.1 to 182.0 cm) and a median body mass index (BMI) of 25.5 kg/m² (range, 19.5 to 35.5 kg/m²) (Table 1).

Gap (M-S) showed that the vertical, long, and lateral averages differed by only -0.03 cm, 0.07 cm, and 0.06 cm, respectively (Fig. 3A). Furthermore, the standard deviation was within 0.5, confirming the consistency of the results. In the vertical direction, the mean difference between Gap (M-C) (range, -0.05 to 0.65) and Gap (S-C) (range, -0.05 to 0.76) was 0.04 cm (p = 0.03), and in the longitudinal direction, the mean difference between Gap (M-C) (range, -0.31 to 0.47) and Gap (S-C) (range, -0.29 to 0.88) was 0.35 cm (p = 0.52), and the lateral direction showed a mean difference of 0.11 cm (range, -0.24 to 0.72 and -0.24 to 0.75, respectively) (p = 0.91) (Fig. 3B, 3C).

The mean translation vector value of Gap (M-C) was 0.39 cm (range, 0.08 to 0.78), while the mean translation vector value of Gap (S-C) was 0.43 cm (range, 0.08 to 0.89). The mean difference between the two groups was 0.04 cm (p < 0.0001; 95% confi-
Surface-guided radiotherapy

Table 1. Patient characteristics (n = 125)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>71.3 ± 7.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.5 ± 6.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5 ± 2.9</td>
</tr>
<tr>
<td>Risk group</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>25 (20.0)</td>
</tr>
<tr>
<td>High</td>
<td>51 (40.8)</td>
</tr>
<tr>
<td>Very high</td>
<td>49 (39.2)</td>
</tr>
<tr>
<td>Treatment aim</td>
<td></td>
</tr>
<tr>
<td>Definitive</td>
<td>71 (56.8)</td>
</tr>
<tr>
<td>Post prostatectomy</td>
<td>53 (42.4)</td>
</tr>
<tr>
<td>Palliative</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Radiation field</td>
<td></td>
</tr>
<tr>
<td>Pelvis</td>
<td>87 (69.6)</td>
</tr>
<tr>
<td>Prostate only</td>
<td>38 (30.4)</td>
</tr>
</tbody>
</table>

Values are presented as median ± standard deviation or number (%).

BMI, body mass index.

The setup time for Halcyon with the surface guide was 7.53 minutes (range, 5 to 10 minutes) and 6.73 minutes (range, 5 to 8 minutes) for TomoTherapy with skin marking, resulting in a difference of 0.8 minutes between the two groups (p < 0.0001) (Fig. 3D).

Discussion and Conclusion

Comparison of the skin-marking and surface-guide setups after CBCT showed a negligible difference in the couch shift value of less than 1 mm in all directions, unaffected by patient age, BMI, and height.

A previous study on surface-guide setup in radiotherapy for prostate cancer reported a median vector offset of 0.47 cm, comparable to our finding of 0.43 cm. The study also noted a faster setup time than with the skin-marking guide [17]. Additionally, several studies have shown that applying surface guides to the pelvis and lower extremities results in a translational difference of 0.6 cm [18], whereas in the head and neck it ranges from 0.1 to 0.3 cm [5,9], and 0.24 to 0.87 cm in the breast and thorax [14,15,18,19]. A difference as large as 1 cm can be observed in the abdomen [5,18] (Table 2). In contrast to the breast, head, and neck, surface contour is not a reliable indicator of the position of internal organs in the prostate.

To evaluate accuracy of surface guides in prostate setup, we conducted a study that revealed a disparity between the surface-guide setup and the final shift value that was similar to that observed in other body areas. Our findings confirm that surface guides are a reasonably accurate method for setup in prostate cancer treatment compared with skin marking. However, several studies have reported that the translational difference of skin marking is greater than that of surface guide [14,15,17–19], suggesting that the latter is a more accurate method. Our study observed a translational difference of 0.39 cm in the skin-marking setup compared with the surface-guide setup.
with the 0.52 cm reported previously [17]. This suggests that our setup method, based on drawing a long reference line on the patient’s body, is a more accurate alternative to using a tattoo point. However, if the reference skin marking is long, the setup is accurate, but the patient’s discomfort may increase. Therefore, this study confirms that SGRT is accurate enough to replace our accurate long reference line, which may reduce patient discomfort.

In addition, our study confirms that the differences in the vertical direction were greater compared to CBCT, indicating similar findings for both skin marking and SGRT. These observations may be attributed to couch sagging in Halcyon, highlighting the potential for enhanced accuracy with the availability of in-bore type SGRT.

While this study focused on applying surface guides as an alternative to skin marking in prostate cancer treatment, surface guides have potential uses in various other applications. For example, these systems offer valuable applications, such as maskless setup for head and neck treatments and reliable patient identification [8-10], wherein the body contour of the patient can serve as a means of identification [1-3,12]. Additionally, when combined with four-dimensional computed tomography (4DCT) imaging, surface guidance enhances treatment accuracy through the gating system, ensuring precise targeting [2,8,20]. This approach also enables us to capture vital patient information, including identification and weight loss, while adapting radiotherapy to account for the daily size changes of surface-adjacent tumors. The integration of augmented reality holds promises in projecting internal patient data onto the surface, further augmenting the setup process [1,3,12].

There are several limitations to the present study. First, performing two setups and to CBCTs would ensure accurate comparison of the two methods; however, given the increased exposure to radiation and potential inconvenience to the patient, we adopted a different approach. To mitigate bias introduced by the initial setup, the patient was stood up and underwent a reset procedure with SGRT for the second setup after completing the first setup with skin marking. Second, performing two setups on the same patient while measuring the setup time would improve the accuracy of our data. However, setup times are typically very short (usually 20 seconds to 1 minute), so accurately measuring them can be challenging. To address this, we determined the overall treatment preparation time by measuring the time from setup initiation to completion just after CBCT image guidance. We then compared this time to that of a prostate treatment patient receiving TomoTherapy with a skin-marking guide. To ensure a more accurate comparison, it is essential to use the same equipment. Nevertheless, our institution had two dedicated treatment rooms, SGRT-Halcyon and skin marking with TomoTherapy, specifically for prostate cancer patients during the study, and thus this comparison was conducted based on these methods. The difference between the surface guide and skin marking was less than 1 minute. Notably, these data were collected when the device was first introduced, so some proficiency issues may have occurred. However, we anticipate that there is currently very little disparity in setup times between the two methods.

In conclusion, surface-guided radiotherapy in prostate EBRT is reliable and could replace skin marking as an accurate and efficient patient identification and setup method.

Table 2. Translational differences of skin marking and surface guide

<table>
<thead>
<tr>
<th>Study</th>
<th>Anatomic location</th>
<th>Translational differences (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Skin marking</td>
<td>Surface guide</td>
</tr>
<tr>
<td>Stanley et al. [18]</td>
<td>Pelvis/lower extremities</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>Abdomen</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Chest/upper extremities</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
<td>1.40</td>
</tr>
<tr>
<td>Jimenez et al. [15]</td>
<td>Breast</td>
<td>0.59</td>
</tr>
<tr>
<td>Kugele et al. [14]</td>
<td>Breast</td>
<td>0.42</td>
</tr>
<tr>
<td>Hattel et al. [19]</td>
<td>Breast</td>
<td>0.54</td>
</tr>
<tr>
<td>Heinzerling et al. [20]</td>
<td>Thoracic and abdomen</td>
<td>0.54</td>
</tr>
<tr>
<td>Lee et al. [9]</td>
<td>Nasopharynx</td>
<td>–</td>
</tr>
<tr>
<td>Haraldsson et al. [5]</td>
<td>Central nerve system</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Head and neck</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Thorax</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Abdomen</td>
<td>–</td>
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</tbody>
</table>

Statement of Ethics

This study was approved by the Institutional Review Board at Asan Medical Center (IRB No. S2023-0461-0001).
Conflict of Interest

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

Funding

None.

Author Contributions

Conceptualization, Kim YS, Song SY. Investigation and methodology, Lee J, Kim YS, Kim YJ. Writing of the original draft, Lee J, Kim YS. Writing of the review and editing, Kim YS, Lee J, Kim YJ. Formal analysis, Lee J, Goh Y. Data curation, Kim YS, Lee J, Yang E, Kim HU.

Data Availability Statement

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

References

Comparison between 1-week and 2-week palliative radiotherapy courses for superior vena cava syndrome

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Purpose: The aim of this study was to evaluate the effectiveness of palliative radiation therapy (RT) for superior vena cava (SVC) syndrome from lung cancer and to compare the 2-week and 1-week schedules.

Materials and Methods: A retrospective study was conducted on lung cancer patients with palliative RT for SVC syndrome. Patients received 30 Gy in 10 fractions (2-week group) or 20 Gy in 5 fractions (1-week group) between July 2012 and June 2022. Treatment outcomes were evaluated at 1 to 2 months after RT. The tumor response and recanalization were evaluated based on the computed tomography (CT).

Results: Of the 39 patients, 24 received a 2-week course RT and 15 received a 1-week course of RT. The most common SVC-associated symptoms were edema (51.3%) and dyspnea (43.6%). There were no significant differences in performance status, histology, and grade of SVC. Symptom relief in symptomatic patients was comparable (85.7% in the 2-week group vs. 91.6% in the 1-week group; p = 0.581). There were no significant differences between the 2-week and 1-week groups in recanalization rates (62.5% vs. 60.0%; p = 0.876), tumor responses (75% vs. 60.0%; p = 0.876), and 6-month overall survival rates (29.2% vs. 36.4%; p = 0.726). In each of the two groups, one patient was consulted for re-irradiation. The median survival were 3.7 months for the 2-week group and 4.4 months for the 1-week group.

Conclusion: In patients with SVC syndrome, the palliative effect of a 1-week course was equivalent to that of a 2-week course. Given the poor prognosis, a 1-week course may be an option.

Keywords: Superior vena cava, Lung cancer, Radiotherapy, Palliative

Introduction

Superior vena cava (SVC) syndrome is a condition caused by the obstruction of blood flow from the head, arms, and upper torso to the heart. Approximately 90% of SVC obstructions are related to thoracic malignancies, which externally compress the SVC with a mass effect or directly invade the SVC [1]. This obstruction leads to increased venous pressure, resulting in symptoms with a wide range of severity, from face and arm swelling to life-threatening symptoms such as central airway obstruction, severe laryngeal edema, and cerebral edema with confusion. Lung cancer is the most common malignancy causing SVC syndrome, accounting for more than 70% of all cases [1,2]. The incidence of SVC obstruction at presentation is 4.2% in patients with lung cancer and is more frequent in small cell lung cancer (SCLC) than in non-small cell lung cancer (NSCLC) [3].

Various treatment options are available for the management of SVC syndrome, including steroids, chemotherapy, intervention, and radiation therapy (RT). Endovascular recanalization is the standard first-line treatment for patients with life-threatening symptoms [4-6]. Intravascular stenting provides rapid relief from symptoms. However, most cases of SVC syndrome are not considered an oncologic emergency and do not require urgent management [7]. In patients without life-threatening symptoms, palliative RT is an effec-
Palliative RT for SVC syndrome

The severity of SVC syndrome was evaluated using the grading system proposed by Yu et al. [12] (Supplementary Table S1).

2. Radiotherapy
CT simulation was performed for all patients in the supine position, under free breathing three-dimensional CT. The gross tumor volume (GTV) included the tumor causing the SVC obstruction through encasement or direct invasion. The clinical target volume (CTV) was generated by adding a 5-mm isotropic margin to the GTV. CTV could be tailored to the size and extent of the tumor. If the tumor was too large to be treated in its entirety, the doctor determined the extent of the target volume. The CTV generally included the area from the upper border of the right atrium to the thoracic inlet.

The planning target volume was created by expanding the CTV by 5 mm or more. RT planning was performed using the Eclipse RT planning system (Varian Medical Systems, Palo Alto, CA, USA). Three-dimensional conformal RT (3D-CRT) planning was mainly used and based on the physician’s preference or the need for organ preservation, intensity-modulated radiotherapy or volumetric-modulated arc therapy techniques were also employed. RT was delivered using 6- or 10-MV photons from a linear accelerator (Varian Medical Systems). The total dose and number of fractions were determined based on the patient’s condition and the physician’s preference. Both RT schedules continuously delivered treatment once daily for 5 days a week.

3. Evaluation and statistics
Follow-up examinations included history taking, physical examination, laboratory tests, CT, magnetic resonance imaging, and positron emission tomography/CT (or when metastasis was suspected), depending on the patient’s condition, stage, and risk factors. The interval of follow-up was also adjusted depending on the patient and the disease. Recanalization was defined as the restoration of flow in patients with complete obstruction before RT and an increase in the luminal diameter of at least 20% in patients with incomplete obstruction (a visible contrast agent on the SVC on initial CT) before RT. The tumor response was evaluated based on the Response Evaluation Criteria in Solid Tumors v1.1 compared to the baseline on a follow-up CT scan. Additionally, the overall tumor response is defined as more than a partial response. Cause of death was evaluated with medical record. The immediate cause defined as the final disease or condition resulting in death. According to the definition provided by Nichols et al. [13] tumor burden was defined as cause of death, resulting from (1) cachexia, (2) no other specific and/or pathophysiologic mechanisms of death, and/or (3) the lung tumor volume being the primary factor leading to fatal respiratory failure.

Differences between the 1-week and 2-week RT courses were

Materials and Methods

1. Patients
This retrospective study was approved by the Institutional Review Board of our institution of Kyungpook National University Chilgok Hospital (No. 2020-04-051). The requirement for informed consent was waived because of the retrospective nature of the analyses. We reviewed the medical records of patients with lung cancer who underwent palliative RT for SVC syndrome between July 2012 and June 2022 at our institution. Patients included were treated with either a 2-week course (30 Gy in 10 fractions) or a 1-week course (20 Gy in 5 fractions) of palliative RT. During the study period, 46 patients with SVC syndrome caused by lung cancer were treated with palliative RT. Of these, seven patients were excluded from the analysis for the following reasons: four due to the use of alternative dose-fractionation regimens other than the standard 1-week or 2-week courses, two due to a lack of follow-up evaluation and one due to discontinued RT. No patients died during RT. The remaining 39 patients were enrolled in this study. All patients had a diagnostic chest computed tomography (CT) image at the time they were referred for palliative RT. Among them, 24 received 30 Gy in 10 fractions (2-week group), whereas 15 received 20 Gy in 5 fractions (1-week group). Patient characteristics and treatment details, including radiation dose, fraction size, and treatment response, were obtained from medical records. Lung cancer diagnosis was based on histological confirmation. SVC syndrome diagnosis was based on clinical symptoms or signs, and SVC obstruction observed on CT images. The severity of SVC syndrome was evaluated using the grading system.
compared using Pearson chi-square test for parametric variables. Overall survival (OS) was estimated using the Kaplan-Meier method, and survival duration was calculated from the starting date of RT until the date of death or the last follow-up. Logistic regression was used to evaluate factors influencing symptom relief. Univariate and multivariate analyses were performed using the Cox proportional hazards model to determine the association between the clinical factors and survival outcomes. Backward selection Cox regression analysis was performed using a multivariate model. Statistical analyses were performed using SPSS version 22 (IBM, Armonk, NY, USA) and the R software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics are shown in Table 1. Of total the 39 pa-

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>2-week group</th>
<th>1-week group</th>
<th>p-value</th>
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<tr>
<td>Age (yr)</td>
<td>62 (38–81)</td>
<td>62 (44–80)</td>
<td>63 (38–81)</td>
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<tr>
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<td>32 (77.1)</td>
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<td>14 (92.9)</td>
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<td>Female</td>
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<td>6 (25.0)</td>
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<td>Index of symptom b)</td>
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<tr>
<td>Dyspnea</td>
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<td>22 (91.7)</td>
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<td>2 (13.3)</td>
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<td>After RT within 1 month</td>
<td>19 (48.7)</td>
<td>12 (50.0)</td>
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<td>10 (41.7)</td>
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<td>Plan</td>
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<td>0.302</td>
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<td>3D-CRT</td>
<td>34 (87.2)</td>
<td>20 (83.3)</td>
<td>14 (93.3)</td>
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<td>IMRT</td>
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<td>0 (0)</td>
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<td>3 (12.5)</td>
<td>1 (6.7)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (range) or number (%).
ECOG, Eastern Cooperative Oncology Group; SVC, superior vena cava; RT, radiation therapy; 3D-CRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; VMAT, volumetric modulated arc therapy.

a) At the time of palliative RT for SVC syndrome.

b) Percentages sum to over 100% because patients had one or more symptoms.
patients, 26 (66.7%) had NSCLC and 13 (33.3%) had SCLC. The onset of SVC syndrome in the 2-week group occurred in 70.8% of cases due to disease progression following previous treatment, and the remaining 29.2% occurred at the time of the initial diagnosis of lung cancer. Of the 1-week patients, 53.3% occurred at the time of initial lung cancer diagnosis, and the remaining 46.7% occurred due to disease progression. And in both groups, patients had distant metastasis (70.8% in the 2-week group and 93.3% in the 1-week group; p = 0.090). The most common symptoms of SVC syndrome were edema (51.3%) and dyspnea (43.6%), while 15.4% of the patients were asymptomatic. SVC syndrome grades 0–2 accounted for the majority of patients in both groups (91.7% in the 2-week group and 93.3% in the 1-week group; p = 0.617). Steroids and chemotherapy were administered to the majority of patients. In both groups, 3D-CRT was the most commonly used RT planning technique (83.3% in 2-week group and 93.3% in 1-week group).

