Aims and Scope

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

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

The ROJ is published quarterly on the last day of March, June, September, and December, one volume per year. Any physicians or researchers throughout the world can submit a manuscript if the scope of the manuscript is appropriate. Articles in the following categories will be published: original articles, invited review articles, case reports, editorials, and letters to the editor related to basic or clinical radiation oncology. All of the manuscripts are peer-reviewed.

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Publisher Hong-Gyun Wu
Editor-in-Chief Sang Min Yoon

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Tel: +82-2-6966-4930 Fax: +82-2-6966-4945 E-mail: support@m2-pi.com

Published on September 30, 2022

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This paper meets the requirements of KS X ISO 9706, ISO 9706-1994 and ANSI/NISO Z39. 48-1992 (Permanence of paper)
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Stereotactic body radiation therapy for pancreatic cancer: a potential ally in the era of immunotherapy?

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Pancreatic cancer (PC) is an aggressive malignancy with a poor prognosis. In 2022, 9,238 new cases of PC were expected to occur, and PC was ranked as the ninth leading primary site among the major cancers in Korea [1]. The incidence rates of PC have been on the rise and are predicted to increase over the next several decades, and PC is expected to be the fourth most common cause of cancer-related deaths by 2022 in Korea [1,2]. Curative surgical resection is the only chance for long-term survival; however, surgical resection is often limited due to many people being diagnosed at an advanced stage and the proximity of the pancreas to major vessels that cannot be replaced or removed.

Although the role of radiotherapy (RT) in PC has been controversial, it has been consistently proven that RT has a proven effect in controlling local disease [3,4]. Previous studies on PC showed that there were high rates of local recurrence or progression that led to the development of pain, gastrointestinal obstruction, bleeding, and other morbidities associated with the primary disease site, impairing the quality of life with chemotherapy and/or surgery alone [3,5]. Therefore, improving local control remains an important aim of RT in patients with PC, regardless of distant disease control. Moreover, RT has become an important modality by better systemic control with an improved chemotherapeutic regimen, and modern radiotherapy techniques with high-precision help local control in a multimodal setting with an acceptable side effect.

Stereotactic body radiotherapy (SBRT) is a modern RT technique that has various benefits compared with conventional RT and has been widely applied as a local therapy for the treatment of several types of malignancies [6]. SBRT enables conformal delivery of high radiation during a short period with reduced irradiation to surrounding normal tissues over conventional RT, and SBRT is considered to have different tumoricidal mechanisms [7,8]. SBRT for PC has been vigorously applied during the last decade for definitive or neoadjuvant aims due to the short treatment duration with limited acute toxicity, which is less disruptive to effective systemic treatment than chemoradiation therapy (CRT) [9]. A previous study that compared conventional CRT with SBRT showed that SBRT could be a feasible alternative to CRT for the treatment of PC [10].

In addition to these advantages of SBRT, it is worth noting that SBRT could promote antitumor immune response through various mechanisms, which could not be expected from conventional CRT [11-13]. However, because SBRT or immune checkpoint inhibitors (ICIs) alone is not sufficient to induce an effective immune response in PC, it could be a novel strategy to combine ICIs with SBRT to overcome resistance to immunotherapy, which means a shift from this “cold tumor” to “hot tumor” [8,13-15]. In the current study to be mentioned in this editorial, Reddy et al. [16] analyzed 68 pa-
tients with borderline resectable (BRPC) or locally advanced pancreatic cancer (LAPC) who received anti-programmed cell death-1 (PD-1) antibody and 5-fraction SBRT after chemotherapy to investigate the role of pre- and post-SBRT neutrophil-to-lymphocyte ratio (NLR).

After a median follow-up period of 10.7 months, the median overall survival (OS) after SBRT was 22.4 months, with a 2-year OS rate of 47.3%. The current study did not compare SBRT plus ICIs with SBRT alone, so the superiority of combination therapy with ICIs cannot be directly evaluated. However, given that most of the patients included in the current study had LAPC, the treatment outcome is considered promising compared to the previously reported treatment results of SBRT for PC with a median OS of 17 months from a meta-analysis [9]. In addition, one of the strengths of the present study is that all patients received standard multi-agent chemotherapy, including FOLFIRINOX or gemcitabine/nab-paclitaxel regimen prior to SBRT and ICIs, given that previous studies included patients who received various chemotherapeutic regimens that could be less effective than the current standard regimens [9].

Recently, the results of a randomized phase 2 trial of SBRT plus pembrolizumab and trametinib versus SBRT plus gemcitabine for locally recurrent PC were reported [17]. A total of 170 patients were enrolled, and after a median follow-up of 13 months, SBRT plus pembrolizumab and trametinib showed a superior median OS (14.9 months vs. 12.8 months, p = 0.021). The authors concluded that SBRT could be a novel immunostimulatory strategy, and SBRT plus pembrolizumab and trametinib could be a new potential treatment option for patients with locally recurrent PC. Although the efficacy of SBRT plus ICIs for PC is not clearly defined, and more evidence is still needed, there are ongoing clinical trials being conducted that aim to assess the feasibility of SBRT combined with immunotherapy [15].

Meanwhile, Reddy et al. [16] showed that the post-SBRT NLR was a significant prognostic factor associated with OS on multivariate analysis. Patients with post-SBRT NLR ≥ 3.2 had a median OS of 15.6 months versus 27.6 months in patients with post-SBRT NLR < 3.2. The authors suggested that the change in NLR was largely due to a decrease in lymphocyte counts after SBRT. The difference in absolute lymphocyte counts was statistically significant compared to the pre-SBRT and post-SBRT values, but not for absolute neutrophil counts. Interestingly, a similar phenomenon has been reported in patients who receive CRT. Chadha et al. showed that post-CRT lymphopenia was associated with a poor prognosis in patients who received induction chemotherapy followed by CRT for LAPC [18].

There is a general consensus that multiple immune cell types exist in the tumor microenvironment (TME) and play an important role in cancer biology [19]. Neutrophils may act as tumor-promoting leukocytes, leading to a negative correlation between neutrophil density and patient survival. However, lymphopenia is associated with immune escape of tumor cells from tumor-infiltrating lymphocytes [20]. Therefore, the NLR might be related to the balance between the inflammatory pathway and antitumor immune function, and a high circulating NLR could be a biomarker of poor prognosis in various cancers [19]. Although the potential role of NLR for PC as a prognostic and predictive marker remains to be determined, NLR in PC could be a promising and convenient biomarker, as shown in a meta-analysis [21].

Reddy et al. [16] also showed that a larger target volume of SBRT correlated with a decreased lymphocyte count. In the present study, log_{CTV} (clinical target volume) had a negative correlation with the post-SBRT absolute lymphocyte count. The authors hypothesized that some RT-related factors, such as target volume or planning, might affect the outcome of patients after RT. These results are in line with those of previous studies. Wild et al. [12] analyzed serial total lymphocyte counts in patients with LAPC who received SBRT or CRT. They observed that SBRT was associated with significantly less lymphopenia than CRT after RT, implying that the RT technique could be associated with lymphopenia, which is related to survival. In addition, Chadha et al. [18] demonstrated that higher splenic doses were associated with the risk of developing severe lymphopenia after CRT in the analysis of dose-volume histogram parameters, including the mean splenic dose and percentage of the splenic volume received at least certain dose levels. These results may be related to the immunomodulatory effect of RT, but further studies are warranted to elucidate the precise mechanism.

The current study does not provide a clear answer for the role of SBRT in the immunotherapy era in the treatment of PC. However, it is interesting in that it provides a number of possibilities and discusses the need for further research on this subject. In addition to the already proven role of SBRT in PC, further research on SBRT must be conducted to answer these unsolved questions regarding the optimal conditions for the immunomodulatory effect of SBRT in terms of the optimal candidate, dose, volume, fractionation scheme, and timing associated with ICIs. As long as these questions remain, we must hold the belief that there is still hope for the role of RT in the treatment of this devastating disease.

Conflict of Interest

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


Radiotherapy, volume reduction, and short-term surgical outcomes in the treatment of large myxoid liposarcomas

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Purpose: While tumor volume reduction following radiation has been documented in myxoid liposarcomas, it is unclear whether large tumors experience similar volume reduction to smaller tumors.

Materials and Methods: MRI studies performed before and after completion of pre-operative radiation therapy (RT) were examined. Tumor sizes were noted and categorized as large versus small based on size >10 cm. Tumor volumes were calculated, and operative duration and major wound complications were recorded.

