Aims and Scope

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

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

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Rectal cancer is one of the most prevalent cancers in the world. In many countries, the current standard of care is long-course chemoradiation (CRT), followed by total mesorectal excision. Some efforts have been made by intensifying radiation or chemotherapy components of the neoadjuvant therapy to further decrease the local recurrence and augment surgery's feasibility and improve the oncological outcomes. This paper reviews recent intensified neoadjuvant interventions in locally advanced rectal cancer (LARC) in terms of efficacy and treatment-related toxicity. Many maneuvers have been made so far to improve the oncological outcomes of rectal cancer with intensified neoadjuvant long-course CRT. Some of these approaches seem compelling and deserve further study, while some have just increased the treatment-related toxicities without evident benefits. Those endeavors with greater pathological complete response than the standard of care may make us await the long-term results on survival rates and chronic treatment-related toxicity. After introduction of neoadjuvant CRT for LARC there have been many efforts to improve its outcomes. Here, this study gathered most of these efforts that intensified the neoadjuvant therapy with some being promising and some being futile.

Keywords: Radiotherapy, Neoadjuvant therapy, Rectal cancer, Neoadjuvant therapy, Chemoradiotherapy

Introduction

Rectal cancer is one of the most prevalent types of cancers, affecting both men and women. Based on the GLOBOCAN 2018 report, rectal cancer is the 8th most diagnosed cancer and the 10th deadliest one [1]. Nearly 700 thousand new rectal cancer cases were diagnosed in 2018, which is estimated to be 60% higher in 2030. On the other hand, about 310 thousand deaths were caused by rectal cancer in 2018, which is expected to reach 480 thousand in 2030 [1,2]. A considerable proportion of patients with rectal cancer presents with the locally-advanced disease that confers poorer outcomes than the early-stage disease and mandates multi-disciplinary management.

Currently, the mainstay treatment for locally advanced rectal cancer (LARC) is total mesorectal excision (TME), either open or using minimally invasive methods like robotic or laparoscopic surgery [3]. Compared to the colon, the cancers of the rectum harbor distinct considerations, including the limited space to obtain sufficient margins and to dissect lateral lymph node in the true pelvis [3,4]. Due to these considerations, adjuvant chemoradiation (CRT) has increased the survival of rectal cancer patients and decreased the likelihood of local recurrence (LR). The delivery of CRT before surgery was suggested 15 years ago and showed that, with similar efficacy, it could decrease the long-term toxicities compared to the postoperative CRT. So, this approach became the standard of care. Besides, preoperative CRT reduces the tumor size, sterilizes the operation field from cancer cells, and augments the chance of sphincter preservation [5,6].
Radiotherapy Intensification

Based on the dose-response models for rectal cancer that showed better responses obtained by increasing total radiation dose [11], various RT techniques have been introduced to deliver higher doses of external beam radiation to increase local control (Table 1). Despite the promising results in terms of feasibility and good toxicity profile, the impact of these techniques on long-term outcomes and survival is not clear.

One of the most studied RT techniques is delivering a boost dose to the gross tumor through external beam photons. The landmark trial of MD Anderson by Janjan et al. [12] was the first to document the feasibility and favorable rate of sphincter preservation with the addition of concomitant boost to the gross tumor versus the historical method of neoadjuvant CRT. In this study, patients received a 45-Gy pelvic RT plus continuous infusion SFU (300 mg/m²) for 5 days per week. In addition, a 7.5-Gy boost was administered to tumor plus 2–3 cm margin in 5 fractions during the last week with a 6-hour interval from the pelvic irradiation.

Yang et al. [13] investigated the efficacy and safety of a combined preoperative regimen, including volumetric modulated arc

Table 1. Radiotherapy intensification studies in locally advanced rectal cancer underwent neoadjuvant chemoradiation and oncologic outcomes and adverse effect

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Study arms</th>
<th>N</th>
<th>pCR</th>
<th>Toxicity</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janjan et al. [12], 2000</td>
<td>Single arm: concomitant boost to tumor with 3DCRT</td>
<td>45</td>
<td>31%</td>
<td>Acute GI toxicity G3: 9.5%</td>
<td>3-yr DFS: 95.4%</td>
<td>3-yr OS: 85.9%</td>
</tr>
<tr>
<td>Hernando-Requejo et al. [14], 2014</td>
<td>Single arm: concomitant boost to mesorectum with IMRT</td>
<td>74</td>
<td>30.60%</td>
<td>Acute GU toxicity G3: 5.4%</td>
<td>3-yr DFS: 81%</td>
<td>3-yr OS: 86.8%</td>
</tr>
<tr>
<td>Osti et al. [16], 2014</td>
<td>Single arm: concomitant boost to mesorectum with IMRT</td>
<td>65</td>
<td>17%</td>
<td>G3-4 Overall toxicity: 15%</td>
<td>3-yr DFS: 56.0%</td>
<td>3-yr OS: 75.3%</td>
</tr>
<tr>
<td>Alongi et al. [16], 2017</td>
<td>Single arm: concomitant boost to the hypermetabolic areas</td>
<td>40</td>
<td>ND</td>
<td>Acute GI toxicity G2: 15%</td>
<td>1-yr DFS: 100%</td>
<td>1-yr OS: 100%</td>
</tr>
<tr>
<td>Badakhshi et al. [17], 2017</td>
<td>Retrospective: concomitant boost to mesorectum with 3DCRT</td>
<td>141</td>
<td>9.90%</td>
<td>Acute GU toxicity G2: 12.5%</td>
<td>3-, 5-, and 10-yr DFS rates were 91.9%, 88.9%, and 79.3%, respectively</td>
<td>3-, 5-, and 10-yr OS rates were 91.9%, 84.6%, and 52.9%, respectively</td>
</tr>
<tr>
<td>Wang et al. [18], 2019</td>
<td>CRT alone vs. CRT plus Concomitant boost and consolidation CAPOX</td>
<td>120</td>
<td>13.3% vs. 23.3% (p = 0.157)</td>
<td>G3-4 toxicities 18.3% vs. 25.0% (p = 0.016)</td>
<td>3-yr DFS: 56.0% (p = 0.349)</td>
<td>3-yr OS: 75.3% vs. 88.5% (p = 0.553)</td>
</tr>
<tr>
<td>Yang et al. [13], 2019</td>
<td>Single arm: concomitant boost to mesorectum with VMAT</td>
<td>26</td>
<td>32</td>
<td>Two cases with G3 dermatitis</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Valentini et al. [11], 2019</td>
<td>Two arms: concomitant boost to bulky site vs. concurrent biweekly oxaliplatin</td>
<td>534</td>
<td>24.4% vs. 23.8% (NS)</td>
<td>Neurological any grade: 1.7% vs. 21.7% (G3: 0% vs. 0.5%; p = 0.001)</td>
<td>5-yr DFS: 74.7% vs. 73.8% (p = 0.444)</td>
<td>5-yr OS: 80.4% vs. 85.5% (p = 0.155)</td>
</tr>
</tbody>
</table>

pCR, pathological complete response; DFS, disease-free survival; OS, overall survival; 3DCRT, three-dimensional conformal radiation therapy; ND, not defined; IMRT, intensity-modulated radiation therapy; GI, gastrointestinal; GU, genitourinary; CRT, chemoradiotherapy; CAPOX, capecitabine and oxaliplatin; VMAT, volumetric modulated arc therapy; NS, not significant; G, grade.
therapy (VMAT) along with a simultaneous integrated boost consisting of 58.75 Gy (2.35 Gy per fraction) to mesorectum and 50 Gy (2 Gy per fraction) for other pelvic lymph node stations, with concurrent capecitabine. In this single-arm study, good sphincter preservation and pCR rates were achieved. The initial results also revealed good tolerance and a low occurrence rate of adverse side effects.

The effect of integrated-boost using intensity-modulated radiation therapy (IMRT) on the pCR has also been investigated by Hernando-Requejo et al. [14]. In this single-arm study 46 Gy in 23 fractions was prescribed for the pelvic nodes and mesorectum and 57.5 Gy in 23 fractions was prescribed as the boost dose concurrently with oral capecitabine. The results revealed that the concomitant-boost was known to be a well-tolerated treatment, even though no specific differences in overall and disease-free survival in comparison with other studies were found in patients with pCR.

Osti et al. [15] in a retrospective single-arm study, evaluated the impact of concomitant boost to the high-risk area with three-dimensional conformal radiotherapy (3DRT) technique in rectal cancer patients. The boost dose was 10 Gy delivered in 10 fractions twice a week while the intermediate risk areas received 45 Gy in 25 daily fractions. The results indicated that the RT treatment intensification might have a positive biological effect. However, the results have not yet been confirmed, and a more extended follow-up period was claimed to be needed.

The role of RT dose intensification through integrated boost was also inspected in the study by Alongi et al. [16], which had a non-randomized design. It was a prospective study in LARC within 10 cm of the anal verge. The methods were described as using high-dose volumes receiving a 6-Gy boost, including the hyper-metabolic areas defined as maximal standardized uptake value (SUVmax) over 5 within a co-registered positron emission tomography scan of the corresponding mesorectum. Prophylactic areas received 54 Gy in 30 fractions. Oral capecitabine were taken twice a day for 5 days every week. This technique seemed to be practicable. Although it was indicated that the sensitivity and specificity of SUVmax values were in association with the best node down-staging and downsizing, the initial outcomes of this study did not confirm any benefits in terms of tumor regression and response rate [16].

A retrospective study by Badakhshi et al. [17] described the effects of concomitant boost with 3DCRT on long-term clinical outcomes in LARC. All patients received 45 Gy with concurrent SFU but some also had a 5.4-Gy boost to the mesorectum and the gross tumor volume. The authors suggested that the concomitant boost is associated with improved overall survival (OS). Interestingly, there were no significant differences in treatment-related toxicities between the standard and boost therapy [17]. However, the small group of patients who received the boost dose faded any possible conclusions.

On a randomized trial, Wang et al. [18] analyzed whether a more intensified CRT could yield a promising clinical result in LARC; patients were divided into two different groups. One received 50 Gy pelvic IMRT (Arm A), and the other obtained 50 Gy pelvic RT plus a concomitant 5 Gy boost (0.2 Gy per fraction) to the primary lesion, followed by a cycle of CAPOX (capecitabine plus oxaliplatin) 2 weeks after the end of CRT (Arm B). Both arms were given capecitabine 625 mg/m^2 and oxaliplatin 50 mg/m^2 as concurrent chemotherapy. The final results demonstrated the pCR advantage of the concomitant boost at the expense of delayed postsurgical wound healing. The authors believed this finding would warrant further attention.

A long-term analysis of the INTERACT trial investigated the two different intensification regimens of preoperative capecitabine-based CRT, in which the patients randomized into either a concomitant RT boost to the bulky tumor or to concurrent biweekly oxaliplatin (130 mg/m^2). All patients received 45 Gy in 25 fractions to the pelvis. The concomitant boost group received 10 Gy boost in twice weekly one-gray fractions. In conclusion, the concomitant boost group significantly obtained better tumor regression grade (TRG) patterns in the surgical specimen. Thus, no distinguishable differences were found in clinical outcomes between the two arms. Nevertheless, according to the boost efficacy on TRG along with its lower toxicity and good compliance, it should be considered a treatment of choice for clinical T3 lesions [11].

As discussed above, many studies have been carried out on the intensification of RT in rectal cancer. Although they stated promising findings in the short-term, we should wait for the long-term outcomes in LR, OS, and chronic toxicities of the treatments.

**Concurrent Chemotherapy Intensification**

Using systemic therapy concurrently with RT is usually done with lower doses than chemotherapy alone. These doses are known to have radio-sensitizing effect that make tumors more susceptible to the impact of RT. Numerous preliminary reports have been published on the results of different chemotherapy regimens combined with neoadjuvant irradiation and standard concomitant systemic therapies to meet the endpoint criteria of local control and pCR (Table 2).

In the most famous study, the ACCORD12 trial, the aim was to inspect the efficacy of two different CRT regimens in resectable rectal cancer patients. In order to fulfill this purpose, a 3-year follow-up was put into work. Each patient was randomly assigned to CRT with either CAP45 (45-Gy RT in combination with capecit-
CAP (Arm A) or the same schedule with biweekly BEV 5 mg/kg (Arm B). The results of this study support the data described previously in single-arm studies about the practicability of adding BEV to a standard neoadjuvant capecitabine-based CRT regimen, as well as its potential role in down-staging.

A phase II trial investigated the preoperative RT with two different parallel chemotherapy regimens: (1) capecitabine (1,200 mg/m²/daily for 5 days a week) plus irinotecan (50 mg/m² weekly × 4), and (2) capecitabine (1,650 mg/m²/daily for 5 days a week) plus oxaliplatin (50 mg/m²/weekly × 5). The efficacy results for both arms were similar to other reported studies. Thus, the authors were uncertain to recommend a second agent plus capecitabine for concurrent chemorhaphy, but they suggested further studies using irinotecan [23].

Bazarbashi et al. [24] studied the effect of adding weekly cetuximab to capecitabine concurrent with RT. The authors concluded that this combination was attainable with acceptable toxicity in LARC, and it was associated with better pCR compared to historical controls.

The addition of systemic therapies based on the molecular profile of tumors has been investigated in rectal cancer patients in a phase II trial by Gollins et al. [25]. In this investigation, the significance of pre-treatment and post-resection RAS mutations was evaluated through treatment with a preoperative chemotherapy regimen consisting of capecitabine, irinotecan (60 mg/m² weekly from week 1 to 4), and cetuximab (weekly from week 0 to 5). As a result, this regimen was proved to be acceptable and met its primary R0 re-

Table 2. Concurrent chemotherapy intensification

<table>
<thead>
<tr>
<th>Study, year</th>
<th>RT dose</th>
<th>Study arm</th>
<th>N</th>
<th>pCR</th>
<th>Toxicity</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. [21], 2013</td>
<td>50.4 Gy</td>
<td>Concurrent CAP vs. CAP/IRI</td>
<td>231</td>
<td>28.6% vs. 37.5% (p = 0.247)</td>
<td>ND</td>
<td>5-yr DFS: 80.8% vs. 72.7%; p = 0.685</td>
<td>5-yr OS: 88.4% vs. 90.4%; p = 0.723</td>
</tr>
<tr>
<td>Salazar et al. [22], 2015</td>
<td>45 Gy</td>
<td>Concurrent CAP + BEV vs. CAP alone</td>
<td>90</td>
<td>16% vs. 11% (p = 0.54)</td>
<td>G3-4 toxicity: 16% vs. 13%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Wong et al. [23], 2015</td>
<td>50.4 Gy in 1.8-Gy fx</td>
<td>Concurrent CAP + OX vs. CAP + IRI</td>
<td>104</td>
<td>21% vs. 10%</td>
<td>ND</td>
<td>4-yr DFS: 62% vs. 68%</td>
<td>4-yr OS: 75% vs. 85%</td>
</tr>
<tr>
<td>Bazarbashi et al. [24], 2016</td>
<td>50.4 Gy</td>
<td>Concurrent CAP + cetuximab</td>
<td>50</td>
<td>0.04</td>
<td>Cetuximab-induced skin reactions (33%), radiation-induced skin toxicity (13%) and diarrhea (20%)</td>
<td>4-yr DFS: 80%</td>
<td>4-yr OS: 93%</td>
</tr>
<tr>
<td>Gollins et al. [25], 2017</td>
<td>45 Gy</td>
<td>Single arm: Concurrent CAP + cetuximab + IRI</td>
<td>82</td>
<td>0.17</td>
<td>G3: 47%</td>
<td>37.4-mo DFS: 67%</td>
<td>37.4-mo OS: 80%</td>
</tr>
<tr>
<td>Haddad et al. [26], 2017</td>
<td>50–50.4 Gy</td>
<td>Concurrent CAP + OX vs. CAP alone</td>
<td>63</td>
<td>34% vs. 13% (p = 0.072)</td>
<td>G3 diarrhea: 22% vs. 0%; p = 0.006</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>ACCORD 12/0405 PRODIGE [19,20], 2012, 2017</td>
<td>Concurrent CAP + OX vs. CAP alone</td>
<td>598</td>
<td>19.2% vs. 13.9% (p = 0.09)</td>
<td>Acute G3-4: 25.4% vs. 10.9%; p &lt; 0.001</td>
<td>5-yr DFS: 66.1% vs. 63.1%; p = 0.9</td>
<td>5-yr OS: 82% vs. 73%; p = 0.3</td>
<td></td>
</tr>
</tbody>
</table>

RT, radiotherapy; pCR, pathological complete response; DFS, disease-free survival; OS, overall survival; CAP, capecitabine; BEV, bevacizumab; OX, oxaliplatin; IRI, irinotecan; ND, not defined.
section endpoint. Also, there was a non-significant enhancement in progression-free survival (PFS) and OS for RAS wild-type in comparison to anytime-mutated tumors.

A clinical trial by Haddad et al. [26] investigated the effects of adding oxaliplatin (60 mg/m^2 weekly for 5–6 cycles) to capecitabine based CRT in LARCs. This particular trial evaluated down-staging as a short-term replacement for PFS. In conclusion, this study revealed that the addition of oxaliplatin to CRT might benefit down-staging in the short term. Given that oxaliplatin is still experimental, the article suggested such a regimen might be beneficial in patients suspected of having positive circumferential resection margins in pre-treatment magnetic resonance imaging.

As seen above, augmenting the systemic part of the neoadjuvant treatment although have been feasible but conferred little benefit so far. Most authors of such trials suggested further studies with some of the agents. To sum up, the standard of care is still using fluorouracil or capecitabine plus RT as the concurrent systemic regimen.

### Induction or Consolidation Systemic Therapy

Adding more chemotherapy in the pre-RT and post-RT windows is a way of intensification of neoadjuvant therapy in rectal cancer. Some RT effects are durable even after the last fraction and using systemic therapy in this time-frame would have some radio-sensitizing effects along those effects harbored by the full-dose systemic therapy itself. A good example of adding more systemic therapy before or after CRT is called total neoadjuvant therapy (TNT). In this method induction chemotherapy is usually followed by CRT with or without consolidation chemotherapy [27].

Higher toxicities are expected during TNT due to the increased intensity of the chemotherapeutic agents, but no grade 4 toxicities were reported in the included papers (Table 3). Grade 3 leukopenia was a common adverse effect in most studies, occurring in 10%–13% of the patients. Radiation dermatitis was also seen in about 6% of the cases [28–30]. However, complete clinical or pathological responses were achieved in 17% to 42% of the cases. The highest complete response rate was reported in a regimen of 50.6 pelvic RT in 22 cycles, followed by 4 cycles of CAPOX [28–30].

Spanish GCR-3, a phase II randomized trial, was designed to measure the benefits of adding chemotherapy before CRT and surgery. Patients with distal or middle third rectal cancer were randomly assigned to two different arms; preoperative CRT followed by surgery and four cycles of postoperative CAPOX or four cycles of induction CAPOX followed by CRT and surgery. In conclusion to this

### Table 3. Induction or consolidation systemic therapy

<table>
<thead>
<tr>
<th>Study, year</th>
<th>RT dose</th>
<th>Study arm</th>
<th>N</th>
<th>pCR</th>
<th>Toxicity</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fernandez-Martos et al. [31], 2015</td>
<td>–</td>
<td>CRT then surgery and adjuvant CAPOX vs. induction CAPDX then CRT then surgery</td>
<td>108</td>
<td>13% vs. 14%</td>
<td>ND</td>
<td>5-yr: 64% vs. 62%; p = 0.85</td>
<td>5-yr: 78% vs. 75%; p = 0.64</td>
</tr>
<tr>
<td>Fernandez-Martos et al. [32], 2019</td>
<td>50.4 Gy</td>
<td>mFOLFOX6 + aflibercept vs. mFOLFOX6 alone</td>
<td>180</td>
<td>22.6% vs. 13.8% (p = 0.15)</td>
<td>Hypertension: 24.3% vs. 1.5%, Postoperative complications: 15.5% vs. 12.9%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Fokas et al. [28], 2019</td>
<td>50.4 Gy in 28 fx</td>
<td>Induction FOLFOX vs. consolidation FOLFOX</td>
<td>311</td>
<td>17% vs. 25%</td>
<td>37% vs. 27%</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Masi et al. [33], 2019</td>
<td>50.4 Gy</td>
<td>Single arm: induction FOLFOXIRI + BEV</td>
<td>49</td>
<td>0.364</td>
<td>Neutropenia: 41.6%, Diarrhea: 12.5%</td>
<td>2-yr: 80.45%</td>
<td>ND</td>
</tr>
<tr>
<td>OPRA trial [35], 2020</td>
<td>54 Gy</td>
<td>Induction vs. consolidation FOLFOX or CAPOX</td>
<td>324</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Conroy et al. [36], 2020</td>
<td>50 Gy</td>
<td>CRT alone vs. induction mFOLFIRINOX then CRT</td>
<td>461</td>
<td>11.7% vs. 27.5% (p &lt; 0.001)</td>
<td>ND</td>
<td>3-yr DFS: 78% vs. 77%; p = 0.9</td>
<td>3-yr MFS: 81% vs. 83%; p = 0.06</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3-yr DFS: 68.5% vs. 75.7%</td>
<td>3-yr MFS: 71.7% vs. 78.8%</td>
</tr>
</tbody>
</table>

RT, radiotherapy; pCR, pathological complete response; DFS, disease-free survival; OS, overall survival; CRT, chemoradiotherapy; CAPOX, capecitabine and oxaliplatin; FOLFOX, 5FU + leucovorin + oxaliplatin + irinotecan; mFOLFOX, modified FOLFOX; BEV, bevacizumab; ND, not defined.

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trial, both treatment methods approached similar results. However, the group with systemic therapy before CRT and surgery showed lower acute toxicity and better overall compliance; therefore, it warranted further investigation [31].

In the Spanish GEMCAD 1402 study, adding aflibercept (4 mg/kg every 2 weeks for 6 cycles) to the induction modified FOLFOX (SFU, leucovorin, and oxaliplatin) followed by CRT and TME yielded better pCR and similar surgical complications than the induction modified FOLFOX alone [32]. These results granted to go for a phase III trial with this approach.

TNT is recognized as a new standard for rectal cancer treatment. To test this hypothesis, in CAO/ARO/AIO-12 trial, patients were divided into two arms. Arm A received induction chemotherapy using three cycles of FOLFOX before SFU/oxaliplatin CRT (SFU 250 mg/m² on days 1 to 14 and 22 to 35 and a 2-hour infusion of oxaliplatin 50 mg/m² on days 1, 8, 22, and 29 of RT), and Arm B received consolidation chemotherapy after CRT. The induction or consolidation regimens were as follows: oxaliplatin 100 mg/m² + leucovorin 400 mg/m² + continuous 46-hour infusion of SFU 2,400 mg/m², repeated on day 15 for a total of 3 cycles. It was concluded that CRT followed by consolidation chemotherapy resulted in better compliance with CRT but worse compliance with chemotherapy compared with Arm A. Only the CRT followed by chemotherapy fulfilled the predefined trial hypothesis of a 10% better pCR rate. Accordingly, this sequence was set for the baseline group for future trials on TNT [28].

As it is known, the CRT alone does not achieve the effective control of distant metastases as is expected. The addition of induction chemotherapy plus BEV in phase II single-arm trial named TRUST was examined. Patients underwent 6 cycles of induction FOLFOXIRI plus BEV, followed by CRT and BEV. The authors claimed that this strategy might be able to improve distant disease control in LARC [33].

OPRA, a phase II multi-institutional study, evaluated selective non-operative management (NOM) in LARC in those with clinical response to avoid unnecessary surgery [34]. Patients with stage II or III who were eligible for TME were randomized to receive SFU or capecitabine-based CRT plus induction versus consolidation FOLF-OX/CAPOX as two forms of TNT. Those who achieved a clinical complete or near-complete response were offered NOM while those with residual disease underwent TME. The 3-year preliminary results demonstrated that by delivering TNT, we would not just enhance the patient’s quality of life but also, we would be able to shorten the time needed before ileostomy reversal. Also, it was established that avoiding surgery in patients with tumors that respond to CRT will minimize over-treatment without compromising survival. In contrast to induction chemotherapy, more patients with consolidation chemotherapy were suggested to achieve NOM [35].

Conroy et al. [36] conducted PRODIGE 23, a clinical phase III trial to validate the TNT approach in LARC prospectively. The efficacy of 6 courses of mFOLFIRINOX as induction chemotherapy followed by CRT and TME within 3 months was compared to the control group consisting of only preoperative CRT and TME. The induction regimen consisted of 6 cycles of modified FOLFIRINOX (oxaliplatin 85 mg/m², leucovorin 400 mg/m², irinotecan 180 mg/m² D1, and 5FU 2.4 g/m² over 46 hours) every 14 days. Adjuvant chemotherapy with mFOLFOX6 or capecitabine was allowed depending on the center’s interest. Although the OS data has yet to be mature, the benefit of total neoadjuvant therapy on pCR, DFS, and metastasis-free survival was shown.

Several robust studies have been listed above that addressed the efficacy and safety of adding induction or consolidation systemic therapy. The most popular method in this setting is TNT that seems to become a famous paradigm in the near future. Considering this approach’s relative novelty, high pCR and metastasis-free survival and DFS rates in the TNT studies made us eagerly expect the long-term results regarding the OS rates and chronic toxicities.

Conclusion

Three main approaches exist to intensify the neoadjuvant chemoradiotherapy for rectal cancer. Many investigators with various practical backgrounds have examined the efficacy and safety of intensified regimens prospectively and retrospectively. It seems that the TNT has a brighter future, considering the strength of results and power of the clinical trials. We should keep in mind that LARC has a relatively high survival rate with current therapies, and there is an availability of various agents in the advanced setting. Thus, long follow-ups are needed to see the effect of different approaches on overall survival.

Conflict of Interest

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

Acknowledgments

We would like to thank Tara Haddad (Faculty of Art and Science, University of Toronto) for contributing to the draft.

References


Purpose: About 40% of men diagnosed with prostate cancer (Pca) are ≤65 years of age. This study evaluates the risk of second cancer among young Pca patients treated with surgery or radiation.

Materials and Methods: This is a retrospective review of 150,915 men aged ≤65 years at Pca diagnosis treated with surgery or radiation registered in the Surveillance, Epidemiology, and End Results (SEER) database between 1973 and 2014. Incidence rates of second rectum/rectosigmoid junction (RJ), bladder, and lung cancer in each treatment group were reported with adjustment for potential confounders. Cumulative incidence functions were used to summarize the risk of second cancer after completing initial treatment.