At 1–2 months following the completion of RT, among the symptomatic patients (excluding those who were asymptomatic), 87.8% experienced symptom relief (Table 2). Reduction in SVC-associated symptoms was observed in 85.7% of the 2-week group and 91.6% of the 1-week group (p = 0.581) in symptomatic patients. The recanalization rates were 62.5% in the 2-week group and 60.0% in the 1-week group (p = 0.876), and the tumor response rates were 75.0% and 60.0%, respectively (p = 0.323). Consultations for re-irradiation of SVC were observed in one patient from the 2-week group and one patient from the 1-week group. The patient who received the 2-week course of RT was consulted for retreatment 5 months after completing RT. This patient’s treatment was interrupted due to hospital-acquired pneumonia after receiving 21 Gy in 7 fractions. The patient who received the 1-week course of RT was consulted 2 months after RT and did not receive re-irradiation determined by the radiation oncologist. Logistic regression analysis indicated that the RT schedule, use of steroids, and concurrent chemotherapy did not have a significant impact on symptom relief (Table 3). At the time of analysis, 35 patients had died. Of these, six patients died outside of the hospital, such as in hospice care, so we could not evaluate the cause of death for them. Of the remaining 29 patients, 28 died of cancer-specific causes, while one died attributed to other specific cause, which was renal failure from underlying chronic kidney disease (Supplementary Table S2). Among the 28 patients who died from cancer-specific reasons, the immediate causes of death were tumor burden in 10 patients, pneumonia in eight patients, and

### Table 2. Treatment outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>2-week group</th>
<th>1-week group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom relief (n = 33)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall response</td>
<td>29 (87.8)</td>
<td>18 (85.7)</td>
<td>11 (91.6)</td>
<td>0.614</td>
</tr>
<tr>
<td>No response</td>
<td>4 (12.2)</td>
<td>3 (14.3)</td>
<td>1 (8.4)</td>
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<tr>
<td>Revascularization</td>
<td></td>
<td></td>
<td></td>
<td>0.876</td>
</tr>
<tr>
<td>Overall response</td>
<td>24 (61.5)</td>
<td>15 (62.5)</td>
<td>9 (60.0)</td>
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</tr>
<tr>
<td>No response</td>
<td>15 (38.5)</td>
<td>9 (37.5)</td>
<td>6 (40.0)</td>
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<tr>
<td>Tumor response</td>
<td></td>
<td></td>
<td></td>
<td>0.323</td>
</tr>
<tr>
<td>Overall response</td>
<td>27 (69.2)</td>
<td>18 (75.0)</td>
<td>9 (60.0)</td>
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</tr>
<tr>
<td>Stable disease</td>
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<td>5 (20.8)</td>
<td>5 (33.3)</td>
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</tr>
<tr>
<td>Progression disease</td>
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<td>1 (4.2)</td>
<td>1 (6.7)</td>
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<tr>
<td>Consultation for retreatment</td>
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<td>2 (5.2)</td>
<td>1 (4.2)</td>
<td>1 (6.7)</td>
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</tr>
<tr>
<td>No</td>
<td>37 (94.8)</td>
<td>23 (95.8)</td>
<td>14 (92.3)</td>
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</tr>
</tbody>
</table>

Values are presented as number (%).

<sup>a</sup>This analysis refers only to the patients who have symptoms associated with the superior vena cava syndrome (a total of 33 patients).

### Table 3. Factors affecting symptom relief

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Symptom relief</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>1.149 (0.945–1.397)</td>
<td>0.463</td>
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<tr>
<td>RT scheme</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2-week</td>
<td>21</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-week</td>
<td>12</td>
<td>4.852 (0.189–124.371)</td>
<td>0.340</td>
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</tr>
<tr>
<td>Onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>10</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease progression</td>
<td>23</td>
<td>1.122 (0.075–16.857)</td>
<td>0.934</td>
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<td>ECOG performance status</td>
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<td></td>
<td></td>
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<td>0–2</td>
<td>22</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–4</td>
<td>11</td>
<td>0.145 (0.013–1.594)</td>
<td>0.114</td>
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</tr>
<tr>
<td>Steroid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>25</td>
<td>1.201 (0.078–18.406)</td>
<td>0.896</td>
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<tr>
<td>CCRT</td>
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<td></td>
<td></td>
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</tr>
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<td>6</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>27</td>
<td>1.600 (0.137–18.723)</td>
<td>0.708</td>
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</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; CCRT, concurrent chemoradiation therapy; HR, hazard ratio; CI, confidence interval.
metastatic complications in eight patients. Dyspnea (55.2%) and general weakness (20.7%) were frequently observed. However, no patients were determined to have died as a direct result of SVC syndrome. The mean follow-up duration was 6 months. The median survival was 3.7 months in the 2-week group [95% confidence interval (CI), 2.020–5.380] and 4.4 months in the 1-week group (95% CI, 2.612–6.188). Not finding a statistically significant difference in the OS rate based on the RT schedule (29.2% in the 2-week group and 36.4% in the 1-week group; p = 0.726) (Fig. 1). Both univariate and multivariate analyses showed that the treatment schedule was not related to OS (Table 4).

**Discussion and Conclusion**

Our study demonstrated that the 2-week and 1-week course of palliative RT were equally effective for the relief of symptoms of metastatic complications in eight patients. Dyspnea (55.2%) and general weakness (20.7%) were frequently observed. However, no patients were determined to have died as a direct result of SVC syndrome. The mean follow-up duration was 6 months. The median survival was 3.7 months in the 2-week group [95% confidence interval (CI), 2.020–5.380] and 4.4 months in the 1-week group (95% CI, 2.612–6.188). Not finding a statistically significant difference in the OS rate based on the RT schedule (29.2% in the 2-week group and 36.4% in the 1-week group; p = 0.726) (Fig. 1). Both univariate and multivariate analyses showed that the treatment schedule was not related to OS (Table 4).

**Table 4. Factors affecting overall survival after RT**

<table>
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<tr>
<th>Variable</th>
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<th>Multivariate</th>
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<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
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<td>35</td>
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<td>1.988 (0.683–5.788)</td>
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<tr>
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<td>1.085 (0.522–2.256)</td>
<td>0.827</td>
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</tr>
</tbody>
</table>

RT, radiation therapy; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SVC, superior vena cava; HR, hazard ratio; CI, confidence interval.

<sup>a</sup>Asymptomatic patients were included in the count of those who achieved symptom relief.
SVC syndrome caused by lung cancer. In symptomatic patients, symptom relief was achieved in 85.7% of the 2-week group and 91.6% of the 1-week group, with no significant difference. And there was no statistically significant difference in recanalization, tumor response, and overall survival between the 2-week course RT and the 1-week course RT.

Historically, palliative RT has been widely advocated for SVC syndrome. However, currently, the SVC stenting has emerged as the first line treatment for SVC obstruction, offering symptom relief in up to 89%, with a stent patency rate of more than 90% [14–16]. This intervention is particularly crucial for patients who require urgent management, with life-threatening symptoms such as larynx swelling, airway obstruction, and cerebral edema [12]. Endovascular stenting can provide more rapid palliation compared to radiation therapy and chemotherapy. However, despite the advantages of the SVC stenting, it is not suitable for all patients. Stenting can be challenging for those with bleeding tendencies due to thrombocytopenia caused by previous treatments or underlying comorbidities. In addition, the lack of necessary equipment or specialists in some medical facilities may further limit its use. For these conditions, palliative RT may still be a good option. Previous studies have demonstrated that RT, using various dose-fractionation schemes, is effective in relieving symptoms of SVC syndrome, with symptom relief achieved in 70%–90% of patients [8–10]. In our study, a reduction in SVC-associated symptoms was achieved in 87.5% of symptomatic patients. These results were consistent with a previous study. Furthermore, the 1-week course RT showed an equivalent effect on symptom reduction to the 2-week course RT.

Patients with SVC syndrome caused by malignancy are known to have a poor prognosis, with a median life expectancy of approximately 6 months [1]. Our study also showed a poor prognosis, with a median survival of 3.7 months in the 2-week group and 4.4 months in the 1-week group. By the time a patient with SVC syndrome is referred for palliative RT, most patients are already in the advanced stage of the disease, having experienced the failure of prior treatments and/or the presence of distant metastases. Furthermore, we found that tumor response was not associated with OS in both univariate and multivariate analyses. Recanalization of the SVC also had no effect on OS. Most of the patients in our study had grade 0–2 SVC syndrome and may have already developed collaterals to compensate for SVC occlusion prior to RT [17,18].

The major concern with a 1-week course of palliative RT is that symptom relief could be of shorter duration of palliation effects compared to a longer course, leading to the need for additional interventions. The selection of palliative treatment should encompass not only the reduction of patient complaints but also the evaluation of symptom stability and the duration of palliation effects [19]. In previous palliative RT studies, the durability of the treatment effect between short and long course regimens appears to vary depending on the metastatic site and cancer type. In painful bone metastases, a single fraction of 8 Gy has been shown to be as safe and effective as a longer course of palliative RT (30 Gy in 10 fractions) in terms of pain relief [20]. However, the retreatment rate in the group receiving a single dose of 8 Gy was much higher than that in the 30 Gy in 10 fraction groups (28% vs. 2%). Similarly, Olafsdottir et al. [21] found that a short course (20 Gy in 5 fractions) for esophageal cancer had a retreatment rate of 32.0% compared with 18.9% for a long course (30 Gy in 10 fractions). Conversely, Rades et al. [22] found that a 1-week course (20 Gy in 5 fractions) and a 2-week course (30 Gy in 10 fractions) for metastatic epidural spinal cord compression were similarly effective in motor function, ambulatory rate, and local progression-free survival and maintained effects for up to 6 months. In our study, we were unable to directly analyze the sustainability of treatment effect. It was challenging to discern, based on medical records, whether symptoms originated from a recurrence or aggravation of SVC syndrome or from systemic disease progression. In addition, most patients were in end-stage disease. Radiological assessment of tumor progression was also challenging as few patients had serial CT scans due to their short survival time.

Other considerable short-course RT regimens, such as 16–17 Gy delivered in 2 fractions, have been previously reported effective as palliative thoracic RT. Kramer et al. [23] compared the effectiveness of 16 Gy in 2 fractions and 30 Gy in 10 fractions regimens for palliative RT in patients with NSCLC experiencing hemoptysis, chest pain, dysphagia, and dyspnea. They reported that although 30 Gy in 10 fractions maintained a longer treatment effect and showed better survival, 16 Gy in 2 fractions was equally effective in relieving symptoms over the initial 39 weeks. Sundstrom et al. [24] compared 17 Gy in 2 fractions (daily 8.5 Gy) as a palliative thoracic dose with 42 Gy in 15 fractions (daily 2.8 Gy) and 50 Gy in 25 fractions. They concluded that 17 Gy in 2 fractions is equally effective in symptom palliation and survival in advanced NSCLC patients. Additionally, a study by Senkus-Konefka et al. [25] evaluated the efficacy of two different RT regimens 20 Gy in 5 fractions and 16 Gy in 2 fractions, for patients with inoperable symptomatic NSCLC. Their analysis showed no significant difference in symptom relief between the two RT regimens, indicating similar effectiveness. Although there is limited evidence to support the use of 2-fraction RT for SVC syndrome, its potential as a shorter and more convenient treatment option could make it a viable choice for selected patients. Further research is needed to establish its efficacy and safety.

This study has several limitations. First, as a retrospective study, it may be prone to inherent bias and heterogeneity between the
two groups, and the small sample size may have limited the robustness of the findings. However, considering the lack of reports on the optimal palliative dose for lung cancer patients with SVC syndrome, the study findings may prove valuable in guiding clinical treatment decisions. Second, SVC syndrome is typically observed in patients with locally advanced or metastatic disease. These patients represent a heterogeneous group with complicating comorbidities and complex clinical scenarios in which various treatments overlap. Thus, stratifying these patients or distinguishing the sole efficacy of palliative RT is challenging. Similarly, it was not possible to distinguish from the medical record whether symptoms following radiation were due to recurrence or aggravation of SVC syndrome or systemic disease progression. This limitation prevented analysis of the duration of symptom relief. Finally, Treatment-related toxicity is one of major considerations in therapeutic decision-making. However, RT-related toxicity could not be assessed due to the retrospective design of this study. Moreover, distinguishing the cause of their symptom was challenging as they might be multifactorial, arising from RT, other treatments, or the progression of the disease.

In conclusion, a 1-week course of RT for SVC syndrome caused by lung cancer offered equivalent effectiveness in symptom relief, tumor response, and recanalization compared to a 2-week course of RT. There was no significant difference in the consultation for re-irradiation. Given the poor prognosis for lung cancer patients with SVC syndrome, a 1-week course of RT could be a viable option for efficient symptom management.

**Statement of Ethics**

This retrospective study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of our institution of Kyungpook National University Chilgok Hospital (No. 2020-04-051). The informed consent was waived because of the retrospective nature of this study.

**Conflict of Interest**

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

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**Author Contributions**

Conceptualization, Lee JE. Investigation and methodology, Park J. Writing of the original draft, Park J. Writing of the review and editing, Lee JE, Park J. Formal analysis, Park J. Data curation, Park J.

**Data Availability Statement**

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

**Supplementary Materials**

Supplementary materials can be found via https://doi.org/10.3857/roj.2023.00626.

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Palliative RT for SVC syndrome


Feasibility of artificial intelligence-driven interfractional monitoring of organ changes by mega-voltage computed tomography in intensity-modulated radiotherapy of prostate cancer

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Purpose: High-dose radiotherapy (RT) for localized prostate cancer requires careful consideration of target position changes and adjacent organs-at-risk (OARs), such as the rectum and bladder. Therefore, daily monitoring of target position and OAR changes is crucial in minimizing interfractional dosimetric uncertainties. For efficient monitoring of the internal condition of patients, we assessed the feasibility of an auto-segmentation of OARs on the daily acquired images, such as megavoltage computed tomography (MVCT), via a commercial artificial intelligence (AI)-based solution in this study.

Materials and Methods: We collected MVCT images weekly during the entire course of RT for 100 prostate cancer patients treated with the helical TomoTherapy system. Based on the manually contoured body outline, the bladder including prostate area, and rectal balloon regions for the 100 MVCT images, we trained the commercially available fully convolutional (FC)-DenseNet model and tested its auto-contouring performance.

Results: Based on the optimally determined hyperparameters, the FC-DenseNet model successfully auto-contoured all regions of interest showing high dice similarity coefficient (DSC) over 0.8 and a small mean surface distance (MSD) within 1.43 mm in reference to the manually contoured data. With this well-trained AI model, we have efficiently monitored the patient’s internal condition through six MVCT scans, analyzing DSC, MSD, centroid, and volume differences.

Conclusion: We have verified the feasibility of utilizing a commercial AI-based model for auto-segmentation with low-quality daily MVCT images. In the future, we will establish a fast and accurate auto-segmentation and internal organ monitoring system for efficiently determining the time for adaptive replanning.

Keywords: Artificial intelligence, Image-guided radiotherapy, Intensity-modulated radiotherapy, Prostate cancer, X-ray tomography, Patient monitoring

Introduction

High-dose (> 70 Gy) radiotherapy (RT) for localized prostate cancer requires careful consideration of target position changes and the state of adjacent organs-at-risk (OARs), such as the rectum and bladder. Previous studies have shown that interfractional displacement of the prostate gland can vary from 0 to 20 mm due to the changes in the rectum and bladder filling [1-8]. Changes in rectal volume can increase the risk of biochemical and local failure [1,9-14]. An increase in rectal volume receiving ≥ 60 Gy can elevate the...
AI-driven organ monitoring by MVCT image

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The risk of grade ≥ 2 rectal toxicity, including rectal bleeding, pain or discomfort during bowel movements, diarrhea, and incontinence [15–20]. The occurrence of acute and late gastrointestinal and genitourinary complications can limit prescription dose escalation.