Results: The median largest tumor dimension was 12.4 cm before RT and 8.7 cm after RT. The median tumor volume was 298.9 cm³ before RT and 106.9 cm³ after RT. There was no significant difference in the mean percent tumor volume reduction between large tumors and small tumors (p = 0.11, 56.3% vs. 64.5%). Operative duration most strongly correlated to post-RT MRI volume (R²=0.674, p<0.001). Despite volume reduction, tumors that were large on presentation were more likely to experience major wound complications post-operatively.

Conclusion: Radiation appears to be as effective at reducing myxoid liposarcoma tumor volume in large and small tumors. However, large tumors on presentation appear more likely to experience wound complications despite tumor volume reduction. Future studies should investigate disease-related outcomes as a factor of volume reduction in myxoid liposarcoma.

Keywords: Myxoid liposarcoma, Soft tissue sarcoma, Radiotherapy, Neoadjuvant radiation

Introduction

Myxoid liposarcoma (MLS) is the most common subtype of liposarcoma and represents approximately 5% of all adult soft tissue sarcomas (STS) [1,2]. Characteristics of MLS include a t(12:16) translocation and perhaps a more favorable prognosis compared to other liposarcomas despite an unusual predilection for extrapulmonary metastasis [3,4]. Intermediate- and high-grade STS, including MLS, are typically treated with combination surgery and radiotherapy (RT), which have been shown to improve local control when compared to surgery alone. While RT for STS can be performed pre- and post-operatively, pre-operative RT has the advantages of fewer late complications and the potential to improve resectability prior to surgery, leading to a shift toward neoadjuvant RT in the treatment of STS in recent years [5–7].

Several historical studies have suggested that MLS may be more likely to respond to RT than other subtypes of STS, with high rates of regression and even reports of complete clinical response after RT [8–12]. However, older series are difficult to interpret due to inclusion of different subtypes of liposarcoma, changes in diagnostic criteria, and variations in radiation techniques. More recent studies have demonstrated an objective response of MLS to neoadjuvant
RT with substantial reductions in tumor volume and changes in tumor morphology after RT as well as higher rates of local control after neoadjuvant RT and surgical resection when compared to other STS subtypes [13–15].

While the effects of RT in MLS have been previously described, the response of MLS to RT specifically based on initial tumor size has not been robustly evaluated. In STS, tumor size impacts ease of resection, rate of post-operative wound complications, and prognosis [16]. The differential response to RT in MLS tumors of different sizes has the potential to inform individualized treatment protocols as well as impact pre-operative planning, but studies specifically examining this are lacking. Accordingly, the purpose of this study was to compare the response of large and small MLS tumors to a standardized protocol of neoadjuvant radiation therapy and to assess surgical complications in these patients.

**Materials and Methods**

Following Institutional Review Board of Rush University Medical Center approval (ORA No. 21101407-IRB01), our institutional sarcoma database was retrospectively reviewed to identify all patients with MLS from 2000 to 2021. Initial query returned a total of 86 patients. The following exclusion criteria were applied: those with limited information in the medical record (n = 21), those without histological confirmation of MLS (n = 6), those who presented with previous incomplete excisions from outside hospitals without tumor size information (n = 6), and those who were not primarily treated surgically for their MLS at our institution (n = 8). Patients were additionally excluded if magnetic resonance imaging (MRI) of their tumors were not available both within one month prior to initiation of radiotherapy (RT) and within one month after completion of RT (n = 21) (Fig. 1). After the above exclusion criteria were applied, the records of 24 patients were reviewed retrospectively.

Basic patient and tumor variables were collected, including age, sex, race, and primary tumor location. The presence of a round cell component on the histological specimen was noted and recorded as a categorical variable. In two cases, information regarding presence of round cell component was unavailable and treated as missing data. Race was coded as a categorical variable defined as Caucasian and non-Caucasian. The majority of tumors were located in the thigh (91.7%, n = 22) and the remaining two (8.3%) were located in the calf. Operative duration was recorded in minutes and major wound complications were defined as described by O’Sullivan et al [17]. These complications were defined as a secondary operation under anesthesia for wound repair or non-operative wound management involving invasive procedures, readmission for antibiotics or wound care, or persistent deep packing for 120 days. Operative duration was unavailable in one patient.

Tumor size measurements in craniocaudal, transverse, and anteroposterior dimensions were recorded from available radiologists’ reports. When a measurement was not noted in the report, one author (LL) recorded the missing size measurements. All pre-RT tumor sizes were recorded from MRI studies performed within one month prior to the initiation of RT. All post-RT tumor sizes were recorded from MRI studies performed within one month after completion of RT. Tumor volume was calculated using the ellipsoid formula:

\[
\text{volume} = \frac{4}{3} \pi \times a \times b \times c,
\]

where \(a\), \(b\), and \(c\) are the tumor dimensions in craniocaudal, transverse, and anteroposterior dimensions. True tumor specimen size was recorded as the largest dimension on pathology after surgical resection. Percent tumor necrosis was recorded from corresponding pathology reports upon final surgical resection. All pathology specimens were reviewed by board-certified, fellowship-trained musculoskeletal pathologists with expertise in sarcoma. Tumor necrosis was estimated by the pathologists according to a departmental protocol which relies on the gross appearance and percentage of necrotic cells in various sections. In these irradiated tumors, necrosis percentage is used as an indicator of response to treatment; therefore, both necrosis and fibrosis are included. Tumor necrosis data was available in 22 of 24 patients.

![Consort chart of patient selection process for those included for study](https://doi.org/10.3857/roj.2022.00094)
Large tumors were determined to be those with a largest dimension greater than 10 cm and small tumors were determined to be those with a largest dimension smaller than 10 cm. Tumors were categorized as large and small according to pre-RT MRI largest dimension, post-RT MRI largest dimension, and final tumor specimen size. While a tumor size cutoff of 5 cm is more commonly used for staging purposes, a tumor size of 5 cm typically does not impose significant operative challenges. Therefore, we focused on tumors greater than 10 cm in size as these cases may experience greater benefit from volume reduction for surgical complexity.

All patients underwent wide, local excision of their MLS within 6 weeks of completion of neoadjuvant RT and all margins were negative. All patients underwent neoadjuvant RT prior to surgery, receiving a cumulative 50 Gy over 25 fractions. Four patients underwent interdigitated chemotherapy and radiation. The chemotherapy regimen was a combination of doxorubicin and ifosfamide in all four patients.

Categorical variables were described using frequencies and percentages and compared with chi-squared or Fisher exact test. Continuous data were reported as mean with range or median with interquartile range (IQR) and compared using Mann-Whitney U Test or paired t-test. Linear regression analysis was performed to analyze the relationship between volume reduction and tumor necrosis as well as between various size and volume measurements with operative duration. Statistical significance was set to $p < 0.05$, and all analyses were performed on SPSS version 26.0 (IBM, Armonk, NY, USA) and RStudio version 1.4 (Integrated Development for R. RStudio; PBC, Boston, MA, USA).

**Results**

The median largest tumor dimension on pre-RT MRI was 12.4 cm (IQR 7, 16) and the median tumor volume prior to radiation for the entire cohort was 298.9 cm$^3$ (IQR 71.4, 830.8). Both MLS size and volume were significantly reduced following preoperative RT in the entire group (both $p < 0.001$). After RT, the median largest tumor dimension on MRI was 8.7 cm (IQR 6.3, 14) and the median tumor volume was 106.9 cm$^3$ (IQR 30.0, 362.6) ([Fig. 2](#fig2)). Tumors with largest dimension greater than 10 cm on pre-RT MRI had a mean volume of 829.8 cm$^3$ (range, 220.2 to 2,813.4) whereas the smaller

![Fig. 2. Axial magnetic resonance imaging (MRI) of myxoid liposarcoma with (A) largest dimension of 16 cm on presentation and (B) largest dimension of 14 cm after radiotherapy (RT). Axial MRI of myxoid liposarcoma with (C) largest dimension of 5.5 cm on presentation and (D) largest dimension of 2.1 cm after RT.](https://doi.org/10.3857/roj.2022.00094)
tumor group had a mean volume of 76.2 cm$^3$ (range 4.0 to 241.9 cm$^3$) ($p < 0.001$). Patient age ($p = 0.68$), gender ($p = 0.81$), race ($p = 0.09$), and presence of round cell component ($p = 0.47$) did not differ between the two groups. Pooled patient demographics and tumor characteristics can be seen in Table 1.