Results: Men treated with external beam radiation (BEAM), brachytherapy (SEED), or combined radiation all exhibited a statistically significant increased incidence of second bladder cancer compared to men treated with surgery (adjusted incidence rate ratio [IRR]: 2.09, 1.91, and 2.04, respectively). Incidence of rectum/RJ cancer was also significantly increased in men receiving BEAM and combined radiation (adjusted IRR: 1.58 and 1.98, respectively). There were also significant differences in the cumulative incidence of second bladder cancer after receiving any form of radiation compared to surgery.

Conclusion: Pca survivors ≤65 years of age at Pca diagnosis had an increased risk of second bladder and rectum/RJ cancer after BEAM and combined radiation treatment after adjusting for confounding factors. Second bladder cancer incidence after either form of radiation treatment was increased even at 5 years after a Pca diagnosis.

Keywords: Prostate cancer, Second cancer, Radiotherapy, Prostatectomy

Introduction

Prostate cancer is the second most common cancer in men, behind only skin cancer. There will be an estimated 191,930 new prostate cancer cases diagnosed in 2020; 40% will occur in men ≤65 years of age [1]. Not all men diagnosed with prostate cancer, however, will die from the disease. It has been estimated that 3.1 million men who have at some point been diagnosed with prostate cancer are alive today [2]. Prostate cancer survivors face many challenges, including the risk of a second primary cancer [3,4]. This challenge is more pronounced in younger men due to their longer post-diagnosis life expectancy.

Many factors may contribute to the risk of second primary cancer among prostate cancer survivors. Some are similar to those in men with no prior cancer diagnosis, such as lifestyle, environmental exposure, and genetic susceptibility. External beam radiation (BEAM), brachytherapy (permanent seed implants or high-dose-rate brachytherapy, SEED), or a combination of the two are used as less invasive alternatives to surgery for treating localized prostate cancer; radiation has been shown to increase the risk of bladder...
and rectal cancer [5].

Many studies have reported on the risk of second cancer after prostate cancer treatment while including men of all ages at the time of diagnosis [6–28]. These studies may underestimate the risk of second cancer due to under-reporting from limited follow-up for older patients. So far, no study only evaluates the risk of second cancer in men ≤ 65 years of age. The purpose of this study is to report the risk of bladder and rectal/rectosigmoid junction (RJ) cancer, using the risk of lung cancer as a reference, after prostate cancer diagnosis among this younger cohort. This information is much-needed for cancer treatment consent when discussing options at the time of prostate cancer diagnosis, and for guidance for second cancer screening for young men diagnosed with prostate cancer.

Materials and Methods

Eligible patients (n = 150,915) were identified in the 1973–2014 multi-primary SEER (Surveillance, Epidemiology, and End Results) database. Patients ≤ 65 years of age at diagnosis with prostate cancer as their first malignancy were included. Patients were excluded from further analysis if they were diagnosed by autopsy or death certificate; had second cancer diagnosis less than 12 months following a prostate cancer diagnosis; had less than 12 months of follow-up after prostate cancer diagnosis; were listed as having received a form of radiation therapy that was not BEAM, SEED, or a combination of both; or received post-operative radiation treatment after radical prostatectomy. Selected patients were separated into four categories based on treatment received for primary prostate cancer: 92,679 underwent surgery without any form of radiation, 36,225 underwent BEAM alone, 13,001 underwent SEED alone, and 9,010 underwent both BEAM and SEED.

We identified the urinary bladder and the rectum/RJ as organs of interest in which to monitor second cancer events. These organs were chosen due to their proximity to the prostate, thus being more likely to receive incidental radiation during therapy. We also monitored second lung cancer as a reference group.

1. Statistical analysis

Descriptive statistics characterizing the study cohort were generated and compared between treatment modality groups. Continuous variables were compared using ANOVA, and categorical variables were compared using the chi-square test. To account for varying lengths of follow-up, we calculated the incidence rates (IR) of any second cancer, and specific second diagnoses of bladder, rectum/RJ, and lung cancers, for each treatment modality. Incidence rates were calculated as the number of observed second cancers over the number of person-years at risk (reported per 100 person-years). Person-years at risk were defined as the time from 12 months post-prostate cancer diagnosis to second cancer diagnosis of any type, death, or end of follow-up, whichever occurred first. Subjects with less than 12 months of follow-up post-prostate cancer diagnosis were excluded, and second events with a latency of less than 12 months were discarded to avoid including occurrences of cancers that likely antedated the treatment for prostate cancer. With an offset of person-years at risk, Poisson regression was used to generate incidence rate ratios comparing the risk of second cancer between treatment modalities. Multivariate Poisson models were generated to adjust for potential confounders, including age at primary prostate cancer diagnosis, race, and year of primary prostate cancer diagnosis. Cumulative incidence functions were used to graphically summarize the risk of any second cancer diagnosis and specific cancer diagnosis of interest over time, by treatment modality, in order to account for the presence of many competing risks. For the lung, bladder, and rectum/RJ cumulative incidence analyses, subjects with a subsequent malignancy of any other type were censored at the time of the second malignancy. Subjects alive and free from subsequent malignancy throughout available follow-up were censored at the date of the last follow-up. The Kaplan-Meier method was used to graphically summarize overall survival from the time of primary prostate cancer diagnosis to death from any cause; and was also used to graphically summarize second cancer-free survival from 12 months post-primary prostate cancer diagnosis to second malignancy or death, whichever occurred first. SAS 9.2 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

Results

Patient characteristics can be seen in Table 1. There were significant differences in age, year of primary cancer diagnosis, and race among patients treated with surgery, BEAM, SEED, and combined radiation.

The incidence rate per 100 person-years, incidence rate ratio (IRR), and IRR adjusted for race, age at primary prostate cancer diagnosis, and year of primary prostate cancer diagnosis are reported in Table 2 (detailed information regarding statistical analysis is included in Supplement A, B). The adjusted IRRs for any second malignancy and lung cancer after treatment for BEAM, SEED, and combined radiation, compared with surgery, were significantly higher (Table 2). The adjusted IRRs for bladder cancer after treatment for BEAM, SEED, and combined radiation, compared with surgery, were 2.09 (95% confidence interval [CI], 1.88–2.32), 1.91 (95% CI, 1.61–2.26), and 2.04 (95% CI, 1.70–2.45), respectively. The
Table 1. Study patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Surgery (n = 92,679)</th>
<th>BEAM (n = 36,225)</th>
<th>SEED (n = 13,001)</th>
<th>Combined (n = 9,010)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years at risk</td>
<td>886,757.2</td>
<td>297,935</td>
<td>99,396.6</td>
<td>75,740.1</td>
<td></td>
</tr>
<tr>
<td>Age at prostate cancer diagnosis (yr)</td>
<td>58.2 ± 5.3</td>
<td>59.7 ± 4.7</td>
<td>59.0 ± 4.8</td>
<td>58.8 ± 4.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Year of primary diagnosis</td>
<td>2,000.5 ± 9.2</td>
<td>1,998.0 ± 10.5</td>
<td>2,004.8 ± 9.8</td>
<td>2,002.9 ± 6.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>77,443 (83.6)</td>
<td>26,947 (74.4)</td>
<td>10,356 (79.7)</td>
<td>6,288 (69.8)</td>
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</tr>
<tr>
<td>Black</td>
<td>11,213 (12.1)</td>
<td>7,246 (20.0)</td>
<td>1,962 (15.1)</td>
<td>2,318 (25.7)</td>
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</tr>
<tr>
<td>Other</td>
<td>3,218 (3.5)</td>
<td>1,755 (4.8)</td>
<td>563 (4.3)</td>
<td>353 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>805 (0.9)</td>
<td>277 (0.8)</td>
<td>120 (0.9)</td>
<td>51 (0.6)</td>
<td></td>
</tr>
<tr>
<td>SEER historic stage A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Localized/regional</td>
<td>70,615 (76.2)</td>
<td>22,209 (61.3)</td>
<td>12,594 (96.9)</td>
<td>8,167 (90.6)</td>
<td></td>
</tr>
<tr>
<td>Un-staged</td>
<td>489 (0.5)</td>
<td>234 (0.7)</td>
<td>102 (0.8)</td>
<td>88 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Distant</td>
<td>96 (0.1)</td>
<td>1003 (2.8)</td>
<td>19 (0.2)</td>
<td>39 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Blank</td>
<td>21,479 (23.2)</td>
<td>12,779 (35.3)</td>
<td>286 (2.2)</td>
<td>716 (8.0)</td>
<td></td>
</tr>
<tr>
<td>Any second cancer diagnosis</td>
<td>9,796 (10.6)</td>
<td>4,807 (13.3)</td>
<td>1,298 (10.0)</td>
<td>1,018 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>1,620 (1.8)</td>
<td>1,000 (2.8)</td>
<td>186 (1.4)</td>
<td>166 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>828 (0.9)</td>
<td>625 (1.7)</td>
<td>170 (1.3)</td>
<td>137 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Rectum/RJ</td>
<td>370 (0.4)</td>
<td>219 (0.6)</td>
<td>49 (0.4)</td>
<td>59 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Age at second cancer diagnosis (yr)</td>
<td>69.2 ± 7.4</td>
<td>69.3 ± 7.1</td>
<td>67.1 ± 5.9</td>
<td>67.5 ± 6.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Latency of second cancer diagnosis (yr)</td>
<td>9.7 ± 6.0</td>
<td>8.8 ± 5.9</td>
<td>7.0 ± 4.2</td>
<td>7.6 ± 4.9</td>
<td></td>
</tr>
</tbody>
</table>

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

BEAM, external beam radiation; SEED, brachytherapy; SEER, Surveillance, Epidemiology, and End Results; RJ, rectosigmoid junction.

Table 2. Incidence rate and ratio (IRR) with adjustment for age, year of primary prostate cancer diagnosis, and race

<table>
<thead>
<tr>
<th></th>
<th>Total person-years</th>
<th>Incidence rate per 100 person-years (95% CI)</th>
<th>IRR (95% CI)</th>
<th>Adjusted IRR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modelling any second malignancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>886,757.2</td>
<td>1.10 (1.08, 1.13)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>BEAM</td>
<td>297,935</td>
<td>1.61 (1.57, 1.66)</td>
<td>1.46 (1.41, 1.51)*</td>
<td>1.35 (1.30, 1.40)*</td>
</tr>
<tr>
<td>SEED</td>
<td>99,396.6</td>
<td>1.31 (1.24, 1.38)</td>
<td>1.18 (1.12, 1.25)*</td>
<td>1.20 (1.13, 1.27)*</td>
</tr>
<tr>
<td>Combined</td>
<td>75,740.1</td>
<td>1.34 (1.26, 1.43)</td>
<td>1.22 (1.14, 1.30)*</td>
<td>1.22 (1.14, 1.30)*</td>
</tr>
<tr>
<td>Modelling lung second malignancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>886,757.2</td>
<td>0.18 (0.17, 0.19)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>BEAM</td>
<td>297,935</td>
<td>0.34 (0.32, 0.36)</td>
<td>1.84 (1.70, 1.99)*</td>
<td>1.60 (1.48, 1.74)*</td>
</tr>
<tr>
<td>SEED</td>
<td>99,396.6</td>
<td>0.19 (0.16, 0.22)</td>
<td>1.02 (0.88, 1.19)</td>
<td>1.11 (0.95, 1.30)</td>
</tr>
<tr>
<td>Combined</td>
<td>75,740.1</td>
<td>0.22 (0.19, 0.26)</td>
<td>1.20 (1.02, 1.41)*</td>
<td>1.22 (1.03, 1.43)</td>
</tr>
<tr>
<td>Modelling bladder second malignancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>886,757.2</td>
<td>0.09 (0.087, 0.10)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>BEAM</td>
<td>297,935</td>
<td>0.21 (0.19, 0.23)</td>
<td>2.25 (2.03, 2.49)*</td>
<td>2.09 (1.88, 2.32)*</td>
</tr>
<tr>
<td>SEED</td>
<td>99,396.6</td>
<td>0.17 (0.15, 0.20)</td>
<td>1.83 (1.55, 2.16)*</td>
<td>1.91 (1.61, 2.26)*</td>
</tr>
<tr>
<td>Combined</td>
<td>75,740.1</td>
<td>0.18 (0.15, 0.21)</td>
<td>1.94 (1.62, 2.32)*</td>
<td>2.04 (1.70, 2.45)*</td>
</tr>
<tr>
<td>Modelling rectum/RJ second malignancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>886,757.2</td>
<td>0.04 (0.04, 0.05)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>BEAM</td>
<td>297,935</td>
<td>0.07 (0.06, 0.08)</td>
<td>1.76 (1.49, 2.08)*</td>
<td>1.58 (1.33, 1.87)*</td>
</tr>
<tr>
<td>SEED</td>
<td>99,396.6</td>
<td>0.05 (0.04, 0.07)</td>
<td>1.18 (0.88, 1.59)</td>
<td>1.30 (0.96, 1.76)</td>
</tr>
<tr>
<td>Combined</td>
<td>75,740.1</td>
<td>0.08 (0.06, 0.10)</td>
<td>1.87 (1.42, 2.46)*</td>
<td>1.98 (1.50, 2.61)*</td>
</tr>
</tbody>
</table>

BEAM, external beam radiation; SEED, brachytherapy; RJ, rectosigmoid junction.

*Adjusted for race (unknown/other groups combined), age at primary prostate diagnosis (linear), and year of primary prostate diagnosis (piecewise linear with spline knots at 25th [1995] and 75th percentile [2008]). Poisson model with offset for follow-up time used to calculate IRRs.

*Indicates statistical significance at alpha = 0.05 level.
adjusted IRRs for rectum/RJ cancer after treatment for BEAM, SEED, and combined radiation, compared with surgery, were 1.58 (95% CI, 1.33–1.87), 1.30 (95% CI, 0.96–1.76), and 1.98 (95% CI, 1.50–2.61), respectively. The adjusted IRRs for lung cancer after treatment for BEAM, SEED, and combined radiation, compared with surgery, were 1.60 (95% CI, 1.48–1.74), 1.11 (95% CI, 0.95–1.30), and 1.22 (95% CI, 1.03–1.43), respectively.

The cumulative incidence of second cancer is depicted in Fig. 1 (detailed statistical analysis provided in Supplement C). When comparing all second cancers’ cumulative incidences, there were noticeable differences between men treated with surgery and any form of radiation (Fig. 1A). Cumulative incidences of second lung, bladder, and rectum/RJ cancer were higher in men treated with any form of radiation than in men treated with surgery (Fig. 1A, 1C, and 1D, respectively). Cumulative incidences of second lung, bladder, and rectum/RJ cancer at 5 years after prostate cancer diagnosis are listed in Table 3. At 5 years after prostate cancer diagnosis, cumulative incidences of lung and bladder cancer were different between men treated with surgery and any forms of radiation.

Overall survival and second cancer-free survival are shown in Fig. 2. Men treated with BEAM had worse overall survival and second cancer-free survival.

**Discussion and Conclusion**

Radiation-induced secondary cancer is generally considered to arise 5 years or more after receiving radiation, and to be located within the radiation field, to be a different histological type of primary cancer, and to not be present at the time of radiation treatment [29]. We observed that differences in the cumulative incidence of second bladder cancers were apparent between men treated with surgery and men treated with either form of radiation at 5 years of diagnosis. There was a higher incidence of lung cancer for men treated with either form of radiation, compared to men treated with surgery. These observations suggest that men elected to receive radiation might have other health-related factors con-

![Fig. 1.](https://doi.org/10.3857/roj.2020.00857)
tributing to second cancer development. This hypothesis was also supported by the findings of Hegemann et al. [23] after their review of second cancer incidence after radiation, radiation after surgery, and surgery alone in a population-based clinical cancer registry in Bavaria. The authors suggested that a higher incidence of second cancer after radiation alone is likely related to advanced age and lifestyle habits.

Our study observed that second lung cancer rates were significantly elevated in men receiving BEAM or combined radiation compared to men treated with surgery, and others have also noted similar findings [24]. This is intriguing in part because lung tissue is not expected to receive radiation doses during radiation treatment regardless of treatment modality to the pelvis. On the other hand, smoking is a known risk factor for lung cancer. Smokers may have higher rates of respiratory insufficiency that result in increased risks when subject to general anesthesia, thus making them more likely to receive radiation as opposed to surgery. In fact, the incidence rates of primary lung cancer in the general population of men ≤ 65 years is 0.28 per 100 person-years [1], compared with 0.18 and 0.34 per 100 person-years for men treated with surgery and BEAM respectively. Furthermore, smoking is a risk factor for bladder cancer, and a difference in smoking rates between treatment groups may partially explain the increased second bladder cancer risk in patients receiving radiation therapy. The incidence rates of primary bladder cancer in men younger than 65 years of age were 0.10 per 100 person-years, as reported in the SEER database [1]. In our study cohort, the incidence rates of bladder cancer in men treated with BEAM, SEED, and combined radiation were 0.21, 0.17, and 0.18 per 100 person-years comparing with 0.09 per 100 person-years in men treated with surgery. The fact that increased incidence of bladder cancer was observed 5 years post-prostate cancer diagnosis also suggested that radiation may

### Table 3. Cumulative incidence of second cancer at 5 years after prostate cancer diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Cumulative incidence (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any second malignancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>3.01</td>
<td>2.90–3.13</td>
</tr>
<tr>
<td>BEAM</td>
<td>4.73</td>
<td>4.50–4.96</td>
</tr>
<tr>
<td>Combine</td>
<td>4.46</td>
<td>4.03–4.92</td>
</tr>
<tr>
<td>SEED</td>
<td>4.25</td>
<td>3.89–4.62</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>0.44</td>
<td>0.40–0.48</td>
</tr>
<tr>
<td>BEAM</td>
<td>1.01</td>
<td>0.90–1.12</td>
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<td>Combine</td>
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<td>0.61–0.99</td>
</tr>
<tr>
<td>SEED</td>
<td>0.65</td>
<td>0.52–0.81</td>
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<tr>
<td>Bladder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>0.22</td>
<td>0.19–0.26</td>
</tr>
<tr>
<td>BEAM</td>
<td>0.51</td>
<td>0.43–0.59</td>
</tr>
<tr>
<td>Combine</td>
<td>0.41</td>
<td>0.29–0.57</td>
</tr>
<tr>
<td>SEED</td>
<td>0.42</td>
<td>0.31–0.55</td>
</tr>
<tr>
<td>Rectum/RJ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>0.16</td>
<td>0.13–0.18</td>
</tr>
<tr>
<td>BEAM</td>
<td>0.20</td>
<td>0.16–0.25</td>
</tr>
<tr>
<td>Combine</td>
<td>0.31</td>
<td>0.21–0.46</td>
</tr>
<tr>
<td>SEED</td>
<td>0.15</td>
<td>0.09–0.23</td>
</tr>
</tbody>
</table>

BEAM, external beam radiation; SEED, brachytherapy; RJ, rectosigmoid junction; CI, confidence interval.

Fig. 2. Overall survival and second cancer-free survival. (A) Overall survival after first prostate cancer diagnosis. (B) Second cancer-free survival (over time at risk). BEAM, external beam radiation; SEED, brachytherapy.
Incidence rates of primary rectum/RJ cancer in men younger than 65 years of age were 0.08 per 100 person-years, as reported in the SEER database [1]. In our study cohort, the incidence rates of rectum/RJ cancer in men treated with surgery, BEAM, SEED, and combined radiation were 0.04, 0.07, and 0.05 per 100 person-years, respectively. The relatively low incidence rate of second rectum/RJ cancer in our control cohort (men treated with surgery for prostate cancer) compared with the incidence rate of rectum/RJ cancer as a primary diagnosis in the general population might be related to intrinsic limitations of data reporting or other factors beyond the scope of this investigation. Further, incidences of rectum/RJ cancer after any form of radiation were comparable to the incidence in the general population, suggesting that the increase in incidence in men treated with radiation might be exaggerated when comparison was made with the incidence after surgery.

Regardless of the cause of second cancers, our observation reflects the status of second cancer risk in men younger than 65 treated with some form of radiation as reported to the SEER database. There was about 100% increased risk of second bladder cancer in men receiving radiation compared with men treated with surgery. The risk of second bladder cancer observed in our study was higher than in published series including men of all ages. Brenner et al. [26] reported an increased risk of bladder cancer and rectal cancer (77% and 105% at 5 and 10 years, respectively) after radiation compared to surgery after reviewing the SEER database. At the time of prostate cancer diagnosis, the median ages of men were 70.3 years for men treated with radiation and 71.4 years for men treated with surgery, with <10% of men from either group <60 year of age. Nieder et al. [27] reported that the relative risk of bladder cancer after external beam radiotherapy, brachytherapy, and combined radiation after more than 10 years of follow-up compared to radical prostatectomy was 1.83, 0.47, and 1.64, respectively, as reported to the SEER database. Moon et al. [19] reported statistically significant increased odds of bladder cancer (odds ratio [OR] = 1.63; 95% CI, 1.44–1.84) after external beam radiation for prostate cancer, compared with men who received no prostate cancer-directed radiation. After reviewing the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) disease registry, Boorjian et al. [28] reported patients treated with radical prostatectomy were approximately half as likely to have post-treatment bladder cancer as patients who underwent radiation therapy (hazard ratio = 0.51; 95% CI, 0.29–0.89). After reviewing a large French-Canadian population-based cohort of prostate cancer patients, Bhojani et al. [30] reported 40% increased incidence (hazard ratio = 1.4; p = 0.02) of bladder cancer for men post-radiation for prostate cancer compared to men post-surgery.

Our study has several weaknesses due to the retrospective design and inherent deficiencies of data reported to the SEER program. There was no information about patients’ performance status, medical co-morbidities, or family history of cancer in the SEER database. These factors might have influenced the choice of prostate cancer treatment and, therefore, second cancer risk. Additionally, there are potential issues of under-reporting of second cancers, especially in elderly patients, to the SEER database. Our study population, comprised of men ≤65 years of age when diagnosed with prostate cancer, may mitigate this risk.

Despite the above-stated weaknesses, our observations, together with others, underscore the challenges prostate cancer survivors face, in the years after prostate cancer diagnosis. Higher risks of any second malignancy, including lung, bladder, and rectal/RJ cancers, among young men treated with radiation for prostate cancer compared with surgery, regardless of underlying causes, suggests that early and continuous vigorous second cancer screening practice may be beneficial for younger prostate cancer survivors.

In conclusion, compared to men treated with surgery, younger prostate cancer survivors had an increased risk of second malignancy, including lung, bladder, and rectum/RJ cancer, after treatment with external beam or combined radiation. The cause of the observed increase in second cancer risk in men treated with radiation is likely multifactorial. Although the true extent of increase in second cancer risk (specifically second rectum/RJ cancer) after radiation requires further investigation, second cancer screening should be an essential aspect of post-treatment survivorship care plan for young prostate cancer survivors.

Conflict of Interest

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

Acknowledgements

We thank Mrs. Laura Finger for her excellent editorial and administrative assistance.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2020.00857.
References


Purpose: In radiotherapy for head and neck cancer, it is crucial to define the appropriate treatment volume to determine treatment outcome and toxicity. We examined the feasibility of omitting elective high retropharyngeal lymph node (RPLN) irradiation in patients with oropharyngeal cancer.

Materials and Methods: We performed a retrospective review of 189 patients with oropharyngeal squamous cell carcinoma who were treated with definitive or postoperative radiation therapy between 2009 and 2016. Of them, 144 (76.2%) underwent ipsilateral RPLN irradiation up to the superior border of the C1 vertebral body, while the other 45 (23.8%) were irradiated up to the transverse process of the C1 vertebra. High RPLN-treated and spared group were propensity matched based on key clinical variables.

Results: During the follow-up period, only three patients (one in the high RPLN-treated group and two in the high RPLN-spared group) developed RPLN recurrence. There were no significant between-group differences in 5-year locoregional failure-free survival (82.8% vs. 90.6%; p = 0.14), distant metastasis-free survival (93.1% vs. 93.3%; p = 0.98) and RPLN failure-free survival (99.3% vs. 95.0%; p = 0.09). In the matched groups, high RPLN-spared patients received a lower mean ipsilateral parotid gland dose (mean, 20.8 Gy vs. 29.9 Gy; p < 0.001) and had a lower incidence of chronic xerostomia (grade 0, 43.5% vs. 13.0%; p = 0.023) at 1 year after radiotherapy compared with high RPLN-treated patients.

Conclusion: Omission of ipsilateral high RPLN irradiation seems safe, and reduces the incidence of chronic xerostomia in patients with oropharyngeal squamous cell carcinoma.

Keywords: Oropharyngeal cancer, Retropharyngeal lymph node, Locoregional recurrence, Xerostomia

Introduction

The incidence of tobacco-associated head and neck squamous cell carcinoma has steadily declined over the past few decades, whereas the incidence of human papillomavirus (HPV)-induced oropharyngeal cancer (OPC) has been increasing [1–3]. Patients with HPV-induced OPC are younger and have fewer comorbidities and a more favorable prognosis than those with tobacco-associated squamous cell carcinoma [4–6]. While cisplatin-based concurrent chemoradiotherapy (CCRT) is the standard treatment for OPC, some patients who present at an early stage are candidates for primary surgery [7]. Patients with HPV-induced OPC show a good response to CCRT, and the 5-year overall survival is approximately 80% to 90% [8]. However, the treatment-related morbidity is considerable. Almost all patients suffer from acute oral mucositis, chronic xerostomia, and loss of taste [9]. Since patients with HPV-induced OPC are generally young and likely to survive their disease, treatment-related toxicity is concerning [10–12].
Intensity-modulated radiation therapy allows conformal dose distribution around the tumor and organs-at-risk. Delineation of the clinical target volume (CTV) and organs-at-risk is very important because treatment outcomes and toxicities depend on treatment plan. However, physicians often disagree about the optimal target definition. In nasopharyngeal, oropharyngeal, and hypopharyngeal cancers, there is a risk of metastasis to the retropharyngeal lymph nodes (RPLNs) [13]. Since high RPLNs are located adjacent to the parotid glands and pharyngeal constrictor muscles, irradiation of these regions has been shown to compromise the quality of life (QOL) of patients with head and neck cancer [14,15]. According to consensus guidelines for the delineation of neck node levels, in patients with primary pharyngeal involvement, the bilateral RPLNs should be treated up to the upper edge of the C1 vertebral body/hard palate cranially [13]. However, previous studies indicate that sparing the contralateral high RPLN is associated with minimal risk of failure and improves QOL [16–18]. Kjems et al. [19] argued that ipsilateral RPLN sparing is safe in patients with OPC in whom the posterior pharyngeal wall is not involved. In this study, we aimed to evaluate the safety and feasibility of omitting ipsilateral high RPLN irradiation in patients with OPC. Background and purpose should be stated clearly.