Image-guided radiotherapy (IGRT) is crucial in minimizing daily uncertainties in delivering the dose to the target and protecting adjacent OARs by matching patient setup with reference images [21–24]. In addition, the daily in-room imaging enables daily evaluation of delivered doses to the target three-dimensionally [25]. However, radiation-based in-room imaging techniques such as megavoltage (MV) or kilovoltage (kV) cone beam computed tomography (CBCT) or MV fan beam CT have limited image quality due to the physical principles of image acquisition and the need for real-time fast imaging or minimization of additional radiation dose associated with imaging [26]. Therefore, evaluating the patient’s dose, considering their daily internal condition, is mainly carried out by utilizing the high-quality simulation kVCT image that has been adjusted to align with the organ structure of the daily CT image [27]. In the last 10 years, three adaptive radiation therapy (ART) platforms—Ethos (Varian Medical Systems, Palo Alto, CA, USA), MRIdian (ViewRay Inc., Mountain View, CA, USA), and Unity (Elekta AB, Stockholm, Sweden)—have been introduced for clinical application. These platforms utilize onboard imaging-based deformable auto-segmentation of structure sets [28]. However, the accuracy of deformable image registration (DIR) depends on factors like the interface areas of deformation, the transformation framework (asymmetric or symmetric), the registration algorithm, and the mapping direction (forward or backward) [29]. Furthermore, auto-contouring based on DIR can lead to incorrect results in specific situations, such as image artifacts and substantial positional or volumetric changes in regions-of-interest (ROIs) [30]. As a result, manual adjustments might be necessary for these outcomes, potentially consuming a significant amount of time. Additionally, the implementation of online ART carries the risk of unintended modifications to the treatment plan, thereby increasing the demand for radiation oncologists to evaluate and approve plans in real-time [28].

Therefore, in practical terms, monitoring interfractional organ variations for individual patients by contouring ROIs directly on the low-quality daily CT images and notifying the medical staff if the degree of variation exceeds a certain tolerance can be an additional option for efficiently implementing ART within conventional RT platforms. However, manual delineation of the target and OARs on low-quality images can be prone to observer variability and too time-consuming to be repeated on each daily image in clinical practice, especially for institutions with limited manpower.

Recent studies have shown that artificial intelligence (AI)-driven technology can effectively reduce the workload in time-consuming, repetitive tasks [31–35]. In the clinical practice of RT planning, AI-based accurate OAR auto-contouring is crucial to establish an efficient workflow by standardizing contouring criteria while reducing workload. Several commercial solutions, such as Therapanacea Annotate (TheraPanacea, Paris, France), AccuContour (Manteia Technology, Xiamen, China), AI-Rad Companion (Siemens Healthineers, Erlangen, Germany), Contour ProtégéAI (MIM Software Inc., Cleveland, OH, USA), and OncoStudio (OncoSoft Inc., Seoul, South Korea), have been developed and globally distributed for AI-based auto-segmentation using planning CT (kV fan beam CT) without user interaction. Consequently, these advancements have brought about significant changes in the clinical workflow within the field of radiation therapy practice. In a recent study by Chung et al. [36], the clinical performance of AI-based auto-segmentation was evaluated using 180 abdominopelvic kVCT images. The dataset comprised a training set of 91.7% and a validation set of 8.3%, and the study involved the participation of ten radiation oncologists specializing in gynecologic cancer from six different institutions [36]. The findings indicated that medical staffs who were part of this project were predominately content (7 out of 10) with the AI-based auto-segmentation, which led to a reduction of 30 minutes in contouring time and an enhancement in consistency across institutions [36]. Nonetheless, the current commercial software options lack AI models for auto-segmentation on low-quality daily CT images. Among the various software available, the OncoStudio software has a feature that allows its user to train and test the AI model integrated into OncoStudio, utilizing user-defined datasets for research purposes.

We anticipate that an autonomous AI-driven system designed for the automated tracking and alerting of interfractional patient conditions will enhance treatment quality in institutions with limited manpower resources. If this AI-driven solution can (1) automatically segment low-quality daily CT images, (2) analyze the patient’s internal condition structurally based on the state depicted in the simulation kVCT image, and (3) notify the medical staff through messaging if the degree of variation exceeds the pre-defined tolerance, it may help to establish an efficient workflow to provide instructions for adaptive treatment planning. This study aimed to evaluate the feasibility of using a commercial AI-based solution to auto-segment MVCT images for interfractional monitoring of organ changes in RT for prostate cancer.

Materials and Methods

1. Preparation of MVCT dataset
We selected 100 prostate cancer patients who received RT using TomoTherapy system (Accuray Inc., Madison, WI, USA). During the
IGRT process, the MVCT images were acquired in a supine position. Patients were instructed to urinate for 1–1.5 hours before treatment. However, strict adherence to this protocol was not enforced. Additionally, no other bladder-filling training was provided. To ensure patient setup alignment with the reference kVCT image used for treatment planning, MVCT imaging was performed by aligning with the three-dimensional (3D) bony structure and subsequently adjusting the couch to the optimal position. The MVCT scan range was set from the sacral promontory level to the lower margin of the ischium and was partially adjusted based on the bladder volume. This scan range was maintained consistently for MVCT imaging six times during each patient’s RT course. The MVCT images were collected with a slice resolution of 6 mm in the scan direction, and 22–34 slices were obtained for each patient treatment, focusing on the bladder volume and its dose distribution, regardless of the total prescription dose. Two radiation oncologists manually contoured the body outline, the bladder including prostate area (Blad+Pros), and the rectal balloon on the MVCT images using the OncoStudio software. The prostate and bladder are quite challenging to distinguish, even in high-quality kVCT images, as they are closely adjacent and exhibit similar densities. Therefore, it is advantageous to delineate the prostate volume using magnetic resonance images fused with the simulation kVCT images during conventional RT planning. Consequently, the differentiation between the prostate and bladder in low-quality MVCT images becomes even more demanding. Our study aims to monitor relative changes in ROIs by reviewing daily CT images based on the patient's internal condition as depicted in the kVCT images. Therefore, we opted to review the combined prostate and bladder volumes for segmentation on the MVCT images to assess whether there are simultaneous meaningful relative changes in both volumes. When contouring the body outline, the segmentation by the image intensity (Hounsfield unit [HU]) threshold might be an option in the autonomous segmentation system. However, it sometimes encounters limitations unexpectedly due to image artifacts, increased noise levels, or the presence of a treatment table, immobilization devices, implants, etc. Therefore, we included the body outline as a target segmentation ROI. To train the AI model with appropriate hyperparameters (i.e., empirically determined settings through multiple trials), we analyzed and compared the image intensity distribution in each ROI on the MVCT image with that of the kVCT image using MIM Maestro version 7.1.4 software. Compared to kVCT images, using MVCT images for contouring ROIs can produce uncertain results among different observers [37]. To ensure consistency in contouring, the initial contouring was performed by one radiation oncologist without prior patient information, followed by a subsequent

![Fig. 1. Illustration of image fusion between the simulation kVCT and MVCT and comparison of the segmented regions of interest, namely, body outlines (blue line for kVCT and light blue line for MVCT), rectal balloon (yellow line for kVCT and brown line for MVCT), and Blad+Pros (pink line for kVCT and light pink line for MVCT). kVCT, kilovoltage computed tomography; MVCT, megavoltage computed tomography; Blad+Pros, bladder including prostate area.](https://doi.org/10.3857/roj.2023.00444)
review by another oncologist. Fig. 1 illustrates the image fusion process between the simulation kVCT image and MVCT images and a comparison of ROIs in the MIM software.

2. Training condition of a commercial AI model
The OncoStudio software is a commercially available AI-based auto-segmentation tool that enables automatic detection and segmentation of CT images without human intervention. The software employs a convolutional neural network (CNN) based on a U-Net structure combined with a 3D version of fully convolutional DenseNet (FC-DenseNet) as the backbone (Fig. 2) [38]. To input into the CNN, all cases were resampled to a voxel spacing of 2 mm in the x- and y-directions and randomly resampled in the z-direction to a voxel spacing between 1 mm and 5 mm, and the image intensity values (HU) were linearly normalized into the range of [0, 1], with a truncated range of [-200, 350]. Due to GPU memory limitations, the CNN was trained on a patch level with a 3D patch size of 256 × 256 × 16 from the volumetric CT images and output the 3D patch of multi-label segmentation. The CNN was trained using the sum of cross-entropy and dice loss, with an Adam optimizer [39] and an initial learning rate of 2 × 10^-4. Data augmentation techniques, such as randomized crop, random intensity shift by 70 HU, random zoom scaling by 0.2, and random blurring by 0.3, were employed during training to reduce overfitting and improve generalization. The AI model was trained on two 24 GB Quadro RTX A5000 GPUs (NVIDIA, Santa Clara, CA, USA). Out of a total of 100 MVCT and contoured datasets, 80 MVCT datasets were utilized for training, 10 datasets were allocated for validation, and another 10 datasets were reserved for independent testing. The above training condition was set empirically, showing the successful performance in MVCT segmentation.

3. Performance evaluation metrics
The dice similarity coefficient (DSC), which is the most commonly used metric for evaluating image segmentation, was used to compare the results of automatic segmentation using an AI model with manual segmentation during the training process. The DSC was calculated based on the overlap area between the predicted and ground truth regions, and a well-trained model would achieve a higher DSC score (i.e., Dice score), which is defined as follows:

\[
\text{Dice score} = \frac{2|A \cap B|}{|A| + |B|} = \frac{2TP}{2TP + FP + FN}.
\]

The overlap area between the predicted region A and the ground truth region B is multiplied by 2 and divided by the sum of regions A and B, which can also be defined using the true positive (TP), false positive (FP), true negative (TN), and false negative (FN) components of the confusion matrix. In general, in AI training, the loss is trained to decrease. Since a higher Dice score indicates better performance, the loss function is usually implemented using the formula below by taking the negative value of the Dice score. As the two regions become more similar, the Dice score approaches 1, and the Dice loss approaches 0, which can be interpreted as a well-trained model.

\[
\text{Dice loss} = 1 - \text{Dice score}.
\]

We utilized not only the Dice loss but also a dual cross-entropy loss [40] to expedite the optimization of the AI model during the training process in OncoStudio. As a result, the overall loss values shown in the AI model did not converge to 0 and exhibited negative values. When evaluating the precision of segmentation, the Hausdorff distance, which indicates the maximum distance differ-
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ence between two contour surfaces, is commonly used as an assessment metric. However, for this study, which aims to detect anomalies through tracking overall relative errors rather than local errors within the ROI, the mean surface distance (MSD), capable of showing how much, on average, the surface varies between two contour surfaces, was employed as the evaluation metric. The formula for calculating MSD is as follows:

\[
MSD = \frac{1}{n_S + n_{S'}} \left( \sum_{p \in S} d(p, S') + \sum_{p' \in S'} d(p', S) \right),
\]

where, \( S \) and \( S' \) represent the outer surfaces of two segmentations, \( d(p, S') \) denotes the distance between a point \( p \) on surface \( S \) and the surface \( S' \), which is calculated as the minimum of the Euclidean norm: \( \min_{p'} \| p - p' \|_2 \). Here, \( n_S \) and \( n_{S'} \) denote the number of points on the surface \( S \) and the surface \( S' \), respectively.

This study used the rigid registration function of MIM Maestro version 7.1.4 software to fuse kVCT and MVCT images based on bony structures rather than utilizing the real image alignment information used in each treatment session, as illustrated in Fig. 1. The ROIs, namely, body outline (blue lines), rectal balloon (brown lines), and Blad+Pros (pink lines) of the kVCT images, segmented during the RT planning process, served as a reference for analyzing changes in the centroid positions (x, y, and z in mm) and volumes (mL) of the ROIs within each MVCT image. Additionally, to evaluate the consistency of MVCT image quality, changes in the mean and median image intensities (HU) of each ROI were analyzed with reference to those assessed in the first MVCT image. During the comparative analysis of the body outline region, only the contours within the fused area with the MVCT images from the entire region of the kVCT image were used.

**Results**

1. Analysis of MVCT and kVCT images

The image intensity of a CT image refers to the level of brightness or darkness of a pixel in a CT image, which is determined by the amount of X-ray absorption by the tissues within the body. The areas of the body that absorb more X-rays appear brighter on the CT image, while areas that absorb fewer X-rays appear darker. The image intensity can be adjusted by changing the window width and window level, which are settings that control the range of pixel values displayed on the image. By adjusting these settings, specific tissues or structures of interest can be highlighted, and the visibility of subtle abnormalities can be improved.

The MVCT images were acquired using high-energy X-rays up to 3.5 MV \([41,42]\), which penetrate deeper into the body and are primarily used for imaging bony structures and implanted devices, while the kVCT images were acquired using kilovoltage X-rays up to 120 kVp, which are better suited for imaging soft tissue. Compared to kVCT images, MVCT images exhibit higher noise levels and lower contrast and spatial resolution. Fig. 3 illustrates the clear differentiation of bone, soft tissue, and cavity regions in kVCT images.

**Fig. 3.** Comparison of the image intensity histograms, plotted using Hounsfield unit (HU) value on the x-axis and the percentage of voxel counts on the y-axis, between body outline (blue line for kVCT and light blue line for MVCT) and rectal balloon (yellow line for kVCT and brown line for MVCT) volumes in kVCT and MVCT images for ten patients. kVCT, kilovoltage computed tomography; MVCT, megavoltage computed tomography.
leading to a sharp distribution of image intensity values (HU) within the contoured body outline and rectal balloon volumes. However, the distributions in MVCT images were relatively blunt. The HU distributions in the kVCT and MVCT images were analyzed using the “contour histogram” and “statistics for contour” functions implemented in MIM Maestro version 7.1.4 software. For the body outline volume, the HU distribution in the kVCT image showed two sharp peaks near -100 HU and 60 HU, respectively, within the range of -135 HU to 120 HU. In the MVCT image, however, two blunt peaks were formed near -70 HU and 50 HU, respectively, within the range of -200 HU to 350 HU. For the rectal balloon volume, the HU distribution in the kVCT image showed a sharp peak mostly centered at -995 HU, while the peak distribution was relatively wider and centered at -930 HU in the MVCT image. The mean HU ± standard deviation of the body outline volume for kVCT and MVCT images for 10 patients was 14.4 ± 176.8 and 10.7 ± 151.7, respectively, while the mean HU ± standard deviation for the rectal balloon volume was -825.5 ± 298.4 and -711.3 ± 291.3, respectively.

2. Training result of FC-DenseNet model

Fig. 4 shows the training result of the FC-DenseNet model implemented in the OncoStudio software, using 80 MVCT image sets of 80 patients and manually segmented datasets. As the Dice score approached 1, the loss value (the gold line) decreased exponentially. The loss gradually decreased and stabilized over time. By epoch 100, the validation set’s loss value had been reduced from the initial -4.55 to the final -4.80, confirming the effectiveness of the training. DSC and MSD metrics were employed to compare AI-generated auto-contours against manual contours for 10 test datasets to evaluate the AI model’s auto-segmentation performance in MIM Maestro version 7.1.4 software. As depicted in Fig. 5, the DSC and MSD scores for the body outline, rectal balloon, and Blad+Pros regions were all over 0.88 and within 1.43 mm, respectively. Specifically, for the body outline, the mean DSC value was measured at 0.992 ± 0.001 (min–max, 0.991–0.994), alongside the MSD value of 0.117 ± 0.022 mm (min–max, 0.088–0.171). Regarding the rectal balloon, the mean DSC value was observed at 0.967 ± 0.011 (min–max, 0.939–0.974), and, while the MSD value was recorded as 0.245 ± 0.176 mm (min–max, 0.150–0.737). For the Blad+Pros, the corresponding DSC values was 0.915 ± 0.021 (min–max, 0.887–0.961), while the associated MSD value was 0.932 ± 0.418 mm (min–max, 0.200–1.426).

When training FC-DenseNet without applying data augmentation techniques and using the same dataset, DSC and MSD metrics were evaluated on the same ten MVCT datasets for testing. As depicted in Fig. 6, in the absence of data augmentation, the minimum DSC values for body outline, rectal balloon, and Blad+Pros decreased to 0.83, while the maximum MSD increased to 6.31 mm. In detail, evaluating the AI-generated auto-contours against manual contours, the mean DSC values for the body outline was 0.994 ± 0.001 (min–max, 0.992–0.995), with the MSD value of 0.097 ± 0.023 mm (min–max, 0.069–0.149). The mean DSC value for the rectal balloon was 0.951 ± 0.044 (min–max, 0.828–0.971), with the MSD value of 0.871 ± 1.917 mm (min–max, 0.180–6.313). For Blad+Pros, the mean DSC value was 0.907 ± 0.023 (min–max, 0.877–0.940), with the MSD values of 1.173 ± 0.346 mm (min–max, 0.512–1.664).