The mean absolute volume reduction was 409.0 cm$^3$ (range, 112.5 to 1,100.2 cm$^3$) in the large tumor group and 47.4 cm$^3$ (range, -10.1 to 146.3 cm$^3$) in the small tumor group. One tumor grew over the course of RT. There was no significant difference in the mean percent tumor volume reduction between the large tumor group and the small tumor group ($p = 0.11$). The mean percent tumor volume reduction in the large tumor group was 56.3% (range, 22.4% to 90.9%) compared to 64.5% (range, -18.4% to 91.7%) in the small tumor group. Relative percent volume reduction did not correlate with percent tumor necrosis on final specimen evaluation ($R^2 = 0.07$, $p = 0.23$). There was also no difference in tumor necrosis seen in large tumors versus small tumors as determined by pre-RT MRI ($p = 0.81$).

Operative duration did not differ when tumors were categorized as large and small based on pre-RT MRI largest dimension ($p = 0.07$); however, operative duration was significantly greater when tumors were categorized based on post-RT MRI largest dimension ($p = 0.006$) as well as when categorized based on pathology tumor specimen size ($p = 0.003$) (Table 2). Linear regression analysis revealed significant correlation between operative duration and pre-RT MRI tumor volume ($R^2 = 0.606$, $p < 0.001$), operative duration and post-RT MRI volume ($R^2 = 0.674$, $p < 0.001$), and operative duration and tumor specimen size ($R^2 = 0.597$, $p < 0.001$).

Only one patient required non-primary wound closure and underwent a flap reconstruction with a split thickness skin graft. There were six total major wound complications in the entire group. When tumors were categorized based on pre-RT MRI largest dimension, five of the six complications occurred in the large tumor group. When categorized based on post-RT MRI largest dimension, two of the six complications occurred in the large tumor group. And when categorized based on tumor specimen size, three of the six complications occurred in the large tumor group (Table 3). Low

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>39.9 (14-84)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>Female</td>
<td>18 (75.0)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>18 (75.0)</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>Round cell component</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Not present</td>
<td>18 (75.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>MRI largest dimension (cm)</td>
<td></td>
</tr>
<tr>
<td>Pre-RT</td>
<td>12.4 (7, 16)</td>
</tr>
<tr>
<td>Post-RT</td>
<td>8.7 (6.3, 14)</td>
</tr>
<tr>
<td>Final tumor specimen size (cm)</td>
<td>8.3 (4.5, 12.8)</td>
</tr>
<tr>
<td>MRI volume (cm$^3$)</td>
<td></td>
</tr>
<tr>
<td>Pre-RT</td>
<td>298.9 (71.4, 830.8)</td>
</tr>
<tr>
<td>Post-RT</td>
<td>106.9 (30.0, 362.6)</td>
</tr>
<tr>
<td>Tumor categorization</td>
<td></td>
</tr>
<tr>
<td>Pre-RT MRI size</td>
<td></td>
</tr>
<tr>
<td>Large, ≥ 10 cm</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>Small, &lt; 10 cm</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Post-RT MRI size</td>
<td></td>
</tr>
<tr>
<td>Large, ≥ 10 cm</td>
<td>11 (45.8)</td>
</tr>
<tr>
<td>Small, &lt; 10 cm</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>Final tumor specimen size</td>
<td></td>
</tr>
<tr>
<td>Large, ≥ 10 cm</td>
<td>10 (41.7)</td>
</tr>
<tr>
<td>Small, &lt; 10 cm</td>
<td>14 (58.3)</td>
</tr>
</tbody>
</table>

Values are presented as mean (range) or number (%). MRI, magnetic resonance imaging; RT, radiotherapy.

Table 2. Operative duration in large and small tumors

<table>
<thead>
<tr>
<th>Tumor categorization</th>
<th>Operative duration (min)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-RT MRI size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large, ≥ 10 cm</td>
<td>67 (46, 141)</td>
<td></td>
</tr>
<tr>
<td>Small, &lt; 10 cm</td>
<td>46 (44, 55)</td>
<td></td>
</tr>
<tr>
<td>Post-RT MRI size</td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>Large, ≥ 10 cm</td>
<td>78 (52, 141)</td>
<td></td>
</tr>
<tr>
<td>Small, &lt; 10 cm</td>
<td>45 (44, 55)</td>
<td></td>
</tr>
<tr>
<td>Final tumor specimen size</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Large, ≥ 10 cm</td>
<td>99 (62, 141)</td>
<td></td>
</tr>
<tr>
<td>Small, &lt; 10 cm</td>
<td>46 (44, 52)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range Q1, Q3). MRI, magnetic resonance imaging; RT, radiotherapy.

Table 3. Major wound complications in large and small tumors

<table>
<thead>
<tr>
<th>Tumor categorization</th>
<th>Major wound complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-RT MRI size</td>
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</tr>
<tr>
<td>Large, ≥ 10 cm</td>
<td>5</td>
</tr>
<tr>
<td>Small, &lt; 10 cm</td>
<td>1</td>
</tr>
<tr>
<td>Post-RT MRI size</td>
<td></td>
</tr>
<tr>
<td>Large, ≥ 10 cm</td>
<td>2</td>
</tr>
<tr>
<td>Small, &lt; 10 cm</td>
<td>4</td>
</tr>
<tr>
<td>Final tumor specimen size</td>
<td></td>
</tr>
<tr>
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<tr>
<td>Small, &lt; 10 cm</td>
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MRI, magnetic resonance imaging; RT, radiotherapy.
overall numbers precluded a powered statistical analysis. Individual patient and tumor characteristics can be seen in Table 4.

Discussion and Conclusion

The sensitivity of MLS to radiation therapy was first documented more than 50 years ago, and more recent studies have provided objective evidence of MLS tumor response to RT [10,11]. In our series, there was a significant reduction in tumor size and volume after neoadjuvant RT, with a proportional reduction in median tumor volume of 64%. This finding is consistent with previous studies that examined MLS tumor size reduction after RT. Pitson et al. [13] observed a 59% reduction in tumor volume in MLS after RT and other studies have consistently demonstrated large decreases in tumor volume after RT, highlighting the radiosensitivity of MLS [2,13,14,18,19].

The principle aim of this study was to examine the response to neoadjuvant RT in MLS tumors of different sizes. In soft tissue sarcoma, tumor size is an important prognostic factor and is associated with rates of local recurrence, post-operative wound complications, and overall survival [20–22]. It is important for clinicians to understand the effects of neoadjuvant RT in large versus small MLS tumors, as this has the potential to impact individualized treatment planning. To our knowledge, this is the first report to specifically examine the response to neoadjuvant RT in differently sized MLS tumors. In our study, there was no significant difference in mean percent volume reduction after RT between large and small MLS tumors. These results indicate that neoadjuvant RT is as effective at reducing the volume of large MLS tumors as small tumors. Large tumor size is associated with inferior disease-free survival and local control, and substantially decreased tumor size after RT likely contributes to the excellent local control rates observed in MLS [15,23–25]. Reducing the volume of large tumors also has the potential to facilitate surgical resection and reduce surgical morbidity, thereby improving functional outcomes without sacrificing local control. In this study, all resected tumor specimens had negative margins, even in very large tumors with greatest dimension greater than 20 cm at presentation. This indicates a benefit in terms of ease of resection after neoadjuvant RT which is important for treatment planning, especially for very large tumors or those in

Table 4. Individual patient and tumor details of included cases

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<th>Pre-RT Post-RT Specimen size (cm)</th>
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C, Caucasian; NC, non-Caucasian; RT, radiotherapy; P, primary; MWC, major wound complication.
critical locations which may otherwise not be as amenable to resection. In addition to decreased tumor volume, changes in MLS tumor histology with more mature lipoma-like areas observed after RT and increased distance of the tumor from the neurovascular bundle after RT, may also contribute to an increase in resectability [14,18]. Furthermore, tumors that are initially deemed not resectable due to large size or proximity to the neurovascular bundle may become resectable after RT due to reduction in tumor volume, though further studies are necessary to determine if these results are applicable in primary unresectable MLS.

Our results also demonstrated no difference in tumor necrosis between large and small tumors after RT. This indicates that, in addition to a similar reduction in tumor volume after RT, the pathological response to RT is similar between large and small MLS tumors. Studies have suggested that rates of tumor necrosis correlate with clinical outcome, with a recent meta-analysis showing that rates of necrosis less than 90% are associated with increased recurrence risk and inferior overall survival in STS patients [26]. Based on the results of our study, clinicians can expect rates of necrosis in large MLS tumors that are comparable to small tumors after RT, and this may positively impact outcomes in these patients.