Materials and Methods

1. Patient selection
The Institutional Review Board of Seoul National University Hospital and Seoul National University Bundang Hospital approved this study (No. B-1805-471-402). The informed consent was waived. We retrospectively reviewed 189 patients with pathologically proven oropharyngeal squamous cell carcinoma who received radiotherapy (RT) at the aforementioned hospitals between January 2009 and December 2016. The inclusion criteria were age > 18 years and the Eastern Cooperative Oncology Group performance status of 0–2. The exclusion criteria were presence of distant metastasis or initial evidence of RPLN involvement.

2. Treatment
Of the 189 patients, 160 (84.7%) received intensity-modulated radiation therapy, and 29 (15.3%) received three-dimensional conformal radiotherapy. Definitive radiotherapy typically included a dose of 67.5–70 Gy to high-risk regions. Patients treated postoperatively or after induction chemotherapy received 60–63 Gy to high-risk regions. The doses for intermediate- and low-risk areas were 54–56 Gy and 42–48 Gy, respectively. Among all patients, 62 (32.8%) received definitive CCRT, 53 (28.0%) underwent induction chemotherapy followed by CCRT/RT alone, 60 (31.7%) were offered surgery and postoperative CCRT/RT alone, 5 (2.6%) underwent induction chemotherapy followed by surgery and postoperative CCRT/RT alone, and 9 (4.8%) were treated with definitive RT alone. After radiotherapy, patients were evaluated at 2 weeks after treatment. They were initially followed up every 1–2 months, followed by every 3 months for a year, every 3–4 months for 2 years, and every 6 months thereafter. During follow-up, physical examination, nasopharyngeal laryngoscopy, and imaging studies including contrast-enhanced neck computed tomography and/or magnetic resonance imaging were performed. Symptoms related to xerostomia were evaluated using the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer toxicity scale at each follow-up visit [20].

3. RPLN evaluation
To evaluate the coverage of the dose to the RPLN and parotid gland, we retrospectively reviewed each patient’s treatment plan. According to consensus guidelines, the cranial border of the RPLN is the upper edge of the C1 vertebral body/hard palate [13]. Patients were classified into the high RPLN-treated group (n = 144) when the CTV sufficiently encompassed the RPLNs between the upper edge of the C1 vertebral body and the inferior border of the transverse process of the C1 vertebra. The remaining patients (n = 45) were classified into the high RPLN-spared group.

4. Statistical analysis
To compare clinical variables according to high RPLN treatment status, Student t-test, Wilcoxon rank sum test, and chi-square test were used, as appropriate. To control for differences in characteristics between the two groups according to high RPLN treatment status, we conducted the propensity score matching analysis. The selected variables were primary site, T-stage, distances of the gross tumor volume (GTV) from parotid, RT technique, and surgery. Using propensity scores, the high RPLN spared group and treated group were matched with a 1:2 nearest-neighbor matching protocol with a caliper width of 0.3 standard deviations. A multivariate Cox proportional hazard model and Kaplan-Meier survival analysis were used to determine factors associated with recurrence outcomes. Statistical analyses were performed using R software (version 3.5.3; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at p < 0.05.

Results

1. Patient characteristics
Table 1 summarized patient characteristics of the two groups according to high RPLNs treatment status. The median follow-up
Table 1. Patients' characteristics in the entire cohort and propensity score matched cohort

<table>
<thead>
<tr>
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<th>Entire cohort (before matching)</th>
<th>Matched cohort (after matching)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-RPLNs spared (n = 45)</td>
<td>High-RPLNs treated (n = 144)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65.4 ± 9.2</td>
<td>65.1 ± 9.6</td>
</tr>
<tr>
<td>Follow-up duration (mo)</td>
<td>59.6 ± 22.9</td>
<td>56.4 ± 26.4</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>40 (88.9)</td>
<td>121 (84.0)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (11.1)</td>
<td>23 (16.0)</td>
</tr>
<tr>
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</tr>
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<td>68 (47.9)</td>
</tr>
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<td>Ex-smoker</td>
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<tr>
<td>HPV status</td>
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<td></td>
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<tr>
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<td>10 (22.2)</td>
<td>34 (23.6)</td>
</tr>
<tr>
<td>Positive</td>
<td>25 (55.6)</td>
<td>79 (54.9)</td>
</tr>
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<td>p16 status</td>
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<td>1 (0.7)</td>
</tr>
<tr>
<td>Soft palate</td>
<td>2 (4.4)</td>
<td>6 (4.2)</td>
</tr>
<tr>
<td>Tongue base</td>
<td>16 (35.6)</td>
<td>8 (5.6)</td>
</tr>
<tr>
<td>Tonsil</td>
<td>24 (53.3)</td>
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</tr>
<tr>
<td>Vallecular</td>
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<tr>
<td>2b</td>
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<td>74 (51.4)</td>
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<td>2c</td>
<td>6 (13.3)</td>
<td>17 (11.8)</td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Prescribed dose (Gy)</td>
<td>65.7 ± 3.2</td>
<td>66.3 ± 2.6</td>
</tr>
<tr>
<td>Radiotherapy technique</td>
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<tr>
<td>3D-CRT</td>
<td>4 (8.9)</td>
<td>25 (17.4)</td>
</tr>
<tr>
<td>IMRT</td>
<td>41 (91.1)</td>
<td>119 (82.6)</td>
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<tr>
<td>Parotid to GTVpn distance (cm)</td>
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<td>&lt; 0.5</td>
<td>10 (22.2)</td>
<td>65 (45.1)</td>
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<td>≥ 0.5 and &lt; 1</td>
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<td>42 (29.2)</td>
</tr>
<tr>
<td>≥ 1</td>
<td>18 (40.0)</td>
<td>37 (25.7)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).
RPLNs, retropharyngeal lymph nodes; HPV, human papillomavirus; AJCC, American Joint Committee on Cancer; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; GTVpn, gross tumor volume for primary tumor mass and lymph node metastases.

https://doi.org/10.3857/roj.2021.00381
time was 66 months (range, 2 to 136 months), and the median age was 64 years (range, 43 to 90 years). Of the entire cohort, high RPLNs were treated in 144 (76.2%) and spared in 45 (23.8%). There were no significant between-group differences in age, sex, smoking, HPV/p16 status, and clinical T/N stages. The distances of the GTV from the parotid and anatomic subsites were significantly associated with the high RPLN treatment status. The high RPLNs of patients with tongue-base primary tumors were often spared because the tongue base is located relatively far from the high RPLN. After propensity score matching, a subset of 69 patients were chosen for matched pairs, which exhibiting similar baseline characteristics based on our propensity score model.

2. Pattern of failure

Of the 189 patients, 36 (19.0%) showed recurrence after radiotherapy. The median time to failure was 11 months (range, 3 to 50 months). The failure patterns are shown in Fig. 1E. The incidences of local, regional, and distant failure were 9.0%, 10.1%, and 5.8%, respectively. Table 2 demonstrates the results of the univariate and multivariate Cox proportional hazard analyses for locoregional failure-free survival (LRFFS). Multivariate analysis revealed that old age was associated with poor prognosis, and HPV positivity was associated with a favorable prognosis. Kaplan-Meier analysis showed that high RPLN treatment was not significantly associated with LRFFS, and RPLN failure-free survival in the entire and the matched cohort (Fig. 1A–1D). When comparing the two groups for entire cohort, the 5-year rates of LRFFS, RPLN failure-free survival, distant metastasis-free survival, and overall survival were 82.8% and 90.6% (p = 0.14), 99.3% and 95.0% (p = 0.09), 93.1% and 93.3% (p = 0.98), and 85.7% and 87.2% (p = 0.34) in the treated and spared groups, respectively.

Table 3 summarizes the characteristics of the patients who developed RPLN recurrence. One patient (1/144, 0.07%) presented with RPLN failure combined with local recurrence from palate to the skull base. Two (2/45, 4.4%) patients in the high RPLN-treated group developed RPLN recurrence; one of them had simultaneous lung metastasis and the other had RPLN failure with level II nodal failure. The patient with regional recurrence alone was successfully managed with stereotactic body radiation therapy (SBRT) to the RPLN area, level II neck dissection, and postoperative CCRT. No evidence of RPLNs recurrence until 22 months after SBRT. The other two patients died from disease progression.

3. Ipsilateral parotid dose and xerostomia

Table 4 shows the results of elective high RPLNs treatment. After matching, patients in the high RPLN-treated group had a signifi-

![Fig. 1. Kaplan-Meier plot for clinical outcomes of (A, B) locoregional failure-free survival (LRFFS), and (C, D) retropharyngeal failure-free survival (RPFFS) according to high RPLNs treatment status in the entire cohort and in the matched cohort. (E) The distribution of first failure pattern. RPLNs: retropharyngeal lymph nodes.](https://doi.org/10.3857/roj.2021.00381)
significantly higher mean ipsilateral parotid dose than those in the high RPLN-spared group (29.9 Gy vs. 20.8 Gy; \( p < 0.001 \)). Significantly more patients in the high RPLN-spared group fulfilled the Quantitative Analyses of Normal Tissue Effects in the Clinic criteria for parotid gland dose constraints (unilateral parotid mean dose < 20 Gy) than in the high RPLN-treated group (39.1% vs. 6.5%; \( p < 0.001 \)) [21]. Consequently, the incidence of chronic xerostomia at one year after radiotherapy was significantly lower in the high RPLN-spared group than in the high RPLN-treated group (no chronic xerostomia, 43.5% vs. 13.0%; \( p = 0.023 \)). Fig. 2 represents the dose distribution of the high RPLN-treated group and the high RPLN-spared group. Comparing two patients with similar clinical conditions, high RPLNs sparing seems to be an effective way of reducing radiation dose for bilateral parotid glands. High RPLNs spared patient had lower mean doses to ipsilateral parotid gland (17.7 Gy vs. 24.7 Gy), and contralateral parotid gland (7.0 Gy vs. 12.8 Gy) than high RPLNs treated patient.

**Discussion and Conclusion**

OPC has been associated with a risk of RPLN metastasis, with RPLN involvement in approximately 10%–20% of patients [22–24]. Since RPLNs are anatomically difficult to approach, standard neck dissection does not include these nodes. Thus RPLN metastasis must be diagnosed based on radiographic findings alone, this makes it difficult to diagnose RPLN accurately [25]. These nodes can be effectively treated using CCRT. However, this may significantly compromise patients’ QOL, since these nodes are located proximal to radiosensitive structures such as the parotid gland, posterior pharyngeal wall, and pharyngeal constrictor muscles. Therefore, there is ongoing debate regarding the delineation of radiotherapy fields. According to consensus guidelines, the cranial border for RPLN

---

**Table 2.** Univariate and multivariate survival analysis for locoregional failure-free survival

<table>
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<tr>
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<td>95% CI</td>
<td>p-value</td>
<td>HR</td>
<td>95% CI</td>
<td>p-value</td>
<td></td>
</tr>
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<td>Age</td>
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<td>1.03–1.11</td>
<td>0.001</td>
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<td>1.02–1.11</td>
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<td>Clinical T stage, T3/4</td>
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<td>0.074</td>
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<td>0.90–4.45</td>
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<td>1.09–7.33</td>
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<td>2.35</td>
<td>0.89–6.20</td>
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<tr>
<td>Positive</td>
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<td>0.13–0.71</td>
<td>0.005</td>
<td>0.40</td>
<td>0.17–0.92</td>
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<tr>
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<td>0.47</td>
<td>0.18–1.25</td>
<td>0.130</td>
<td>0.38</td>
<td>0.14–1.04</td>
<td>0.061</td>
<td></td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; HPV, human papillomavirus.

**Table 3.** Demographics and treatment of patients with RPLN recurrences

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th></th>
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<th>Patient 2</th>
<th></th>
<th></th>
<th>Patient 3</th>
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<tbody>
<tr>
<td>Age (yr)</td>
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<td>63</td>
<td>70</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage (AJCC 7th)</td>
<td>cT4N1M0</td>
<td>cT2N2bM0</td>
<td>cT1N3M0</td>
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</tr>
<tr>
<td>Location</td>
<td>Primary</td>
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<tr>
<td></td>
<td>Soft palate</td>
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<td>Tonsil</td>
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<tr>
<td>High-RPLNs to GTV (cm)</td>
<td>( \leq 1 )</td>
<td>( \leq 1 )</td>
<td>( &gt; 1 )</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Treatment</td>
<td>Purpose</td>
<td>Radial</td>
<td>Radial</td>
<td></td>
<td></td>
<td></td>
<td>Radial</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treated</td>
<td>Spared</td>
<td></td>
<td></td>
<td></td>
<td>Spared</td>
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</tr>
<tr>
<td>Recurrence</td>
<td>First failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Disease-free interval (mo)</td>
<td>11</td>
<td>16</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

AJCC, American Joint Committee on Cancer; RPLNs, retropharyngeal lymph nodes; GTV, gross tumor volume.
treatment is the upper edge of the C1 vertebral body/hard palate [13]. Unlike nasopharyngeal cancer, most OPCs are located inferior to the lateral process of the C1 vertebra. Due to their anatomic location, metastasis to a high RPLN requires retrograde lymphatic flow from the OPC, and metastases to these nodes are considered rare. Tang et al. [23] showed that RPLN metastasis is associated with increased nodal burden. None of our patients with single node positivity exhibited RPLN metastasis. This suggests that RPLN metastasis occurs late in the disease course, and the treatment of RPLN should be individualized based on each patient’s risk level.

Due to the excellent prognosis of HPV-induced OPC, there has been an increasing interest in the QOL of patients with OPC [1,12]. Currently, treatment de-escalation, which can be achieved by lowering the dose or reducing the field of radiation, has received attention. Since Eisbruch et al. [26] reported three marginal RPLN failures in 80 patients with OPC, it has been recommended that RPLNs be treated bilaterally. However, in their prospective study, Spencer et al. [16] showed that sparing the contralateral RPLN and high level II nodes is safe and improves the QOL of patients with head and neck cancer. There is consensus regarding contralateral high RPLN sparing [17,18]. However, the safety of sparing ipsilateral RPLNs has not been sufficiently evaluated. Previously, Kjems et al. [19] reported that ipsilateral RPLNs were excluded from the elective target volume in 469 patients with OPC without posterior pharyngeal wall involvement; only one of them developed RPLN recurrence. In that study, the CTV encompassed the GTV with an additional 14-mm margin, and ipsilateral RPLNs were not included in the CTV unless the RPLN areas were close to the GTV or the posterior pharyngeal wall was involved.

In our study, three RPLN recurrences (1.6%) occurred among 189 patients with OPC who showed no evidence of RPLN metastasis at initial diagnosis. Of the three patients with recurrence, the RPLNs of one (1/144, 0.07%) was treated and those of the others (2/45, 4.4%) were untreated. One patient in the high RPLN-spared group developed RPLN recurrence with pulmonary lymphangitic metastasis. In this patient, there was a short distance (≤1 cm) from the primary GTV to the high RPLN. Retrospectively, we believe this patient would have benefited from high RPLN treatment. Another patient in the high RPLN-spared group developed RPLN recurrence and subsequent level II nodal failure at 50 and 62 months after RT, respectively. This patient underwent SBRT to treat isolated RPLN recurrence. After SBRT, there was no evidence of RPLN recurrence until the last follow-up. However, this patient developed level II recurrence with extracapsular extension and underwent modified radical neck dissection and postoperative CCRT without RPLN treatment. Currently, there is no evidence of recurrence or severe toxicity after the third course of RT. Historically, RPLN recurrence

---

Table 4. Ipsilateral parotid mean dose and patient reported xerostomia in the entire cohort and propensity score matched cohort

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort (before matching)</th>
<th>Matched cohort (after matching)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-RPLNs spared(n = 46)</td>
<td>High-RPLNs treated (n = 144)</td>
<td>p-value</td>
</tr>
<tr>
<td>Mean ipsilateral parotid dose (cGy)</td>
<td>2,021.7 ± 477.2 (480-2,987)</td>
<td>2,907.7 ± 801.1 (1,575-6,875)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&gt; 20 Gy</td>
<td>21 (46.7)</td>
<td>14 (9.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>18 (40.0)</td>
<td>14 (9.8)</td>
<td>0.026</td>
</tr>
<tr>
<td></td>
<td>6 (13.3)</td>
<td>9 (6.2)</td>
<td>0.014</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (21.7)</td>
<td>1 (2.2)</td>
<td>0.014</td>
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</tbody>
</table>

Xerostomia ≥ Grade 1

<table>
<thead>
<tr>
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<th>Entire cohort (before matching)</th>
<th>Matched cohort (after matching)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-RPLNs spared(n = 23)</td>
<td>High-RPLNs treated (n = 46)</td>
<td>p-value</td>
</tr>
<tr>
<td>At 6 month</td>
<td>No</td>
<td>Yes</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>8 (17.8)</td>
<td>9 (20.9)</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Unknown</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>33 (73.3)</td>
<td>33 (73.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>At 12 month</td>
<td>No</td>
<td>Yes</td>
<td>0.023</td>
</tr>
<tr>
<td></td>
<td>16 (35.6)</td>
<td>23 (51.1)</td>
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<tr>
<td></td>
<td>Yes</td>
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<td>0.023</td>
</tr>
<tr>
<td></td>
<td>21 (46.7)</td>
<td>35 (76.1)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

RPLNs: retropharyngeal lymph nodes.

Values are presented as average ± standard deviation or number (%).
was considered difficult to salvage. Modern radiotherapy techniques make it possible for RPLN re-irradiation with tolerable toxicity and good local control [27,28]. However, treatment for RPLN failure is still challenging because of its close proximity to critical structures such as the carotid artery, and careful patient selection is necessary to ensure safe outcomes following RPLN sparing [22,28,29].

Here, we present evidence that RPLN recurrence is rare, and careful sparing of the RPLN helps reduce chronic xerostomia in patients with OPC. Patients in the high RPLN-spared group had a lower ipsilateral parotid dose and, consequently, less chronic xerostomia at 1 year than those in the high RPLN-treated group in entire cohort (grade 0, 35.6% vs. 14.6%; p = 0.014) and matched cohort (grade 0, 43.5% vs. 13.0%; p = 0.023). As sparing of the high RPLN could result in more RPLN recurrences in some settings, the high RPLNs should be treated in patients with risk factors such as posterior pharyngeal wall involvement, bulky nodal burden, and primary tumor mass near the high RPLNs. Further studies are needed to identify the risk factors for RPLN recurrence for ensuring the safety of high RPLN sparing.

**Conflict of Interest**

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

**References**


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**Fig. 2.** Dose distribution comparison of adjuvant radiotherapy plans using volume modulated arc therapy technique for two tonsil cancer patients staged pT1N2bM0, who were (A–C) treated for high RPLNs (retropharyngeal lymph nodes) and (D–F) spared for high RPLNs. CTV, clinical target volume.


Purpose: This study was conducted to evaluate prognosis of patients with level I/II axillary lymph node metastases from occult breast cancer (OBC).

Materials and Methods: Data of 53 patients with OBC who received axillary lymph node dissection (ALND) positive/negative (+/–) breast-conserving surgery between 2001 and 2013 were retrospectively collected at seven hospitals in Korea. The median number of positive lymph nodes (+LNs) was 2. Seventeen patients (32.1%) had >3 +LNs. A total of 48 patients (90.6%) received radiotherapy. Extents of radiotherapy were as follows: whole-breast (WB; n = 11), regional lymph node (RLN; n = 2), and WB plus RLN (n = 35).

Results: The median follow-up time was 85 months. Recurrence was found in four patients: two in the breast, one in RLN, and one in the breast and RLN. The 5-year and 7-year disease-free survival (DFS) rates were 96.1% and 93.5%, respectively. Molecular subtype and receipt of breast radiotherapy were significantly associated with DFS. Patients with estrogen receptor negative, progesterone receptor negative, and human epidermal growth factor receptor 2 negative (ER-/PR-/HER2-) subtype had significantly lower 7-year DFS than those with non-ER-/PR-/HER2- tumor (76.9% vs. 100.0%; p = 0.03). Whole breast irradiation (WBI) was significantly associated with a higher 7-year DFS rate (94.7% for WBI group vs. 83.3% for non-WBI group; p = 0.01). Other factors including patient’s age, number of +LNs, taxane chemotherapy, and RLN irradiation were not associated with DFS.

Conclusion: Patients with OBC achieved favorable outcome after ALND and breast-targeting treatment. Molecular subtype and receipt of WBI was significant factors for DFS.

Keywords: Unknown primary neoplasms, Breast neoplasm, Lymph nodes, Radiotherapy

Introduction

Cancer of unknown primary site (CUP) is a rare disease entity in which metastatic cancerous lesions present without any evidence of primary tumor. In most patients with CUP, the disease tends to disseminate early and respond poorly to systemic agents [1]. However, there are favorable subsets of patients who have experienced prolonged survival after treatment for putative primary origin [1,2].
Cases of axillary lymph node adenocarcinoma with unknown primary site (AxCUP) which is detected in females are one of the favorable subsets of CUP [1]. AxCUP in females is generally regarded as a presentation of occult breast cancer (OBC). Hence, it has been recommended that AxCUP in females needs to be managed as per the treatment for primary breast cancer [3].

OBC accounts for only 0.1%–1.0% of all breast cancer cases [4,5]; therefore, there was little evidence regarding optimal treatment strategies for OBC. Recent studies reported that axillary lymph node dissection (ALND) along with breast-targeting treatment such as mastectomy or breast-conserving surgery (BCS) resulted in favorable survival among patients with OBC [5–7]. The addition of postoperative radiotherapy to surgical treatment was associated with improved survival when compared to surgery alone [5,8]. Nonetheless, there is little consensus regarding which area should be irradiated for patients with OBC. Given that patients with OBC have no cancerous lesion in the ipsilateral breast even after detailed imaging studies, it is questionable whether the breast needs to be irradiated or not. Moreover, it is unknown whether prophylactic radiotherapy to uninvolved regional lymph nodes (RLNs), such as supravacular lymph nodes (SCN) or internal mammary lymph nodes (IMN), has prognostic impact in patients with OBC with axillary lymph node involvement.

In this study, we evaluated prognosis and patterns of failure in patients with axillary lymph node metastasis from OBC.

Materials and Methods

1. Patients and treatments
Females who received breast-conserving treatment (BCT) including ALND and/or BCS for OBC between January 2001 and December 2013 were included in this study. OBC was defined as adenocarcinoma or poorly differentiated carcinoma in axillary lymph nodes without an evidence of primary breast tumor on physical examination and imaging studies including mammography, breast ultrasonography (US), magnetic resonance imaging (MRI) of the breast, chest computed tomography (CT), or positron emission tomography-computed tomography (PET-CT). Patients were ineligible for inclusion in this study if they had cancerous lesions in other organs other than the axillary lymph nodes, previous history of other cancer, or previous radiotherapy. Patients who had mastectomy with subsequent identification of primary breast tumor on pathologic evaluation were excluded from this study. Seven hospitals that are members of the Korean Radiation Oncology Group provided data of 53 patients who met the inclusion criteria of this study. The Institutional Review Board of each hospital approved this study. The informed consent was waived.

Mammography and either breast US or breast MRI were performed in all patients. All four patients who did not undergo breast MRI were evaluated with breast US and PET-CT. ALND and/or BCS was administered to all patients. Blind upper outer quadrantectomy was performed in 11 patients, while 42 patients underwent no breast surgery. The median number of dissected lymph nodes was 17 (range, 3 to 62). Immunohistochemical staining for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) of tumor in lymph nodes was performed. ER/PR positivity was defined as an Allred score of 3–8 by immunohistochemistry (IHC). HER2 positivity was defined as either staining 3+ by IHC or 2+ by IHC with positive fluorescence in situ hybridization (FISH) or silver in situ hybridization (ISH). Taxane-based chemotherapy was provided to 71.7% of patients. Neoadjuvant systemic treatment was administered before ALND in five patients (9.4%). Among 15 patients with HER2-positive tumor, eight patients (53.3%) underwent anti-HER2 agents. Patient’s characteristics are shown in Table 1. Radiotherapy was provided to all but five patients. Fields and doses of radiotherapy were decided according to each institutional policy. Whole breast or RLNs was treated with a total dose of 40.05–50.4 Gy at 1.8–2.67 Gy per fraction. Three patients received intensity-modulated radiotherapy, while others underwent three-dimensional conformal radiotherapy. Details of radiation fields are depicted in Table 2.

2. Statistical analysis
Overall survival (OS), disease-free survival (DFS), and breast cancer-free survival (BCFS) were defined as the interval from the date of ALND or the first day of neoadjuvant systemic treatment to death, cancer recurrence, and ipsilateral breast cancer occurrence, respectively. Survival probability was estimated using the Kaplan–Meier method and the log-rank test was used to compare survival between groups with different variables. Factors with a significance at p < 0.05 on univariate analysis were included in a multivariate Cox stepwise regression analysis. Statistical significance was calculated at 95% confidence level (p < 0.05). Statistical analyses were performed using SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA).

Results
The median follow-up time was 85 months (range, 7 to 178 months). Recurrence was found in four patients (7.5%): two (3.7%) in the ipsilateral breast, one (1.9%) in RLN, and one (1.9%) in the ipsilateral breast and RLN (Table 3). No patient showed distant metastases. Cancer in the ipsilateral breast occurred in three patients (5.6%) within 7 to 93 months after the completion of treatment.
of the three patients who developed breast cancer, one did not have breast irradiation while two received radiotherapy to the ipsilateral breast for the treatment of OBC. The 5-year DFS, BCFS, and OS of all patients were 96.1%, 98.0%, and 96.0%, respectively. The 7-year DFS, BCFS, and OS of all patients were 93.5%, 95.4%, and 96.0%, respectively. In the univariate analyses, molecular subtype and receipt of breast radiotherapy were significant factors for DFS. Patients with ER-/PR-/HER2- subtype had significantly lower 7-year DFS than those with non-ER-/PR-/HER2- tumor (76.9% vs. 100.0%; p = 0.03). In addition, whole breast irradiation (WBI) was significantly associated with a higher 7-year DFS rate (94.7% for WBI group vs. 83.3% for non-WBI group; p = 0.01) (Fig. 1). However, in multivariate analyses, there were no factors significantly associated with DFS. Other factors such as patient’s age, number of metastatic lymph nodes, ratio of positive lymph nodes, types of breast surgery, RLN irradiation, and taxane chemotherapy were not related to patient’s DFS.