3. Analysis of interfractional MVCT images

Fig. 7 compares six MVCT images acquired for IGRT of a randomly selected prostate cancer patient. In the simulation kVCT image of

![Fig. 4. The training outcome of the fully convolutional DenseNet (FC-DenseNet) model for MVCT auto-segmentation, depicting the fluctuating patterns of dice similarity coefficient for individual regions-of-interest and the overall loss value during 100 epochs of training. MVCT, mega-voltage computed tomography.](https://doi.org/10.3857/roj.2023.00444)
**Fig. 5.** Distributions of dice similarity coefficient (DSC) and mean surface distance (MSD) scores of the automatically segmented body outline (blue), rectal balloon (orange), and Blad+Pros (grey) regions in reference to the manually segmented reference regions-of-interest across ten test datasets. Blad+Pros, bladder including prostate area.

**Fig. 6.** Distributions of dice similarity coefficient (DSC) and mean surface distance (MSD) scores of the automatically segmented ROIs by AI model trained with and without dataset augmentation, namely, body outline (blue for AI model with augmentation, orange for AI model without augmentation), rectal balloon (grey for AI model with augmentation, yellow for AI model without augmentation), and Blad+Pros (royal blue for AI model with augmentation, green for AI model without augmentation), in reference to the manually segmented reference ROIs across 10 test datasets. Examples of the segmentation results on the MVCT image are shown above. AI, artificial intelligence; ROI, region-of-interest, MVCT, megavoltage computed tomography; Blad+Pros, bladder including prostate area.
Fig. 7. Comparison of MVCT images acquired at different time points during treatment sessions and the simulation kVCT image overlaid with contours segmented on six MVCT images. kVCT, kilovoltage computed tomography; MVCT, megavoltage computed tomography.
Fig. 7, all ROIs segmented from six MVCT images are overlaid, allowing for a rough observation of the patient’s internal structural changes. To quantitatively compare and analyze these changes, as shown in Figs. 8–10, the DSC, MSD, centroid differences, and volume differences were analyzed in the six MVCT images based on the ROIs in the kVCT image. For the body outline, the DSC was above 0.97, MSD was within a maximum of 2.48 mm, and the centroid differences were all within 1.20 mm along the x, y, and z axes, indicating good agreement. However, in terms of volume, differences of up to 460 mL were observed in the last MVCT image. For the rectal balloon, the mean DSC was 0.81 ± 0.06 (min–max, 0.75–0.89), the mean MSD was 2.83 ± 1.09 mm (min–max, 1.40–4.05), and centroid differences were within 2.10 mm along the x-axis (with a mean of 1.03 ± 0.56 mm), 7.60 mm along the y-axis (with a mean of 4.72 ± 2.31 mm), and 8.60 mm along the z-axis (with a mean of 1.13 ± 3.98 mm). Volume differences of up to 48 mL (with a mean of 17.96 ± 16.61 mL) were observed for the rectal balloon. For the Blad+Pros region, the mean DSC was 0.75 ± 0.11 (min–max, 0.55–0.87), the mean MSD was 4.56 ± 2.93 mm (min–max, 2.02–10.04), and centroid differences were within 1.30

Fig. 8. Distribution of dice similarity coefficient (DSC) and mean surface distance (MSD) scores for the body outline (blue), rectal balloon (orange), and Blad+Pros (grey) regions segmented on the six MVCT images, assessed in reference to the regions-of-interest segmented on the simulation kVCT image. kVCT, kilovoltage computed tomography; MVCT, megavoltage computed tomography; Blad+Pros, bladder including prostate area.

Fig. 9. Distribution of centroid differences—x (blue), y (orange), and z (grey) in mm—for the body outline, rectal balloon, and Blad+Pros regions segmented on the six MVCT images, assessed in reference to the regions-of-interest segmented on the simulation kVCT image. kVCT, kilovoltage computed tomography; MVCT, megavoltage computed tomography; Blad+Pros, bladder including prostate area.

Fig. 10. Distribution of volume (mL) differences for the body outline (blue), rectal balloon (orange), and Blad+Pros (grey) regions segmented on the six MVCT images, assessed in reference to the regions-of-interest segmented on the simulation kVCT image. kVCT, kilovoltage computed tomography; MVCT, megavoltage computed tomography; Blad+Pros, bladder including prostate area.
mm along the x-axis (with a mean of 0.08 ± 0.80 mm), 3.30 mm along the y-axis (with a mean of 0.30 ± 1.76 mm), and 14.80 mm along the z-axis (with a mean of 6.63 ± 5.49 mm). Volume differences of up to 208 mL (with a mean of 74.01 ± 76.14 mL) were observed for the Blad+Pros region. The intensity (HU) of MVCT images was quantitatively analyzed for variations in the remaining five MVCT images based on the initial MVCT image, as depicted in Fig. 11. For the body outline and Blad+Pros regions, the mean HU differences were within 8.04 ± 5.26 HU and 9.51 ± 6.17 HU, respectively, and the median HU differences were within 8.00 ± 5.35 HU and 6.00 ± 4.18 HU, respectively, indicating no significant observed changes. However, the average and median HU differences were relatively largely fluctuated for the rectal balloon, within 90.36 ± 34.92 HU and 110.00 ± 42.82 HU, respectively.

**Discussion and Conclusion**

This study aimed to assess the feasibility of commercial software in establishing a system that can track interfractional patient organ changes using low-quality MVCT images, possibly enabling ART efficiently. This is particularly important in terms of cost-effectiveness. This research evaluated the feasibility of utilizing the AI model in OncoStudio for the automated segmentation of ROIs in low-quality MVCT images.

To ensure stable auto-segmentation performance during the training of the FC-DenseNet model in OncoStudio, we established a successful training condition through trial and error. These included factors such as dataset composition and quantity, voxel spacing, 3D patch size, data augmentation conditions, image intensity (HU) range, and learning rate. DenseNet, which connects all layers densely using dense connectivity patterns, has been known for its remarkable performance and low computational requirements compared to other architectures. In the training process of this model, growth rate and model depth were set to 16 and 5, respectively, corresponding to the settings used for training the auto-segmentation model on the kVCT image in the OncoStudio. While we initially trained the model on 259 datasets from 23 patients, we found that increasing the number of patients significantly impacted model performance. To achieve stable results, we determined that a minimum of 100 patients was required. However, due to data limitations, 80 patients were used for training, 10 for validation, and 10 for testing, and it was ensured that the images used for training and validation were not utilized in testing.

For the voxel spacing in the training process, while the initial training was performed with a fixed z-axis spacing of 3 mm, 1 mm-interval random sampling of 1–5 mm spacing was determined for more precise training considering variations in MVCT scan slice thickness (2–6 mm) and the complex 3D volume structure. In this case, when the 3D patch size was set to 384 × 384 × 16 under the condition of a 2 × 2 × 3 mm³ resolution, the training speed decreased and memory usage increased, but there was not a significant impact on segmentation performance. Therefore, the training process was conducted with a 3D patch size of 256 × 256 × 16, which allowed it to encompass the entire body region. To augment the dataset, factors such as variations in image quality such as image intensity (HU) distribution and noise level that affect image sharpness and blurring, and organ size due to patient anatomy were taken into account to determine the contrast range (HU), the random intensity (HU) shift, the random zoom scaling, and the random blurring. The learning rate should be set to a suitable value to ensure stable training with increased epochs. Through trial and error, it was found that a learning rate of around 2 × 10⁻⁴ was appropriate to prevent sudden increases in loss and convergence to zero DSC values during training. By optimizing the training conditions through these processes, the AI model produced outcomes that closely matched those obtained through manual segmentation, as depicted in Fig. 5. Data augmentation is crucial to ensure the stability of the model performance due to the lower image quality of MVCT images compared to kVCT images. A larger dataset comprising more than 100 patients is necessary to achieve further improvements beyond the developed model. This expansion is anticipated to potentially raise overall DSC above 0.9 and maintain MSD within 1 mm.

We observed slight changes (up to 9.51 HU) in the image intensities (HU) of the six MVCT images, as depicted in Fig. 11, with the

![Image intensity differences (HU)](image-url)
exception of the rectal balloon. These changes are expected to have a minimal impact on auto-segmentation performance due to the application of random HU shifts (within a range of 70 HU) during data augmentation. However, in the case of the rectal balloon, the blurred image quality at the boundary between the rectal wall area and the air layer can result in variations in the proportion of tissue invasion within the segmented ROI. As previously reported in the literature [37], determining the ROI boundaries is highly uncertain due to the poor image quality of MVCT images. The uncertainty can be further pronounced when the rectum is filled with gas due to physiological phenomena. This is a limitation inherent in the auto-segmentation of low-quality MVCT images.

In a previous study by Shelley et al. [43], an auto-segmentation model for the rectum in MVCT images of prostate cancer patients was developed. This model was based on the Chan-Vese algorithm and implemented in MATLAB. They trained the model using 26 MVCT images from 10 prostate cancer patients and validated it with 30 additional MVCT images. The performance of this model resulted in a DSC of approximately 0.78 when comparing auto-Contours against manual contours. Although the rectum’s structure is more intricate than the ROIs utilized in this study, making direct comparison challenging, our results demonstrated the superior performance of the auto-segmentation model (FC-DenseNet) regarding the DSC score, achieving a DSC score above 0.88 for the Blad+Pros region.

While monitoring the patient's internal condition through six MVCT scans, the DSC values for both the rectal balloon and Blad+Pros regions scored below 0.9. The MSD values were up to 4 mm and 10 mm, respectively, indicating significant variations in the shape and volume of the ROIs. Additionally, disparities in centroid positions were noted, with the rectal balloon and Blad+Pros areas showing differences of up to 8.6 mm and 14.8 mm along the z-axis, respectively. The presence of gas in the patient's rectum due to physiological factors could contribute to an increased segmentation volume in the superior direction of the rectal balloon. Similarly, variations in bladder filling could lead to notable changes in the superior direction of the Blad+Pros region. In clinical practice, online image registration for IGRT primarily focuses on aligning with the positions of the prostate and rectal balloon, particularly in regions receiving the highest radiation doses. This approach contrasts with the rigid registration outcomes between MVCT and kVCT based on bony structures, as employed in this study using MIM software. Given these considerations, the variations observed in the y- and z-axes direction of the rectal balloon in this study could be relatively reduced during actual treatment scenarios. However, even if rectal balloon position variations were minimized, whole-body centroid shifts would still occur, which might necessitate the conventional DIR-based approach for patient dose estimation if we are concerned.

The changes in bladder volume and abdominal body volume vary from patient to patient due to individual conditions. Factors like meals, fluid intake, and timing of urination are quite challenging to control, especially in elderly patients. This study observed trends where the body outline and Blad+Pros volumes changed by up to 460 mL and 208 mL, respectively. However, at present, determining the threshold for adaptive planning based on these changes remains difficult. Therefore, accumulating patient tracking data for a larger patient population and statistically analyzing the impact of varying degrees of changes in each ROI on the patient’s internal dose distribution is required further. This will help determine levels of risk for significant changes, requiring the medical staff's confirmation, in MSD, centroid position, and volume.

In conclusion, we have verified the feasibility of utilizing a commercial AI-based model for auto-segmentation with low-quality daily MVCT images. Additionally, this approach facilitates effective interfractional tracking of organ changes during RT. Our future objective is to establish an automatic system capable of swiftly and accurately segmenting all ROIs within the daily MVCT images. Moreover, if any segmentation errors are identified, we aim to rectify them within a 5-minute.

Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board of Yonsei University Wonju College of Medicine (IRB No. CR323049). Given that this study utilized previously acquired tomographic images to develop an AI model to improve the radiotherapy quality, written informed consent from individual participants was not required as all data used were anonymized. The study procedures were conducted in accordance with the ethical standards outlined in the Declaration of Helsinki.

Conflict of Interest

The authors declare that they have no financial conflicts of interest related to this work. However, they acknowledge that they have used the OncoStudio software in this study and have provided feedback to the software developers in the past.

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**Author Contributions**

Conceptualization, Choi HJ, You SH. Investigation, Lee Y, Kim H. Formal analysis, Eum YJ, You SH. Writing of the original draft, Lee Y, Choi HJ. Writing of the review and editing, Kim S, Kim MS, Cha H, You SH.

**Data Availability Statement**

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

**References**


Outcome of dose-escalated intensity-modulated radiotherapy for limited disease small cell lung cancer

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Purpose: An optimal once-daily radiotherapy (RT) regimen is under investigation for definitive concurrent chemoradiotherapy (CCRT) in limited disease small cell lung cancer (LD-SCLC). We compared the efficacy and safety of dose escalation with intensity-modulated radiotherapy (IMRT).

Materials and Methods: Between January 2016 and March 2021, patients treated with definitive CCRT for LD-SCLC with IMRT were retrospectively reviewed. Patients who received a total dose <50 Gy or those with a history of thoracic RT or surgery were excluded. The patients were divided into two groups (standard and dose-escalated) based on the total biologically effective dose (BED, α/β = 10) of 70 Gy. The chemotherapeutic regimen comprised four cycles of etoposide and cisplatin.

Results: One hundred and twenty-two patients were analyzed and the median follow-up was 27.8 months (range, 4.4 to 76.9 months). The median age of the patients was 63 years (range, 35 to 78 years) and the majority had a history of smoking (86.0%). The 1- and 3-year overall survival rates of the escalated dose group were significantly higher than those of the standard group (93.5% and 50.5% vs. 76.7% and 33.3%, respectively; p = 0.008), as were the 1- and 3-year freedom from in-field failure rates (91.4% and 66.5% vs. 73.8% and 46.9%, respectively; p = 0.018). The incidence of grade 2 or higher acute and late pneumonitis was not significantly different between the two groups (p = 0.062, 0.185).

Conclusion: Dose-escalated once-daily CCRT with IMRT led to improved locoregional control and survival, with no increase in toxicity.

Keywords: Small cell lung carcinoma, Limited disease, Radiotherapy, Radiotherapy dosage, Intensity-modulated radiotherapy

Introduction

Small cell lung cancer (SCLC) is a rapidly progressive cancer if not controlled with appropriate intervention [1]. Only one-third of patients with SCLC are diagnosed with limited disease that can be encompassed within the radiotherapy (RT) field [2]. Given that SCLC is a relatively radiosensitive tumor [3] and the number of surgical candidates for very early-stage SCLC is small, RT is the main local treatment modality. Based on the Japan Clinical Oncology Group study 9104 [4], National Cancer Institute of Canada Clinical Trials Group data [5], and Yugoslavia data [6], concurrent chemoradiotherapy (CCRT) is the standard of care for limited disease small cell lung cancer (LD-SCLC) to improve survival.

The prescribed RT dose for SCLC has traditionally been lower
than that for non-small-cell lung cancer due to the difference in radiosensitivity between the two tumor types [3]. However, recent studies have trialed modified schedule or escalated-dose RT to overcome locoregional recurrences after conventional-fractionated CCRT. The Intergroup 0096 study demonstrated that patients treated with a 45 Gy/30 fractions twice-daily schedule showed longer overall survival (OS) compared to those treated with 45 Gy/25 fractions once-daily [7], while the CONVERT [8] and CALGB 30610 [9] trials showed a similar OS in the 45 Gy/30 fractions twice-daily group compared to the conventional RT group. Despite the accelerated RT schedule showing improved survival [7], it also increased treatment-related toxicities and deteriorated the patients’ quality of life [7,8,10].

Conventional RT remains the standard scheme for LD-SCLC in many institutions [11] because two hospital visits per day tends to reduce patient compliance. Therefore, in our institution, we escalated the total dose but maintained a single daily dose of curative intent CCRT in patients with LD-SCLC. We analyzed the clinical outcomes of the patients with the aim to prove the efficacy of dose escalation.

Materials and Methods

1. Patients (study population)

We retrospectively reviewed patients with LD-SCLC who were treated with RT from January 2016 to March 2021 at our institution. Patients who were initially diagnosed, pathologically confirmed, treated with definitive aim CCRT with intensity-modulated radiotherapy (IMRT), and irradiated with a total dose of ≥ 50 Gy were included. Patients who had no follow-up chest computed tomography (CT) after treatment, a history of other malignancy in the 2 years prior to SCLC diagnosis, and experience of RT or surgery in the thoracic cavity were excluded (Fig. 1). This study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2023-0815). Informed consent was waived based on the retrospective nature of this study.