In this study, we observed significantly shorter operative times in the small tumor group when compared to the large tumor group. Smaller pre-RT size, post-RT size, and pathology specimen size were all correlated with shorter operative duration. However, the strongest correlation was with post-RT size, indicating that tumor size immediately prior to surgery is a more important factor than tumor size at presentation. Shrinking MLS tumors with neoadjuvant RT may contribute to ease of resection and lead to shorter operative times. Operative duration is an independent risk factor for surgical complications. A contemporary meta-analysis showed that the likelihood of developing a complication approximately doubled with operative times exceeding 2 hours and that there was a 14% increase in likelihood of complications for every 30 minutes of additional operative time [27]. Reducing tumor volume with neoadjuvant RT has the potential to reduce operative time and, in turn, reduce complications and costs associated with increased operative duration [28].

Despite advances in STS treatment, post-operative wound complications remain a major source of morbidity and have been reported in up to 56% of surgical cases [21]. There were six total major wound complications in our study with a rate of 25%, similar to prior reports. Previous studies have investigated factors that influence the risk for post-operative wound complications, including tumor size and location, timing of radiation pre- or post-operative, and radiation field size [16,21,29]. Tumor size and tumor volume have been found in multiple studies to be predictors of post-operative wound complications, and a study by Ziegele et al. [21] demonstrated that tumor volume may be a stronger predictor of complication risk than tumor size based on largest diameter. Larger volume of resection contributes to development of wound complications by leading to larger soft tissue dead space with increased potential for formation of seromas, hematomas, and infection. The significant reduction in both tumor volume and tumor size seen in our cohort after neoadjuvant RT has the potential to reduce post-operative wound complications in these patients. It is important to note that in our study, most wound complications occurred in the large tumor group when this was assessed based on pre-RT size. However, when evaluating complications based on pathology specimen size after resection, the number of complications in the large and small tumor groups were similar, though small numbers prevented statistical analysis. These results indicate that tumors that are large on presentation may still be more likely to have wound complications after resection, regardless of reduction in tumor size after RT. This is likely due to the larger radiation field size needed for neoadjuvant RT in larger tumors. The association between neoadjuvant RT and increased wound complications has been well documented, and the rate of complications increases with the magnitude of the radiated area [16,21,29]. It is important for clinicians to recognize that even if RT leads to reduced tumor size, tumors that are large prior to RT may still be more prone to post-operative wound complications.

This study does have several limitations, principally, the retrospective nature of the study and the small sample size. STS are rare tumors and our sample size was further restricted by limiting our population to patients with MLS who had undergone neoadjuvant RT, though we note that our cohort is among the largest in similar studies. There is also potential error in MRI volume measurements, though all tumor volume measurements were reported by board-certified radiologists specially trained in musculoskeletal pathology or performed by a single researcher to reduce interobserver variability. The use of neoadjuvant chemotherapy in some patients may also affect the ability to draw conclusions from histological evaluation of tumor response, as chemotherapy itself causes tumor necrosis. However, the identical protocol for neoadjuvant RT in all patients is a strength of the study. Finally, we did not examine long-term outcomes including disease-free and overall survival as this was outside the scope of this study. Further investigation with longer follow-up is necessary to determine the effect of RT on long-term outcomes in large versus small MLS tumors.

Our results demonstrate a significant reduction in tumor volume and size seen after RT in MLS and support the use of neoadjuvant radiation therapy in these tumors. Based on our data, neoadjuvant RT is as effective at reducing tumor volume and generating tumor
necrosis in large tumors as in small tumors. Use of RT in large MLS tumors has the potential to increase ease of surgical resection as well as reduce operative time; however, large tumors on presentation seem more prone to major wound complications regardless of volume and size reduction. Additional studies are required to further examine the effect of neoadjuvant RT on rates of complications and on oncologic outcomes in large MLS tumors so that clinicians may be as informed as possible when creating individualized treatment protocols for these patients.

Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board (ORA No. 21101407-IRB01).

Conflict of Interest

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

Funding

None.

Data Availability Statement

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

References

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Radiation in large myxoid liposarcomas

Introduction

Brachytherapy is one of the most important treatment modalities for gynecological cancers. The comprehensive global cancer statistics from the International Agency for Research on Cancer indicate that gynecological cancers accounted for 19% of the 5.1 million estimated new cancer cases in the world [1]. As per GLOBOCAN 2020 project data, breast cancer, cervical cancer, ovarian cancer, and uterine cancer are among the top-10 common cancers in females worldwide [2]. Gynecological cancers can be treated by various treatment modalities and the most common treatment modalities are surgery, radiation therapy, chemotherapy, and targeted therapy. Surgery is one of the treatment options for the early stage of cervical carcinoma other than local radiotherapy in the form of brachytherapy. However, the majority of patients present with either bulky or locally advanced diseases, so these patients are treated by concurrent chemoradiation with external beam radiotherapy followed by brachytherapy [3]. High-dose rate (HDR) brachytherapy was initially used for cervical cancers in many countries, but later on, it was integrated into treatment plans for...
vaginal cancers also [4].

In HDR brachytherapy, the dose optimization is done by the treatment planning system (TPS) to calculate the prescribed dose at the desired location and optimization is performed to reduce the dose to the nearby organs-at-risk (OAR). The prescribed dose is calculated by the TPS at desired location by varying the dwell times and dwell positions of a radioactive source along specified applicator paths. In intracavitary brachytherapy (ICBT) of cervical cancers, various types of applicators for HDR brachytherapy treatment are in use. The most common method for the ICBT treatment of cervical cancer is the Manchester system. The Manchester system-based ICBT approach is a more widely accepted method [5-9]. The Manchester system is characterized by doses to four points: Point A, Point B, bladder, and rectum. The duration of the implant is based on the dose rate at Point A, which is located 2 cm superior to the cervical os and 2 cm lateral to the cervical canal. Point B is defined as 3 cm laterally to Point A if the central canal is not displaced. If the tandem displaces the central canal, Point A moves with the canal, but Point B remains fixed at 5 cm from the midline.

In HDR brachytherapy, the applicator is first inserted into the patient, then the patient undergoes a CT-scan with the applicator inside and the same CT-scan is then transferred to the TPS. With the help of these computerized TPSs, the desired patient plan is created. In brachytherapy, the algorithm mostly used in TPS for dose calculations is based on the formalism presented by the American Association of Physicists in Medicine (AAPM) Task Group No. 43 Report (TG-43). The TG-43 does not take heterogeneity correction within the human body into account and this formalism considers a bare source in the center of water for calculations [10,11]. However, in practice, various types of metallic central tandems and vaginal cylinders are used for the brachytherapy treatment of gynecological cancers [16] and TG-43 formalism effectively ignores the attenuation caused by metallic applicators and vaginal cylinders, which might lead to under dosage of the target while overestimating the dose to the OAR. So when the applicator geometry is not included in the TPS, there will be variation in the TPS calculated doses due to the different dosimetrical properties of these applicators [17].

The cervix applicator set studied in this study, consists of metallic central tandem of various angulations and vaginal cylinders of different diameters as shown in Fig. 1. These are Varian CT compatible applicators used in Varisource iX / Varisource 200/ GammaMed Plus iX / GammaMed Plus afterloader (Varian Medical Systems, Palo Alto, CA, USA) having Catalog number GM11004040. Although various types of applicators are in use for the brachytherapy treatment of cervical cancer, however, the attenuation in dose caused by this type of applicator and the applicator material has not been yet investigated. The attenuation of these applicators has been measured so that an accurate dose to the target and the organs at risk can be estimated when such applicators are used for cervical cancer treatment. In this study, the overestimation of dose by the BrachyVision TPS 11 (Varian Medical Systems) for these applicators was evaluated. The dose overestimation by TPS was obtained for tandem and cylinder assembly by using EBT3 Gafchromic films. Furthermore, a novel method, that is, well-type ionization chamber was used to find the attenuation due to various applicators used in gynecological brachytherapy, and the results obtained were compared with the results obtained by using Gafchromic films. In most of the other studies performed for such measurements, either only film dosimetry was done or a 0.125-mL ion chamber was used for dose measurements. The use of a 0.125-mL ion chamber for brachytherapy is cumbersome whereas the use of well-type ionization chamber for such measurements is relatively easy.

Materials and Methods

This study has been carried out in the tertiary care hospital and the hospital is equipped with various state of art radiotherapy equipment. The HDR brachytherapy unit GammaMed Plus iX, has been used for this study. The GammaMed Plus iX is the 5th generation afterloader and has 24 channels. The GammaMed Plus iX afterloader and control software is designed to be fully compatible with hospital networks and enhance HDR and pulsed-dose rate (PDR) brachytherapy treatments. The HDR unit is fully integrated with the BrachyVision (version 11) TPS and the ARIA oncology information. The 192Ir radioactive source is housed in this GammaMed Plus iX afterloader HDR unit. The GammaMed Plus iX 192Ir HDR source consists of a 3.50-mm-long 192Ir core with a diameter of 0.70 mm, enclosed in a 0.90-mm-diameter and 4.52-mm-length AISI 316 L stainless steel capsule (density of 7.8 g/cm³) [18-20]. The 192Ir source emits a wide spectrum of relatively low energies, mostly in the range of 201–884 keV with an average value of 360 keV.