Discussion and Conclusion

In this study, we found that patients with OBC presenting as AX-CUP achieved favorable outcome after ALND and BCT including WBI and systemic treatment. Tumor subtype of non-ER-/PR-/HER2- and administration of WBI was significantly associated with for OBC. Of the three patients who developed breast cancer, one did not have breast irradiation while two received radiotherapy to the ipsilateral breast for the treatment of OBC. The 5-year DFS, BCFS, and OS of all patients were 96.1%, 98.0%, and 96.0%, respectively. The 7-year DFS, BCFS, and OS of all patients were 93.5%, 95.4%, and 96.0%, respectively. In the univariate analyses, molecular subtype and receipt of breast radiotherapy were significant factors for DFS. Patients with ER-/PR-/HER2- subtype had significantly lower 7-year DFS than those with non-ER-/PR-/HER2- tumor (76.9% vs. 100.0%; p = 0.03). In addition, whole breast irradiation (WBI) was significantly associated with a higher 7-year DFS rate (94.7% for WBI group vs. 83.3% for non-WBI group; p = 0.01) (Fig. 1). However, in multivariate analyses, there were no factors significantly associated with DFS. Other factors such as patient’s age, number of metastatic lymph nodes, ratio of positive lymph nodes, types of breast surgery, RLN irradiation, and taxane chemotherapy were not related to patient’s DFS.

Table 1. Patient’s characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>54 (32–79)</td>
</tr>
<tr>
<td>≤ 50</td>
<td>22 (41.5)</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>31 (58.5)</td>
</tr>
<tr>
<td>Breast MRI</td>
<td></td>
</tr>
<tr>
<td>Done</td>
<td>49 (92.5)</td>
</tr>
<tr>
<td>Not done</td>
<td>4 (7.5)</td>
</tr>
<tr>
<td>Breast US</td>
<td></td>
</tr>
<tr>
<td>Done</td>
<td>49 (92.5)</td>
</tr>
<tr>
<td>Not done</td>
<td>4 (7.5)</td>
</tr>
<tr>
<td>PET-CT</td>
<td></td>
</tr>
<tr>
<td>Done</td>
<td>50 (94.3)</td>
</tr>
<tr>
<td>Not done</td>
<td>3 (5.7)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
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<tr>
<td>CMF</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>AC</td>
<td>9 (17.0)</td>
</tr>
<tr>
<td>AC-T</td>
<td>36 (67.9)</td>
</tr>
<tr>
<td>AT</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Taxol-carboplatin</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>None</td>
<td>4 (7.5)</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td></td>
</tr>
<tr>
<td>Done</td>
<td>26 (49.1)</td>
</tr>
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<td>27 (50.9)</td>
</tr>
<tr>
<td>Number of dissected LNs</td>
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<tr>
<td>≤ 18</td>
<td>17 (3–62)</td>
</tr>
<tr>
<td>&gt; 18</td>
<td>28 (52.8)</td>
</tr>
<tr>
<td>Number of positive LNs</td>
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</tr>
<tr>
<td>≤ 3</td>
<td>2 (0.0–31)</td>
</tr>
<tr>
<td>4–9</td>
<td>36 (67.9)</td>
</tr>
<tr>
<td>&gt; 9</td>
<td>13 (24.5)</td>
</tr>
<tr>
<td>Ratio of positive LNs</td>
<td>4 (7.6)</td>
</tr>
<tr>
<td>Molecular subtype&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>ER+ or PR+ HER2-</td>
<td>15 (28.3)</td>
</tr>
<tr>
<td>ER+ or PR+ HER2+</td>
<td>11 (20.8)</td>
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<tr>
<td>ER- PR- HER2+</td>
<td>4 (7.5)</td>
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<tr>
<td>ER- PR- HER2-</td>
<td>17 (32.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (11.3)</td>
</tr>
</tbody>
</table>

Values are presented as median (range) or number (%). LNs, lymph nodes; MRI, magnetic resonance imaging; US, ultrasonography; PET-CT, positron emission tomography-computed tomography; CMF, cyclophosphamide, methotrexate, and fluorouracil; AC, doxorubicin and cyclophosphamide; AC-T, doxorubicin and cyclophosphamide followed by paclitaxel or docetaxel; AT, doxorubicin and paclitaxel or docetaxel; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

<sup>a</sup>Five patients received neoadjuvant systemic treatment before axillary lymph node dissection. Of the five patients, one showed pathological complete response of axillary lymph nodes in surgical specimens.

Table 2. Extent of radiotherapy according to lymph node status

<table>
<thead>
<tr>
<th>Extent of radiotherapy</th>
<th>Number of positive lymph nodes ≤ 3</th>
<th>&gt; 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast alone</td>
<td>11 (30.7)</td>
<td>-</td>
</tr>
<tr>
<td>Breast &amp; SCN</td>
<td>6 (16.7)</td>
<td>8 (47.1)</td>
</tr>
<tr>
<td>Breast &amp; axilla &amp; SCN</td>
<td>9 (25.0)</td>
<td>6 (35.3)</td>
</tr>
<tr>
<td>Breast &amp; axilla &amp; SCN &amp; IMN</td>
<td>4 (11.1)</td>
<td>2 (11.7)</td>
</tr>
<tr>
<td>Axilla alone</td>
<td>1 (5.9)</td>
<td>-</td>
</tr>
<tr>
<td>Axilla &amp; SCN</td>
<td>1 (2.7)</td>
<td>-</td>
</tr>
<tr>
<td>No radiation</td>
<td>4 (11.1)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Total</td>
<td>36 (100)</td>
<td>17 (100)</td>
</tr>
</tbody>
</table>

Values are presented as number (%). SCN, supraclavicular lymph nodes; IMN, internal mammary lymph nodes.

Table 3. Sites of recurrence according to radiotherapy field

<table>
<thead>
<tr>
<th>Radiotherapy field</th>
<th>Sites of recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breast</td>
</tr>
<tr>
<td>No radiotherapy (n = 5)</td>
<td>0</td>
</tr>
<tr>
<td>RLN alone (n = 2)</td>
<td>1</td>
</tr>
<tr>
<td>Breast alone (n = 11)</td>
<td>0</td>
</tr>
<tr>
<td>Breast + RLN (n = 35)</td>
<td>1</td>
</tr>
</tbody>
</table>

RLN, regional lymph node.
improved DFS. Patients in whom the ipsilateral breast was not irradiated had more frequent recurrence than those who received whole breast radiotherapy.

AxCUP in females is generally thought to be a metastases from primary breast cancer [2]. Therefore, thorough evaluation including breast imaging, pathologic diagnosis, and molecular-profiling is recommended to search for the primary breast lesion [3]. Defining OBC is likely to depend on what diagnostic tests are available at the time of diagnosis. About 70% of patients with OBC as defined by mammography present primary breast cancer on pathologic specimen after mastectomy [2]. With the introduction of more advanced imaging modalities like breast MRI, primary breast cancer could be identified in about two-thirds of mammographically defined OBC [9]. In our study, all but four patients were confirmed to have no lesions in the breasts by MRI. Four patients in whom breast MRI was not performed were examined using both breast imaging and pathologic examination.

**Fig. 1.** Disease-free survival according to breast radiotherapy.

**Table 4.** Prognostic factors for disease-free survival

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>DFS (%)</th>
<th>p-value</th>
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<td></td>
<td></td>
<td>5-yr</td>
<td>7-yr</td>
<td>Univariate</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50</td>
<td>22</td>
<td>95.2</td>
<td>89.6</td>
<td>0.26</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>31</td>
<td>96.8</td>
<td>96.8</td>
<td></td>
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<tr>
<td>Number of metastatic LNs (pathologic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 3</td>
<td>36</td>
<td>97.1</td>
<td>93.2</td>
<td>0.70</td>
</tr>
<tr>
<td>&gt; 3</td>
<td>17</td>
<td>94.1</td>
<td>94.1</td>
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<tr>
<td>≤ 0.2</td>
<td>36</td>
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<tr>
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<td></td>
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</tr>
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<td>75.0</td>
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<td>38</td>
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</tbody>
</table>

DFS, disease-free survival; LNs, lymph nodes; SCN, supraclavicular lymph nodes; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; IMN, internal mammary lymph nodes.
US and PET-CT and proven to have no primary breast lesion. Therefore, cases included in our study were truly OBC defined by contemporary imaging modalities. In such cases, it is challenging for oncologists to select the appropriate treatment to manage occult lesions in the ipsilateral breast.

Total mastectomy has been frequently used in patients with OBC. A study showed that 39% of OBC cases were treated with mastectomy based on the Surveillance, Epidemiology and End Results (SEER) database [8]. Similarly, 38% of Korean patients with OBC received mastectomy according to data of the Korean Breast Cancer Society cancer registry [4]. Besides, another study showed that mastectomy was more often performed than BCT if OBC patients were managed at non-academic centers (39.5% vs. 25.2%; p < 0.001) [5]. Complete removal of ipsilateral breast tissue could be an option for treatment of OBC. However, several recent studies noted that BCT is as effective as mastectomy for OBC in terms of achieving favorable survival outcome [4,5,7]. The 5-year OS rate ranges from 82% to 92% after mastectomy and was between 92% and 97% after BCT in patients with OBC presenting as AxCUP [4,5]. Likewise, we also found in the present study that survival outcome was good with BCT in patients with OBC. Given the favorable outcome with BCT which was observed in several other studies, it is reasonable and safe to provide BCT to patients with OBC.

In cases where breast conservation is planned, radiotherapy is an essential treatment for axillary presentation of OBC. In a study comparing survival outcomes of OBC according to treatment modalities, combination of ALND and radiotherapy was significantly associated with better survival than ALND alone or observation [5]. The benefit of radiotherapy was also confirmed in OBC patients with mastectomy or having a large number of metastatic lymph nodes [8]. Even if radiotherapy has been proven to be important in the management of OBC, there is little information regarding which area should be covered with radiotherapy. Most recent studies on OBC analyzed population-based data which had unavailable details of radiotherapy [4,5,8]. Even in studies presenting information about radiotherapy, almost all patients had WBI [7,10]. Thus, it has been difficult to evaluate the impact of ipsilateral breast irradiation in patients with OBC. In our study, we analyzed patients’ data from multiple hospitals where diverse radiation fields were applied. Through this analysis, we expected to evaluate the prognostic significance of breast radiotherapy in patients with OBC.

Radiotherapy to the ipsilateral whole breast can be taken for granted in the management of axillary presentation of OBC. However, as seen in our study, various radiation fields have been in use (Table 2). It was not uncommon to include the ipsilateral breast in the radiation field in patients with OBC. Previously, there were a couple of studies reporting unfavorable prognosis in OBC when breast radiotherapy was omitted. However, the studies are old and did not adopt breast MRI for the diagnosis of OBC in a large proportion of patients [11,12]. Thus, such reports cannot provide sufficient evidence for deciding the radiotherapy field for OBC defined using contemporary imaging modalities. Particularly, in OBC cases where the absence of breast lesion was confirmed using highly sensitive imaging modalities like breast MRI, there could be an attempt to exclude the breast from the irradiation field. In this study, we found that the 5-year DFS was significantly better in patients with whole breast irradiation than in those without breast radiotherapy among patients who underwent BCT. It is likely that females with OBC presenting as AxCUP have some subclinical cancer in the ipsilateral breast, which was undetectable even with contemporary imaging modalities. With the administration of radiotherapy to the breast, such subclinical primary breast cancer might be eliminated in patients with OBC. Therefore, ipsilateral WBI is thought to contribute in improving outcome of patients with OBC presenting as AxCUP. However, since the current analysis was conducted in a small cohort, further studies are necessary to determine the role of WBI in patients undergoing BCT for AxCUP.

We could not find an association between prophylactic irradiation of RLN and patient’s outcome in the current study. However, considering that the range of number of positive lymph nodes (+LNs) was wide among patients included in our study, it is difficult to objectively evaluate the impact of RLN radiotherapy through this analysis. The 5-year DFS was comparable between the patients with less than four +LNs and those with four or more +LNs in our study. Given that most patients with four or more +LNs underwent SCN or IMN radiotherapy, it is probable that the poor prognosis in patients with large number of lymph node metastasis was offset by RLN irradiation. Further studies are necessary to know the impact of RLN radiotherapy in the axillary presentation of OBC.

We acknowledge the limitations of this study. Even though we collected data from multiple hospitals, the number of cases was still small. Since only four recurrences were noted among our patients, it was difficult to perform multivariate analyses of prognostic factors for survivals. In addition, the extent of radiotherapy varied across the participating hospitals. Only a small number of patients received radiotherapy to RLNs without breast irradiation. Therefore, it is probable that the significance of WBI could not be sufficiently evaluated. Given that the axillary presentation of OBC is a rare disease entity, it is necessary to collaborate with institutions in order to determine optimal strategies for the treatment of OBC.

Despite these drawbacks, our study has important implications for the determination of optimal radiation field for OBC with axillary lymph node involvement. As the sensitivity of imaging modalities increases, there might be attempts to exclude the ipsilateral...
breast from the radiation field in the management of AxCUP in females. Our study demonstrated the importance of the extent of radiotherapy in these patients. Even in patients confirmed to have no lesion in the breast by contemporary imaging studies, it is necessary to include the ipsilateral breast in the radiation field in females with OBC presenting as AxCUP.

**Conflict of Interest**

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

**References**

Combination of yttrium–90 radioembolization with stereotactic body radiation therapy in the treatment of portal vein tumor thrombosis

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Introduction
Portal vein tumor thrombosis (PVTT) is a common complication of tumors involving the liver, occurring in about 40%–60% of cases of hepatocellular carcinoma (HCC) [1]. PVTT is commonly associated with portal vein (PV) hypertension, impaired liver function, and liver failure. Prognosis of PVTT is poor, with median survival ranging from 2 to 5 months with best supportive care [2,3]. There is currently no widely accepted consensus for the management of PVTT. Treatment options include systemic therapy, surgery, arterially directed therapies such as radioembolization, or external beam radiation. The most evident survival advantages can be attributed to

Purpose: Portal vein tumor thrombosis (PVTT) from cancer involving the liver carries a dismal prognosis, with median overall survival (OS) ranging from 2 to 5 months. While treatment with yttrium-90 (90Y) radioembolization alone may improve outcomes, overall prognosis remains poor. We hypothesize that the combination of 90Y radioembolization to the parenchymal component of the tumor and stereotactic body radiation therapy (SBRT) to the vascular component is a safe and effective means of improving outcomes.

Materials and Methods: A single center retrospective review identified 12 patients with cancers involving the liver who received both 90Y radioembolization and SBRT to the PVTT between May 2015 to August 2020. Primary endpoint was the 90-day toxicity rate by the Common Terminology Criteria for Adverse Events version 5.0. Secondary endpoints were the best response rate based on the Response Evaluation Criteria in Solid Tumors v1.1, local control rate, portal vein (PV) patency rate, and median OS.

Results: Patients received a median 90Y dose of 104.3 Gy (range, 83.3 to 131.7 Gy) and a median 5-fraction SBRT dose of 32.5 Gy (range, 27.5 to 50 Gy). There were no late toxicities reported, and only 7 acute grade 1 toxicities reported: elevation of liver function tests (17%), nausea (17%), fatigue (17%), and esophagitis (8%). Local control was 83%. 58% of patients had a patent PV after treatment. With a median follow-up time of 28 months, 1-year OS was 55% with a median OS of 14 months.

Conclusion: Combination 90Y radioembolization and SBRT appears to be safe and effective in the treatment of PVTT. Larger prospective studies are warranted to better evaluate this combination treatment approach.

Keywords: Liver, Portal vein, Hepatocellular carcinoma, Therapeutic embolization, Stereotactic body radiotherapy
surgery, with a median overall survival (OS) up to 37 months, although many patients with advanced cancer are poor surgical candidates [4–6].

Yttrium-90 (90Y) radioembolization is one viable treatment option in patients unable to undergo surgery. However, objective response rates with 90Y radioembolization alone in patients with PVTT are approximately 50% [7]. There is growing evidence that stereotactic body radiation therapy (SBRT) is also a potentially viable option for PVTT, although SBRT is rarely used alone to cover the entire area of disease in the liver [8–11]. Here, we hypothesize that the combination of 90Y radioembolization to the parenchymal component of the tumor and SBRT to the vascular invasion component is a safe and effective means of improving outcomes.

Materials and Methods

1. Data collection

We retrospectively identified 12 patients with cancers involving the liver and associated PVTT who received both 90Y radioembolization and SBRT to the PVTT between May 2015 and August 2020. The Institutional Review Board of City of Hope National Medical Center (No. 21240) approval was obtained for this study. The informed consent was waived as this was a retrospective study. Demographic, clinical, and treatment factors were recorded. Primary endpoints were treatment complication rate and toxicity rate by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All toxicities ≤ 3 months (90 days) after treatment completion were considered acute, and all others were considered late. Toxicities were reported during weekly on treatment visits and 1–3 month follow-up visits by the attending or resident physician. When quantifying hepatic impairment, the following criteria were used based on the CTCAE v5.0: grade 1, alanine aminotransferase/aspartate aminotransferase (ALT/AST) 1–3.0 times the upper limit of normal (ULN) or bilirubin 1–1.5 times ULN; grade 2, ALT/AST 3–5 times ULN or bilirubin 1.5–3 times ULN; grade 3, ALT/AST 5–20 times ULN or bilirubin 3–10 times ULN; grade 4, ALT/AST > 20 times ULN or bilirubin > 10 times ULN. For the purposes of our analysis, we chose to use the term “elevated liver function tests (LFTs)” to capture this toxicity. Toxicity data is recorded for all patients using a “toxicity assessment” smartsheet on the Epic electronic medical record system. This is a regular part of our workflow and is almost always filled out.

Secondary endpoints were the best response rate, PV patency rate, 1-year OS rate, and median OS. Best response rates were determined based on the Response Evaluation Criteria in Solid Tumors criteria (RECIST v1.1). Treatment response was evaluated based on the vascular component of treatment. A complete response (CR) was defined as no tumor within the PV, a partial response (PR) was defined as decreased tumor within the PV, stable disease (SD) was defined as stable tumor within the PV, and progressive disease (PD) was defined as tumor growing within the PV. PV patency was determined based on radiologist report and viewing the scan for confirmation. 1-year OS rate was based on the time from start of SBRT to the time of death or most recent follow-up.

2. Treatment

All patients were reviewed in a weekly multidisciplinary tumor board dedicated to upper gastrointestinal malignancies. It is our general principle to use 90Y radioembolization followed by SBRT to treat patients all patients who are not surgical candidates with HCC with PVTT. Reasons that may preclude a patient from surgery include comorbidities such as cirrhosis and diffuse or multifocal disease. Our approach has been to deliver 90Y radioembolization to the parenchymal component of the tumor followed by SBRT to the vascular invasion component of the tumor. SBRT was typically planned from the start. When we first started this combination treatment modality, we waited until after 90 days after 90Y radioembolization to initiate SBRT because we typically do not see the maximum effect of 90Y until after 90 days. However, our experience has progressively shown that PVTT does not respond to 90Y alone, so we have been more routinely offering SBRT sooner within 1–3 months and not wait 90 days to evaluate response. Fig. 1 illustrates the overall timeline for 90Y radioembolization and SBRT treatment planning and evaluation.

For 90Y radioembolization, all patients underwent a standardized pretreatment workup consisting of clinical evaluation, laboratory and imaging assessment, a mapping angiographic procedure, and technetium-99 macroaggregated albumin scintigraphy. 90Y-microspheres (Sirtex, Woburn, MA, USA) were administered to the appropriate segmental or lobar feeding arteries. Our institutional practice is to give the 90Y activity that will result in the intended volume of the liver receiving between 80 to 150 Gy. There were no whole liver 90Y treatments in this cohort. After treatment, patients routinely underwent a limited positron emission tomography/computed tomography (PET/CT) scan to visualize areas of inflammation to approximate 90Y uptake.

For SBRT treatments, all patients underwent a four-dimensional CT simulation scan. Patients received IV contrast and were immobilized using a VacLoc. In patients with adequate lung function, end expiratory breath holding was used to minimize breathing-related liver motion, otherwise respiratory gating was used. The gross tumor volume (GTV) defined as the primary lesion in the PV was delineated using the CT simulation image and/or fused magnetic resonance imaging (MRI) scan. For patients undergoing respiratory
gating, the internal target volume (ITV) was delineated similarly, making sure to include the primary lesion in all phases of breathing during which the patient will be treated. The planning target volume (PTV) was defined as the GTV or ITV plus a 5-mm radial margin. Dose was prescribed to 95% of the PTV. For treatment planning for 5-fraction SBRT, dose constraints commonly used were liver $V_{15} < 700$ mL, duodenum $D_{max} < 32$ Gy, esophagus $D_{max} < 35$ Gy, and spinal cord $D_{max} < 30$ Gy. To limit hot spots, max dose within the target was limited to $< 110\%$. Unfortunately, there was no method to account for the prior radiation dose delivered to the normal liver via $^{90}$Y radioembolization. Generally, SBRT to the vascular invasion component of the tumor contributed very little radiation to the normal liver given its focused target area. However, if there is concern for normal liver receiving too much radiation from both treatments, the limited PET/CT scan obtained after $^{90}$Y can be used to crop the SBRT treatment volume off of overlapping liver volumes. For treatment delivery, image guidance with cone beam CT was used to verify positioning before each treatment. Fiducial markers were used in select patients. SBRT was delivered every other day up to a total of 5 fractions.

3. Statistical analysis

Descriptive statistics such as medians for continuous variables and frequencies for categorical variables were used to describe patient characteristics. Median follow-up time (from the completion of SBRT) was calculated with the reverse survival method. Survival analyses were performed using Kaplan-Meier analysis and Cox regression for univariate analysis. All analyses were done using the statistical software SPSS version 26 (IBM, Armonk, NY, USA). All tests used a significance level $< 0.05$.

**Results**

1. **Patient demographics**

A total of 12 patients received the combination of $^{90}$Y and SBRT for PVTT from May 2015 to August 2020. Baseline patient characteristics were gathered and shown in Table 1. None of the patients had any prior treatment such as surgical resection, liver transplant, or systemic therapy. Most patients were 65 years or older (68%), male (68%), had a primary diagnosis of HCC (75%), the Eastern Cooperative Oncology Group (ECOG) performance status of 0 (58%), Child–Pugh class A (75%), with PVTT in the left or right PV (75%). Patients received a median $^{90}$Y dose of 104.3 Gy (range, 83.3 to 131.7 Gy) to a median volume of 846 mL (range, 675 to 1,068 mL). Most patients had a 1- to 3-month interval between $^{90}$Y and SBRT (75%). Patients received a median SBRT dose of 32.5 Gy in 5 fractions (range, 27.5 to 50 Gy in 5 fractions) to a median volume of 91.3 mL (range, 14.7 to 623.2 mL). The most common fractionation was 30 Gy in 5 fractions. There were three patients with progression of parenchymal disease in the time between $^{90}$Y and SBRT. These three patients with disease progression had a larger PTV volume (range, 266.1 to 623.2 mL) than patients who did not have disease progression (range, 14.7 to 192.4 mL) to cover additional areas of parenchymal disease.

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Most patients were treated using end expiration breath-hold (75%), and the remaining were treated using respiratory gating. Fifty-eight percent of patients received some form of maintenance therapy after local treatment such as sorafenib, lenvatinib, bevaccizumab, or nivolumab.

2. SBRT related toxicities
A summary of SBRT related toxicities can be seen in Table 2. Of the 12 patients in this study, 17% developed acute grade 1 elevation of LFTs, 17% developed acute grade 1 nausea, 17% developed acute grade 1 fatigue, and 8% developed acute grade 1 esophagitis. The total rate of grade 1 toxicity was 59%. There were no grade 2+ acute toxicities or late toxicities or treatment complications reported. As mentioned above, the interval between $^{90}$Y and SBRT was shortened from over 3 months to 1–3 months after our experience showed PVTT rarely responds to $^{90}$Y alone. After shortening the interval, we observed no increase in acute toxicities in patients treated with a 1- to 3-month interval (5/8 patients) vs. patients treated with >3-month interval (2/4 patients), although sample sizes are too small to draw any conclusions. Individual patient level demographics and toxicities can be seen in Table 3.

3. Response rates and survival
Based on RECIST criteria v1.1, the CR rate was 8%, the PR rate was 42%, the SD rate was 33%, and the PD rate was 17%. After shortening the interval between $^{90}$Y and SBRT from over 3 months to 1–3 months, we observed no difference in response rates in patients treated with a 1- to 3-month interval (7/8 patients with CR+PR+SD) vs. patients treated with >3-month interval (3/4 patients), although sample sizes are too small to draw any conclusions. Individual patient level demographics and toxicities can be seen in Table 3.

Table 1. Summary of patient demographics, clinical factors, and treatment variables (n = 12)

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<thead>
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<th>Value</th>
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<td>≥ 65</td>
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</tr>
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<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
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<tr>
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</tr>
<tr>
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<td>Previous treatments</td>
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<td>Maintenance therapy afterwards</td>
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</tbody>
</table>

Values are presented as median (range) or number (%). HCC, hepatocellular carcinoma; ECOG, Eastern Cooperative Oncology Group; PVTT, portal vein tumor thrombosis; PV, portal vein; $^{90}$Y, yttrium-90; SBRT, stereotactic body radiation therapy; PTV, planning target volume.