2. Treatment

1) Radiotherapy

Four-dimensional CT simulation was performed as the standard protocol, and the gross tumor volume (GTV) was delineated in the most expiratory phase. For patients who underwent induction chemotherapy, post-chemotherapy tumors, including all initial tumor sites, were delineated as the GTV. The clinical target volume (CTV) was delineated to cover the adjacent nodal area or ambiguous tumor margin in 48 patients (39.3%). The internal target volume (ITV) was added to the GTV or CTV to allow for respiratory tumor motion. The planning target volume (PTV) was expanded 3–7 mm from the ITV. All treatment was planned using IMRT with a total dose in the range of 50–66 Gy and conventional fractionation. Thereafter, the biological equivalent dose (BED) was calculated using the linear quadratic formula [12] to equally compare different treatments with different radiation doses per session using an α/β of 10. To evaluate the radiation dose irradiated to normal organs, the maximum dose, mean dose irradiated to each organ and Vx were measured, where Vx refers to the volume of the area irradiated more than x Gy. All patients were treated with image-guided radiotherapy (IGRT) with cone-beam CT conducted at least once a week. Using IGRT, the early response of tumor could be checked during treatment period, which allowed for adjustments to the treatment plan to reduce the treatment volume, as well as the normal organ radiation dose (e.g., lungs, esophagus, and heart).

2) Chemotherapy

The standard chemotherapy regimen included four cycles of platinum-based combination treatment as follows: etoposide 100 mg/m²/day over 3 hours on days 1–3, cisplatin 70 mg/m² over 1 hour on day 1, and carboplatin at an area under the concentration–time curve of 5 over 1 hour on day 1. Chemotherapy was administered after the evaluation of hematologic toxicity and performance status by clinicians every 3 weeks. Two patients switched etoposide with irinotecan due to toxicity (irinotecan 65 mg/m²/day over 90 minutes on days 1 and 8). A total of 103 patients (84.4%) were administered 1–2 cycles of induction chemotherapy before CCRT due to old age, bulky tumor, or prompt start of treatment.

3. Evaluation after treatment and toxicities

Following completion of CCRT, chest CT was performed 1 month later, followed by every 3 months for the evaluation of treatment response and surveillance of disease progression for the first 2
years, and every 6 months until 5 years. The maximum treatment response after definitive CCRT was decided by clinicians with the aid of chest CT and fluorodeoxyglucose positron emission tomography-CT if deemed necessary. In cases without radiation-induced pneumonitis, a complete response was defined as disappearance of the primary lesion or no obvious metabolic hyperactivity. A partial response required ≥ 30% decrease in the sum of the longest diameters (SLD) of target lesions. Between complete response and partial response, near complete response was considered in cases with ambiguous chest CT imaging; for example, radiation pneumonitis obscuring the total primary lesion with a minimal residual solid part with unclear metabolic activity. A progressive disease required ≥ 20% increase in the SLD and stable disease was defined as being neither partial response nor progressive disease.

Brain magnetic resonance imaging was performed at the time of initial diagnosis. Prophylactic cranial irradiation (PCI) was considered for patients without brain metastasis and with a partial or complete disease response after thoracic CCRT. PCI was selectively administered according to age, performance, and patient preference.

Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. [13] After the completion of RT, RT-associated toxicity was graded as acute when it occurred within 3 months, and as late when it occurred after 3 months.

4. Statistical analysis
Locoregional failure (LRF) was defined as tumor recurrence in the ipsilateral hemithorax and regional lymph node(s) and was subdivided into in-RT-field failure (IFF) and out-RT-field failure (OFF). Between the date of IFF and OFF, the LRF date was recorded as the earlier. Freedom from IFF (FFIFF), freedom from OFF (FFOFF), freedom from LRF (FFLRF), and freedom from distant metastasis (FFDM) were calculated from the date of diagnosis to the date of failure or the last follow-up (the date of the most recent cancer-associated clinical visit).

The disease progression date was recorded as the earliest date of any recurrence or the date of death in patients without recurrence. The survival status of the patients and the date of death were obtained through the national health insurance database. For the patients who died, the date of death was obtained and for the patients who remained alive, May 31, 2023, was recorded as the date of death. Additionally, progression-free survival (PFS) and OS were calculated from the date of diagnosis to the date of disease progression and death, respectively.

The Pearson chi-square test and independent sample t-test were used to compare the characteristics of patients in both groups. The Kaplan–Meier method was used to analyze the survival outcomes, and log-rank tests were used to evaluate the statistical significance between two groups. Clinical and therapeutic factors that may affect IFF and OS were analyzed, including factors that were significantly different between the two groups, using the Cox proportional hazard model in univariate analysis. Thereafter, multivariate analysis was performed using the backward elimination method in the Cox proportional hazard model including the factors with p-value < 0.1 in univariate analysis or clinicians thought might be affecting each survival outcomes. Decided at clinician’s discretion, the overall stage was additionally included in the FFIFF analysis, and overall stage and whether PCI was performed were included in the OS analysis. A p-value < 0.05 was considered statistically significant. SPSS version 21 (IBM, Armonk, NY, USA) was used for all statistical analyses.

Results
1. Patient and disease characteristics
A total of 122 patients were analyzed, with a median follow-up period of 27.8 months (range, 4.4 to 76.9) (Table 1). The median age of the patients was 63 years (range, 35 to 78 years) and the majority of patients were male (104 patients, 85.2%), and had a history of smoking (105 patients, 86.0%). A total of 109 patients (89.3%) had a primary tumor of ≤ 7 cm and 114 patients (93.4%) had nodal metastasis. Only two patients had stage I disease according to the 8th staging system of American Joint Committee on Cancer (AJCC) [14] and all the patients had LD according to the International Association for the Study of Lung Cancer recommendation [15].

The patients were divided into a standard group, irradiated with a total dose of < BED10 70 Gy (median 63.5 Gy; range, 60.0 to 68.6 Gy) and a dose-escalated group, irradiated with a total dose of ≥ BED10 70 Gy (median 73.7 Gy; range, 71.1 to 80.5 Gy). In the standard group, 53 patients (88.3%) had stage III compared to 40 patients (64.5%) in the dose-escalated group (p = 0.005). Additionally, the standard group showed a tendency toward higher nodal stage (p = 0.053), but there was no significant difference in forced vital capacity, forced expiratory volume in one second, and underlying interstitial lung disease or chronic obstructive pulmonary disease between the two groups. The diffusing capacity of the lung for carbon monoxide (DLCO) was better in the dose-escalated group (p = 0.011).

A total of 103 patients (84.4%) were treated with induction chemotherapy and 45 patients (36.9%) underwent PCI after definitive CCRT for thoracic disease (Table 2). Forty-eight patients (39.3%) had CTV for thoracic RT, including 25 (41.7%) in the standard group.
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and 23 (37.1%) in the dose-escalated group. The median PIV was 292.2 mL (range, 39.5 to 742.3 mL) and 190.8 mL (range, 77.7 to 801.0 mL) in the standard and dose-escalated groups, respectively (p = 0.005).

2. Treatment outcomes

The median OS was 23.1 months (95% confidence interval [CI], 17.2–29.0) months and 38.7 months (95% CI, 28.4–49.0) in the standard and dose-escalated groups, respectively, with 1- and 3-year OS rates of 76.7% and 33.3% and 93.5% and 50.5%, respectively (p = 0.008) (Fig. 2). Fig. 3A–3E shows the Kaplan–Meier method survival curves of FFLRF, FFIFF, FFOFF, FFDM, and PFS, respectively. The median FFIFF was unreached in the dose-escalated group, but showed a significant difference compared to that of the standard group at 1 and 3 years (standard group 73.8% and 46.9% vs. dose-escalated group 91.4% and 66.5%, respectively; p = 0.018).

Moreover, the 3-year FFLRF was 40.5% and 52.8% in the standard and dose-escalated groups (p = 0.028), while the 3-year FFDM was 28.4% and 50.6%, respectively (p = 0.034). None of the patients showed disease progression immediately after CCRT, and objective response ratio was 97.5% (n = 119) (Table 3).
of RT field recurrence or distant metastasis. The most frequent failure pattern contained distant metastasis in both groups.

4. Acute and late toxicities
Among all patients, 26 (21.3%) showed grade 2 or higher acute radiation pneumonitis and 28 (23.0%) showed grade 2 or higher acute radiation-induced esophagitis. Grade 2 or higher acute esophagitis occurred in 19 patients (31.7%) in the standard group and nine patients (14.5%) in the dose-increase group, showing a statistically significant difference between the two groups (p = 0.024) (Table 5). Grade 2 or higher late radiation pneumonitis or fibrosis was identified in 19 patients (15.6%) of all patients and only one patient suffered from grade 2 late esophagitis. None of the patients presented with grade 4 or 5 toxicity. Additionally, V₅, V₁₀, V₂₀ of the lungs and mean dose of the heart were lower in the dose escalated group with statistically significant difference (Supplementary Table S1).

5. Prognostic factors
In univariate analysis for FFIFF, DLCO, CCRT regimen including cisplatin, and BED₁₀ ≥ 70 Gy showed a significant favorable correlation. But in multivariate analysis only DLCO, and the CCRT regimen showed statistical significance with a hazard ratio (HR) of 0.980 (95% CI, 0.962–0.999; p = 0.036) and 0.502 (95% CI, 0.270–0.932; p = 0.029), respectively (Table 6). BED₁₀ ≥ 70 Gy showed favorable tendency but was not statistically significant (HR = 0.566; 95% CI, 0.311–1.028; p = 0.062). For OS, in multivariate analysis, the CCRT regimen remained statistically significant, with a HR of 0.498 (95% CI, 0.314–0.790; p = 0.003) and also BED₁₀ ≥ 70 Gy showed a significant favorable correlation with a HR of 0.620 (95% CI, 0.392–0.981; p = 0.041) (Table 7).

Discussion and Conclusion
Our study showed improved local control in the RT field, with a 1-year FFIFF of 91.4% in the dose-escalated group compared to the standard group. Additionally, for FFIFF, BED₁₀ ≥ 70 Gy showed a favorable correlation in univariate analysis and was marginally significant in multivariate analysis. Furthermore, the dose-escalated group showed improved OS, with a median OS of 23.1 months and 38.7 months in the standard and dose-escalated groups, respectively. Therefore, we consider the possibility that improvement in

<table>
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<tr>
<th>Treatment</th>
<th>Standard dose (n = 60)</th>
<th>Escalated dose (n = 62)</th>
<th>p-value</th>
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<tr>
<td>Etoposide/cisplatin</td>
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<td>Treatment volume</td>
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<tr>
<td>GTV (mL)</td>
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<td>PTV (mL)</td>
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<td>RT regimen</td>
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<td>RT dose (Gy)</td>
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<td>RT duration (day)</td>
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<td>46 (38–65)</td>
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<td>PCI, yes</td>
<td>22 (36.7)</td>
<td>23 (37.1)</td>
<td>0.961</td>
</tr>
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</table>

Values are presented as number (%) or median (range).
CCRT, concurrent chemoradiation therapy; GTV, gross tumor volume; PTV, planning target volume; RT, radiotherapy; PCI, prophylactic cranial irradiation.

Fig. 2. Overall survival.
Fig. 3. Other survival outcomes: (A) freedom from locoregional failure, (B) freedom from in-field failure, (C) freedom from out-of-field failure, (D) freedom from distant metastasis, (E) progression-free survival. BED, biologically equivalent dose.

**Panel A**
- **Freedom from locoregional failure (%)**
- **Number at risk:**
  - 62: 46, 28, 17, 10, 6
  - 60: 32, 16, 14, 12, 7
- **Time (mo):** 0, 12, 24, 36, 48, 60
- **p = 0.028**

**Panel B**
- **Freedom from in-field failure (%)**
- **Number at risk:**
  - 62: 51, 31, 21, 12, 6
  - 60: 35, 17, 15, 12, 7
- **Time (mo):** 0, 12, 24, 36, 48, 60
- **p = 0.018**

**Panel C**
- **Freedom from out-of-field failure (%)**
- **Number at risk:**
  - 62: 46, 30, 17, 10, 6
  - 60: 33, 21, 16, 12, 7
- **Time (mo):** 0, 12, 24, 36, 48, 60
- **p = 0.137**

**Panel D**
- **Freedom from distant metastasis (%)**
- **Number at risk:**
  - 62: 39, 31, 19, 10, 6
  - 60: 26, 17, 14, 10, 7
- **Time (mo):** 0, 12, 24, 36, 48, 60
- **p = 0.034**

**Panel E**
- **Progression-free survival (%)**
- **Number at risk:**
  - 62: 34, 24, 15, 11, 7
  - 60: 24, 13, 12, 12, 9
- **Time (mo):** 0, 12, 24, 36, 48, 60
- **p = 0.083**
High-dose IMRT for limited disease SCLC

Several retrospective and prospective studies have compared 45 Gy/30 fractions twice-daily with various once-daily regimens with a total dose of 45–70 Gy [7-10,16,17]. Although comparing survival rates between studies warrants caution, the median OS of the dose-escalated group in our study was not inferior to that of 45 Gy/30 fractions twice-daily groups in other studies, ranging from 23.0 to 31.4 months [7-10,16,17]. In the CONVERT [8] trial in 2017, the median OS of the 45 Gy twice-daily group was 30 months compared to 25 months in the 66 Gy once-daily group (p = 0.14). Moreover, the CALGB 30610 [9] trial presented in 2023 reported a median OS of 28.5 months and 30.1 months in the 45 Gy twice-dail-

Table 3. Treatment response

<table>
<thead>
<tr>
<th></th>
<th>Standard dose (n = 60)</th>
<th>Escalated dose (n = 62)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>2 (3.3)</td>
<td>2 (3.2)</td>
<td>0.903</td>
</tr>
<tr>
<td>Near complete response</td>
<td>7 (11.7)</td>
<td>6 (9.7)</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>49 (81.7)</td>
<td>53 (85.5)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>2 (3.3)</td>
<td>1 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%).
The p-value was calculated for the distribution of the five response categorical variables with Fisher’s exact test.

Table 4. Initial patterns of failure according to the RT field

<table>
<thead>
<tr>
<th></th>
<th>Standard dose (n = 60)</th>
<th>Escalated dose (n = 62)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No recurrence</td>
<td>16 (26.7)</td>
<td>23 (37.1)</td>
<td>0.086</td>
</tr>
<tr>
<td>Locoregional recurrence</td>
<td>8 (13.3)</td>
<td>1 (1.6)</td>
<td>0.025</td>
</tr>
<tr>
<td>Isolated in-RT field</td>
<td>3 (5.0)</td>
<td>6 (9.7)</td>
<td>0.430</td>
</tr>
<tr>
<td>Isolated out-of-RT field</td>
<td>3 (5.0)</td>
<td>6 (9.7)</td>
<td>0.481</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>18 (30.0)</td>
<td>22 (35.5)</td>
<td>0.762</td>
</tr>
<tr>
<td>Combined with locoregional</td>
<td>12 (20.0)</td>
<td>4 (6.4)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Values are presented as number (%).
RT, radiotherapy.