The unit is also provided with various applicators for brachytherapy treatment. The cervix applicators studied in this article include various vaginal cylinders and central metallic tandems. The vaginal cylinders are made up of polyetheretherketone (PEEK) having diameters of 20 mm, 23 mm, 26 mm, 30 mm, and 35 mm, and three types of stainless steel central metallic tandems having angulations of 0°, 20°, and 30° as shown in Fig. 1.

For the source strength verification of the GammaMed Plus iX unit, HDR 1000 Plus well-type ionization chamber, and the elec-
A well-type ionization chamber is often used in brachytherapy for dosimetric purposes. The well-type ionization chamber is provided with a unique source holder for each brachytherapy source and is commonly referred to as a source jig. To obtain the attenuation due to the various cervix applicators, the source jig was replaced with water equivalent elasto-gel to mimic the various vaginal cylinder sizes, as shown in Fig. 4. Now the measurements were made first with elasto-gel and then with the applicator assembly.

1) Case 1
The plan which was created for the treatment of the patients was executed on HDR 1000 Plus well-type ionization chamber using elasto-gel of appropriate diameter as shown in Fig. 5A. The total charge collection by the electrometer was noted down.

2) Case 2
In the second case, again the same plan was executed using HDR 1000 Plus a well-type ionization chamber but now instead of elasto-gel, the same tandem and vaginal cylinder assembly were used.
Fig. 2. Representative dose in color wash for 6 Gy prescription to Point A in multiplanar view and three-dimensional view.

Fig. 3. (Top) Applicator surface taped with EBT3 Gafchromic films. (Bottom) Tandem and vaginal cylinder assembly wrapped in elasto-gel bolus.

and the charge collection was measured as shown in Fig. 5B.

Pertinently in both the above cases, only the charge collection was measured and the calibration factor of the well-type chamber was not used in calculations which ensured that the calibration factor will not affect the final results obtained. It was also ensured in both the above cases that the distal end of the tandem and vaginal cylinder assembly and the distal end of the elasto-gel was placed at the same position in the base of the well-type ionization chamber and both were 12 cm deep within the well of the chamber. This ensured that the dwell positions of the $^{192}$Ir source in both the cases within the chamber were the same. Thus, in both cases, there was no difference in the comparative positions of the $^{192}$Ir source within the chamber.

A similar procedure was repeated for other patients wherein the patient was first inserted with appropriate tandem and vaginal cylinder assembly and then a plan was created on TPS and the same plan was executed with Gafchromic film taped on the surface of the applicator. Subsequently, the charge collection using a well-type ionization chamber was also measured. In this way, the results were obtained for all the different combinations of tandem and
vaginal cylinder assembly.

The measured dose recorded by the Gafchromic films and the TPS calculated dose were compared using paired t-test, analyzed on the data editor of SPSS version 20 (IBM, Armonk, NY, USA). Also, the charge collected by well-type ionization chamber with elasto-gel and tandem-vaginal cylinder assembly was compared using the same test. A p-value less than 0.1 were considered significant.

Results

The dosimetric results were obtained both by using Gafchromic films and well-type ionization chamber. The mean overestimation of dose by the TPS was calculated for each tandem and vaginal cylinder assembly, using Gafchromic films. The results for 0°, 20°, and 30° angulated central tandems when used along with various diameters of vaginal cylinders are given in Tables 2–4, respectively. The mean percentage attenuation obtained by using a well-type ionization chamber due to 0°, 20°, and 30° central tandems when used along with various diameters of vaginal cylinders was also calculated and are given in Tables 5–7, respectively. Fig. 6 shows the mean overestimation of dose by the TPS for each tandem and vaginal cylinder assembly. The graphical representation of mean percentage attenuation for each tandem and vaginal cylinder assembly obtained by using a well-type ionization chamber is shown in Fig. 7.

It can be observed from the above tables that the maximum overestimation of dose by TPS is for 35-mm diameter vaginal cylinder when used along with 30° curvature central tandem and is 7.47% and is least for 0° central tandem when used with 20-mm vaginal cylinder and is 4.78%. The percentage attenuation values obtained by using well-type ionization chambers also showed that the maximum attenuation was by 35-mm diameter vaginal cylinder when used along with 30° curvature central tandem and is 6.82%, the least attenuation is for 0° central tandem when used with 20-mm vaginal cylinder and is 3.52%.

The results of the statistical analysis in both Gafchromic mea-
Fig. 5. (A) Setup used to obtain charge collection when water equivalent elasto-gel. (B) Setup used to obtain charge collection when tandem and vaginal cylinder assembly was used.

measurements and for well-type ionization chamber measurements showed that there is a significant decrease in dose when 30° angled central tandem is used with a 35-mm vaginal cylinder ($p < 0.10$). However, for all other measurements, the difference was not significant ($p > 0.10$).

Discussion and Conclusion

In this study, the attenuation due to PEEK vaginal cylinders when used with stainless steel central tandems has been studied. The dosimetric influence of various vaginal cylinders, when used with different types of central tandems in brachytherapy, has been obtained using EBT3 Gafchromic films. In this study, a novel method that is the use of a well-type ionization chamber to find the attenuation due to various applicators used in brachytherapy was used and the results obtained were quite similar to the measurements using Gafchromic films.

The dose at the surface of the tandem and vaginal cylinder assembly was obtained by placing the Gafchromic films on the surface of the applicator. The dose recorded on the films was measured by using an Epson scanner with IMRT OmniPro software. The effect of tandem and vaginal cylinder assembly on net charge collection versus the charge collection with water equivalent elasto-gel was also studied using a well-type ionization chamber. The results obtained from these two methods gave effective attenuation due to tandem and vaginal cylinder assembly and the results in both the methods were analogous to each other with little variation.

The heterogeneity of the medium is not taken into account by the TPSs using the TG-43 algorithm for dose calculations. The TG-43 formalism effectively ignores the attenuation caused by vaginal cylinders and by metallic applicators, and thus the TPS calculated target, and OAR doses are overestimated and are presented in this study.

The percentage overestimation of dose by TPS for various tandem and vaginal cylinder assembly obtained in this study are shown in Tables 2–4. The percentage attenuation was also calculated for various tandems when used with different types of vaginal cylinders in well-type ionization chamber and it also showed almost the same trend with little respective variation and can be seen in Tables 5–7.

Sampath et al. [17] have studied the influence of central vaginal cylinders in HDR $^{192}$Ir brachytherapy with different diameter applicators. They have analyzed the dosimetric influence due to various vaginal cylinders of diameters 2.0, 2.5, 3.0, and 3.5 cm. They measured the dose by using a 0.125-mL ion chamber and the Oncentra planning system (Elekta, Stockholm, Sweden) was used for the dose calculation. The dose measured with the ion chamber was compared with EDR2 radiographic films. The authors conclude that the difference in TPS calculated and a measured dose is significant when high-density vaginal cylinders are used in measurement, which is consistent with our study. Parsai et al. [24] have studied the dose attenuation around Fletcher-Suit-Delclos due to stainless steel tube for HDR brachytherapy by using Monte Carlo calculations. The authors conclude that the patients may be receiving less dose due to metallic applicators. The authors further added that the anisotropy function has a predominant influence on dose reduction, whereas the radial dose function does not fluctuate too much as a result of attenuation. The authors suggested that the anisotropic and radial dose function of source in water used in treatment planning systems based on TG-43 formalism may be replaced with corresponding parameters of source applicator assembly.

In conclusion, this study is a step forward towards a better dose delivery in HDR ICBT treatment and evaluates the dose variation due to the brachytherapy TPS. The commercially available TPS used in brachytherapy calculates dose at various locations by using TG-43 formalism. To verify the TPS calculated doses, in vitro dose measurements of various tandems and vaginal cylinders by using EBT3 Gafchromic films were performed and the percentage attenuation due to various tandems and vaginal cylinders was also calculated by using a well-type ionization chamber.