Table 2. Summary of toxicities, response rates, and PV patency

<table>
<thead>
<tr>
<th>Value</th>
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<tbody>
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<td>SBRT related toxicities</td>
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<td>Acute grade 1 elevated LFTs</td>
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<tr>
<td>Acute grade 1 nausea</td>
</tr>
<tr>
<td>Acute grade 1 fatigue</td>
</tr>
<tr>
<td>Acute grade 1 esophagitis</td>
</tr>
<tr>
<td>Late toxicities</td>
</tr>
<tr>
<td>Best response by RECIST v1.1</td>
</tr>
<tr>
<td>Complete response</td>
</tr>
<tr>
<td>Partial response</td>
</tr>
<tr>
<td>Stable disease</td>
</tr>
<tr>
<td>Progressive disease</td>
</tr>
<tr>
<td>PV patency after treatment</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

Values are presented as number of patients (%). PV, portal vein; SBRT, stereotactic body radiation therapy; LFT, liver function test; RECIST, Response Evaluation Criteria in Solid Tumors.
tients with CR+PR+SD), although sample sizes are too small to draw any conclusions. The local control rate (CR+PR+SD) was 83% (Fig. 2). On follow-up imaging, 58% patients had a patent PV. With a median follow-up of 29 months, 1-year OS was 55% and median OS was 14 months (Fig. 3). A summary of response rate, PV patency rate, and 1-year OS rate can be seen in Table 2. Individual patient level demographics, response rates, and 1-year OS rates can be seen in Table 3.

A univariate analysis was performed to determine predictors for improved OS (Table 4). The only variable to be significantly associated with improved OS was treatment response, dichotomized into CR+PR+SD versus PD (p < 0.001). Age, sex, diagnosis, performance status, Child–Pugh, location of PVTT, 90Y dose, total SBRT dose, PTV volume, interval between 90Y and SBRT, and receiving maintenance therapy after local treatment were not significantly associated with OS. Fig. 3 shows the Kaplan–Meier curve comparing OS for responders to 90Y-SBRT versus non-responders. Median OS for treatment responders was 33 months versus 2 months for treatment non-responders (p < 0.001).

Discussion and Conclusion

There is currently insufficient data supporting the safety of combination therapy. Previous consensus statements have stated previous 90Y radioembolization as a relative contraindication to SBRT due to concern of the liver receiving too much radiation [12]. However, there has been a growing number of radiation oncologists comfortable with offering SBRT after 90Y radioembolization based on anecdotal evidence that it can be delivered safely. In this retrospective analysis, we show that the combination of 90Y and SBRT is safe and well tolerated in the treatment of PVTT.

### Table 3. Individual patient level demographics and outcomes

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<th>ECOG PS</th>
<th>Child–Pugh</th>
<th>90Y dose (Gy)</th>
<th>90Y volume (ml)</th>
<th>SBRT dose (Gy)</th>
<th>SBRT volume (ml)</th>
<th>Response</th>
<th>PV patency</th>
<th>OS (mo)</th>
<th>SBRT related toxicities</th>
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<td>50</td>
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</tr>
<tr>
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<td>M</td>
<td>Asian</td>
<td>HCC</td>
<td>0</td>
<td>B</td>
<td>110.6</td>
<td>89.7</td>
<td>1</td>
<td>30</td>
<td>91.8</td>
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<td>12+</td>
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<tr>
<td>3</td>
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<td>A</td>
<td>124.7</td>
<td>1.011</td>
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<td>99.9</td>
<td>810</td>
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<td>107.3</td>
<td>870</td>
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<td>623.2</td>
<td>PR</td>
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<td>Asian</td>
<td>CCC</td>
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<td>A</td>
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<td>45</td>
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<td>PR</td>
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<td>107.3</td>
<td>870</td>
<td>5</td>
<td>45</td>
<td>623.2</td>
<td>PR</td>
<td>Yes</td>
<td>33</td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group performance status; SBRT, stereotactic body radiation therapy; PV, portal vein; OS, overall survival; HCC, hepatocellular carcinoma; CCC, cholangiocarcinoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; +, still alive; LFT, liver function test.
Fig. 3. (A) Kaplan-Meier curve for all patients. Median overall survival (OS) was 14 months. (B) Kaplan-Meier curve comparing $^{90}$Y-SBRT responders (CR+PR+SD) versus non-responders (PD). Median OS for responders was 33 months versus 2 months for non-responders ($p < 0.001$). SBRT, stereotactic body radiation therapy; $^{90}$Y, yttrium-90; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 4. Univariate analysis for predictors of overall survival

<table>
<thead>
<tr>
<th>Predictor</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Cholangiocarcinoma vs. HCC</td>
<td>0.832</td>
</tr>
<tr>
<td>Neuroendocrine liver metastasis vs. HCC</td>
<td>0.863</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
</tr>
<tr>
<td>$\geq 65$ vs. $&lt; 65$</td>
<td>0.511</td>
</tr>
<tr>
<td>Sex</td>
<td>0.888</td>
</tr>
<tr>
<td>Male vs. female</td>
<td></td>
</tr>
<tr>
<td>Child–Pugh classification</td>
<td>0.358</td>
</tr>
<tr>
<td>B vs. A</td>
<td></td>
</tr>
<tr>
<td>Dose fractionation</td>
<td></td>
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<tr>
<td>30–35 Gy vs. $&lt; 30$ Gy in 5 fx</td>
<td>0.915</td>
</tr>
<tr>
<td>40–45 Gy vs. $&lt; 30$ Gy in 5 fx</td>
<td>0.819</td>
</tr>
<tr>
<td>50+ Gy vs. $&lt; 30$ Gy in 5 fx</td>
<td>0.781</td>
</tr>
<tr>
<td>PTV volume (mL)</td>
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<tr>
<td>50–100 vs. $&lt; 50$</td>
<td>0.866</td>
</tr>
<tr>
<td>100–250 vs. $&lt; 50$</td>
<td>0.736</td>
</tr>
<tr>
<td>250–500 vs. $&lt; 50$</td>
<td>0.607</td>
</tr>
<tr>
<td>500+ vs. $&lt; 50$</td>
<td>0.429</td>
</tr>
<tr>
<td>Treatment response</td>
<td></td>
</tr>
<tr>
<td>Responders (SD+PR+CR) vs. non-responders (PD)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

HCC, hepatocellular carcinoma; PTV, planning target volume; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Recently, published data has suggested that the combination of arterial therapy and SBRT can be performed safely with good short-term outcomes. A randomized clinical trial by Yoon et al. [13], prospectively compared transarterial chemoembolization (TACE) plus external beam radiotherapy versus sorafenib in HCC with macroscopic vascular invasion. It was found that first-line treatment with TACE plus SBRT was well tolerated and had improved progression-free survival (PFS), objective response rate, and OS compared to sorafenib. Hardy-Abeloos et al. [14] retrospectively identified 68 patients with HCC who received SBRT after TACE and 31 patients who received SBRT after $^{90}$Y radioembolization. The rate of grade $\geq 3$ toxicities were similar between TACE-SBRT and $^{90}$Y-SBRT (13% vs. 9.4%). One-year LC rate for $^{90}$Y-SBRT was 97%, and the median OS for $^{90}$Y-SBRT was not reached after 18 months. In the $^{90}$Y-SBRT arm, 14 patients (45%) achieved a CR, while 5 patients (16%) achieved a PR. Fourteen patients (14%) had PVTT (8 in the TACE-SBRT arm and 6 in the $^{90}$Y-SBRT arm), but this study did not specifically analyze this population. The current study supports this previous report that combination $^{90}$Y radioembolization and SBRT can be performed safely. In the current study, no acute or late grade $\geq 3$ toxicities were identified. Several factors may account for this. Firstly, the current study had a lower median SBRT dose of 32.5 Gy in 5 fractions compared to a median SBRT dose of 40 Gy in 5 fractions in the previous study. Furthermore, our median PTV volume was smaller at 91.3 mL compared to 103.1 mL. Also, less parenchyma was included in the PTV since the SBRT was only targeting the PVTT. Our sample size was also much smaller, which may account for the lack of patients reporting grade $\geq 3$ toxicities.

The efficacy of combination therapy in the current study is also encouraging. One patient (8%) who achieved a CR and 5 patients (42%) achieved a PR in the current study. This is lower than seen in the previous report of combination therapy, where CR and PR were 45% and 16% respectively. Similarly, the current study’s 1-year OS rate was also lower at 55% with a median OS of 14 months compared to 70% with a median OS not reached after 18 months in the previous trial. However, these findings are expected given the overall worse response rates and survival in patients with PVTT (Fig. 4).

Several previous studies have analyzed the outcomes of combination therapy or SBRT alone in patients with PVTT and demon-
A retrospective study of 37 patients with HCC with PVTT received TACE followed by SBRT found a CR rate of 16.2% and a PR rate of 54% \[15\]. These values are slightly higher than those of our study (8% and 42%, respectively). Furthermore, the 1-year OS rate was 54.1% with a median OS of 15 months, which is closely in line with our study (55% with median OS of 14 months).

Another retrospective study of 24 patients with HCC with PVTT...
treated with SBRT found a CR rate of 8.3% and a PR rate of 45.8% [16]. Another retrospective study of 70 patients with HCC with PVTT treated with SBRT found a 1-year OS rate of 40% with a median OS of 10 months [17]. The current study demonstrated a 1-year OS rate of 55% with a median OS of 14 months.

In the univariate analysis, only response to $^{90}$Y-SBRT was associated with improved OS, with patients who achieved a CR, PR, or SD after treatment had a significantly longer median OS compared to those who had PD (33 months vs. 2 months; p < 0.001) (Fig. 3). This is consistent with two previous studies. One retrospective study examining SBRT for PVTT found that patients who achieved a CR, PR, or SD had a median OS of 13 months versus 4 months for patients who had PD [17]. Another retrospective study examining SBRT for PVTT found that patients with controlled disease had a median OS of 18.8 months versus 7.8 months in those with local progression [18]. This is reasonable, as PD can result in complete occlusion of the PV, eventually leading to liver failure. These two studies also identified other predictors for OS not found in our study, including PVTT location, a biologically effective dose (BED) $> 100$ Gy, and a smaller GTV volume [17,18]. The absence of these associations in the current study may be due to the small sample size of the current study.

While the results of our study are promising, there are several limitations. The analysis is retrospective and single institution, so results will need to be prospectively validated. Furthermore, the sample size of 12 makes it difficult to perform any meaningful statistical analysis examining predictors of improved response or survival. However, as a feasibility study, our goal is to simply report that $^{90}$Y-SBRT for PVTT is safe and can offer adequate LC and improved OS. Larger prospective studies are warranted to better evaluate this combined treatment modality and determine what factors may predict for improved outcomes.

Despite these limitations, our study shows that the combination of $^{90}$Y radioembolization and SBRT is a safe and well-tolerated treatment for PVTT. There were no recorded grade 2+ toxicities. Successful treatment may result in improved survival. As always, having a multi-disciplinary approach to treating advanced liver cancer with PVTT is the best approach to maximizing patients’ quality of life and survival.

**Conflict of Interest**

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

**References**

13. Yoon SM, Ryoo BY, Lee SJ, et al. Efficacy and safety of transarterial chemoembolization plus external beam radiotherapy vs...


Dose-volume histogram parameters and patient-reported EPIC-Bowel domain in prostate cancer proton therapy


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2 Department of Health Sciences Research, Mayo Clinic, Scottsdale, AZ, USA

Purpose: To analyze rectal dose and changes in quality of life (QOL) measured with the Expanded Prostate Cancer Index Composite (EPIC) bowel domain in patients being treated for prostate cancer with curative-intent proton beam therapy (PBT) within a large single-institution prospective registry.

Materials and Methods: Data was collected from 243 patients with localized prostate cancer treated with PBT from 2016 to 2018. The EPIC survey was administered at baseline, end-of-treatment, 3, 6, and 12 months, then annually. Dose-volume histogram (DVH) parameters for the rectum were computed, and rectal dose was analyzed using BED ($\alpha/\beta = 3$), EQD$_{2Gy}$, and total dose. Repeated measures mixed models were implemented to determine the effect of patient, clinical, and treatment factors (including DVH) on patient-reported bowel symptom burden (EPIC-Bowel).

Results: Treatment overall resulted in changes in EPIC-Bowel scores (baseline score = 93.7), most notably at end-of-treatment (90.6) and 12 months (89.7). However, they returned to baseline at 36 months (92.9). On multivariate modeling, rectal BED $D_{25}^{\text{Gy}}$ $\geq$ 23% was significantly associated with decline in QOL scores measuring bother ($p < 0.01$; 4.06 points different).

Conclusion: Rectal doses, specifically BED $D_{25}^{\text{Gy}}$ $\geq$ 23%, are significantly associated with decline in bowel bother-related QOL in patients undergoing definitive radiotherapy for localized prostate cancer. This study demonstrates BED as an independent predictor of bowel QOL across dose fractionations of PBT.

Keywords: Prostatic neoplasms, Radiation therapy, Quality of life

Introduction

Prostate cancer is the most common cancer in American men, with roughly 200,000 new cases and 30,000 deaths annually [1]. Quality of life (QOL) issues are important for prostate cancer patients who generally survive for years after therapy [2-5]. External beam irradiation is one of the treatment options for localized prostate cancer. Proton beam therapy (PBT) is a unique form of radiotherapy (RT) that delivers high-dose, targeted particles to tumors while minimizing radiation dose to surrounding healthy tissue [6,7]. Previous research has generally included clinician evaluated toxicities resulting from PBT [8-11]. However, the relationship between dose volume parameters and quality of life using the Expanded Prostate Cancer Index Composite (EPIC) scores remains unclear.

The EPIC survey measures health-related quality of life across a variety of disease-specific domains such as urinary, bowel, and sexual function [12]. Furthermore, the survey has expanded on previous instruments like the University of California Los Angeles Pros-
tate Cancer Index (UCLA-PCI) to capture irritative and hormone therapy-related side effects [13]. Thus, the survey provides a comprehensive and valuable measure of QOL as patients self-report their symptoms throughout the course of treatment.

Previous studies have demonstrated statistically and clinically significant changes in EPIC-Bowel scores for patients receiving PBT for prostate cancer [14,15]. We sought to investigate this further with analysis of the survey subdomains across different fraction schemes, using conventional fractionation, hypofractionation and extreme hypofractionation. We present a prospective analysis on how PBT affects QOL in patients undergoing curative treatment for prostate cancer.

Materials and Methods

1. IRB statement

The Institutional Review Board of Mayo Clinic Arizona approved the study and all patients provided written informed consent (No. 19-007866). This trial was registered with ClinicalTrials.gov (NCT01255748).

2. Eligibility criteria

Adult males undergoing definitive radiotherapy for localized prostate cancer from January 1, 2016 to December 31, 2018 were originally assessed for eligibility. To be included, patients must have received proton RT with curative intent, and completed at least one pre-RT and one post-RT EPIC questionnaire. Patients with node-positive or metastatic disease were excluded. The final number of patients enrolled was 243.

3. Radiation therapy

Patients underwent computed tomography (CT) simulation with pelvic immobilization, a full bladder, and a rectal balloon. Carbon fiducial markers were placed prior to simulation. Some patients also had a rectal spacer placed between the prostate and rectum at the discretion of the treating physician. A treatment planning magnetic resonance imaging (MRI) was obtained and co-registered with CT images for target delineation. In patients who could not undergo MRI scans, treatments were planned using CT, positron emission tomography (PET), and bone scans. The clinical target volume (CTV) encompassed the entire prostate gland and proximal seminal vesicles. In cases of T3b disease, the entire seminal vesicles were included in CTV. An optimization target volume (OTV) was created from the CTV using a margin of 2–3 mm posteriorly and 3 mm elsewhere. Treatment was delivered with right and left lateral beams. The constructed OTV included an additional 5 mm in the beam direction distally and proximally due to range uncertainty. Usual proton beams were oriented laterally left and right. Image guidance with matching to carbon fiducial markers was performed to confirm daily set up.

For the purpose of this study, conventional fractionation denotes dose per fraction between 1.8 and 2 Gy (relative biological effectiveness [RBE]). Hypofractionation was defined as treatment regimens of more than 5 fractions with over 2 Gy (RBE) per fraction. Extreme hypofractionation (stereotactic body radiation therapy [SBRT]) was defined as treatments of 5 fractions or less, typically ≥ 6 Gy (RBE) per fraction. Spot scanning proton beam was used for all treatments.

4. Dosimetric data

Rectal dose-volume histogram (DVH) parameters collected from treatment plans were computed with D$_d$ signifying dose (Gy) delivered to a percentage of rectal tissue volume. V$_d$ denoted the percentage of rectal volume receiving at least a given dose (Gy). Assuming an alpha-beta ratio of 3, both the biologically effective dose (BED = $D \times (1 + \frac{d}{a/\beta})$) and equivalent dose in 2 Gy fractions (EOD$_{2\text{Gy}} = D \times \left(\frac{d + \frac{a}{\beta}}{2\text{Gy} + \frac{a}{\beta}}\right)$) of each rectal DVH parameter was calculated [16]. We assumed the rectum to have an alpha-beta ratio of 3 for BED and EOD$_{2\text{Gy}}$ calculations.

Institutional guidelines for conventional fractionation, hypofractionation, and extreme fractionation were utilized when determining rectal dose constraints. For conventional fractionation: $V_{50}$ (Gy) ≤ 50%; hypofractionation: $V_{15}$ (Gy) ≤ 15%; and extreme hypofractionation: $V_{33}$ (Gy) ≤ 15%. For the hypofractionation schemes, the higher dose constraints were approximately 10% greater than conventional fractionation protocols: BED of 98.5 Gy (65 Gy nominal) for conventional, 110 Gy (61 Gy nominal) for hypofractionation, and 108 Gy (33.5 Gy nominal) for extreme hypofractionation.

5. Toxicity assessments

Toxicity was measured with the Common Terminology Criteria for Adverse Events (version 5.0).

6. QOL measures

The EPIC is a survey tool used to measure health-related QOL through assessment of urinary, bowel, sexual, and hormonal burden during treatment of prostate cancer [12]. Patients completed the EPIC-50 and AUASI-17 (American Urological Association Symptom Index) at the following intervals: baseline, end of treatment, and 3, 6, 12, 24, and 36 months. A higher EPIC score implies less bowel symptom burden. Previous analyses have established the minimally
important difference (MID) as 4–6 points within the EPIC-Bowel domain [17,18].

7. Statistical analysis
Rectal dose was analyzed using BED (alpha/beta = 3), EQD_{2Gy}, and total dose. Univariate analysis utilizing repeated measures mixed models was utilized to determine the "best" DVH parameter associated with differences in patient-reported QOL. An outcome-oriented approach (with alpha-adjustment to control for family-wise error) was used to determine the optimal dichotomization of the DVH parameter of interest with the largest association to changes in patient-reported QOL. Multivariate repeated measures mixed models with unstructured covariance matrices were implemented to determine the effect of patient, clinical, and treatment factors (including DVH) on patient-reported bowel symptom burden (EPIC-Bowel overall, function, and bother scores).

Results

1. Patient and tumor characteristics
The present analysis includes 243 patients from January 1, 2016 to December 31, 2018, treated for prostate cancer in accordance with institutional protocols. Patient and tumor characteristics are displayed in Table 1. The median pre-RT PSA (prostate-specific antigen) value was 6.1 ng/mL (range, 0.3–1289), median T stage was T1c (range, T1b–T3b), median Gleason score was 7 (range, 6 to 10), and median age was 71 years (range, 52 to 91 years).

2. Radiotherapy characteristics and outcomes
The median follow-up time was 20 months (range, 2.5 to 40 months). Dose fractionations are presented in Table 2. Conventional fractionation was used in 117 patients (48%), with a median dose of 1.8 Gy and range of 1.8–2.0 Gy. Moderate hypofractionation was used in 84 patients (34%), with a median dose of 2.5 Gy and a range of 2.5–3.0 Gy. Extreme hypofractionation was used in 42 patients (17.3%), with all patients receiving 7.6 Gy. Moderate rectal BED_{mean} was 12.45 Gy (range, 1.74 to 50.5 Gy) and median rectal EQD_{2Gy} was 7.47 Gy (range, 1.04 to 30.32 Gy). Median post-RT PSA at first follow-up was 0.22 ng/mL (range, 0 to 29.71 ng/mL). One patient (0.4%) died by the last follow-up due illness unrelated to cancer and radiation treatment.

3. DVH analyses
DVH parameters were determined by BED, EQD_{2Gy}, and total dose. Each continuous parameter was tested for associations with significant decline in EPIC scores at intervals of 5% in volume and 5 Gy for dose. The univariately significant DVH parameters are displayed in Table 3. For table brevity, large ranges of non-significant values are listed at intervals of 10 Gy instead of 5 Gy. Across BED and EQD_{2Gy}, significant parameters included D_{2Gy}, D_{5Gy}, D_{10Gy}, and D_{15Gy}. For total dose, D_{2Gy}, D_{5Gy}, D_{10Gy}, D_{15Gy}, V_{6Gy}, and V_{8Gy} were significant. Based on statistical significance and clinical interpretability, BED D_{2Gy} (Gy) was selected as the "best" continuous predictor for differences in EPIC-Bowel scores over time.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>71 (52–91)</td>
</tr>
<tr>
<td>Race</td>
<td>White: 227 (93.4) Other: 16 (6.6)</td>
</tr>
<tr>
<td>ECOG status</td>
<td>0: 198 (81.5) 1: 44 (18.1) 2: 1 (0.4) 1 or 2: 45 (18.5)</td>
</tr>
<tr>
<td>Pre-RT PSA (ng/mL)</td>
<td>6.140 (0.3–1289)</td>
</tr>
<tr>
<td>T stage</td>
<td>T1-T2a: 188 (77.4) T2b-T2c: 32 (13.2) T3-T4: 22 (9.1)</td>
</tr>
<tr>
<td>Gleason score</td>
<td>6 (group 1): 35 (14.4) 7 (group 2 or 3): 146 (60) 3+4 (group 2): 91 (37.4) 4+3 (group 3): 55 (22.6) 8 (group 4): 36 (14.8) 9–10 (group 5): 26 (10.7)</td>
</tr>
<tr>
<td>Biopsy cores taken</td>
<td>13 (2–34)</td>
</tr>
<tr>
<td>Biopsy cores positive</td>
<td>5 (1–25)</td>
</tr>
<tr>
<td>MRI results</td>
<td>Extraprostatic extension: 27 (11.1) Seminal vesicle invasion: 5 (2.1)</td>
</tr>
<tr>
<td>Androgen deprivation therapy</td>
<td>Yes: 155 (63.8) No: 88 (36.2)</td>
</tr>
</tbody>
</table>

Values are presented as median (range) or number (%).
ECOG, Eastern Cooperative Oncology Group; RT, radiotherapy; PSA, prostate-specific antigen; MRI, magnetic resonance imaging.
Table 2. Dose fractionation with BED and EQD\(_{2\text{Gy}}\) transformations

<table>
<thead>
<tr>
<th>Dose fractionation (SBRT)</th>
<th>Prostate</th>
<th>Rectum</th>
<th>Total number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38 Gy/5 fx</td>
<td>230.5</td>
<td>98.8</td>
<td>134.3</td>
</tr>
<tr>
<td>60 Gy/20 fx</td>
<td>180</td>
<td>77.1</td>
<td>120</td>
</tr>
<tr>
<td>67.5 Gy/25 fx</td>
<td>189</td>
<td>81</td>
<td>128.3</td>
</tr>
<tr>
<td>70 Gy/28 fx</td>
<td>180</td>
<td>77.1</td>
<td>128.3</td>
</tr>
</tbody>
</table>

Bed, biologically effective dose; EQD\(_{2\text{Gy}}\), equivalent dose in 2 Gy fractions; SBRT, stereotactic body radiation therapy.

Table 3. Univariate analysis of DVH parameters used in selecting BED D\(_{25}\) Gy (\(p = 0.027\)) as the optimal predictor for differences in EPIC-Bowel, to be evaluated through subsequent multivariate analysis

| DVH parameters and EPIC-Bowel QOL

| DVH parameters and EPIC-Bowel QOL

Table 3. Univariate analysis of DVH parameters used in selecting BED D\(_{25}\) Gy (\(p = 0.027\)) as the optimal predictor for differences in EPIC-Bowel, to be evaluated through subsequent multivariate analysis

BED, biologically effective dose; EQD\(_{2\text{Gy}}\), equivalent dose in 2 Gy fractions; SBRT, stereotactic body radiation therapy.

https://doi.org/10.3857/roj.2021.00388
4. EPIC scores
Globally, treatment had expected effects over EPIC-Bowel scores which returned to baseline over time, with a median baseline score (93.7), end-of-treatment (90.6), 3 months (92.1), 6 months (92.7), 12 months (89.7), 24 months (93.3), and 36 months (92.9). EPIC score decline from baseline was significant at end-of-treatment ($p = 0.04$) and 12 months post-treatment ($p < 0.01$). However, within 24 months, patient QOL demonstrated a return to pre-RT levels ($p = 0.99$).

Extreme hypofractionation was associated with a 4.58 point decrease in total EPIC-Bowel scores ($p < 0.01$) when compared to conventional fractionation, while hypofractionation was not associated with a significant decline (-1.42 points, $p = 0.07$). Both extreme hypofractionation (-4.06 points, $p < 0.01$) and hypofractionation (-2.47 points, $p < 0.01$) were significantly associated with decline in bowel function compared to conventional fractionation. Extreme hypofractionation was significantly associated with a decrease in bother scores (-5.12 points, $p < 0.01$), while hypofractionation was not (-0.40 points, $p = 0.66$).

Rectal dose affected QOL with the strongest DVH signals noted for BED $D_{25}$ (Gy) with an optimal cut point of $\geq 23\%$. This parameter was significant after controlling for age, body mass index (BMI), race, Eastern Cooperative Oncology Group (ECOG) performance status $\geq 1$, Gleason score, clinical T stage, androgen deprivation therapy (ADT) use, and fractionation schedule. For overall EPIC-Bowel scores, the dose of BED $D_{25}$ (Gy) $\geq 23\%$ was associated with an average decrease of 2.73 points compared to those $< 23\%$ ($p < 0.01$). The effects of radiotherapy on bowel were subdivided into the domains of function and bother. A dose of BED $D_{25}$ (Gy) $\geq 23\%$ did not significantly affect bowel function (-1.44 points, $p = 0.13$). However, reported bother was significantly worse ($p < 0.01$) with a score difference of 4.06 points (Fig. 1).

**Discussion and Conclusion**

In a single, large prospective registry ($n = 243$), we determined BED to be an independent predictor for bowel-related QOL. Overall, EPIC-Bowel scores were significantly affected by BED $D_{25}$ (Gy) $\geq 23\%$ ($p < 0.01$). On multivariate modeling, this parameter was significantly associated with a decline in QOL scores measuring bother ($p < 0.01$, 4.06 points different) as opposed to function.