Table 5. Acute and late toxicities using CTCAE v5.0

<table>
<thead>
<tr>
<th></th>
<th>Standard dose (n = 60)</th>
<th>Escalated dose (n = 62)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Pneumonitis</td>
<td></td>
<td></td>
<td>0.062</td>
</tr>
<tr>
<td>Grade 1</td>
<td>18 (30.0)</td>
<td>21 (33.9)</td>
<td></td>
</tr>
<tr>
<td>Grade 2–3</td>
<td>17 (28.3)</td>
<td>9 (14.5)</td>
<td></td>
</tr>
<tr>
<td>Esophagitis</td>
<td></td>
<td></td>
<td>0.024</td>
</tr>
<tr>
<td>Grade 1</td>
<td>7 (11.7)</td>
<td>13 (21.0)</td>
<td></td>
</tr>
<tr>
<td>Grade 2–3</td>
<td>19 (31.7)</td>
<td>9 (14.5)</td>
<td></td>
</tr>
<tr>
<td>Late Pneumonitis/fibrosis</td>
<td></td>
<td></td>
<td>0.185</td>
</tr>
<tr>
<td>Grade 1</td>
<td>19 (31.7)</td>
<td>29 (46.8)</td>
<td></td>
</tr>
<tr>
<td>Grade 2–3</td>
<td>12 (20.0)</td>
<td>7 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Esophagitis</td>
<td></td>
<td></td>
<td>0.492</td>
</tr>
<tr>
<td>Grade 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2–3</td>
<td>1 (1.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Table 6. Univariate and multivariate analysis for freedom from in-field failure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th></th>
<th>Multivariate#</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Age, ≥ 70 yr</td>
<td>1.031 (0.462–2.300)</td>
<td>0.941</td>
<td>-</td>
</tr>
<tr>
<td>Sex, female</td>
<td>0.851 (0.382–1.888)</td>
<td>0.693</td>
<td>-</td>
</tr>
<tr>
<td>ECOG performance status, ≥ 1</td>
<td>3.113 (0.967–10.021)</td>
<td>0.057</td>
<td>2.954 (0.910–9.594)</td>
</tr>
<tr>
<td>Smoking, smoker</td>
<td>0.949 (0.534–1.687)</td>
<td>0.859</td>
<td>-</td>
</tr>
<tr>
<td>Chronic lung disease, yes</td>
<td>1.942 (0.988–3.817)</td>
<td>0.054</td>
<td>-</td>
</tr>
<tr>
<td>DLCO, continuous value</td>
<td>0.978 (0.960–0.996)</td>
<td>0.019</td>
<td>0.980 (0.962–0.999)</td>
</tr>
<tr>
<td>T stage, 3–4</td>
<td>1.214 (0.686–2.146)</td>
<td>0.506</td>
<td>-</td>
</tr>
<tr>
<td>N stage, 3</td>
<td>1.578 (0.817–3.050)</td>
<td>0.174</td>
<td>-</td>
</tr>
<tr>
<td>Overall stage, III</td>
<td>1.777 (0.859–3.674)</td>
<td>0.121</td>
<td>-</td>
</tr>
<tr>
<td>Induction CTx, yes</td>
<td>2.528 (0.907–7.041)</td>
<td>0.076</td>
<td>-</td>
</tr>
<tr>
<td>CCRT regimen, etoposide with cisplatin</td>
<td>0.511 (0.284–0.920)</td>
<td>0.025</td>
<td>0.502 (0.270–0.932)</td>
</tr>
<tr>
<td>PTV, continuous value</td>
<td>1.001 (1.000–1.003)</td>
<td>0.098</td>
<td>-</td>
</tr>
<tr>
<td>BED$_{10} ≥ $70</td>
<td>0.506 (0.284–0.900)</td>
<td>0.020</td>
<td>0.566 (0.311–1.028)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; DLCO, carbon monoxide diffusion capacity; CTx, chemotherapy; CCRT, concurrent chemoradiation therapy; PTV, planning target volume; BED, biologically equivalent dose; HR, hazard ratio; CI, confidence interval.
#Multivariate analysis was performed using the backward elimination method in the Cox proportional hazard model.

https://doi.org/10.3857/roj.2023.00591
Table 7. Univariate and Multivariate Analysis for Overall Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate HR (95% CI)</th>
<th>p-value</th>
<th>Multivariate$^{a}$ HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, ≥ 70 yr</td>
<td>1.631 (0.926–2.870)</td>
<td>0.090</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Sex, female</td>
<td>0.751 (0.386–1.459)</td>
<td>0.398</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>ECOG performance status, ≥ 1</td>
<td>0.703 (0.405–1.222)</td>
<td>0.211</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Smoking, smoker</td>
<td>1.103 (0.697–1.744)</td>
<td>0.676</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Chronic lung disease, yes</td>
<td>1.535 (0.885–2.663)</td>
<td>0.127</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>DLOC, continuous value</td>
<td>0.987 (0.971–1.003)</td>
<td>0.122</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>T stage, 3–4</td>
<td>1.595 (1.016–2.509)</td>
<td>0.042</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>N stage, 3</td>
<td>1.417 (0.848–2.367)</td>
<td>0.183</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Overall stage, III</td>
<td>1.599 (0.908–2.814)</td>
<td>0.104</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>GTV, continuous value</td>
<td>1.003 (1.000–1.006)</td>
<td>0.042</td>
<td>1.003 (1.000–1.006)</td>
<td>0.074</td>
</tr>
<tr>
<td>PTV, continuous value</td>
<td>1.001 (1.000–1.002)</td>
<td>0.035</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Induction CTx, yes</td>
<td>1.130 (0.597–2.141)</td>
<td>0.707</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>CCRT regimen, etoposide with cisplatin</td>
<td>0.448 (0.284–0.705)</td>
<td>0.001</td>
<td>0.498 (0.314–0.790)</td>
<td>0.003</td>
</tr>
<tr>
<td>BED$_{eq}$ ≥ 70</td>
<td>0.547 (0.347–0.861)</td>
<td>0.009</td>
<td>0.620 (0.392–0.981)</td>
<td>0.041</td>
</tr>
<tr>
<td>PCI, yes</td>
<td>0.805 (0.501–1.291)</td>
<td>0.367</td>
<td></td>
<td>–</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; DLOC, carbon monoxide diffusion capacity; CTx, chemotherapy; CCRT, concurrent chemoradiation therapy; GTV, gross tumor volume; PTV, planning target volume; BED, biologically equivalent dose; HR, hazard ratio; CI, confidence interval.

$^{a}$Multivariate analysis was performed using the backward elimination method in the Cox proportional hazard model.

ly group and 70 Gy once-daily groups, respectively (p = 0.498).

However, few studies have compared the once-daily regimen [18,19] for dose escalation. Kim et al. [18] showed a 3-year OS of 53.6% in the dose-escalated group irradiated with > 54 Gy, and Tomita et al. [19] showed a median OS equal to 41.0 months in the standard fractionation group (≥ 54 Gy). In the current study, we reveal that the use of a once-daily regimen with IMRT achieves a median OS of more than 3 years, with acceptable toxicity in all patients. To the best of our knowledge, this study is the first to use IMRT in all patients and represents an important basis to clarify the optimal once-daily regimen with a modern RT technique.

The PTV were significantly larger in the standard group compared to those in the dose-escalation group (p = 0.005), but there was no significant difference in the GTV (p = 0.316), indicating no significant difference in the total primary and nodal gross tumor volumes. However, the overall TNM stage according to the 8th edition of AJCC [17] was significantly higher (p = 0.005) in the standard group, which may impact disease control or OS. Although most studies and guidelines divide SCLC into limited or extensive stages [20,21], several studies have announced the prognostic value of TNM staging in patients with SCLC [22,23]. To account for this, we performed additional multivariate analysis, including factors related to tumor extent, and found no statistically significant factors related to FFIFF and OS. However, as this is a limitation of our retrospective study, long-term follow-up with more patients and further randomized controlled studies considering patients and disease characteristics are needed.

The criterion for dividing the two groups in this study was BED$_{eq}$ 70 Gy, and in terms of the RT regimen, its total dose reaches approximately 60 Gy in 2 Gy per fraction. A phase I study presented in 1998 sought to investigate the maximum tolerative dose (MTD) in SCLC starting with the fourth cycle of chemotherapy. The authors reported 70 Gy/35 fractions (BED$_{eq}$ 80 Gy) as the MTD, which led to grade 4 or more acute esophagitis in 33% of patients, with no cases of acute pneumonia [24]. Moreover, by implementing concurrent chemotherapy and conformal RT, the CONVERT [8] and CALGB 30610 [9] trials reported 19% and 17.5% of grade 2 or more acute esophagitis with 66 Gy/33 fractions and 70 Gy/35 fractions, respectively. Although prospective studies have introduced high doses [8,9,25], in retrospective studies [10,16,17], most of the institutions have only attempted modest dose escalations, increasing gradually from 50 Gy or more in conventional RT. In our institution, we employ dose escalation in selective patients with consideration for their age, performance, other morbidities, and dose constraints for normal organs. Among the few studies that have compared once-daily regimens, one showed no significant difference in complications based on 54 Gy [26] and another study showed better PFS and OS based on the same dose [18]. Therefore, we set a dose that was slightly higher than this as the standard and converted it into BED$_{eq}$ considering the diversity of the dose per fraction.

This study has a few limitations that warrant discussion, largely owing to its retrospective nature. First, some information could not be obtained, even after thoroughly reviewing the patients’ medical records, because some patients had participated in clinical phase III double-blind trials for which we could not establish whether the patients had received the systemic agent or not. However, only a
small number of the included patients participated in such trials. Second, regarding treatment toxicity, data for grade 1 toxicity may have been missed when it was based on the patient's subjective symptoms. However, as CTCAE version 5.0 defines grade 2 or higher toxicity as that requiring medication, toxicity of grade 2 or higher could be investigated without omission in relation to the prescribing history, which may be clinically important. Finally, the patient and disease characteristics, such as DLCO, overall stage, PTV and chemotherapy regimen may have varied between the two groups. Unlike the previous three factors, chemotherapy regimen was found to have significant effect on the survival rate in univariate and multivariate analyses. However, as we had no strict criteria on chemotherapy such as dose and time intervals, and also included a small number of double-blind trials of systemic therapy, the influence of additional confounders cannot be ruled out when interpreting results related to chemotherapy. Therefore, a well-designed randomized trial that can compensate for these group differences should be conducted.

Like the standard dose group, the most common failure pattern in the dose-escalated group included distant metastases. Therefore, the need for systemic therapies that can control distant metastases more efficiently and exhibit fewer side effects will continue to be important to extend the survival period. Several ongoing trials have introduced various drugs concurrently (NCT04602533, NCT04624204, NCT03811002) or as consolidation (NCT03540420, NCT03703297) [27]. If the standard regimen of systemic therapy changes according to the results of these trials, additional studies on the optimal RT regimen and the interaction between systemic therapy and RT will be needed.

In conclusion, dose-escalated once-daily CCRT with an IMRT technique over 70 Gy in BED_10 affordably improved survival and local tumor control without increasing toxicity. A prospective study will be designed to overcome the limitations of these retrospective outcomes.

**Funding**

None.

**Author Contributions**

Conceptualization, Choi W, Song SY; Investigation and methodology: Yang E, Joo JH, Song SY; Writing of the original draft: Yang E, Song SY; Writing of the review and editing: Yang E, Shin YS, Joo JH, Choi W, Kim SS, Choi EK, Song SY; Formal analysis: Yang E, Shin YS; Data curation: Yang E, Lee J, Song SY.

**Data Availability Statement**

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

**Supplementary Materials**

Supplementary materials can be found via https://doi.org/10.3857/roj.2023.00591.

**References**

7. Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung can-

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Developing prompts from large language model for extracting clinical information from pathology and ultrasound reports in breast cancer

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Purpose: We aimed to evaluate the time and cost of developing prompts using large language model (LLM), tailored to extract clinical factors in breast cancer patients and their accuracy.

Materials and Methods: We collected data from reports of surgical pathology and ultrasound from breast cancer patients who underwent radiotherapy from 2020 to 2022. We extracted the information using the Generative Pre-trained Transformer (GPT) for Sheets and Docs extension plugin and termed this the “LLM” method. The time and cost of developing the prompts with LLM methods were assessed and compared with those spent on collecting information with “full manual” and “LLM-assisted manual” methods. To assess accuracy, 340 patients were randomly selected, and the extracted information by LLM method were compared with those collected by “full manual” method.

Results: Data from 2,931 patients were collected. We developed 12 prompts for Extract function and 12 for Format function to extract and standardize the information. The overall accuracy was 87.7%. For lymphovascular invasion, it was 98.2%. Developing and processing the prompts took 3.5 hours and 15 minutes, respectively. Utilizing the ChatGPT application programming interface cost US $65.8 and when factoring in the estimated wage, the total cost was US $95.4. In an estimated comparison, “LLM-assisted manual” and “LLM” methods were time- and cost-efficient compared to the “full manual” method.

Conclusion: Developing and facilitating prompts for LLM to derive clinical factors was efficient to extract crucial information from huge medical records. This study demonstrated the potential of the application of natural language processing using LLM model in breast cancer patients. Prompts from the current study can be re-used for other research to collect clinical information.

Keywords: Automatic data processing, Artificial intelligence, Natural language processing, Breast cancer, Clinical reports

Introduction

In radiation therapy for breast cancer patients, numerous clinical factors are considered. For instance, when the National Comprehensive Cancer Network panels [1] recommend comprehensive regional nodal irradiation for pN1 patients, it also recommends considering clinical factors such as whether the primary tumor is small or there is only one metastasis. Indeed, clinical decision to irradiate full regional lymph nodes or not depend on clinical factors including age, nuclear grade, molecular subtype, resection margin status, lymphovascular invasion and extranodal extension [2–5] as well as TNM stage. Thus, pathologic factors and radiologic findings are carefully reviewed to make an optimal decision in clinical practice. Radiation oncologists manually reviewed the medical record of...
each patient, seeking important factors to support their decision. When collecting clinical information for research work, medical reports are thoroughly reviewed, factors are manually classified, and the case report form is constructed. This process is labor-intensive, costly, and time-consuming. However, automation of these processes has been challenging due to difficulties in processing unstructured, narrative-style reports generated from diagnostic workup for breast cancer patients.

Recent advances in natural language processing (NLP) play a pivotal role in solving complex problems like the challenges mentioned above. NLP makes it possible to reliably extract important information from free text, and many fields of medicine, including radiation oncology, could benefit from these techniques [6]. In the field of NLP, state-of-the-art large language models (LLMs) like GPT-4 (Generative Pre-trained Transformer 4) have shown outstanding abilities in understanding and generating human language [7]. This enables LLMs to comprehend textual data and establish contextual connections, leading to revolutionary achievements. Further, this capability allows LLMs to analyze complex medical data, extract crucial information, and support decision-making. As such, the effective utilization of LLMs offers tremendous potential in the automation of traditional medical chart review.

To use LLM effectively, “prompts” must be properly developed. Prompts are input sentences or phrases for LLM to perform a specific action. The content and structure of these prompts greatly influence the output and performance of LLMs [8]. Depending on the prompt, LLM model determine which information to process and what type of answers to generate. Thus, design of proper prompts is key to maximizing the capabilities of LLMs, given that inappropriate prompts can cause models to misunderstand or produce unexpected results. In particular, in the field of radiation oncology, research on prompt engineering is required for LLM to extract accurate information from unstructured medical reports.

In this study, prompts were developed to extract the required information using LLM from surgical pathology reports and preoperative ultrasound reports of breast cancer patients. The time and cost needed to develop the prompt was assessed and compared with manual methods. Also, the accuracy of the extracted information was evaluated by comparing it with information collected manually.

**Materials and Methods**

We collected data from breast cancer patients who received postoperative radiotherapy (RT) from 2020 to 2022 in our institution. Male breast cancer patients, patients who received palliative RT, and patients who did not undergo surgery at our institution were excluded. For the study population, the findings from the earliest breast ultrasound within one year before the surgery and the report from surgical pathology were collected. The overall study schema is depicted in Fig. 1.

As the target LLM, we selected the ChatGPT and accessed it with an extension program of Google Sheets, named as GPT for Sheets and Docs (https://gptforwork.com). This plugin, developed by Talarian, is an application that allows the GPT model to be used directly in Google Sheets and provides additional custom features. This makes using various LLM models such as GPT3 and ChatGPT models in Google Sheets possible. In this study, we used the ChatGPT (gpt-3.5-turbo) model.

From the ultrasound reports, prompts were designed to extract and organize factors related to the clinical stage. To determine the clinical T stage, we designed prompts to extract the size and location of the largest suspected cancerous mass within the breast. To extract information about the clinical N stage, we designed prompts to extract the number of suspected metastatic lymph nodes for each nodal area. In addition, information about laterality and tumor location was also extracted.

In the surgical pathology report, prompts were designed to extract factors like tumor size and number of metastatic lymph nodes, which determines the pathological stage. We also designed prompts to extract clinical factors such as histologic grade, neoadjuvant chemotherapy status, resection margin status, molecular subtype, lymphovascular invasion, and extracapsular extension. In addition, we designed prompts to extract factors, such as surgery type and metastatic lymph node ratio.

To evaluate the efficiency and accuracy of the extraction method using LLM, we compared three methods of collecting clinical information from medical records. First, the “full manual” method was done by JYS, a resident physician in Radiation Oncology. The method is a way to manually collect information from the medical records of each patient, and to ensure 100% accuracy, the information was verified by another physician after collection. Second, the “LLM-assisted manual” method was done by the same resident physician who did the “full manual” method, but with the assistance of the information already collected using LLM. Lastly, the “LLM” method used LLM alone to extract information of clinical factors. To establish comparability throughout the three methods, 340 patients were randomly selected using the RAND function in Microsoft Excel to extract information. We calculated the sample size to represent the accuracy of the entire 2,913 cases with a confidence level of 95% and a margin of error of 5%.

The accuracy and time- and cost-efficiency were assessed using the following methods. First, the accuracy of the “LLM” method...
was assessed by regarding the information collected by the “full manual” method as the ground truth and comparing the data collected with both methods. The accuracy rate was calculated by each factor. Also, the time spent to collect the information, to design prompts, or to trim information collected by LLM was measured. Since only 340 patients were included in “full manual” and ‘LLM-assisted manual’ methods, a factor of 8.57 (2,931/340) was multiplied by the measured time to extrapolate, and establish comparability between the three methods. Furthermore, the cost spent to collect the information was estimated. In the “full manual” and “LLM-assisted manual” methods, the cost was estimated by multiplying the measured time by US $7.4 per hour, which is South Korea’s minimum wage in 2023. In the “LLM-assisted manual” and “LLM” methods, the estimated cost for prompt design and the GPT application programming interface (API) fee was measured. Since the “LLM” method was performed on entire patients, the cost for 340 patients was calculated by dividing the total GPT API fee by 8.57.