The attenuation due to metallic central tandem and the vaginal

https://doi.org/10.3857/roj.2022.00199
### Table 2. Comparison of mean in vivo doses and calculated (TPS) doses in ICBT with 0º central tandem and vaginal cylinder assembly

<table>
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<th>Serial No.</th>
<th>Vaginal cylinder diameter (mm)</th>
<th>Angulation of central tandem (º)</th>
<th>Prescribed dose (Gy)</th>
<th>Mean dose at surface of applicator (Gy)</th>
<th>Deviation (calculated–measured) dose (Gy)</th>
<th>Overestimation of dose by TPS (%)</th>
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TPS, treatment planning system; ICBT, intracavitary brachytherapy. Percentage overestimation is calculated by using the following formula: \( \frac{\text{Measured dose} - \text{Calculated dose}}{\text{Calculated dose}} \times 100\).

### Table 3. Comparison of mean in vivo doses and calculated (TPS) doses in ICBT with 20º central tandem and vaginal cylinder assembly

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<th>Mean dose at surface of applicator (Gy)</th>
<th>Deviation (calculated–measured) dose (Gy)</th>
<th>Overestimation of dose by TPS (%)</th>
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Mean 1.66  Mean 4.93

Mean 0.81  Mean 4.71

TPS, treatment planning system; ICBT, intracavitary brachytherapy.
Percentage overestimation is calculated by using the following formula: 100–\(\frac{\text{Measured dose}}{\text{Calculated dose}}\) x100.

Table 4. Comparison of mean \textit{in vivo} doses and calculated (TPS) doses in ICBT with 30º central tandem and vaginal cylinder assembly

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Mean 1.11  Mean 5.03

Mean 1.08  Mean 4.78

TPS, treatment planning system; ICBT, intracavitary brachytherapy.
Percentage overestimation is calculated by using the following formula: 100–\(\frac{\text{Measured dose}}{\text{Calculated dose}}\) x100.

\(a)\) Using Gafchromic films.
Table 5. Mean attenuation due to 0° central tandem when used with various vaginal cylinders

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Mean 6.40

Mean 5.06

Mean 4.20

Mean 3.91

Mean 3.52

Percentage attenuation by tandem and vaginal cylinder assembly is calculated by using the following formula: \(100 - \frac{nC_2}{nC_1} \times 100\).

Table 6. Mean attenuation due to 20° central tandem when used with various vaginal cylinders

<table>
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<th>Diameter of vaginal cylinder or elasto-gel (mm)</th>
<th>Angulation of central tandem (°)</th>
<th>Prescribed dose (Gy)</th>
<th>Mean charge collected</th>
<th>Attenuation by tandem and vaginal cylinder assembly (%)</th>
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Mean 6.65

Mean 5.24

Mean 4.35

(Continued to the next page)
Table 6. Continued

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<th>Mean charge collected</th>
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Percentage attenuation by tandem and vaginal cylinder assembly is calculated by using the following formula: \( \frac{nC_2}{nC_1} \times 100 \).  

Table 7. Mean attenuation due to 30° central tandem when used with various vaginal cylinders

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<th>Angulation of central tandem (°)</th>
<th>Prescribed dose (Gy)</th>
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Percentage attenuation by tandem and vaginal cylinder assembly is calculated by using the following formula: \( \frac{nC_2}{nC_1} \times 100 \).
cylinders used in brachytherapy treatment of gynecological cancers is more when compared to the attenuation due to water. Thus, the dose to the target as well as OAR is overestimated by the TPS in the HDR brachytherapy and should be taken into consideration while calculating the dose to the target and nearby organs at risk. The under dosage of the target if not considered may otherwise lead to treatment failures.

Statement of Ethics

Ethics approval was not required for this article.

Conflict of Interest

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

Author Contribution

Conceptualization, AAK, MMH. Funding acquisition, SE, ME. Investigation and methodology, AAK, SQW. Writing of the original draft, AAK, AV, MMH. Writing of the review and editing, AAK, AV, SQW, MMH. Software, AV, MMH. Formal analysis, AV, SQW.

Data Availability Statement

The entire data of this article can be provided whenever required.

References


Bone-only oligometastatic prostate cancer: can SABR improve outcomes? A single-center experience

Ángel L. Sánchez-Iglesias, Virginia Morillo-Macías, Ana Santafé-Jiménez, Carlos Ferrer-Albiach

Department of Radiation Oncology, Consorcio Hospitalario Provincial de Castellón, Spain

Purpose: Ablative treatment of oligometastases has shown survival benefit with certain tumors, although these effects still are to be demonstrated in prostate cancer.

Materials and Methods: We analysed the toxicity and clinical control results obtained in patients with bone-only oligometastatic prostate cancer treated with stereotactic ablative radiotherapy (SABR). Retrospective study on patients with metachronous oligoprogression and synchronous de novo bone-only oligometastatic prostate cancer treated with SABR and androgen deprivation therapy.

Results: Treatment schedules varied according to location and organs at risk, with biologically equivalent dose (BED) ≥100 Gy. Fifty-five bone lesions (31 patients) were treated and evaluated for toxicity, local control, progression-free survival (PFS), and overall survival (OS). After a 41-month follow-up, there was minimal acute or chronic toxicity and no G3 toxicity. The local control at 3 and 5 years was 100% and 87.1%, respectively. Median PFS and OS were 43 and 98 months, respectively. The best result in PFS was obtained with BED ≥230 Gy, delaying time to the next systemic therapy by 28.5 months.

Conclusion: The use of SABR in bone oligometastases of prostate cancer is safe with minimal toxicity and excellent results in local control and PFS, delaying the start of the next systemic therapy.

Keywords: Stereotactic body radiotherapy, Bone oligometastases, Prostate cancer, Next systemic therapy

Introduction

Worldwide, prostate cancer is the second most common cancer in men and the fifth leading cause of cancer-related deaths [1]. Historically, the treatment for metastatic prostate cancer has been androgen deprivation therapy (ADT) followed by systemic treatment when this failed. In addition, the use of docetaxel was a major milestone in increasing the overall survival (OS) and clinical response rate in metastatic castration-resistant prostate cancer (mCRPC) [2]. Subsequently, the advent of androgen receptor-targeted agents (ARTAs) has brought about a major breakthrough in this setting [3–6] as well as in metastatic hormone-sensitive prostate cancer (mHSPC) [7–10].

However, not all metastatic patients progress the same way. There is a subgroup with a limited number of lesions with less aggressive behaviour corresponding to the oligometastatic state, defined by Hellman and Weischselbaum [11] as an intermediate state between a localised tumour and widespread metastatic disease.

This patient profile may produce better results when non-invasive and potentially immunogenic local treatment of metastases with stereotactic ablative radiotherapy (SABR) is added to their therapeutic regimens [12]. Furthermore, metastasis-directed therapy (MDT) with SABR in these patients is well tolerated with minimal toxicity, delaying clinical progression with a potential benefit in both metastasis-free survival and new systemic therapy, as demonstrated in several retrospective studies and randomised phase II trials, such as ORIOLE [13] and STOMP [14]. Increasing the time to new systemic therapy could increase quality of life in these
Bone metastases prostate cancer-SABR results

In the case of prostate cancer, metastasis-targeted therapy has been evaluated in mHSPC and mCRPC, with good tolerance and promising results [17,18], although most studies include patients with nodal involvement and few focus on exclusive bone metastases, despite having a cancer-specific mortality 1.58 times higher than exclusive nodal metastases and being the sole site of metastasis in 63.6% of metastatic patients [19]. Next-generation imaging (NGI) tests detect metastases with lower prostatic specific antigen (PSA) levels, allowing earlier diagnosis of these patients [20,21]. The aim of this study was to assess the clinical control and toxicity of SABR on exclusive bone metastases PCa, as well as the time to the next-line systemic treatment (NEST).

Materials and Methods

We retrospectively evaluated patients with ≤5 exclusively bone metastases from prostate cancer, treated at our centre with SABR in the context of oligometastatic disease. All the patients were evaluated by a multidisciplinary committee and signed informed consent for the treatment and for the anonymised use of their data for scientific purposes. Eight patients debuted with de novo oligometastatic disease (“synchronous group”) and the remaining 23 presented with metachronous disease (“metachronous group”). In the first group, seven patients were treated with ADT, external beam radiation therapy (EBRT) for the primary tumour (doses of 76 Gy/38 fractions, 70 Gy/28 fractions, or 62 Gy/20 fractions) and SABR for metastases, while the remaining one received ADT and SABR for metastases. In the other group, 15 patients were treated at diagnosis with EBRT ± ADT and eight underwent surgery ± EBRT ± ADT. The presence of metachronous bone metastases was diagnosed after confirming biochemical recurrence, following the Phoenix criteria [22] in cases treated with EBRT, and the European Association of Urology criteria [23], in surgical patients. After confirming biochemical progression, the imaging tests available at the centre were performed in each case, confirming the presence of metastases: computed tomography (CT) or whole-body magnetic resonance (WBMR) and bone scintigraphy and choline-PET-CT. All patients received ADT for 6 months (metachronous) or 24 months (synchronous) concurrent with irradiation.