The MID for the EPIC-Bowel domain has been established as 4–6 points [17,18]. In other words, this is the threshold for which patients can detect clinically meaningful changes in their symptom
DVH parameters and EPIC-Bowel QOL

burden. However, the MID has not specifically been established for the subdomains. We hypothesize that if the MID for the overall domain is 4 points then a 4.06 difference within the bother subdomain alone is clinically significant.

Potentially, these results can have different applications as we continue modifying radiation dose fractionations for the treatment of prostate cancer. Through the application of BED, we can minimize the risk of patient-reported toxicity regardless of dose fractionation, and compare different plans treated to different dose fractionation schemes. Since the toxicity is related to the biological effect, different doses with a similar biological effectiveness theoretically should impact QOL similarly.

We found extreme hypofractionation to be associated with a statistically and clinically significant decline in overall EPIC-Bowel scores, as well as individual function and bother scores, when compared to conventional fractionation (p < 0.01). Hypofractionation was not clinically significantly associated with a decrease in EPIC-Bowel scores—it was only found to be statistically significant for decrease in bowel function (p < 0.01) compared to conventional fractionation. These findings deserve further study into the effects of the separate fractionation schemes on QOL.

In our prior analysis, we observed a significant decline of the EPIC-Bowel domain associated with BED $V_{35}$ (Gy) > 14.3% (p = 0.01) and EOD$V_{22}$, $V_{22}$ (Gy) > 16.4% (p < 0.003) [19]. We further developed this analysis by optimizing cut points for greatest effect on EPIC-Bowel scores, determining BED $D_{25}$ (Gy) ≥ 23% to be the most significant dosimetric predictor with the most clinically meaningful changes. Additionally, the present analysis evaluates function and bother subscales within the overall EPIC-Bowel domain, which serves to better capture the nature of QOL decline within this patient set.

While the function subscale assessed topics such as bowel urgency, stool quality, and abdominal cramping, the bother subscale assessed how significantly these problems were perceived by patients. The differences in the scale suggest that patients have bother-related to radiation changes, but function was not affected. Thus, patients reported similar stool quality, but perception of the radiation effect on the change was larger than the perceived function. This can be interpreted in multiple ways: that patients can perceive differences in their stool quality for example, even though function is not affected, suggesting higher sensitivity to bother than a functional scale. Alternatively, the volume of the rectum that has developed radiation proctitis is relatively small. While the organ maintains function, but the small volume of rectum with proctitis can produce changes in bother in different subdomains. These findings may provide a more specific understanding of rectal toxicities associated with RT, guiding patient counseling.

Previous studies have supported the separate reporting of function and bother because treatment planning and symptom management may depend on a patients’ perceived experience [20]. Perceived bother may vary between patients based on their individual concerns, as well as their preconceived expectations regardless of organ function, over the course of treatment [21,22]. In a study that prospectively analyzed EPIC-Bowel scores in response to photon radiotherapy (n = 228), on the subscales of function and bother, there were patterns of decline and resolution similar to our findings, with an association with urinary flare symptoms [23]. Another prospective study (n = 226) evaluated QOL and toxicity between passively scattered proton therapy and spot-scanning proton therapy, showing a significant decrement in bowel QOL which persisted through follow-up [19]. Our study is unique because it validates the use of proton radiotherapy across various dose fractionation schemes. Through DVH analysis and statistical modeling that accounted for variations in treatment, patient characteristics, and demographics, this study demonstrates that BED, as a DVH tool, can be used to predict QOL across dose fractionations.

One limitation of the present study is the difficulty in administration of a 50-item questionnaire. Although the EPIC-50 was used in order to retain granularity in the data collection, this poses certain challenges related to survey fatigue in patients [24], observed by drop-rates in Fig. 1. Newer versions of the questionnaire, such as the EPIC-26 and EPIC-CP [25,26], have been developed to remedy this. Another limitation is that our data was collected from patients exclusive to a single, high-volume academic institution. This could limit generalizability of the results in smaller practices. Furthermore, patients were treated according to physician preference, allowing for more variation in the analysis which may limit the power of certain subgroup analysis. We expect these findings to additionally be applicable to patients receiving photon RT, however different cut points may be necessary.

In summary, this study demonstrates that BED can be used as an independent predictor for bowel QOL across conventional fractionation, hypofractionation and extreme hypofractionation schemes. We specifically determined BED $D_{05}$ (Gy) ≥ 23% to be a statistically and clinically significant parameter for predicting decline in perceived bowel bother QOL. Therefore, BED can be a useful measure in prospective clinical trials to minimize symptom burden for patients undergoing PBT for prostate cancer, even when utilizing different dose fractionations.

**Conflict of Interest**

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

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References

Use of GammaPlan convolution algorithm for dose calculation on CT and cone-beam CT images

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Introduction

Gamma Knife is a well-established radiotherapy treatment system specifically designed to treat intracranial brain lesions. One of the main advantages of Gamma Knife stereotactic radiosurgery (SRS) is its precision, enabling the clinicians to deliver very high doses in a single fraction. The first Gamma Knife device using cobalt-60 ($^{60}$Co) radioisotope was introduced by Lars Leksell in 1967 [1–5]. Since then, several models such as U, B, C, and Perfexion have been developed for stereotactic radiosurgery [4,6–8]. The latest system, Leksell Gamma Knife (LGK) Icon (Elekta Instruments AB, Stockholm, Sweden) with an onboard cone-beam computed tomography (CBCT) imaging system, utilizes 192 $^{60}$Co sources to deliver collimated radiation beams to target areas with high accuracy [9,10]. The sources are fixed inside eight independent moveable sectors, with each sector containing five rings and 24 sources per sector. Each sector can be aligned with one of three collimator sizes (4, 8, or 16 mm) or blocked if the sector is not required for treatment. The collimators are designed to focus the radiation from the individual sources on to a common point in space, referred to as the...
focus position. An SRS treatment with LGK is characterized by a combination of various sector, collimator, and couch positions referred to as shots. A Gamma Knife treatment is based on one or more shots; each shot is characterized by its location in stereotactic space, collimator size (independently set per sector), and contribution to the overall target dose (weight). The shot parameters and their distribution are determined during treatment planning by clinicians. The irradiation time (shot time) required to deliver the prescribed target dose is calculated by accounting for the radioactive decay of the sources and the radiation attenuation properties of various cranial tissues.

Treatment accuracy can be attained with a stereotactic frame rigidly attached to the patient’s head or a specially designed thermoplastic mask with infrared markers for high definition motion management (HDMM) system during treatment. Computed tomography (CT), magnetic resonance imaging (MRI), and angiography are image modalities commonly used in treatment planning.

The onboard CBCT imaging system of the LGK Icon uses an air-cooled X-ray tube with an energy range of 70–120 kVp and a focal spot size of 0.6 mm. The detector consists of a CsI layer and an amorphous silicon thin-film transistor (a-Si TFT) array. Icon can reconstruct imaging volumes of 224 mm × 224 mm × 224 mm with a pixel size of 0.368 mm and a magnification of 1.27. The scan time is typically 30 seconds. Fig. 1 shows a schematic of the LGK Icon CBCT. As the detector is close to the object being scanned, a large proportion of the scattered radiation reaches the detector plane, thereby degrading the image quality. Due to the physical design constraints of the system needed for clearance, the CBCT system is unable to sample data from all angles around the patient with a scanning arc of 200° used for all patients. This results in cone-beam artifacts during image reconstruction, including the appearance of smeared-out structures at the top of the head [11].

The Icon CBCT acquisition offers a choice between two preset modes: a high dose preset (6.3 mGy per scan) for treatment planning simulation scans and a low dose preset (2.5 mGy per scan) for pre-treatment image guidance. Other parameters, including energy (90 kVp), gantry start and stop angles, and field-of-view (FOV), are not variable. Customer acceptance tests of the CBCT system include image quality (spatial resolution, contrast-to-noise, and uniformity) measured with a CatPhan 503 (The Phantom Laboratory, New York, NY, USA) and CBCT precision (treatment and CBCT iso-center coincidence) measured with the QA Tool Plus (Elekta Instruments AB). Commissioning tests also included dosimetry (kVp and CTDI) measured with an Unfors RaySafe X2 detector system (Unfors RaySafe AB, Bilddal, Sweden), geometric accuracy measured with the CatPhan, and image registration accuracy measured using fiducial markers on a STEEY phantom (CIRS, Norfol, VA, USA). The routine quality assurance protocol for the Icon involves daily measurements of coincidence between the imaging and treatment isocenters, to within a tolerance of 0.4 mm with typical measurements less than 0.2 mm. In addition, CBCT image quality (uniformity, spatial resolution, contrast to noise, and geometric accuracy) is verified monthly against manufacturer specifications, as is CBCT dosimetry (CTDI and energy) which is measured biannually.

Dose calculations are performed with Leksell GammaPlan (LGP), using either a simple homogeneous dose algorithm known as TMR10 or a convolution dose algorithm [12,13]. The convolution algorithm accounts for differences in relative electron density data derived from patient CT datasets acquired prior to treatment. In this study, we examine the feasibility of using the onboard CBCT for deriving relative electron density information to be used with the dose convolution algorithm.

Materials and Methods

This study was approved by the Institutional Review Board of Metro South Health, Queensland, Australia (No. 73890). At our center, either high dose preset CBCT or fan-beam CT images are used for treatment planning in LGP with the TMR10 algorithm. TMR algorithms disregard tissue heterogeneities, approximating all tissue in the head as water. Dose distributions in tissues are calculated based on the inverse square law, exponential attenuation in water, output factors, and dose profiles. The inverse square law models the decrease in photon flux and thereby the dose rate in a unit area and at a distance r from the source. The photon flux also undergoes exponential attenuation as the photons in the beam interact with the tissue between the skull surface and the center of the target. In the earlier TMR classic algorithm, the attenuation of the beam is determined entirely by the virtual attenuation coefficient in the tissue. The TMR10 algorithm contains an additional exponential term in which the distance from the source to the skull

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**Fig. 1.** Schematic of the onboard cone-beam computed tomography (CBCT) unit on the Gamma Knife Icon.
surface is multiplied by \( \mu_0 \), the linear attenuation coefficient for the primary \(^{60}\)Co energies. As the photon fluence is dependent on the collimation settings, the various parameters in the inverse square law and exponential attenuation corrections are collimator size and ring specific for the LGK Icon [14].

In the Icon, the sources are aligned with the collimator channels for the 4 mm collimation; therefore, the dose profiles from this collimation are only a function of the distance from the beam axis. However, for the 8 mm and 16 mm collimations, the sources are tilted with respect to the collimator axis, with the tilt angle depending on which ring the source is located in. This results in an overall asymmetric dose profile that is collimator size and ring specific. The parameter used to scale the dose profiles with the depth is closely related to the source-focus distance. The output factors used in the algorithms are also dependent on the collimator size. Output factors are normalized to the largest collimator size (16 mm) and are thus always less than or equal to one [13].

The convolution algorithm used in LGP is similar to those commonly used in other radiotherapy dose calculations. The algorithm convolves a field, describing the total energy released per unit mass (TERMA) from primary photons, with kernels that describe how this energy is distributed by secondary particles (representing primary and scatter dose). In contrast to the TMR algorithms, the convolution algorithm takes tissue heterogeneities in the patient into account and can model dose build-up near tissue interfaces. The convolution algorithm is derived from the planning CT image and the calculation algorithm models the charged particle transport in straight lines, averages local electron density for radiological path length calculations, and is always directed along the central beam axis. For the scattered dose, the TERMA is convolved with a scatter kernel generated by a least-squares fitted solution to Monte Carlo simulated kernels. Simplifications and considerations used include utilizing a single lateral profile and kernel for each collimator size, geometric scaling of the scatter dose profile based on source distance, no kernel scaling based on heterogeneities between the interaction point and dose deposition point, and scaling based on relative electron densities and inverse relative mass density at a point. The simplifications used in this algorithm limit the calculation time, which is an important consideration in same-day treatment planning [13,14]. The electron density information used in the convolution algorithm is derived from the planning CT images of the patient. For accurate dose calculations, it is important that the images do not contain significant artifacts and that the Hounsfield unit to electron density (HU-to-ED) calibration is correct. It should be noted that the onboard CBCT was designed primarily for patient positioning rather than as a tool for treatment dose calculation.

The TMR10 dose calculation was validated during commissioning by comparing dose planes measured by irradiating EBT3 films in the LGK solid water phantom (SWP) with corresponding DICOM RT-dose cubes exported from LGP via gamma analysis in a radiotherapy plan verification program. LGP’s convolution algorithm has been validated by multiple institutions [13]. To validate convCT and convCBCT, measurements were performed using an Exradin A1SL ion chamber in the SWP. The SWP is a spherical solid water phantom of radius 8 cm designed to be affixed to the Gamma Knife frame. The SWP has a higher attenuation coefficient than water at kilovoltage energies (due to higher Z-value), but similar electron density, leading to a discrepancy when the relative electron density of the phantom is calculated using a CT-ED curve based on tissue.

![Fig. 2. Sagittal (A, B) and coronal (C, D) slices through the center of CBCT datasets of the SWP (A, C), and (B, D) of the SWP with a central block removed, respectively. The slice intact SWP (A, C) suffers a relatively small artifact at the superior apex of the phantom in comparison to patient CBCTs. The arrow on the right-hand images (B, D) indicate the low-density slice that was drawn to create a cavity in the dataset. CBCT, cone-beam computed tomography; SWP, solid water phantom.](https://doi.org/10.3857/roj.2020.00640)
sue-equivalent materials. Fig. 2 shows the coronal and sagittal slices of the SWP with and without the central block. As LGP has no functionality to correct this discrepancy, the HU-value of the convCT and convCBCT datasets were estimated from a region-of-interest (contoured using Pinnacle 1 TPS version 16.2.1) then the HU-values of the phantom were rescaled (using a Python script) so that the mean HU of the region-of-interest was equivalent to water (0 HU). In addition, HU values of the voxels corresponding to the chamber bore in the SWP were assigned a value of 0. A plan was created in LGP with a reasonably homogeneous dose distribution in the collecting volume of the detector. A structure (cylinder of 4 mm diameter and 4.2 mm length) approximating the collection volume of the detector was drawn, and the LGP calculated dose was defined as the mean dose to this structure. Plans were generated using TMR10, convCT and the convCBCT. These plans were then exported to the treatment console and delivered to the SWP. The dose measured with the A1SL ion chamber was compared to the LGP calculated dose. The dose difference $D_{\text{diff}}$ was defined as:

$$D_{\text{diff}} = \frac{(D_{\text{LGP}} - D_{\text{Meas}})}{D_{\text{Meas}}} \times 100\%$$ (1)

where $D_{\text{LGP}}$ is the LGP calculated dose and $D_{\text{Meas}}$ is the ion chamber measured dose.

To verify the accuracy of the convCT and convCBCT dose calculations in a non-uniform volume, the plans were recalculated on the SWP after removing a block of solid water from the phantom. The resulting phantom consists of the cylindrical chamber holder of a diameter 2.5 cm inside an air cavity of dimension 8.5 cm $\times$ 6.5 cm $\times$ 10 cm. The removed block included part of the superior surface of the phantom, it was necessary to add a surface structure to both CT datasets by replacing an 8.5 cm $\times$ 6.5 cm area of air in a single slice with low-density material (-450 HU), which was then classified as part of the skull by LGP.

A preliminary study was carried out with the CBCT to establish the relation between HU and the physical and electron densities of tissue equivalent materials. The CIRS Electron Density Head phantom (Model 062M; CIRS) was imaged with the onboard CBCT of the Gamma Knife Icon. The phantom was imaged with water, adipose tissue, breast (50% adipose tissue, 50% glandular tissue), muscle, liver, lung (inhale), trabecular bone, and dense bone tissue. The phantom was imaged in two configurations to quantitatively assess any off-axis variation in HU in the cone beam. In the first configuration, the phantom was imaged at the center of the cone-beam FOV, with the inferior phantom edge being 9 cm from the edge mask adapter and aligned with the superior edge of the first flat surface for mask attachment. This position corresponded with the center of the phantom being 11.5 cm from the edge of the FOV in the longitudinal direction. In the second configuration, the phantom was imaged at the edge of the cone-beam FOV, with the inferior phantom edge aligned with the mask adapter. The phantom was imaged eight times in both configurations, with the phantom rotated by 45° between each measurement in order to assess the variation of HU with the angle. This corresponded to each insert being imaged at eight different angles (0°, 45°, 90°, 135°, 180°, -135°, -90°, and -45° relative to the 12 o’clock position). For each measurement, the central insert was set to be the same material as the insert at 0°. The central insert was used to relate the HU to the electron and physical densities of the material when the phantom was imaged at the center of the cone beam.

The CIRS Electron Density head phantom was also scanned in a Philips Brilliance Big Bore CT scanner (Philips Healthcare, Best, The Netherlands). The phantom was imaged twice in the center of the CT scanner’s FOV. The inserts were first imaged in the default configuration and then imaged with the phantom rotated by 180°, such that the inserts were located on the opposite side of the phantom compared to the first image. This allowed the calculation of the HU difference between the two orientations to assess off-axis variations in the planning CT images.

The convolution algorithm requires relative electron density data to be determined for each voxel in the planning dataset. A computed tomography number versus electron density (CT-ED) curve was determined for the Icon cone-beam CT using the average CT number measured at all positions for each insert in the CIRS Electron Density head phantom. CT-ED curves for CT datasets were based on previously commissioned clinical data based on measurements using the larger diameter Gamma 467 Tissue Characterization Phantom (Sun Nuclear Corporation, Melbourne, FL, USA). LGP does not extrapolate relative electron density values beyond the measured range of the CT-ED curve. Voxels with higher CT numbers than the maximum in the CT-ED curve are set to the electron density of the highest value within the curve, in this case corresponding to dense bone [11].

A retrospective set of 30 Gamma Knife treatment plans generated for patients with multiple brain metastases was selected. Of these plans, 12 targets were located in the frontal lobes, five targets in the temporal lobes, four in the parietal lobes, three in the cerebellum, two in the occipital lobes, and four targets in other sites. The clinical plans were generated with LGP version 11.1 using the TMR10 algorithm. Treatment plans were constructed following our departmental protocol, involving rigid co-registration of simulation CBCTs, CTs (if available) and MR images followed by contouring of target volumes and organs-at-risk. Shot arrangements were set up to cover the target, with iterative manual adjustments.
of shot weights and positions to optimize dose coverage and avoidance of normal tissue and limiting organs-at-risk. In addition, the prescription isodose (typically 50% of the maximum dose) can be adjusted to improve target coverage and selectivity. For plans with multiple targets, the cumulative dose was assessed and adjusted, if necessary. Each plan consisted of at least one target with at least two shots containing a target contour delineated by a radiation oncologist. Simulation CBCTs were used to define the outer contour of the skull and generate electron density information for treatment planning with the convolution algorithm. When available, planning CTs were also used for electron density data for treatment planning using the convolution algorithm. Treatment plans utilizing convolution algorithms on CBCT, and planning CT data were generated by changing the dose algorithm and electron density information used for calculations on the previously generated TMR10 plans. Treatment plans were evaluated using coverage, selectivity, gradient index, and beam-on time to assess changes introduced by using convolution using CBCT and planning CT data when compared to the TMR10 algorithm.

1. Treatment plan evaluation

Plan quality indices used to evaluate treatment plans include coverage, selectivity, gradient index, and beam-on time [3]. Coverage describes the proportion of the target volume (TV) that is covered by the prescription isodose volume (PIV), thus

\[
\text{Coverage} = \frac{\text{Volume}\ (\text{PIV} \cap \text{TV})}{\text{TV}} \tag{2}
\]

Similarly, the selectivity describes the proportion of the PIV that is inside the TV,

\[
\text{Selectivity} = \frac{\text{Volume}\ (\text{PIV} \cap \text{TV})}{\text{PIV}} \tag{3}
\]

The gradient index quantifies the steepness of the dose fall-off. It may be described as the ratio between the half-prescription isodose volume size and the PIV size. Thus, if the planning isodose is 50%, the gradient index is,

\[
\text{Gradient index} = \frac{\text{Volume}\ (\text{PIV}_{50\%})}{\text{Volume}(\text{PIV})} \tag{4}
\]

The beam-on time is defined as the sum of the shot times for all shots on a target.

In clinical use, coverage, selectivity and gradient index are used to assess plan quality and to compare different planning options. Coverage of greater than 0.98 is typical for plans where treatment volume has not been compromised to spare tissue at risk. Selectivity and gradient index vary based on the relative treatment volume size, shape and location. Dose-volume histograms and dose statistics to the target volumes and organs-at-risk can also be used to assess plan quality. Beam-on time can be a practical issue affecting patient comfort and throughput if it is excessive.

Results

For dose measurements performed in the unmodified SWP, the difference in measured and LGP-calculated doses were -0.3%, -0.2%, and +1.8% when the dose was computed using TMR10, convCT, and convCBCT algorithms, respectively. The higher HU for the CBCT dataset is consistent with the expected higher photoelectric effect cross-section at the lower imaging energy (90 kVp vs. 120 kVp for the planning dataset). The higher discrepancy for the convCBCT dose calculation is assumed to be due to the non-uniformity in the HU of the CBCT datasets across the entire scanning volume and the uncertainty in the HU value scaling. For measurements in modified SWP with air cavity, where a block of solid water was removed from the SWP, the difference between measured and LGP calculated doses were -17.0%, -0.5%, and 1.4% for TMR10, convCT, and convCBCT, respectively. The TMR10 algorithm is expected to perform poorly as the air cavity is assigned the density of water. The results indicate that the convolution algorithms accurately model attenuation in this non-homogeneous phantom. Mean HU values of 29 HU and 304 HU for convCT and convCBCT, respectively and these values were used to rescale all voxels in each phantom dataset to a water equivalent relative electron density.

The HU measurements of the inserts imaged (mean ± standard deviation) with the CT and Icon CBCT scanners are shown in Table 1. The HU measurements in Table 1 were used in LGP for to generate CT-ED curves for use with Icon CBCT images. Fig. 3 shows the HU difference between the phantom aligned at the center of the cone beam and the inferior edge of the cone beam.

The mean coverage, selectivity, and gradient index was found to

| Table 1. CT numbers of CIRS phantom inserts imaged in Philips Big Bore Scanner and Gamma Knife CBCT imaging system |
|-------------|------------|-------------|
| Material    | CT HU      | CBCT HU (average) |
| Water       | 1.7 ± 1.6  | 92.6 ± 83.4  |
| Adipose     | -74.4 ± 2.0| -154.4 ± 77.0|
| Dense bone  | 1,121.9 ± 14.5| 1,590.7 ± 212.5|
| Muscle      | 54.1 ± 2.7 | 150 ± 90.6   |
| Lunge (inhale)| -827.9 ± 5.5| -993.7 ± 16.8|
| Breast (50/5)| -40.3 ± 2.8 | 18.1 ± 85.6 |
| Trabecular bone | 288.5 ± 3.3 | 505.9 ± 115.3|
| Liver       | 59.9 ± 2.3 | 170.3 ± 85.3 |

Values are presented as mean ± standard deviation. CT, computed tomography; CBCT, cone-beam CT; HU, Hounsfield unit.
be 0.995 ± 0.008, 0.61 ± 0.13, and 3.3 ± 1.0 for convCT, respectively. Fig. 4 compares the mean coverage, selectivity, gradient index, and beam-on time of LGK treatment plans calculated with the TMR10 algorithm and with convCBCT, respectively. CBCT imaging with LGK Icon generates artifacts produced at the superior end of the scanner due to the non-symmetry of the x-ray tube with the imaging panel is depicted in Fig. 5. Fig. 6 is a box and whisker plot of the mean calculated beam-on times for various treatment plans recalculated using TMR10, convCT, and convCBCT.

Discussion and Conclusion

As seen in Fig. 3, the CT number of all the inserts in the CIRS phantom imaged with CBCT was observed to vary excessively with the insert’s position within the phantom. This was true whether the phantom was imaged in the center or at the edge of the cone-beam FOV. The greatest variation in HU (up to 408 HU) was seen for the dense bone insert when the CIRS phantom was imaged at the center of the cone-beam FOV. The average CT number of the inserts was also dependent on the position of the phantom within the cone-beam FOV, with the largest difference seen for dense bone. The difference in the average CT numbers of this insert when the phantom was imaged in the center and at the edge of the cone-beam FOV was 321 ± 195 HU. There were also large differences in the CT numbers of all other inserts of the CIRS phantom, with the exception of the lung (inhale) insert, where all measured values were near to the minimum HU value of -1000, representing an underestimate in electron density. As expected, the planning fan-beam CT image did not suffer the same HU variation issues as the CBCT.

The very significant changes in HU with respect to the insert position made it difficult to define a suitable CT-ED curve for dose calculations using CBCTs. As there was no way to encode positional variation in LGK’s CT-ED curve, the average CT number of all phantom measurements for each material were used. In addition, the density of dense bone was used as a cut-off value, with all materials with a higher HU set to this density. This was a deliberate choice to minimize the effect of the HU increase in the skull seen away from the center of the FOV in CBCT images and especially prominent at the superior end of the patient’s skull.

Typically, the convolution dose calculation algorithm in LGK uses electron density information from planning CT images. If CBCT images could be used instead, then planning CTs could be excluded from the workflow, as skull definition and electron density could be derived from the CBCT, with the target volume and organ-at-risk delineation performed on fused MRI images. As the CBCT is an integrated part of the Gamma Knife Icon and the whole system is calibrated to use the same stereotactic frame of reference, a high level of positional accuracy is ensured. Furthermore, as CBCT images are acquired with the patient on the treatment couch, the overall treatment process is greatly simplified. However, when using CBCT images for convolution dose calculations, the large variations in CT number and limited FOV must be taken into consideration, especially as the beam travels through the skull. It is imperative to ensure that this does not introduce any systematic dose calculation errors into the final treatment plan. Restricted acquisition angles

Fig. 3. Difference in HU numbers with CIRS phantom aligned along the central axis and near the inferior edge of the cone beam, for each position of the insert in the phantom. HU, Hounsfield unit.
GammaPlan convolution algorithm for dose calculation

Fig. 4. Comparison of treatment plans: (A) gradient index, (B) coverage index, (C) selectivity and (D) beam-on time (TMR10 vs. convolution algorithm).
tend to introduce a significantly higher density artifact at the superior edge of the skull. Such an artifact may be seen in the target coverage for patient #25, which decreased from 0.95 (TMR10) to 0.85 (convCBCT) (see Fig. 4).