Results

In total, 2,931 breast cancer patients treated at our institution were included in this study. Table 1 shows the factors, function types, prompts designed, and their corresponding results in this study. A representative example of a surgical pathology report and an ultrasound report could be found in Supplementary Figs. S1 and S2.

Prompts were developed using the Extract function and the Format function from GPT for Sheets and Docs. The Extract function extracts the required information from the reports. The Format function was used to convert them into a structured format. For future statistical analysis, it is essential to standardize the format of responses. Therefore, the choice or type of response was predetermined through the prompts. When the required information could not be extracted at once, the extraction was performed in two steps. For example, when the information regarding the largest nodule among the nodes with suspected malignancy is needed, the information of the node that corresponds to the condition is first extracted, and then the information on diameter, laterality, and clockwise location is extracted again from that extracted information.

In some cases, simple computations to trim the extracted information were necessary. These were performed using IF, AND, and OR functions in Microsoft Excel. For instance, functions were used to determine the breast cancer subtype based on immunohistochemistry results or to identify whether the breast cancer was located on the inner or outer side based on the laterality and clockwise location. When additional trimming was needed for statistical
Table 1. The factors, function types, prompts designed, and their corresponding results

<table>
<thead>
<tr>
<th>Factors</th>
<th>Function type</th>
<th>Prompt</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultrasound reports</strong></td>
<td><strong>Largest nodule in-formation</strong></td>
<td>Extract</td>
<td>Information about largest nodule in diameter or mass with BI-RADS classification of C4 or higher, if there is no C4 or higher nodule, just say 'no cancer'. If not 'no cancer', answer form is 'longest diameter (e.g., 1.0 cm, 2.5 cm by cm), laterality (e.g., Rt/Lt), orientation [by clockface, e.g., 1H, 11.5H] or by quadrant (e.g., SA, center, UO, IL), BI-RADS classification'. all answer is in a single line.</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td><strong>Format</strong></td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td><strong>Laterality</strong></td>
<td><strong>Format</strong></td>
<td>L1t</td>
<td></td>
</tr>
<tr>
<td><strong>Clockwise orientation</strong></td>
<td><strong>Format</strong></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Metastatic lymph node</strong></td>
<td><strong>Extract</strong></td>
<td>This is sono reading. from now on, you are radiologist, count number of suspicion or enlarged lymph nodes. do not count suspicion breast nodule. Do things step by step. Answer form 'inner: ## / axillary : ## / IMN : ## / SCL : ##' answer in single line. 'inner' means intramammary lymph nodes. 'IMN' means internal mammary lymph nodes. 'SCL' mean supra clavicular lymph nodes.</td>
<td>Inner : N/A / axillary : 5 / IMN : N/A / SCL : N/A</td>
</tr>
<tr>
<td><strong>Pathology reports</strong></td>
<td><strong>Pathological T stage</strong></td>
<td>Extract</td>
<td>The invasive tumor size 또는 종괴의 크기 as a long diameter 또는 the extent of in situ.</td>
</tr>
<tr>
<td><strong>Histologic grade</strong></td>
<td><strong>Extract</strong></td>
<td>II/III</td>
<td></td>
</tr>
<tr>
<td><strong>Surgery type</strong></td>
<td><strong>Extract</strong></td>
<td>Surgery type</td>
<td></td>
</tr>
<tr>
<td><strong>Pathological N stage</strong></td>
<td><strong>Extract</strong></td>
<td>The number of positive or metastatic lymph nodes out of total dissected lymph nodes. If nodes were not dissected or not submitted, just say 'not submitted'.</td>
<td>N1</td>
</tr>
<tr>
<td><strong>Metastatic lymph node ratio</strong></td>
<td><strong>Format</strong></td>
<td>Just say only the number after calculating the ratio of the number of positive or metastatic lymph nodes by the total number of examined or dissected lymph nodes</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Lymph node sampling type</strong></td>
<td><strong>Format</strong></td>
<td>ALND</td>
<td></td>
</tr>
<tr>
<td><strong>Number of metastatic lymph nodes</strong></td>
<td><strong>Extract</strong></td>
<td>Just say the number of metastatic or involved lymph nodes, not total harvested or dissected lymph nodes.</td>
<td>1</td>
</tr>
<tr>
<td><strong>Neoadjuvant chemotherapy</strong></td>
<td><strong>Extract</strong></td>
<td>Just say 'Yes' if this pathologic report described post neo-adjuvant chemotherapy or yp/stages according to AJCC staging system. If not, just say 'No'.</td>
<td>Yes (post-neoadjuvant chemotherapy status)</td>
</tr>
<tr>
<td><strong>Resection margin</strong></td>
<td><strong>Extract</strong></td>
<td>Evaluate the margin status, reviewing this pathologic report. Answer in one of 3 words: 'Clear', 'Close', or 'Positive'. You are breast cancer pathologist.</td>
<td>Clear</td>
</tr>
<tr>
<td><strong>IHC result</strong></td>
<td><strong>Extract</strong></td>
<td>Concatenate the immunohistochemistry results including estrogen, progesterone, Ki-67, and gene amplification results in single line. If there isn't, just say 'N/A'. Don't make multiple lines in answer.</td>
<td></td>
</tr>
<tr>
<td><strong>Format</strong></td>
<td><strong>Extract</strong></td>
<td>Just say 'Positive' if the expression of estrogen receptor is positive or more than 1+, based on AJCC breast cancer staging. Otherwise, just say 'No'.</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Format</strong></td>
<td><strong>Extract</strong></td>
<td>Just say 'Positive' if the expression of HER2 is more than 2+ or FISH amplification is positive, based on AJCC breast cancer staging. Otherwise, just say 'Negative'.</td>
<td>Negative</td>
</tr>
</tbody>
</table>

(Continued to the next page)
Developing LLM prompt to extract data

The accuracy of the information extraction by LLM was calculated by each factor and is shown in Table 2. Regarding all the factors, the average accuracy was 87.7%, which could be translated to roughly 298 out of 340 patients. Among all factors, lymphovascular invasion had the highest accuracy of 98.2%. In contrast, neoadjuvant chemotherapy status and tumor location had the lowest accuracy of 47.6% (162 out of 340) and 63.8% (217 out of 340), respectively.

The time- and cost-efficiency of the information extraction by LLM were also assessed. Regarding the time-efficiency, it took 1.5 hours for designing the prompts for the ultrasound report and 2 hours for the surgical pathology report. Responses to the prompts were outputted in parallel for each cell in the table via the GPT server. The entire response output process took 15 minutes. Trimming the data took approximately 30 minutes in total, and the actual application was completed in a few seconds. In total, approximately 4 hours were needed in extracting clinical factors from 2,931 breast cancer patients. In terms of cost, using the GPT model through the GPT API incurs a fee per token. In the current study, US $6.04 for ultrasound interpretation and US $59.76 for surgical pathology interpretation was charged using the GPT API, for a total of US $65.8. Also, the whole process took 4 hours to design the prompts and trim the data, which could be translated to a wage cost of US $29.6, when applying the minimum wage of South Korea in 2023. The response output process was excluded from the wage cost calculation because the process could be done automatically.

The time and cost spent on collecting the information using “full manual,” “LLM-assisted manual,” and “LLM” methods were measured and estimated for comparison (Table 3). For all 2,913 patients, the time spent for the “full manual,” “LLM-assisted manual,” and “LLM” methods were 122.6 hours, 79.4 hours, and 4 hours, respectively. The estimated cost for “full manual,” “LLM-assisted manual,” and “LLM” methods were US $909.3, $653.4, and $95.4, respectively. By using “LLM-assisted manual” and “LLM” methods compared to the “full manual” method, we could save 43.2 hours and US $255.9, and 118.6 hours and US $813.9 in all 2,913 patients, respectively.

Table 1. Continued

<table>
<thead>
<tr>
<th>Factors</th>
<th>Function type</th>
<th>Prompt</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphovascular invasion</td>
<td>Extract</td>
<td>The lymphatic invasion in pathologic report</td>
<td>Lymphatic emboli: present, minimal</td>
</tr>
<tr>
<td>Extracapsular extension</td>
<td>Extract</td>
<td>The presence or absence or N/A of extracapsular extension in pathology results</td>
<td>Extracapsular extension: N/A</td>
</tr>
</tbody>
</table>

AJCC, American Joint Committee on Cancer; ALND, axillary lymph node dissection; BI-RADS, Breast Imaging Reporting and Data System; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IL, inferio-lateral; IMN, internal mammary lymph node; N/A, not accessible; SA, subareolar; SCL, supraclavicular lymph node; SLNB, sentinel lymph node biopsy; UO, upper-outer.

Table 2. The accuracy of the data extraction by LLM

<table>
<thead>
<tr>
<th>Factor</th>
<th>Correct</th>
<th>Total</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical T stage</td>
<td>279</td>
<td>340</td>
<td>81.9</td>
</tr>
<tr>
<td>Clinical N stage</td>
<td>311</td>
<td>340</td>
<td>91.5</td>
</tr>
<tr>
<td>Tumor location</td>
<td>217</td>
<td>340</td>
<td>63.8</td>
</tr>
<tr>
<td>Surgery type</td>
<td>318</td>
<td>340</td>
<td>93.4</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>162</td>
<td>340</td>
<td>47.6</td>
</tr>
<tr>
<td>Pathologic T stage</td>
<td>295</td>
<td>340</td>
<td>86.7</td>
</tr>
<tr>
<td>Histologic grade</td>
<td>334</td>
<td>340</td>
<td>98.1</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>334</td>
<td>340</td>
<td>98.2</td>
</tr>
<tr>
<td>Resection margin</td>
<td>298</td>
<td>340</td>
<td>87.7</td>
</tr>
<tr>
<td>Lymph node sampling type</td>
<td>295</td>
<td>340</td>
<td>86.7</td>
</tr>
<tr>
<td>Pathologic N stage</td>
<td>314</td>
<td>340</td>
<td>92.4</td>
</tr>
<tr>
<td>Metastatic lymph node ratio</td>
<td>324</td>
<td>340</td>
<td>95.3</td>
</tr>
<tr>
<td>Extracapsular extension</td>
<td>305</td>
<td>340</td>
<td>89.6</td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td>324</td>
<td>340</td>
<td>95.3</td>
</tr>
<tr>
<td>HER2</td>
<td>327</td>
<td>340</td>
<td>96.3</td>
</tr>
<tr>
<td>Ki-67</td>
<td>311</td>
<td>340</td>
<td>91.5</td>
</tr>
<tr>
<td>Triple-negative breast cancer</td>
<td>324</td>
<td>340</td>
<td>95.3</td>
</tr>
<tr>
<td>Overall (average)</td>
<td>298</td>
<td>340</td>
<td>87.7</td>
</tr>
</tbody>
</table>

LLM, large language model; HER2, human epidermal growth factor 2.

Discussion and Conclusion

In the current study, we investigated the efficiency and accuracy of the utilization of LLM in extracting RT-related factors. From 2,931 breast cancer patients, we extracted clinical factors from the reports of ultrasound and surgical pathology. The whole process took 4 hours and cost US $95.4, and the average accuracy was 87.7%.
Developing an effective prompt to get the desired outcome, which is called prompt engineering, is the most crucial point in utilizing LLM. In prompt engineering, the features of LLMs should be well understood by developers. When using an LLM, users may avoid using jargon, instead, should provide all the information needed to generate a response. Also, it is recommended to write the logic leading up to the desired outcome in the prompt, rather than trying to achieve the desired outcome all at once, thereby, the LLM can follow the logical process. For example, in interpreting an ultrasound report, instead of saying, “Identify the clinical T stage,” it is better to say, “Here’s an ultrasound reading of a breast cancer patient, find the mass with the largest diameter and tell me its diameter in centimeters.” Also, these results can be improved with a well-known few-shot learning or fine-tuning method by introducing an example within the prompt and having the LLM replicate the logical flow. Since we could not fully predict the output of LLM, it is essential to modify and correct the prompt through a trial-and-error method, rather than completing it at once. Understanding these features will provide appropriate answers to users when effective prompt engineering is adopted in coding clinical data.

Information extraction by developing prompts from LLM is extremely efficient in terms of both time and expenses, especially when it is applied to a task handling huge data. From raw data of thousand patients to well-organized spreadsheet data, we could save 118.6 hours and US $813.9 by using “LLM” method. After completing the prompt design, the cost of developing the prompt is fixed, which could save expenses for research that needs to be encoded from large data, such as pathological or radiographic findings of patients with breast or prostate cancer treated with radiation therapy. This method is a much-awaited in labor market like South Korea, where the hiring of qualified healthcare provider is expensive and scarce. For the last decade in South Korea, there has

The GPT model, which is employed in the current study, is intended to imitate natural conversations, and does not contain logical thinking [9]. Thus, it does not understand the meaning of sentences but is merely aligning the most likely word to use. In other words, there is no logic in the response it gives. For example, in the current study, we first wanted to separate the location of a breast tumor into inner and outer based on laterality and the clockwise direction from the nipple. Despite many trials and errors, we failed to implement the function in a GPT model. This may be because the GPT model failed to comprehend the logic that the clockwise direction is opposite according to the laterality of the breast in separating inner from outer lesions. Also, another well-known feature of the GPT model is a phenomenon called the hallucination [10]. This is a phenomenon that the model responds with a plausible answer that is incorrect. For example, when the GPT-3.5 is asked “Explain to me the clinical N stage of breast cancer according to the American Joint Committee on Cancer (AJCC) 8th edition,” it comes up with a plausible answer which is an explanation about the pathological N stage. The hallucination was seen time to time in extracting information in the current study. For example, when asked about the diameter of the tumor from the ultrasound report, it sometimes responded with the distance from the nipple. We speculate that this hallucination occurred because the two values are both written in numerical values in centimeter. In another example, the category “Neoadjuvant chemotherapy” was accurate at less than 50%. It could be due to hallucination. Even though there was no information about neoadjuvant chemotherapy in the pathology report, LLM gave a yes or no answer instead of saying that there was insufficient information. A deep understanding in such features of LLMs is crucial to designing prompts and applying it to use.

### Table 3. The time and cost spent on collecting the data using “full manual,” “LLM-assisted manual,” and “LLM” methods

<table>
<thead>
<tr>
<th></th>
<th>Full manual</th>
<th>LLM-assisted manual</th>
<th>LLM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>340 patients</td>
<td>All patients (extrapolated)</td>
<td>340 patients</td>
</tr>
<tr>
<td>Time spent (hr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For data collection</td>
<td>14.3</td>
<td>122.6</td>
<td>8.8</td>
</tr>
<tr>
<td>For prompt design and trimming</td>
<td>-</td>
<td>-</td>
<td>4.0</td>
</tr>
<tr>
<td>Total</td>
<td>14.3</td>
<td>122.6</td>
<td>12.8</td>
</tr>
<tr>
<td>Time saved compared to “full manual”</td>
<td>-</td>
<td>-</td>
<td>1.5</td>
</tr>
<tr>
<td>Estimated cost (US dollar)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual data collection wage cost</td>
<td>106.1</td>
<td>909.3</td>
<td>65.6</td>
</tr>
<tr>
<td>Prompt design and trimming wage cost</td>
<td>-</td>
<td>-</td>
<td>29.6</td>
</tr>
<tr>
<td>GPT API usage fee</td>
<td>-</td>
<td>-</td>
<td>7.7</td>
</tr>
<tr>
<td>Total</td>
<td>106.1</td>
<td>909.3</td>
<td>102.9</td>
</tr>
<tr>
<td>Cost saved compared to “full manual”</td>
<td>-</td>
<td>-</td>
<td>3.2</td>
</tr>
</tbody>
</table>

API, application programming interface; LLM, large language model; Bold, total time and cost.
been a steep growth in wages with the minimum wage almost doubling [12], and that of the healthcare providers are no exception [13]. In addition, the “Act on the Improvement of Training Conditions and Status of Medical Residents” was enacted in 2015, restricting the working hours of medical residents [14]. Due to advantage of the using LLM in large-scale tasks, development, and facilitating prompts are employed in other expert fields as well [15]. The accuracy of the information extracted by prompts using LLM was 87.7%, which is an encouraging result compared to conventional NLP models. Juhn et al. [16] reported 80%-98% accuracy in identifying the presence or severity of allergic conditions through medical record review using an NLP-based model [16]. In addition, Tang et al. [17] reported a low accuracy of 23.4% in biomedical named entity recognition using the ChatGPT, and a higher accuracy of 75.9% in LLM for medical tasks. Although the accuracy of 87.7% in the current study is notable, it should be cautioned to use without supervision. Manual examination should be done to re-examine the extracted information. Alternatively, a hybrid method that we named the “LLM-assisted manual” method could be a reasonable way to compromise in a real-world setting. By referring to the information extracted, one can collect information more efficiently, while still maintaining the level of accuracy of a manual information collection. Recently, the GPT-4 was released and expected to reduce the frequency of hallucinations and improve accuracy [7]. We expect that LLMs specialized in medical tasks may elevate the accuracy of extraction even better [18,19].