Prior to ablative treatment, a planning CT scan was performed using 3-mm thick slices. Each patient was treated with customised immobilization devices and in some cases a 4D-CT scan was performed. The CT was co-registered with the available diagnostic tests for each patient. The planning target volume (PTV) was obtained by adding a 5-mm margin to the bony lesion in all directions. For vertebral lesions, the recommendations published by the International Spine Radiosurgery Consortium [24] were followed. Dose to PTV was prescribed at 100% (complying D99% ≥ 100% and D1 ≥ 110% of the prescribed dose). Treatment was delivered by intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT), flattening filter free to reduce delivery times on linear accelerator. A kilovoltage cone-beam CT (kV-CBCT) was performed on all the patients prior to treatment to verify the positioning. Once the patient is positioned, a slow CBCT is performed, and the clinician manually adjusts the target for accuracy. We stratified the patients by the biologically equivalent doses (BED) received in the SABR treatment: the median BED (α/β: 1.5) was 230 Gy.

Weekly clinical check-ups were carried out during the treatment and 15 days after its conclusion. After 3 months, a further follow-up with PSA and the same imaging test used at diagnosis was performed to assess the patient’s response. Thereafter, follow-ups were programmed every 6 months with an associated imaging test if progression was suspected. Acute and chronic toxicity was determined according to the Common Terminological Criteria for Adverse Events (CTCAE) version 5 [25].

The statistical analyses were carried out with SPSS software (v24.0; IBM Corp., Armonk, NY, USA) and the following factors were evaluated: local progression-free survival (LPFS) understood as relapses within the irradiation field (defined as an increase in the size or uptake of the treated lesions detected in the PET-CT together with an increase in the PSA values), PFS (defined as an increase in PSA >25% post-SABR or the appearance of a new lesion on imaging tests), OS (defined as the time elapsed from the last day of SABR treatment to death from any cause or the last follow-up), and time to the NEST (defined as the time from the end of concurrent ADT treatment with SABR to progression and the start of the subsequent systemic treatment).

Survival analyses were estimated by applying the Kaplan-Meier method, performing the log-rank test to assess differences between the different categories analysed. Cox regression was performed to assess variables that could impact survival. p-values ≤ 0.05 were considered statistically significant.

Results

At the time of diagnosis, the mean age was 65.7 years (range, 45 to 77 years); 80.6% of patients were high or very high-risk, and the median PSA was 14 ng/mL (range, 4.5 to 70 ng/mL). The median time to progression for metachronous lesions was 71 months (range, 14 to 143 months). The median PSA at the time of progression (pPSA) prior to the procedure was 3.7 ng/mL (range, 0.3–97.0 ng/mL). Fourteen lesions were synchronous, 41 were metachronous, and 81.8% were non-spinal. A total of 55 bone lesions were treat-
ed in 31 patients (18 patients were treated with SABR on a single bone lesion, 5 patients on two bone lesions, 5 patients on three lesions, and 3 patients on four bone metastases). The baseline patient characteristics are shown in Table 1.

The most frequent location of metastases was in the iliac bone (34.5%), followed by ribs (16.4%) and pubic bone (10.9%). The location of the lesions is shown in Table 2. The dose and number of fractions administered varied depending on the location and restrictions of the organs at risk. The dose range received (BED1.5) was 130–275 Gy and the most used treatment schedule was 30 Gy/3 fractions (SABR characteristics are shown in Table 2). The treatment was well tolerated and there were no cases of ≥ G3 toxicity; 43.6% of the cases presented acute G1 toxicity and 7.3% experienced G2 toxicity (mainly urinary) due to the treatment of the primary tumour. There was no chronic toxicity in 63.6% of the cases and there was only one G2 case.

The median follow-up time was 41 months (range, 1 to 160 months). The LPFS rate was 94.5% and relapse was only observed in three lesions. Local control at 3 and 5 years was 100% and 87.1%, respectively. BED ≥ 230 Gy had no impact on local control in the multivariate analysis (hazard ratio [HR] = 2.38; 95% confidence interval [CI], 0.21–26.33; p = 0.47), probably due to the small number of events in our series. The other variables analysed showed no trend in the univariate or multivariate analysis, probably due to the limited number of events.

The median PFS was 43 months (95% CI, 19.4–66.5), with 35.2% of patients currently free of disease. Furthermore, the PFS was higher when the BED was stratified (47.4 months vs. 25.5 months in BED ≥ 230 Gy vs. < 230 Gy, respectively; p = 0.037). A trend in PFS was observed in synchronous versus metachronous lesions (52.4 months vs. 29.2 months; p = 0.053), while no differences were found according to the pPSA levels (p = 0.21), number of metastatic lesions (p = 0.44), Gleason index (p = 0.91), or risk group (p = 0.11). Moreover, BED remained a significant factor for PFS in the multivariate analysis (HR = 2.92; 95% CI, 1.18–8.41; p

### Table 1. Baseline characteristics

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

Table 2. SABR characteristics

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<td>Femur</td>
<td>4 (7.3)</td>
</tr>
<tr>
<td>Scapula</td>
<td>3 (5.4)</td>
</tr>
<tr>
<td>Ischium</td>
<td>3 (5.4)</td>
</tr>
<tr>
<td>Tibia</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Spinal</td>
<td></td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>4 (7.3)</td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>3 (5.4)</td>
</tr>
<tr>
<td>Cervical spine</td>
<td>3 (5.4)</td>
</tr>
<tr>
<td>SABR schedule (BED1.5)</td>
<td></td>
</tr>
<tr>
<td>24 Gy/3 fx (152 Gy)</td>
<td>13 (23.6)</td>
</tr>
<tr>
<td>27 Gy/3 fx (189 Gy)</td>
<td>7 (12.7)</td>
</tr>
<tr>
<td>30 Gy/3 fx (230 Gy)</td>
<td>30 (54.5)</td>
</tr>
<tr>
<td>33 Gy/3 fx (275 Gy)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>30 Gy/5 fx (150 Gy)</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>30 Gy/6 fx (130 Gy)</td>
<td>2 (3.6)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

SABR, stereotactic ablative radiotherapy; fx, fraction; BED1.5, biologically equivalent dose with α/β ratio of 1.5 Gy.
The most frequent progression location was distant (30.9%), followed by lymph nodes and mixed locations (5.5% each). The treatments received were ARTA (22.58%), SABR (12.9%) and ADT (12.9%). Metastasis-free survival (MFS) was 61.8%, with a median of 48 months (95% CI, 32.3–63.6). At the time of analysis, 77.4% of the patients were still alive, with a median OS of 98 months (95% CI, 18.1–177.8). There were four cancer-specific deaths and the OS at 3 and 5 years was 82.6% and 77.4%, respectively. We did not find any significant differences in the OS when we considered the decrease in PSA after SABR ($p = 0.77$) (prognostic factors for LPFS, PFS and OS are shown in Table 3).

Finally, in our results we observed a delay in the initiation of the NEST, at 28.5 months.

Fig. 1. Kaplan-Meier curves of survival. (A) Local progression-free survival (LPFS). (B) Progression-free survival (PFS) and (C) Cox regression in patients with BED <230 Gy and ≥230 Gy. (D) PFS in patients with synchronous oligometastatic disease and metachronous oligorecurrent disease. BED, biologically equivalent dose; HR, hazard ratio; CI, confidence interval.
Discussion and Conclusion

In some solid tumour types, local SABR treatment of oligometastatic patients has recently shown survival benefit in a phase II trial (SABR-COMET) [26]. In oligometastatic prostate cancer, the data we have so far show that MDT is safe for the patient, with a good tolerability profile and delaying clinical progression [13, 14]. In this study, we assessed metastasis-targeted therapy with SABR and ADT in patients with bone-only oligometastatic prostate cancer, with satisfactory results in terms of toxicity, local control and time to the NEST.

This study has some limitations, the first being its retrospective nature with a small patient cohort compared to other studies of metastasis-directed therapy, since it was a single-center study, with a small number of patients fulfilling the condition of exclusively bone oligometastatic disease. Other limitations may be heterogeneity in terms of the imaging techniques used (the large majority of choline-PET and a small part conventional imaging tests) and the presence of a minority of synchronous lesions compared to metachronous lesions. On the other hand, a highlight of our study is that it only includes exclusive bone lesions compared to the higher frequency of both bone and lymph node lesions studies in the literature.