In comparison, the measurements in the SWP indicated close agreement between dose and measurement for both convCT and convCBCT algorithms. It should be noted that convCBCT dose estimations at the center of the SWP are expected to be less affected by the two unfavorable influences observed on patient datasets: the target is at the center of the FOV. Therefore, the radiation contributing dose to the target will be attenuated by the full range of the HU-inhomogeneity, thus averaging out the influence of non-uniformity; secondly, the shots do not traverse the artifact at the superior apex of the phantom. This artifact is also reduced as the phantom is smaller than a typical human skull with no higher electron density material equivalent to the bone.

The coverage of Gamma Knife treatment plans generated using the TMR10 algorithm was 0.98 ± 0.02. The plan coverage achieved with convCBCT was 0.98 ± 0.03. Therefore, the choice to use the TMR10 or convolution algorithm with CBCT for treatment planning does not make a significant difference to the coverage of treatment plans (p = 0.13). This is reflected in the mean absolute difference in coverage between plans generated with the two different algorithms, which was 0.001.

The selectivity of Gamma Knife treatment plans generated using the TMR10 algorithm was 0.73 ± 0.14. The selectivity achieved with convCBCT was 0.75 ± 0.15. Therefore, the choice to use the TMR10 or convolution algorithm with CBCT for treatment planning does not make a significant difference to the selectivity of the treatment plans (p = 0.33). This is reflected in the mean absolute difference in selectivity between plans generated with the two different algorithms, which was 0.02.

The gradient index of Gamma Knife treatment plans generated using the TMR10 algorithm was 3.1 ± 0.94. The gradient index achieved with the convolution algorithm using CBCT images was 3.1 ± 0.97. Therefore, the choice to use the TMR10 or convolution algorithm with CBCT for treatment planning does not make a significant difference to the gradient index of treatment plans (p = 0.46). This is reflected in the mean absolute difference in gradient index between plans generated with the two different algorithms, which was 0.0002.

The results for coverage, selectivity, and gradient index are unsurprising because treating the patient as water equivalent will be an excellent approximation for most of the 192 beamlets for most shot positions.

Fig. 6 shows that planning treatments using convCBCT compared to TMR10 increased the average beam-on time from 18.9 ± 5.8 minutes to 21.7 ± 6.6 minutes. The choice of dose calculation algorithm therefore results in a significant increase in the beam-on time (p = 0.048). This was also observed when the plans were calculated with TMR10 and then recalculated with convCT (see Fig. 6). Moving from TMR10 to convCT increased the mean beam-on time by 6.9%. Moving from convCT to convCBCT increased the mean beam-on time by 8.6%. Overall, calculating the treatment plan using convCBCT instead of TMR10 increased the mean beam-on time by 16.2%.

There are three considerations that have a significant influence on the beam-on time. The first is the attenuation from the skull. Every beamlet in a shot will traverse the skull for almost all situations, lowering the dose rate at the shot position and thus increas-
The beam-on time necessary. The second consideration is that
HU values increase towards the edge of the FOV, introducing a
spurious increase in necessary beam-on time. The third consider-
ation is that high-density artifacts near the superior end of the
skull in CBCT images may be traversed by beamlets, introducing
another spurious increase in the beam-on time, particularly for su-
perior targets. These considerations indicate that it is likely that the
beam-on time calculated using convCT is more accurate than the
underestimate calculated using TMR10 or the overestimate using
convCBCT. It should be noted that a factor could potentially be ap-
plied to adjust the prescription dose based on the outcome data
correlated to the treatment plans that have been historically calcu-
lated using TMR10 or similar homogeneous dose algorithms to cor-
rect for the increased beam-on time in the convCT algorithms.

A limitation of this study was that all plans considered were
planned using TMR10 only. However, it should be noted that due to
the practical limitations imposed by the calculation time, centers
using the convolution algorithm will usually plan using TMR10
first, only using the convolution to make small iterative adjust-
ments at the end of the plan construction.

In conclusion, the use of the convolution dose calculation algo-

formation derived from CBCT images. The limitations of the CBCT
imaging due to artifacts introduced by the small FOV and the large
HU variation usually do not significantly impact the quality of the
treatment plan in terms of coverage, selectivity, and gradient index.
However, it is arguable that the limitations of CBCT-based electron
density data may introduce more uncertainties into the dose algo-

Conflict of Interest

No potential conflict of interest relevant to this article was report-
ed.

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Abscopal effect after palliative five-fraction radiation therapy on bone and lymph node metastases from luminal B breast cancer: a case report and clinical implications for palliative radiation therapy

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Introduction

The abscopal effect (from the Latin ab- for “away from” and scopus for “target”) is the regression of tumors at a distance from the irradiated lesions; it was first described in 1953 [1]. In the last several decades, the abscopal effect has been discussed by radiation oncologists as an interesting but extremely rare phenomenon with little hope for application in real practice [2]. The abscopal effect is mediated by immunologic mechanisms. In the immunotherapy era, a new appreciation of the role played by anti-cancer immune systems in orchestrating the anti-tumor effects of radiotherapy (RT) has caused a major spike in interest in the abscopal effect [3]. Here, we have reported a case of metastatic luminal B breast cancer showing the abscopal effect after multi-site five-fraction palliative RT and proposed some ways to increase the probability of occurrence of the abscopal effect.

Case Report

After approval by the Institutional Review Committee of Severance...
Hospital (No. 4-2020-0947), the medical records of patients with breast cancer treated at our institution were examined. A patient who received intensity-modulated radiotherapy (IMRT) was identified and selected for study.

A 37-year-old woman was diagnosed with metastatic luminal B breast cancer (estrogen and progesterone receptor positive and HER2 positive) in April 2018. Metastatic lesions were found in the lungs (bilateral), bone (the spine, sternum, rib, both pelvic bone, and proximal femurs), and lymph nodes (left axillary level I, the left supraclavicular fossa, and the mediastinum). Positron emission tomography (PET) and chest computed tomography (CT) showed multiple metastatic lesions (Figs. 1, 2). She refused to receive any systemic therapy because she was afraid of toxicity caused by chemotherapy and hormone therapy. However, she agreed to receive palliative RT in order to relieve severe pain.

The patient received five fractions of IMRT for painful metastatic bone lesions. The patient had severe pain in the right pelvis, sacrum, and thoracic spine. The initial pain score using the visual analog scale (VAS) was 8. Simulation CT was performed using a custom-made immobilization device. The gross tumor volume (GTV) was contoured with the simulation CT fused with PET and diagnostic CT. The clinical target volume (CTV) was defined as the consideration of microscopic disease, and the planning target volume (PTV) was defined as an adequate margin for the CTV. A total dose of 22.5 Gy was delivered at 4.5 Gy to 100% of the PTV using IMRT to spare normal organs at risk, such as the heart, lung, bowel, and rectum. Linac-based volumetric modulated arc therapy was used for IMRT. After four fractions of RT of the thoracic spine and pelvic bone, the pain subsided (the VAS score reduced from 8 to 2), but there was new-onset pain in the left axilla and sternum (VAS score, 6). Additional RT to the axilla was planned, and the prescribed dose was 25 Gy in 5 Gy. Because the left axillary metastatic mass was large, a simultaneous integrated boost technique was used. The fractional dose of 6 Gy was prescribed to the “core” of axillary mass. The dose distribution for the thoracic spine, pelvic bones, sternum, and axillary mass are shown in Fig. 3. The patient did not have any severe toxicity during RT.

After 3 months of RT, the follow-up pulmonary CT revealed that a large mass involving the left anterior chest wall (irradiated lesion) and metastatic nodules in both lungs (unirradiated lesion) were markedly decreased in size (Fig. 4). Considering that RT was only administered to the chest wall mass, the decrease in the size of metastatic nodules in both lungs might be regarded as the abscopal effect. No other treatment was administered to either lung lesion. Severe pain in the thoracic spine, right pelvis, axilla, and sternum reduced from a VAS score of 8 to 0, from 8 to 2, from 8 to 2, and from 8 to 0, respectively.

As respect to lymphocyte count, total lymphocyte count (TLC) before RT was 3,300/mm$^3$. TLC was decreased to 640 during RT, and TLC was recovered to 1,150 at 1-month follow-up after RT.

However, the patient did not want to receive any further treatment and refused to visit the hospital after 3 months of follow-up. The patient died of the disease 14 months after RT.

Discussion

The abscopal effect has been described as a rare phenomenon in clinical practice. This rarity is caused by the fact that conventional

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**Fig. 1.** Positron emission tomography (PET) revealed multiple metastases (both lungs, bones, and left anterior chest wall mass). (A) Maximum intensity projection image. (B) Fusion axial image of PET and computed tomography.

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RT alone is inadequate to subvert the existing immunosuppression or tolerance characteristics of the microenvironment of an established tumor. However, the ability of RT to prime antitumor responses is likely to be key in not only inducing the abscopal effect but also obtaining therapeutic synergy with immunotherapies [4].

Considering Norman Coleman’s statement that “radiation is a different drug at different doses and fractionation schedules,” the dose and fractionation of RT might be linked to the abscopal effect. Vanpouille-Box et al. [4] provided a mechanistic explanation for the dose dependence of abscopal effects. A shorter course (≤ 3–5 fractions) with increasing dose size per fraction (≥ 6–8 Gy) was associated with activated intrinsic type I interferon (IFN-I) activation via the cGAS/STING pathway and may be the optimal choice of regimen to test abscopal responses. Although there are various dose and fractionation schedules for palliative RT (such as 8/1, 20/5, and 30/10), we believe that the shorter the course, the better the abscopal effect; shorter courses are also preferred for patients’ convenience.

Many groups have insisted that lymphocytes might play a key role in the abscopal effect, and the degree of RT-induced lymphopenia might influence the occurrence of the abscopal effect [5]. Short fractions lead to short periods of circulating lymphocyte depletion and relatively faster recovery. The Yonsei Group found that a large RT target volume was associated with RT-induced lymphopenia and poor survival [6]. Prevention of lymphopenia caused by RT might be needed to achieve the desired abscopal effect. Lambin et al. [5] proposed “lymphocyte-sparing RT” with the principle of “as low as reasonably achievable” in lymphocyte-rich regions in RT treatment planning. Recently, Sung et al. [7] developed a model for lymphocyte and RT, enabling physicians to predict the immunological consequences of different RT dose/fractions. This model could provide an explanation for understanding the abscopal effect.

Emerging data have shed light on the fact that lower tumor burden is associated with better response to immunotherapy [8]. Accordingly, inter-metastasis tumor heterogeneity could be a challenge for the abscopal effect as well as immunotherapy [9]. Weichselbaum, who first proposed the concept of oligometastasis in 1995 [10], suggested multi-site RT or RT to all sites because of the potential benefits of ablating non-immunogenic lesions [3]. Tumor microenvironment profiles are associated with response to immunotherapy. Recent studies have focused on immune checkpoint molecules, such as programmed death (PD)-1, PD-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which are associated with response to immunotherapy. Luke et al. [11] re-

Fig. 2. The dose distribution for the thoracic spine, lumbar spine, pelvic bones, sternum, and axillary mass. The total dose for the thoracic and lumbar spine and pelvic bones was 22.5 Gy in 4.5 Gy and 30 Gy in 6 Gy for the sternum and axillary mass. (A) Axial image. (B) Sagittal image. (C) Coronal image.
ported stereotactic body RT (SABR) outcomes based on local tumor response and tumor gene expression patterns, showing that SBRT increased the expression of innate and adaptive immune genes and decreased the expression of cell cycle and DNA repair genes. The limitation of our report is the lack of biopsy results. There was only an initial pathology report of a mastectomy specimen, and no post-RT pathology report. If there were both pre-RT and post-RT pathologies, additional analysis would be possible. According to changed policies of IRB in 2013, it was impossible to access the patient’s pathological records without the patient’s consent. At the time of writing this case report, the patient had already died and we could not get consent because we couldn’t contact her guardians. Recently, we initiated our phase II study (NCT04017897) to investigate whether immunotherapy plus RT exhibits increased antitumor activity in patients with melanoma [12]. Because we could not analyze various molecular profiles and tumor microenvironment due to absence of pathologic confirmation, we will check various molecular profiles and report changes in tumor microenvironment by obtaining peripheral blood sample and tumor tissue in the prospective study.

Several groups have provided preclinical and clinical evidence that low-dose radiation (doses below the threshold thought to kill...
cancer cells, e.g., 1–20 Gy total with < 1–2 Gy daily dose) might convert the stroma by reducing transforming growth factor-beta (TGF-β) signaling and subsequently increasing the abscopal effect [13,14]. Low dose with high dose RT is currently underway in NCT02710253 at MD Anderson. Low-dose radiation has been used for decades (e.g., whole-lung RT 12–20 Gy for Ewing sarcoma) [15]. Some groups have suggested that irradiating parenchymal sites (e.g., the liver and lung) may be more associated with the abscopal effect because there are inherent differences in the microenvironment of various organs [16].

In summary, a meaningful abscopal effect is an infrequent phenomenon. Dose and fraction (conventional vs. hypofractionated vs. high-ablative dose), use of targeted image-guided techniques with a sharp fall-off of dosing (such as SABR), lymphocyte-sparing RT, tumor burden (oligometastases vs. polymetastases), targets (single site vs. multi-site), use of low-dose radiation, and irradiated sites (parenchymal vs. non-parenchymal) may affect the occurrence of abscopal effects. Furthermore, concomitant use of immunotherapy and the timing and sequence of RT in relation to immunotherapy can influence the abscopal effect and treatment outcomes. With emerging evidence of oligometastasis and the potential role of local ablative therapy, clinicians should be aware of the potential role of RT in immunomodulation.

Conflict of Interest

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

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Intrathyroidal parathyroid carcinoma: a case report and literature review

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Introduction

Parathyroid carcinoma is a rare entity, accounting for 0.4% to 5% of all cases of primary hyperparathyroidism (PHPT). It is the least common endocrine malignancy, with a prevalence of 0.005% of all cancers [1]. Fritz de Quervain first described it in 1904 in a patient who presented with a non-functioning lesion. (De Quervain F, 1904) Twenty-nine years later, Sainton and Millot reported the first functioning parathyroid carcinoma. Parathyroid carcinoma arising in an ectopic location is extremely rare. (Sainton P and Millot J, 1933) Equally unusual is the presence of an intrathyroidal parathyroid gland (0.2%), which originates from inadequate migration of the parathyroid gland(s) from the third and fourth branchial arches during embryogenesis [2].

Preoperative diagnosis of an intrathyroidal parathyroid carcinoma is challenging. Due to its rarity in literature there is a lack of large-scale, multicentric series, thus natural course of parathyroid carcinoma is still unclear, and there is no universal consensus regarding management and follow-up.

Parathyroid carcinoma has a high probability of local recurrence, regional node and distant metastasis. The 5-year survival ranges from 50% to 85%. Complete surgical resection with microscopically negative margins is the primary treatment and offers the best chance of cure. Adjuvant radiation therapy is often considered as it can provide benefits in terms of local control [3].

Here, we report an unusual case of parathyroid carcinoma arising from intrathyroidal parathyroid tissue. According to the review of the related literature, less than 20 cases have been described since 1993, and this is the first case of intrathyroidal parathyroid carcinoma identified in Morocco.
Case Report

A 56-year-old female patient presented to a private practice in January 2018 with medial cervical mass evolving over a 10-month period. Family and past medical history were unremarkable. Neck examination showed enlarged thyroid gland. Thyroid ultrasound demonstrated multinodular goiter with hypoechoic irregular 35 mm nodule and prominent internal vascularity within the right thyroid lobe. These findings raised suspicion of a malignant nodule. No further imaging studies or fine needle aspiration (FNA) was performed. In February 2018, the patient underwent total thyroidectomy without lymph node dissection. Written informed consents were obtained. Pathologic examination of the thyroidectomy specimen showed an irregular gray white nodule measuring 3.5 cm × 3 cm in the right thyroid lobe with local infiltration into the surrounding thyroid tissue as well as vascular invasion compatible with intrathyroidal parathyroid carcinoma. Resection margins were positive. Thymic nodular hyperplasia was found, with normal ectopic parathyroid in the contralateral lobe. Postoperative hypothyroidism was treated with levothyroxine at a dosage of 125 μg/day. The patient was sent to endocrinology department for further testing. Physical examination was normal. Her body mass index was 25 kg/m². Blood tests revealed increased serum intact parathyroid hormone (iPTH) level of 241.9 pg/mL (reference range, 15 to 65 pg/mL). Levels of serum calcium and phosphorus showed no abnormality. Thyroid, renal, and liver function tests were within normal ranges. The patient was vitamin D deficient, with serum 25-hydroxyvitamin D levels of 15.2 μg/L (reference range, 30 to 100 μg/L) and received vitamin D suppletion. Postoperative color Doppler ultrasonography displayed a 5.8 mm × 6.7 mm hypervascular hypoechoic lesion in the right thyroid bed, suggestive of residual disease. Sestamibi parathyroid scintigraphy confirmed hyperfunctioning parathyroid tissue in the right thyroid bed (Fig. 1). Chest, abdomen, and pelvis computed tomography (CT) scans ruled out metastatic disease.

Multidisciplinary board considered re-excision. The possibility of surgical treatment and risk of adverse events was discussed with the patient. She refused further surgery. According to that, radiotherapy as an alternative therapeutic approach was planned. The patient was sent to radiation oncology department for evaluation and was taken up for adjuvant treatment. Simulation was performed using the CT simulator (SOMATOM Sensation Open; Siemens, Erlangen, Germany). The patient was immobilized in supine position with a 5-point head neck and shoulder thermoplastic mask. An intravenous iodine contrast enhanced planning CT with 3-mm slice thick reconstruction was obtained. The CT DICOM images were transferred to the Monaco treatment planning system version 5.11 (Elekta, Stockholm, Sweden) for target delineation. Gross tumor volume (GTV) consisted of the macroscopic residual disease based on the postoperative ultrasonography and seen on the planning CT. A 5-mm isotropic margin was given around GTV to generate high-risk clinical target volume (CTV-HR). A low-risk clinical target volume (CTV-LR) was defined as the CTV-HR with a 5-mm margin, including the thyroid and surgical bed along with drainage lymph nodes in the paratracheal, perithyroidal areas and superior mediastinum, starting 3 mm below the skin (Fig. 2). The planning target volumes (PTVs) were created using a 5-mm expansion around the respective CTVs, except in the skin direction (Fig. 3). All the organs at risk were contoured according to the Radiation Therapy Oncology Group (RTOG) atlas for normal tissue contouring.

Table 1. Dose prescription for the PTVs.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>70 Gy in 35 fractions</td>
</tr>
<tr>
<td>Mid</td>
<td>56 Gy</td>
</tr>
</tbody>
</table>

Two-arc volumetric modulated arc therapy (VMAT) with simultaneous integrated boost (SIB) technique plan was generated using 6-MV photon beams. PTV coverage was acceptable, with a conformity index and homogeneity index of 1.06 and 0.03, respectively (Fig. 2). All the organs at risk received acceptable doses (Table 1). VMAT plan was delivered using Elekta Versa HD. Patient set-up was

![Fig. 1](https://example.com/fig1.png) Early and delayed 99mTc-methoxy-isobutyl-isonitrile (99mTc-MIBI) scintigraphy showed focal uptake in the right anterior neck, suggestive of residual disease.
verified weekly by kV cone-beam CT imaging prior to treatment.

Radiation dermatitis prevention consisted on local hygiene routine and use of emollient and healing creams. The patient tolerated the radiation treatment well and experienced reversible ≤ grade 2 acute toxicity on skin and mucosa according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

At a 3-month follow-up visit after radiation, the serum PTH level dropped to 71.10 pg/mL and a cervical ultrasonography found an empty thyroid bed with no abnormal lymph nodes. After a period of 24-month follow-up, our patient remains asymptomatic. Her calcium and PTH levels are within normal ranges (PTH 55.2 pg/mL) and CT scans showed no signs of local or distant recurrence. The patient is still under regular follow-up till date.

Discussion

Parathyroid carcinoma is an exceedingly rare malignancy and comprises less than 2% of patients with PHPT. It affects equally both genders with a median age of 45 years [4]. The pathogenesis of parathyroid cancer remains unclear. It may occur sporadically or as a part of a genetic syndrome. It has been associated with a rare autosomal dominant inherited disorder known as hyperparathyroidism-jaw tumor syndrome (HPT-JT) due to germline mutations in the CDC73 gene that encodes parafibromin. Less frequently, it is associated with familial isolated hyperparathyroidism and multiple endocrine neoplasia type 1 and type 2A. No established risk factors have been identified. However, cases of parathyroid cancer arising in patients with prior neck radiation exposure or secondary and tertiary hyperparathyroidism from chronic renal failure have been reported [1,4].

Parathyroid glands generally lie behind the thyroid and originate from the third and fourth branchial arches [5]. Aberrant migration during embryogenesis can lead to various ectopic locations within the thymus, along the anterior surface of the carotid sheath or mediastinal. Intrathyroidal location is the most unusual site of an ec-
topic parathyroid gland (0.2%) [3,4].

In the literature, approximately 700 cases of parathyroid carcinoma have been reported to date, and, to the best of our knowledge, less than 20 cases of intrathyroidal parathyroid carcinoma have been previously documented [6–20] (Table 2). We report a parathyroid carcinoma that was completely intrathyroidal, presenting with multinodular goiter leading to initial misdiagnosis.

Patients with parathyroid cancer usually present with manifestations associated with severe hyperparathyroidism and hypercalcemia. In addition to the stigmata of hyperparathyroidism, a palpable neck mass can be present in 30%–75% of cases [1]. Asymptomatic parathyroid carcinoma is rather rare, representing approximately 2% of all. Our case is noticeable, because of the lack of symptoms on presentation except for the enlarged thyroid gland.

In absence of reliable consensual clinical diagnostic criteria, preoperative diagnosis of parathyroid carcinoma is still difficult, especially in case of infiltrative thyroid mass. The presence of multiple thyroid nodules or nodules in the vicinity of normal parathyroid glands can make perioperative and preoperative localization extremely difficult and easily missed. The clinical suspicion of severe hyperparathyroidism can be helpful. Blood sampling tests (serum calcium, iPTH, etc.) and ultrasonography of the neck are the exams of first choice when dealing with a patient with PHPT. A Sestamibi scan and MRI of the cervical area can aid in locating the affected parathyroid gland, although usually these exams cannot differentiate between adenoma and carcinoma. The same goes for FNA since there is a big overlap in cytological features of parathyroid and thyroid nodules [5]. Consequently, final diagnosis is almost always made postoperatively and is only confirmed by histological and pathological examination.

Table 2. Literature review of published intrathyroidal parathyroid carcinoma cases

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Number of cases</th>
<th>Age /Sex</th>
<th>Presentation</th>
<th>Tumor location/size</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ernst et al. [6], 1993</td>
<td>1</td>
<td>52/F</td>
<td>↑ HPT / ↑ Ca</td>
<td>LTN, 2.5 cm</td>
<td>LHT</td>
<td>NED, 4 months</td>
</tr>
<tr>
<td>Crescenzo et al. [7], 1998</td>
<td>2</td>
<td>60/F</td>
<td>Left neck mass, ↑ HPT / ↑ Ca</td>
<td>LTN, 1.5 cm</td>
<td>LHT + IT</td>
<td>NED, 18 months</td>
</tr>
<tr>
<td>Kirstein and Ghosh [8], 2001</td>
<td>3</td>
<td>74/M</td>
<td>↑ HPT</td>
<td>LTN, NR</td>
<td>LHT</td>
<td>NR</td>
</tr>
<tr>
<td>Schmidt et al. [9], 2002</td>
<td>4</td>
<td>76/F</td>
<td>↑ HPT / ↑ Ca</td>
<td>RST, 3.2 cm</td>
<td>RHT + IT</td>
<td>NED, 1 year</td>
</tr>
<tr>
<td>Hussein et al. [10], 2006</td>
<td>5</td>
<td>63/F</td>
<td>↑ HPT / ↑ Ca</td>
<td>LTN, 6.0 cm</td>
<td>LHT</td>
<td>NED, &gt; 1 month</td>
</tr>
<tr>
<td>Foppiani et al. [11], 2007</td>
<td>6</td>
<td>67/F</td>
<td>↑ HPT / ↑ Ca</td>
<td>RIT, 3.0 cm</td>
<td>TT</td>
<td>NED, 5 years</td>
</tr>
<tr>
<td>Herrera-Hernandez et al. [12], 2011</td>
<td>7</td>
<td>14/F</td>
<td>↑ HPT / ↑ Ca</td>
<td>RTN, 2.5 cm</td>
<td>RHT</td>
<td>NED, 18 months</td>
</tr>
<tr>
<td>Quartey et al. [16], 2011</td>
<td>8</td>
<td>55/M</td>
<td>↑ HPT</td>
<td>RTN, 2.4 cm</td>
<td>RHT + IT</td>
<td>NED, 3 months</td>
</tr>
<tr>
<td>Kruljac et al. [14], 2011</td>
<td>9</td>
<td>40/M</td>
<td>Left neck mass, ↑ HPT / ↑ Ca</td>
<td>NR</td>
<td>TT</td>
<td>NED, 10 months</td>
</tr>
<tr>
<td>Lee et al. [13], 2014</td>
<td>10</td>
<td>59/F</td>
<td>MEN type 1 ↑ HPT / ↑ Ca</td>
<td>RTN, 2.1 cm</td>
<td>RHT</td>
<td>NR</td>
</tr>
<tr>
<td>Vila Duckworth et al. [4], 2013</td>
<td>11</td>
<td>51/F</td>
<td>Thyromegaly ↑ HPT / ↑ Ca</td>
<td>RST, 1.4 cm</td>
<td>TT</td>
<td>NED, 2.5 years</td>
</tr>
<tr>
<td>Young et al. [15], 2015</td>
<td>12</td>
<td>33/F</td>
<td>Right neck mass, ↑ HPT / ↑ Ca</td>
<td>LTN, 6 cm</td>
<td>TT + upper RPT</td>
<td>NR</td>
</tr>
<tr>
<td>Tejera Hernandez et al. [3], 2016</td>
<td>13</td>
<td>25/M</td>
<td>Right neck mass, ↑ HPT / ↑ Ca</td>
<td>RTN, 3 cm</td>
<td>RHT</td>
<td>NED, 16 months</td>
</tr>
<tr>
<td>Merazka et al. [17], 2016</td>
<td>14</td>
<td>36/F</td>
<td>Right neck mass, ↑ HPT / ↑ Ca</td>
<td>RTN, 4 cm</td>
<td>TT</td>
<td>NED, 6 months</td>
</tr>
<tr>
<td>Balakrishnan et al. [5], 2018</td>
<td>15</td>
<td>60/F</td>
<td>Right neck mass, ↑ HPT / ↑ Ca</td>
<td>LTN, 3 cm</td>
<td>TT</td>
<td>NED, 6 months</td>
</tr>
<tr>
<td>Alharbi et al. [18], 2018</td>
<td>16</td>
<td>63/M</td>
<td>↑ HPT / ↑ Ca</td>
<td>LTN, 2.7 cm</td>
<td>TT + central and left neck dissection</td>
<td>MD, 3 months</td>
</tr>
<tr>
<td>Cao and Wang [2], 2019</td>
<td>17</td>
<td>56/F</td>
<td>Right thyroid nodule ↑ HPT / ↑ Ca</td>
<td>LTN, 2.7 cm</td>
<td>RHT + RL</td>
<td>NED, 6 months</td>
</tr>
<tr>
<td>Poortmans et al. [19], 2020</td>
<td>18</td>
<td>26/F</td>
<td>Multinodular goiter ↑ HPT / ↑ Ca</td>
<td>LTN, 2.8 cm</td>
<td>TT</td>
<td>NED, 5 years</td>
</tr>
<tr>
<td>Present study</td>
<td>19</td>
<td>56/F</td>
<td>Multinodular goiter ↑ HPT / ↑ Ca</td>
<td>RTN, 3.5 cm</td>
<td>TT + adjuvant RT</td>
<td>NED, 2 years</td>
</tr>
</tbody>
</table>

↑ Ca, hypercalcemia; ↑ HPT, hyperparathyroidism; IT, isthmusectomy; TT, total thyroidectomy; LHT, left hemithyroidectomy; RHT, right hemithyroidectomy; RPT, right para-thyroidectomy; RL, right lymphadenectomy; LTN, left thyroid nodule; RTN, right thyroid nodule; RIT, right inferior thyroid; RST, right superior thyroid; RT, radiotherapy; NR, not reported; NED, no evidence of disease; MD, metastatic disease.