There were several limitations in this study. First, the clinical N stage did not strictly follow the AJCC staging system. The information in the ultrasound report was insufficient to extract whether a lymph node is movable or not. Thus, distinguishing between clinical N1 and N2 solely depended on the number of nodal metastasis or the presence of an internal mammary lymph node metastasis without axillary metastasis, and has discrepancy with the AJCC staging system. Also, the “full manual” method, which is used as a ground truth, is not perfect. Although manual process is the control for the “LLM” process, the “full manual” method does not guarantee 100% accuracy in information collection due to the human error. It could be improved if two or more people could cross-check each other’s collected information to approach 100% accuracy for a solid ground truth. Moreover, using minimum wage in the evaluation of total cost may be inaccurate. Healthcare providers such as doctors or nurses, who would likely collect the clinical information from the medical records in real-life, receive more than a minimum wage. Therefore, the exact cost of manual information collection could be higher. Finally, the extrapolation of time and cost taken in 60 patients into 2,913 patients may be inaccurate. Validation with more data is required.

In conclusion, we showed that using LLM prompts is an efficient way to extract crucial information from the medical records of breast cancer patients and to construct well-fined clinical data. This method is expected to save lots of effort from daily practice and research work. Prompts from the current study can be re-used for other investigators to collect clinical information.

Statement of Ethics
This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. H-2304-072-1422).

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

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Author Contributions
Conceptualization, Choi HS, Song JY, Jang BS. Funding acquisition, Shin KH, Jang BS. Investigation and methodology, Choi HS, Song JY, Jang BS. Project administration, Choi HS. Resources, Shin KH, Chang JH, Jang BS. Supervision, Jang BS. Writing of the original draft, Choi HS, Song JY. Writing of the review and editing, Choi HS, Song JY. Software, Choi HS. Validation, Choi HS. Formal analysis, Choi HS, Song JY. Data curation, Choi HS. Visualization, Choi HS.

Data Availability Statement
The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from Bum Sup Jang upon reasonable request.

Supplementary Materials
Supplementary materials can be found via https://doi.org/10.3857/roj.2023.00633.
References


Bleeding metastasis of renal cell cancer to anal canal treated with radiation

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Introduction

Renal cell cancer (RCC) has the potential to metastasize to various organs, including the anal canal which is reported to be the rarest location. An 88-year-old male patient who had previously been treated for right RCC subsequently developed distant metastases to the prostate, lungs, and small bowel. Four years following nephrectomy, the patient presented with a bleeding anal mass which was excised and has been proven to be an anal canal metastasis of RCC. Seven months post excision, regrowth occurred. The patient underwent stereotactic ablative body radiotherapy resulting in satisfactory regression during the 2-month follow-up period, without episodes of bleeding. The treatment options for metastatic post-nephrectomy disease should be considered with a multidisciplinary approach in order to achieve satisfactory symptom relief.

Keywords: Anal canal, Metastasis, Radiation therapy, Renal cell cancer

Case Report

An 88-year-old male patient was treated for right RCC with open radical nephrectomy in 2017 with a pathology report for clear cell renal carcinoma with focal papillary areas (World Health Organization Grade 4). Medical data history on his comorbidities and previous treatment with radiotherapy are not available. Four years following surgery, the patient presented with a bleeding anal mass which was excised and has been proven to be an anal canal metastasis of RCC. Seven months post excision, regrowth occurred. The patient underwent stereotactic ablative body radiotherapy after nephrectomy and palliative radiotherapy for metastatic disease. In the setting of soft-tissue metastatic RCC occurrence, palliative radiotherapy is described to have certain relief of the symptoms [5]. It has been shown that the use of a total dose of 20–30 Gy leads to enviable local progression-free survival rates [6].

We present a case of an anal canal metastasis from RCC causing rectal bleeding and severe anemia in a male patient. After the initial treatment with surgical excision and regrowth appearance, the lesion was treated with SABR, and symptom relief was achieved. Written informed consent was obtained from the patient.

Renal cell cancer (RCC) has the ability to metastasize to various organs, including the anal canal which is reported to be the rarest location. An 88-year-old male patient who had previously been treated for right RCC subsequently developed distant metastases to the prostate, lungs, and small bowel. Four years following nephrectomy, the patient presented with a bleeding anal mass which was excised and has been proven to be an anal canal metastasis of RCC. Seven months post excision, regrowth occurred. The patient underwent stereotactic ablative body radiotherapy resulting in satisfactory regression during the 2-month follow-up period, without episodes of bleeding. The treatment options for metastatic post-nephrectomy disease should be considered with a multidisciplinary approach in order to achieve satisfactory symptom relief.

Keywords: Anal canal, Metastasis, Radiation therapy, Renal cell cancer
ous surgeries comprehended diabetes mellitus and hypertension and open prostatectomy due to benign prostatic hyperplasia in 2007, respectively. Metastasis from the RCC was diagnosed in 2020 and was initially treated with interferon-alpha but due to the patient’s intolerance to the medication, interruption, and replacement with sunitinib followed. During the treatment, the clinical progression of the metastasis was recognized. Therefore, the treatment was converted to doxorubicin + cyclophosphamide with the achievement of a complete clinical response seen on the chest X-ray performed prior to surgical excision of the anal canal lesion. Further, small bowel metastasis occurred in 2020 presented with hematochezia. Hence, segmental intestinal resection was performed.

Almost 4 years following the index surgery for the RCC, the patient complained of rectal bleeding with present anal mass mimicking hemorrhoid disease. He was initially treated for bleeding hemorrhoid disease. The bleeding was recurrent, and the lesion continued to grow, finally resulting in severe secondary anemia at the beginning of the year 2022. In March 2022 he was admitted to the department for colorectal surgery with anemia and a visible mass in the anal canal (Fig. 1). Add following: erythrocytes count of $3.01 \times 10^6$ U/L, hemoglobin value of 8.2 g/L, hematocrit of 24.4%, neutrophils of 86.6%, C-reactive protein value of 40.4 mg/L, glucose value of 185 mg/dL, serum albumin value of 24.1 g/L, serum creatinine value of 13 U/L, serum urea value of 59 mg/dL, serum total protein value of 47 g/L and serum sodium value of 133 mmol/L. Replacement of blood (4 units) was given in order to correct anemia with hemoglobin value achievement of 12.2 g/L. The patient was operated under spinal anesthesia and the lesion was excised with mucosal defect closure in order to achieve proper hemostasis. The patient’s hospital stay lasted 4 days and the wound was regularly followed and it healed completely after 35 days. The pathology report confirmed R0 resection of RCC metastasis in the anal canal (Fig. 2).

One month after metastasis removal, clinical regrowth was noted. The lesion regrew to an almost identical size as when presented initially over the next 7 months with episodes of bleeding (Fig. 3). Additional R2 resection of the lesion due to bleeding was forced. In addition, the patient was referred to the oncologist where radiation (SABR) was indicated with a total of 25 Gy divided into 10 fractions. Metastasis regression followed with no new episodes of bleeding (Fig. 4). Six months after SABR completion, a complete clinical response was achieved with no macroscopic tumor present in the anal canal. After this time frame, the patient was lost for further follow-up.

Discussion

Approximately 1/3 of the patients diagnosed with RCC present with distant metastases at the initial diagnosis. Twenty to 40% of them will subsequently develop metastases [7]. Distant spread is described to be hematogenous, lymphatic, transcoelomic or by direct invasion [8].

An advanced search of the Cochrane library and PubMed by using the keywords “renal cell cancer,” “metastasis,” and “anal canal” revealed only two case reports of anal canal metastasis from RCC [9,10]. Rare GI tract locations of RCC metastases have also been reported. They are described as solitary or with concomitant involvement of other organs (brain and lungs) as in this case. GI tract organ affection includes the duodenum [9,11], the colon [12], the rectum [3], and the anal canal [9,10]. To the best of our knowledge, the present case is the third report on the occurrence of anal canal metastasis originating from RCC (Table 1).

The diagnosis can be challenging because symptomatology can mimic other primary conditions of the affected organ. It may present with hematochezia [11], rectal bleeding [9], signs of intestinal obstruction, vomiting, and change in stool caliber [13]. Anal canal metastases have been misdiagnosed as hemorrhoids and in some cases treated as such [9]. The same clinical confusion was initially present in this case.

Fig. 1. Clinical presentation of the metastasis in the anal canal.
In general, the indication for SABR in RCC has not yet been clearly defined for different stages of the disease. Surgery remains the standard treatment option for localized RCC. Having in mind the cases with locally advanced RCC and/or the present comorbidities in some patients, radiation therapy should be considered as the proper treatment option. In the multi-center analysis from the International Radiosurgery Consortium of the Kidney, primary inoperable RCC in 96 patients was treated with stereotactic ablative body radiotherapy delivered as single or multiple fractions of more than 5 Gy. The reported cumulative incidence of local failure at 5 years was 5.5% [14]. In the German S3 guideline for renal cell carcinoma stereotactic body radiotherapy is favored for local tumor control. At the same time, the oligometastatic treatment with higher local doses or stereotactic treatment should be considered after interdisciplinary discussion [15].

The use of palliative radiotherapy in patients with metastases occurrence after prior nephrectomy is reported. In the systematic review of Kothari et al. [16], the effect of SABR on extracranial metastatic renal cell carcinoma was analyzed. The reported average marginal range was 15–50 Gy with a range of fractions from single one to 10. Weighted local control was achieved in 89% with a median overall survival range of 11.7–22 months. In the meta-analysis of Zaorsky et al. [17] on the use of stereotactic ablative radiation therapy for extracranial oligometastatic renal cell carcinoma, the 1-year overall survival rate ranged from 48.9–100% with a 1-year local control rate range from 72.4–99.4%.

Due to the lack of data and recommendations for the standard treatment of the metastatic disease to the anal canal from RCC, surgical excision was initially performed in this case. The clinical symptomatic regrowth forced the use of palliative radiation. The used 25 Gy/10 fraction radiation was lower than the standard one for soft-tissue conventional palliative radiation dose. The advanced age of the patient influenced the radiation dose decision.

In the proposed algorithm of the Mayo Clinic on the diagnosis
and treatment of RCC, metastatic stage IV disease should be treated with molecularly targeted therapy +/- cytoreductive nephrectomy. In cases with oligometastases presence, surgical excision or stereotactic body radiotherapy are the treatment options [18].

Metastatectomy is still an effective treatment in selected patients with soft-tissue metastases from RCC. In this case, the surgery failed and led to symptomatic local recurrence. On the contrary, local radiation therapy resulted in satisfactory metastasis regression with no post-radiation bleeding during the follow-up period. Therefore, initial radiotherapy could be the choice of treatment for local metastases in the anal canal from RCC instead of local excision in selected cases. To summarize, the recurrent local metastatic RCC disease requires a multidisciplinary approach in order to achieve symptom relief.

Statement of Ethics
Written informed consent was obtained from the patient.

Conflict of Interest
No potential conflict of interest relevant to this article was reported.
Funding
None.

Author Contributions
Conceptualization, Ulusoy C, Nikolovski A. Investigation and methodology, Ulusoy C, Nikolovski A, Mete SG. Project administration, Ulusoy C. Resources, Mete SG. Supervision, Ulusoy C, Nikolovski A, Mete SG. Writing of the original draft, Nikolovski A. Writing of the review and editing, Ulusoy C, Nikolovski A. Software, Nikolovski A. Validation, Ulusoy C, Mete SG, Nikolovski A. Formal analysis, Ulusoy C, Nikolovski A. Data curation, Mete SG. Visualization, Nikolovski A.

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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.

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THE STANDARD OF CARE¹ FOR STAGE III UNRESECTABLE NSCLC

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STUDY DESIGN The PACIFIC study design, eligibility criteria and assessments have been fully described previously. Eligible patients had histologically and/or cytologically documented Stage IIA or IIB unresectable NSCLC, with a WHO performance score of 0 or 1. Randomization to treatment blocks of 1:1 (durvalumab: placebo) was carried out at trial sites based on the number of patient randomizations in each site. Randomization was stratified on the number of prior lines of chemotherapy, histology, stage and primary tumor site (peripheral vs central), and tumor burden. Treatment allocation was generated centrally and was masked from the investigator and patient. The study was terminated early by the Data Safety and Monitoring Board because of the increased overall survival in the durvalumab group compared with placebo. The data cutoff date was 8 March 2019. Treatment was with durvalumab 10 mg/kg intravenously every 2 weeks for up to 12 months or until confirmed disease progression or confirmed death. There were 5,555 patients enrolled across 269 centers in 17 countries. Median follow-up was 16 months. Henceforth, the term OS will denote overall survival and PD-L1 expression will denote proportion of tumor cells expressing PD-L1. PROMISE endpoints were death or confirmed progressive disease. The primary endpoint was OS in the intention-to-treat population. The OS results demonstrated a significant increase in overall survival (hazard ratio 0.78, 95% CI 0.70-0.88, p < 0.0001) with durvalumab versus placebo in the intention-to-treat population. The 28% reduction in risk of death was consistent in all prespecified subgroups, including patients receiving concurrent chemoradiation therapy. The results were the same in patients with squamous and non-squamous NSCLC and for patients with high and low PD-L1 expression. There was no difference in the incidence of treatment-related death or serious adverse events. The infections were mainly respiratory and the most common grade 3 or higher adverse events were pneumonia, and lung and other respiratory infections. There was no increase in autoimmune adverse events. Treatment-related adverse events were more common in the placebo group. The median OS was 20.7 months longer in the durvalumab group than the placebo group. DURVALUMAB 10 mg/kg plus placebo was superior to placebo alone. The durability of benefit beyond 2 years with durvalumab continues. In the PACIFIC trial, durvalumab was well-tolerated and responses were durable. Median OS in the placebo group was 13.7 months. Median OS from the time of randomization was 23.8 months in the durvalumab group and 18.6 months in the placebo group. Median OS in the overall population was 24.4 months in the durvalumab group versus 20.7 months in the placebo group (HR 0.78, 95% CI 0.70-0.88, p < 0.0001).

UPDATED 5-YEARS OVERALL SURVIVAL IN THE ITT POPULATION

STUDY DESIGN The PACIFIC study design, eligibility criteria and assessments have been fully described previously. Eligible patients had histologically and/or cytologically documented Stage IIA or IIB unresectable NSCLC, with a WHO performance score of 0 or 1. Randomization to treatment blocks of 1:1 (durvalumab: placebo) was carried out at trial sites based on the number of patient randomizations in each site. Randomization was stratified on the number of prior lines of chemotherapy, histology, stage and primary tumor site (peripheral vs central), and tumor burden. Treatment allocation was generated centrally and was masked from the investigator and patient. The study was terminated early by the Data Safety and Monitoring Board because of the increased overall survival in the durvalumab group compared with placebo. The data cutoff date was 8 March 2019. Treatment was with durvalumab 10 mg/kg intravenously every 2 weeks for up to 12 months or until confirmed disease progression or confirmed death. There were 5,555 patients enrolled across 269 centers in 17 countries. Median follow-up was 16 months. Henceforth, the term OS will denote overall survival and PD-L1 expression will denote proportion of tumor cells expressing PD-L1. PROMISE endpoints were death or confirmed progressive disease. The primary endpoint was OS in the intention-to-treat population. The OS results demonstrated a significant increase in overall survival (hazard ratio 0.78, 95% CI 0.70-0.88, p < 0.0001) with durvalumab versus placebo in the intention-to-treat population. The 28% reduction in risk of death was consistent in all prespecified subgroups, including patients receiving concurrent chemoradiation therapy. The results were the same in patients with squamous and non-squamous NSCLC and for patients with high and low PD-L1 expression. There was no difference in the incidence of treatment-related death or serious adverse events. The infections were mainly respiratory and the most common grade 3 or higher adverse events were pneumonia, and lung and other respiratory infections. There was no increase in autoimmune adverse events. Treatment-related adverse events were more common in the placebo group. The median OS was 20.7 months longer in the durvalumab group than the placebo group. DURVALUMAB 10 mg/kg plus placebo was superior to placebo alone. The durability of benefit beyond 2 years with durvalumab continues. In the PACIFIC trial, durvalumab was well-tolerated and responses were durable. Median OS in the placebo group was 13.7 months. Median OS from the time of randomization was 23.8 months in the durvalumab group and 18.6 months in the placebo group. Median OS in the overall population was 24.4 months in the durvalumab group versus 20.7 months in the placebo group (HR 0.78, 95% CI 0.70-0.88, p < 0.0001).
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