*Case also described by Temmim et al. [20].
Surgery is the mainstay in the management of parathyroid carcinoma. Complete surgical resection with microscopically negative margins offers the best chance of cure and it is, therefore, recommended as a gold standard. It requires an en bloc resection of the tumor with ipsilateral thyroid lobectomy and centrocervical lymphadenectomy as well as removal of involved structures or local metastatic lymph nodes. It is of great importance that clear gross margins are obtained, and particular attention must be given to avoid capsular disruption because of the very high risk of local seeding and persistent or recurrent disease [19]. However, many patients fail to receive such treatment and experience subsequent tumor progression, such as in our case. Disease progression rates of 30%–67% have been reported [2,13]. Parathyroid carcinoma has a high recurrence rate and the potential to metastasize to regional nodes and distant sites late in its course. Patients should be closely followed over time [21]. Postoperative assay of serum calcium and PTH level is a simple and important evidence to evaluate the efficacy of treatment and to predict the recurrence of tumor as well. When complete resection is successful, this results in a 90% survival rate, if not the local recurrence rate is as high as 50%–60%. Although repeated surgical interventions have proven beneficial in palliative care, excision of progressive tumor is not consistently curative [19].

Parathyroid carcinoma is not considered to be radiosensitive, thus, no established radiotherapy protocol exists. There is no evidence for the efficacy of radiation treatment as primary therapy in local or metastatic disease. The evidence base for radiotherapy in the adjuvant setting is limited and has only been reported in small case series. The Mayo Clinic series and other studies suggested beneficial effect of adjuvant radiotherapy in preventing tumor regrowth after surgery, with reduced local recurrence and increased disease-free interval. The reported local recurrence rate without radiotherapy is 77%, whereas adjuvant radiotherapy seems to have reduced recurrence by 65% [22-29].

These results provide preliminary support that adjuvant radiotherapy may decrease the strong predilection for locoregional disease progression. However, it should be interpreted with great caution, as the studies dealing with adjuvant radiotherapy were retrospective and included a small number of patients without any comparison, thus no strong conclusion can be drawn. Therefore, the role of postoperative radiotherapy in the management of parathyroid carcinoma remains unclear. It is not recommended as a routine tool but may be of value for highly selected groups. To our knowledge, the present report is the first case of intrathyroidal parathyroid carcinoma to receive adjuvant radiation therapy. Given our patient’s refusal to undergo further surgery, adjuvant radiotherapy to the residual disease seemed essential to reduce the risk of local relapse. No recurrence occurred 2 years after treatment, with PTH level within normal ranges and without significant radiation-related toxicity.

Very few data are available in the literature regarding target volume delineation, dose prescription and fractionation or planning technique for parathyroid carcinoma. In this case, radiotherapy was planned according to the principles of the international guidelines of the Danish Head and Neck Cancer Group (DAHANCA). GTV was accurately outlined on the planning CT, based on examinations, imaging and pathology reports. Following a geometric approach, we defined a CTV–HR including the macroscopic residual tumor GTV plus a 5-mm margin and a CTV–LR adding an additional 5-mm margins. CTV–LR encompassed the operative bed, tracheoesophageal grooves, along with the elective nodal regions at risk for subclinical spread—the central nodal compartment (covered superiorly to the caudal edge of hyoid bone), the upper and lower paratracheal lymph node levels, the upper mediastium (thoracic lymph node levels II, III, and IV covered to the level of the carina). Lateral cervical neck was omitted in a node-negative neck. These CTVs were adjusted on natural anatomic boundaries (bone, air cavities) and excluded the right carotid artery. PTVs contained corresponding CTVs with set-up margins of 5 mm. Using a SIB approach, gross disease was treated to 70 Gy in 35 daily fractions of 2 Gy, and low risk areas received a prophylactic dose of 56 Gy in 35 daily fractions of 1.6 Gy, 5 days a week over 7 weeks.

Our patient didn’t receive concomitant chemotherapy as there is no evidence supporting the efficacy of chemotherapy in parathyroid carcinoma. No standard chemotherapy regimen is available as experience is limited to case reports. A few chemotherapy drugs were used in the metastatic setting, including cyclophosphamide, 5-fluorouracil and dacarbazine as single or combination therapies, but no survival benefit was demonstrated. Denosumab, a monoclonal antibody against RANKL (receptor activator of nuclear factor kappa-B ligand) that inhibits osteoclast maturation, function, and survival can be useful in malignant hypercalcemia treatment [27].

An interdisciplinary team approach including endocrinologists, surgeons, radiation oncologists, and pathologists must be involved to offer patients the best option for cure of this rare disease.

In conclusion, parathyroid carcinoma is a rare disease, usually presenting with clinical signs of severe hypercalcemia, but often disguising as apparently benign PHPT. It is a particularly difficult diagnosis to establish when the disease is detected outside of its typical anatomical sites. Of these, the intrathyroidal occurrence of parathyroid carcinoma can be problematic.

Clinical suspicion prior to surgery is crucial, since specific surgical procedure is the only potentially curative therapy. The combination of high levels of serum calcium, tumor size and an inverted

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(>1) PTH ratio are efficient in orienting towards an oncological surgical approach. The severity of this pathology is due to the severe hypercalcemia aggravating the mortality and to the risk of local recurrence and distant metastases justifying the prolonged monitoring. Adjuvant radiation therapy has been reported to effectively decrease the local relapse rate and to improve the disease-free interval, especially in high-risk patients. Whether adjuvant radiation therapy should become the standard of care in these patients remains a subject of discussion.

Conflict of Interest

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

References


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Lacrimal gland adenoid cystic carcinoma: report of an unusual case with literature review

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Introduction

Adenoid cystic carcinoma (ACC) is a rare malignancy of the secretory glands characterized by slow growth kinetics, prolonged clinical course and perineural invasion. ACC was first described in literature by Theodore Billroth, and was initially named “cylindroma” because of its specific histopathologic characteristics [1]. According to the Surveillance, Epidemiology, and End Results (SEER) database, ACC rising in the eye and orbit, including the lacrimal gland, lacrimal sac, and nasolacrimal duct, accounted for only 1.8% of total patients. The lacrimal gland was most commonly involved in over 80%. ACC is the most common malignant histology of the lacrimal gland, accounting for 25%–40% of all epithelial tumors of the lacrimal gland [2].

Lacrimal gland adenoid cystic carcinomas are rare, aggressive orbital tumors characterized by poor overall prognosis, tendency for local recurrence and metastasis despite aggressive treatment. Treatment continues to be controversial. Many authorities today will often initiate surgery (orbital exenteration with or without bone removal vs. globe-sparing resection) and adjuvant radiotherapy (external beam or proton beam therapy). We introduce a case of lacrimal gland adenoid cystic carcinoma treated with orbital exenteration and adjuvant volumetric modulated arc therapy, and discuss the related literature.

Keywords: Adenoid cystic carcinoma, Lacrimal gland, Orbital exenteration, Adjuvant radiotherapy, Volumetric arc therapy

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Lacrimal gland ACC (LGACC) is associated with poor long-term disease-free survival (DFS) profile that is complicated by complex orbital anatomy and aggressive behavior, high recurrence rates and significant morbidity and mortality. In the literature, the overall tumor-related mortality of LGACC is 10%–87%, with survival rates of less than 50% at 5 years and 20% at 10 years regardless of the local treatment regimens. Perineural invasion is considered an indicator of poor prognosis, because of the inherent risks of spread to the skull base and local recurrence. ACC can metastasize via hematogenous spread to lungs, brain and bone in decreasing order of frequency [3].

Defining a single best treatment strategy has been difficult because of the rarity of lacrimal ACC. The appropriate local therapy for LGACC is a subject of controversy. Some authors advocate con-
servesive surgery followed by external beam radiation therapy (EBRT) or proton beam therapy, whereas others believe that radical surgery probably results in better local control and possibly better long-term survival [4].

This case report provides insight to an individualized treatment approach in a patient with ACC of the left lacrimal gland referring to our institution, and discusses current recommendations from the literature, with a focus on the role of adjuvant radiotherapy.

Case Report

A 45-year-old white man, with a 10 pack-year smoking history, presented to the ophthalmology division of Rabat Hospital with a 9-month history of left-sided painful exophthalmos, red eye and diplopia. On examination, left-sided proptosis and restricted eye motility was noted. The patient’s visual acuity was 20/20, and visual fields were full. Sensation in the V1 and V2 distribution was intact, and he was without facial or cervical lymphadenopathy.

Contrast-enhanced computed tomography (CT) scan of the head and orbits showed a left intra-orbital expansive lesion, characterized by a strong contrast enhancement, pushing back the globe with grade 3 exophthalmos, invading the optic nerve and the orbital canal, without endocranial damage. The image morphology was more in favor of lymphoma. The magnetic resonance imaging (MRI) scan of the head and orbits demonstrated a 4.1 × 1.7 × 2.6-cm left lacrimal gland tumor, infiltrating the superior and lateral rectus muscles, filling the extra-conical fat, encompassing the eyeball without scleral lysis, with osseous destruction of the orbital roof and meningeal enhancement. The tumor invaded the optic nerve over more than 180°, continuing through the optic canal and the lower orbital fissure (Fig. 1).

A biopsy of this mass revealed ACC with perineural invasion. Neck, chest, abdomen and pelvis CT scans ruled out metastatic disease. Clinical stage was cT4eN0M0, according to the American Joint Committee on Cancer staging manual (AJCC 8th edition).

Multidisciplinary head and neck tumor board considered that total orbital exenteration would be necessary to achieve optimal disease control, given the extensive involvement of the lacrimal gland and orbit with perineural invasion. Ultimately, after considering his options, the patient gave his written informed consent for exenteration of the left eye.

The pathological report of the operative specimen confirmed the diagnosis of ACC, measuring 2 × 1.6 × 1.5-cm, optic nerve in contact with the tumor, with perineural invasion, extension in the soft tissues and positive surgical margins (R1). Postoperative MRI found an empty orbital lodge with no sign of residual disease.

The patient was sent to radiation oncology department for evaluation and was taken up for adjuvant treatment. Simulation was performed using the CT simulator (SOMATOM Sensation Open; Siemens, Erlangen, Germany). The patient was immobilized in supine position with a thermoplastic mask covering the head and neck with three fixation points. The patient was instructed to keep his eyes in a fixed position, even during radiotherapy. The planning CT images were acquired from the head to the base of mandible with intravenous iodine contrast enhancement and a slice thickness of 3-mm. The CT DICOM images were transferred to the Monaco treatment planning system version 5.11 (Elekta, Stockholm, Sweden) for target delineation. The acquired images were then co-reg-
istered with diagnostic MRI images to contour the gross tumor volume (GTV) defined before surgery, with the aim of better selecting the clinical target volume (CTV). A 5-mm isotropic margin was given around GTV to generate high-risk CTV (CTV-HR), and was adjusted on the planning CT, including the lacrimal fossa, lateral and superior portions of the orbit, the entire surgical bed and positive margins to consider the microscopic disease. Due to perineural invasion, this volume comprised also a complex “neuronal” volume, including: the upper part of the trigeminal ganglion, where the ophthalmic nerve arises; the entire path of the ophthalmic nerve, extending forward along the lateral wall of the cavernous sinus, below the oculomotor and trochlear nerves and through the superior orbital fissure; and the entire path of the lacrimal nerve, running along the upper border of the lateral rectus, parallel to the lacrimal artery and communicating with the zygomatic branch of the maxillary nerve, finally entering the lacrimal gland. The planning target

Fig. 2. (A, B) Axial views of the planning computed tomography scan showing the target volumes: preoperative GTV in red, CTV-HR and PTV-HR in yellow and green, respectively. (C) Volumetric modulated arc therapy was delivered via to the region of high risk, using a 0.5-cm thick bolus (in blue), to doses of 66 Gy (95% isodose line in orange). GTV, gross tumor volume; CTV, clinical target volume; PV, planning target volume; HR, high risk.

Fig. 3. (A–C) Consecutive axial views from superior to inferior of the planning CT scan with 66 Gy (100%; in red) and 62.7 Gy (95%; in orange) isodose lines.
volume (PTV) was created adding a 5-mm expansion around the corresponding CTV, except in the skin direction (Figs. 2, 3). No elective nodal volume was considered. Organs-at-risk (OARs) were contoured according to the Radiation Therapy Oncology Group (RTOG) atlas for normal tissue contouring. OARs consisted of cord, brainstem, optic chiasm, right eye, right lens, right retina, right optic nerve, temporal lobes and cochleae. A dose prescription of 66 Gy in 2 Gy daily fractions (33 fractions) was given to the PTV to reach the microscopic disease without the limitations placed by an intact globe. Two-arc volumetric modulated arc therapy (VMAT) plan with 6-MV photon beams was set by the medical physicist, using a 0.5-cm thick bolus. Planning goals for the PTV were the following: at least 90% and 95% of the prescribed total dose (PTD) encompassing at least 98% and 95% of PTV, respectively (V 90% ≥ 98% and V 95% ≥ 95%, respectively); and no more than 2% of PTV received more than 107% of the PTD (V 107% ≤ 2%). The following constraints were set for some OARs: for cord, the maximum dose received by 2% of its volume less than 45 Gy (D 2% ≥ 45 Gy); for brainstem, D 2% < 55 Gy; for optic chiasm, D 2% < 60 Gy; for temporal lobes, D 2% < 65 Gy; lastly, the mean dose received by right eye, cochleae and right lens less than 30, 45 and 10 Gy, respectively (D mean < 30, 45 and 10 Gy, respectively). We restricted the right optic nerve mean dose to 48 Gy and a maximum of < 54 Gy. Doses were acceptable for all OARs (Table 1) with homogeneous uniform dose coverage in PTV with 1.08 conformity index. DVH distribution is shown in Fig. 4.

**Table 1. Main dosimetric results for organs-at-risk**

<table>
<thead>
<tr>
<th>Structure</th>
<th>Parameter</th>
<th>Dosimetric results (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord</td>
<td>D max</td>
<td>0.8</td>
</tr>
<tr>
<td>Brainstem</td>
<td>D 2%</td>
<td>45.5</td>
</tr>
<tr>
<td>Optic chiasm</td>
<td>D max</td>
<td>54.2</td>
</tr>
<tr>
<td></td>
<td>D 2%</td>
<td>52.4</td>
</tr>
<tr>
<td>Right optic nerve</td>
<td>D max</td>
<td>28.8</td>
</tr>
<tr>
<td>Left temporal lobe</td>
<td>D 2%</td>
<td>66.7</td>
</tr>
<tr>
<td>Right temporal lobe</td>
<td>D 2%</td>
<td>32.1</td>
</tr>
<tr>
<td>Right retina</td>
<td>D max</td>
<td>22.1</td>
</tr>
<tr>
<td>Right eye</td>
<td>D mean</td>
<td>12.2</td>
</tr>
<tr>
<td>Left cochleae</td>
<td>D mean</td>
<td>22.4</td>
</tr>
<tr>
<td>Right cochleae</td>
<td>D mean</td>
<td>15.5</td>
</tr>
<tr>
<td>Right lens</td>
<td>D max</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Fig. 4. Dose-volume histogram distribution of the following structures: planning target volume (green), chiasma (orange), left temporal lobe (purple), right temporal lobe (cyan), spinal cord (red), brainstem (dark green), right optic nerve (dark blue), right retina (pink), right lens (blue), and right globe (yellow).

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VMAT plan was delivered using Elekta Versa HD. Patient set-up was verified weekly by kV cone beam CT imaging prior to treatment. Systemic therapy was not recommended because of the lack of clear supporting evidence for benefit in this setting. During radiotherapy, the patient was assessed for treatment-related toxicity once a week by the radiation oncologist. The patient tolerated the treatment well and experienced reversible grade 1 periorbital dermatitis according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). No reduction of visual acuity was recorded. There were no treatment interruptions.

After radiotherapy completion, the patient was clinically evaluated every 3–6 months, addressing disease status and late adverse effects. Head and neck MRI and thorax and abdomen CT scans were prescribed on a regular basis every 6 months and 12 months, respectively. After a period of 24-month follow-up, no evidence of local or distant recurrence was found. The patient remains asymptomatic and is still under regular follow-up to date.

**Discussion**

ACC is an uncommon malignancy that arises in secretory glands and accounts for about 1% of all head and neck malignancies. It is the most common primary malignant epithelial tumor of the lacrimal glands and accounts for approximately 1.6% of all orbital tumors [2,5].

LGACC has a propensity for early perineural invasion, bony and intracranial spread. It is associated with aggressive biology and poor prognosis. Despite aggressive local treatment, LGACC show a high rate of local recurrence and late distant metastasis, with significant resultant mortality [4].

It is mainly an adult tumor with a peak incidence defined in the fourth decade of life, although occurrence is possible at any age [2]. The onset of evolution is usually marked by exophthalmos or ptosis, facial asymmetry owing to displacement of the eyeball and swelling of the lacrimal gland. Pain is a cardinal symptom in patients with LGACC, caused by a growth pattern that leads to early peripheral nerve and extraocular muscle invasion. Lacrimation, reduced eye motility, diplopia and visual changes have also been reported in patients with ACC. The duration of symptoms before first ophthalmic consultation is approximately 6 months. Although, the delay in diagnosis or referral is not unique in our case. Ni et al. [6] have reported that fewer than 15% of patients were diagnosed within 2 months and 72% of patients started treatment after 1 year because of delay in diagnosis. Imaging is an important diagnostic tool when establishing a presurgical evaluation of lacrimal gland tumors. MRI is advantageous for early detection of small tumors and for evaluating tumor extension and perineural spread, but it remains unable to differentiate between a malignant and benign tumor [5]. The final diagnosis can only be established after pathological evaluation of a biopsy.

Because of the rare nature of LGACC, a randomized clinical trial is not likely. Consequently, guidance on the best possible treatment must rely on retrospective data and small, single institution series. The optimal management for LGACC remains unresolved.

Surgery is usually the first local treatment in LGACC [7]. Taking the correct surgical approach to these lesions is probably one of the most critical management decisions and can save the patient from unnecessary morbidity and mortality. Residual tumor burden following surgery is a significantly important determinant on both progression-free survival and overall survival. Careful attention should to be paid to minimize gross residual disease at surgery [8]. The rarity of lymph node metastasis (4% to 9%) suggests that lymph node dissection is unnecessary [7,9].

Worldwide, the extent of surgical resection (orbital exenteration with or without bone excision versus globe-preserving surgery) remains an unsolved issue [10]. Because of a historically poor prognosis, orbital exenteration has been the most common surgery for LGACC in the belief that it improves survival [3,11]. However, there is much controversy as to how much radical surgery contributes to the outcome of the patient. In the literature, distant relapse and cancer-related mortality risks are high after orbital exenteration, which highlights the locally invasive and metastatic behavior of this disease [5]. Additionally, comparative case series found that there is no difference in either survival or tumor recurrence for lacrimal gland carcinoma treated with cranio-orbital resection, or eye-preserving tumor excision and radiotherapy [12,13]. Moreover, studies have demonstrated that the quality of life of patients who underwent orbital exenteration is markedly reduced because of functional disability and disfigurement [14]. Consequently, eye-preserving surgery followed by adjuvant radiotherapy has recently gained popularity. Data from the literature suggest that eye-sparing surgery with adjuvant radiotherapy can achieve satisfactory results in patients with T1–T2 orbit-confined lacrimal gland carcinoma [4,15,16]. However, the risk of local recurrence is increased with conserving surgery in patients with advanced-stage disease (T3–T4) at initial diagnosis. Orbital exenteration and adjuvant radiotherapy seems to be a more reasonable option in this group of patients [10,16,17].

In our case, total exenteration was performed after obtaining the informed consent of the patient due to locally advanced disease. However, this surgery can prove challenging given the complex anatomical characteristic of the orbit and the tumor’s tendency to spread along nerve tracts. Negative resection margins could not be obtained.
Adjuvant radiotherapy is recommended after surgical resection, regardless of its extent, especially for patients at high risk of recurrence, including those with an advanced stage tumor and/or multiple unfavorable pathological factors such as bony structure invasion, positive surgical margins, lymphovascular space invasion, or perineural invasion [10,15,17].

Most of the literature available evaluates the use of conventional EBRT. Adjuvant radiation therapy has proven to be effective in preventing locoregional recurrences with local control rates of approximately 50%–80% at 5 years, despite no benefit in survival [10,18]. Addition of radiotherapy following incompletely resected ACC (R0/R1) could decrease the risk of progression, but not following R2 resection [8,17].

Due to the horseshoe-shaped target volume and the proximity to radiosensitive normal structures of lacrimal gland tumors, they might be good candidate for advanced radiotherapy technologies, such as proton beam therapy and intensity-modulated radiation therapy (IMRT) because of their high accuracy and ability to deliver higher radiation doses to the tumor and to spare surrounding tissues. Recently, the introduction of VMAT further improved normal tissue sparing, target coverage and delivery efficiency, compared with conventional IMRT in head-and-neck cancers (HNC) [19]. Very few reports in the literature specifically relates to the use of IMRT or VMAT in LGACC. A case reported by Orlandi et al. [20] presented favorable outcomes in two patients with lacrimal gland cancer treated by postoperative VMAT, with no evidence of disease at 18-month follow-up. To the best of our knowledge, this is the second report describing the use of postoperative VMAT in the management of lacrimal gland malignancies.

In our case, target volumes were selected according to examinations, initial radiological extension of the disease and pathology report. The GTV was accurately outlined on the preoperative MRI and adjusted on the planning CT. Following the international guidelines of the Danish Head and Neck Cancer group (DAHANCA), we defined a CTV-HR including the preoperative GTV plus a 5-mm margin, covering the entire surgical bed and positive margins, along with the lateral orbital wall, superior orbital fissure, orbital roof, and nerve tract up to the skull base. No elective nodal volume was considered because routinely prophylactic nodal irradiation for lacrimal glands malignancies is not recommended [12]. PTV was generated with 5-mm margin for daily setup variation. We prescribed a dose of 66 Gy with standard fractionation to reach the microscopic disease after R1 resection, which was consistent with data reported in the literature. Tumor control is related to radiation dose and that a dose of at least 60 Gy is required to obtain an improved control. In a recent review, von Holstein and coworkers [5] reported fractionation schemes for lacrimal gland ACC and non-ACC epithelial tumors, suggesting a postoperative dose of 66 Gy for ACC with extracapsular spread, positive or close margins or involved nodes.

No concomitant chemotherapy was delivered in our case as there are still no clear data in the literature in favor of this combined approach [10]. Besides, the role of postoperative chemotherapy for LGACC remains unclear.

After 27 months, our patient is free of recurrent disease despite advanced perineural invasion, locally invasive features and positive surgical margins. He experienced minimal acute toxicity and showed no sign of late toxicity at last follow-up. Our case suggests that postoperative VMAT can potentially offer an improved disease control with moderate acute and late side effects for lacrimal gland tumors in the context of a multidisciplinary therapeutic strategy. However, long-term outcome data are not available yet, and additional evidence is required to further elucidate the efficacy and safety of adjuvant VMAT in LGACC.

In conclusion, LGACC is a rare and slowly progressing disease, associated with poor local control, distant metastasis and significant morbidity and mortality rates. Delayed diagnosis, tendency for peri-neural invasion, infiltration to periosteum and local recurrence are factors resulting in poor outcome. To date, optimal treatment is still debated. First treatment conventionally consists in surgery followed by postoperative radiotherapy. Ongoing discussions focus on the optimal dose, fractionation and technique of radiotherapy. ACC is classically considered as a radioresistant tumor, and dose escalation to the focal region of risk is essential to hope for a curative irradiation. New irradiation techniques such as VMAT proved to be effective and safe in irradiating orbital tumors. The role of systemic therapy is yet to be established. Close follow-up after treatment should be undertaken to evaluate both recurrence and radiation-related complications. Larger multicenter studies can yield additional insight and should be planned in the future.

**Conflict of Interest**

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

**References**


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

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

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

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<thead>
<tr>
<th>Initiative</th>
<th>Type of study</th>
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