Our work on oligometastatic bone disease exclusively treated with SABR shows that patients had excellent tolerance to the treatment with only low rates of acute or chronic G2 toxicity, and no cases of ≥ G3 toxicity. There was only one case of acute G2 toxicity related to the treatment of the metastases, in the form of pain. These tolerance data correspond with those reported elsewhere in the literature [27, 28].

Ablative treatment of bone metastases offers excellent local control, as shown by Habl et al. [29] and Rogowski et al. [30], with the latter reporting a local failure rate of 1.7% at 24 months. Our data are consistent with these previous findings, with an LPFS of 100% at 36 months. Of particular note, our analysis shows that the number of metastases, Gleason index, stage at diagnosis, or pPSA levels were not statistically significant predictive factors for survival. The PFS was higher when we stratified the patients according to the BED, which should therefore be considered an independent predictor of PFS after multivariate analysis. BED > 100 Gy have been considered as ablative doses in different tumour primaries. Ost et al. [31] found a correlation between BED exceeding 100 Gy and PFS in cases of prostate oligometastases, and Hurmuz et al. [32] reported the same correlation in LPFS. Our data confirmed the correlation with PFS, but not with LPFS. There was a trend towards higher PFS in patients with synchronous lesions (p = 0.053); no differences were found in BED received (p = 0.78) or in lesions per patient (p = 0.60), finding a lower age (p = 0.019) and a lower percentage of toxic habits in the subgroup of synchronous patients.

All our patients received ADT during the ablative treatment, but

<p>| Table 3. Univariate analysis of prognostic factors |
|---------------------------------|-----|-----|-----|-----|</p>
<table>
<thead>
<tr>
<th></th>
<th>LPFS (mo)</th>
<th>p-value</th>
<th>PFS (mo)</th>
<th>p-value</th>
<th>OS (mo)</th>
<th>p-value</th>
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<td>Gleason score</td>
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</tr>
<tr>
<td>≤ 7</td>
<td>95.0</td>
<td>0.18</td>
<td>40.9</td>
<td>0.91</td>
<td>121.4</td>
<td>0.57</td>
</tr>
<tr>
<td>≥ 8</td>
<td>56.8</td>
<td>0.95</td>
<td>34.5</td>
<td>0.44</td>
<td>76.6</td>
<td>0.50</td>
</tr>
<tr>
<td>Number of metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>88.8</td>
<td>0.09</td>
<td>43.1</td>
<td>0.053</td>
<td>98.9</td>
<td>0.17</td>
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<td>≥ 2</td>
<td>70.9</td>
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<td>34.8</td>
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<td>56.4</td>
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<tr>
<td>Type of metastases</td>
<td></td>
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<tr>
<td>Synchronous</td>
<td>93.2</td>
<td></td>
<td>52.4</td>
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<tr>
<td>Metachronous</td>
<td>79.8</td>
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<td>29.2</td>
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<tr>
<td>Dose BED_{1.5} (Gy)</td>
<td></td>
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<tr>
<td>&lt; 230</td>
<td>88.4</td>
<td>0.45</td>
<td>25.5</td>
<td>0.037</td>
<td>90.9</td>
<td>0.51</td>
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<tr>
<td>≥ 230</td>
<td>91.1</td>
<td></td>
<td>47.4</td>
<td></td>
<td>80.2</td>
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<tr>
<td>pPSA (ng/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt; 3.7</td>
<td>91.3</td>
<td>0.39</td>
<td>46.1</td>
<td>0.21</td>
<td>78.0</td>
<td>0.80</td>
</tr>
<tr>
<td>≥ 3.7</td>
<td>87.9</td>
<td></td>
<td>28.8</td>
<td></td>
<td>91.5</td>
<td></td>
</tr>
<tr>
<td>PSA decline (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>91.1</td>
<td>0.74</td>
<td>5.5</td>
<td>0.77</td>
<td>108.9</td>
<td>0.77</td>
</tr>
<tr>
<td>≥ 30</td>
<td>96.7</td>
<td></td>
<td>43.0</td>
<td></td>
<td>97.3</td>
<td></td>
</tr>
</tbody>
</table>

LPFS, local progression-free survival; PFS, progression-free survival; OS, overall survival; BED_{1.5}, biologically equivalent dose with α/β ratio of 1.5 Gy; pPSA, PSA at the time of progression.
we do not know its possible impact on the results. Some authors [29] did not observe differences if hormonal treatment was added, although Rogowski et al. [30] observed a benefit in patients who underwent ADT during SABR. This provides a possible form of study that would let us compare our series with another group receiving exclusively SABR.

Radiation therapy to the primary tumour improved the OS in patients with metastatic prostate cancer with a low tumour burden, as seen in the HORRAD trial [33] and STAMPEDE trial [34]. Furthermore, a secondary analysis [35] of the STAMPEDE trial data revealed that the number of bone metastases influenced the OS, with this metric being more relevant in patients with ≤ 3 lesions. Therefore, in patients with bone oligometastases, adding ablative treatment of metastases to radiotherapy of the primary tumour, we would likely achieve greater local control of the disease, which could lead to a benefit in terms of OS. Nonetheless, although the data we obtained in our series showed a trend (p = 0.172) in this subgroup of patients, we still lack randomized studies to support this assumption.

Time to next systemic therapy is being used as an exploratory outcome in metastases directed therapies for different tumour types. In two studies of MDT in oligometastatic non-small cell lung cancer, SABR was reported to delay the time to the next systemic therapy [15,16]. Other studies have shown the synergistic action of sequential MDT and ADT in prolonging the castration-sensitivity time and delaying the time to NEST [36,37]. In our series, the time to the next systemic therapy time was 28.5 months and therefore represented promising data that may impact on the quality of life of these patients, who are elderly.

Low PSA levels after SABR on metastases have been associated with a better prognosis [38]. In the setting of mCRPC, an early decrease in PSA levels 4 weeks after the onset of abiraterone acetate may function as a surrogate for OS and PFS [39,40]. However, in our work, we assessed the early decrease in PSA after SABR and did not obtain significant differences in PFS or OS in patients with a decrease in PSA by ≥ 30% at 1 month compared to lower decreases.

In conclusion, our data allow us to conclude that ablative treatment of bone metastases in patients with oligometastatic prostate cancer is a safe treatment that produces minimal toxicity and excellent results in terms of local control. Higher BEDs were associated with better PFS results, thereby delaying the start of the next systemic treatment.

Statement of Ethics

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Castellón Provincial Hospital (Protocol Code: CEIC-108-03).

Conflict of Interest

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

Financial Support

This study was funded by the Castellón Provincial Hospital Foundation.

Author Contributions

Conceptualization, ASI, VMM. Methodology, VMM, ASI. Investigation, VMM, ASI, ASJ. Writing—original draft preparation, ASI, VMM. Writing—review and editing, ASI, VMM, CFA. Funding acquisition, ASI. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data are available on request from the corresponding author.

References


Introduction

Radiotherapy is established as a standard radical treatment for patients with localized prostate cancer. The results of prospective randomized studies confirmed that radiotherapy in low and intermediate risk patients is as effective as a surgical treatment while providing a better safety profile [1]. Separate retrospective studies confirm that in male with high and very high-risk prostate cancer surgery is associated with higher rates of overall and cancer specific survival compared to the external beam radiotherapy [2,3]. However, recently several doses escalated studies that utilized high dose rate brachytherapy (HDRB) boost in addition to pelvic irradiation outperformed surgical treatment and external beam radiotherapy in terms of biochemical control, distant metastatic free and/or cancer specific survival [4-7]. The studies mentioned above validate the use of brachytherapy as the standard method for prostate treatment in high-risk patients.

Purpose: To compare biochemical recurrence-free survival (BRFS) and toxicity outcomes of high dose rate brachytherapy (HDRB) and stereotactic body radiotherapy (SBRT) boost after elective nodal irradiation for high very high-risk prostate cancer.

Materials and Methods: A retrospective analysis was performed in 149 male patients. In 98 patients, the boost to the prostate was delivered by HDRB as 2 fractions of 10 Gy (EQD2 for α/β = 1.5; 66 Gy) or 1 fraction of 15 Gy (EQD2 for α/β = 1.5; 71 Gy). In 51 male patients, SBRT was used for the boost delivery (3 fractions of 7 Gy; EQD2 for α/β = 1.5; 51 Gy) because brachytherapy equipment was out of order.

Results: In 98 patients that received HDRB boost, 3- and 5-year BRFS were 74.6% and 66.8%. Late grade-II genitourinary toxicity was detected in 27, grade-III in 1 case. Grade-II (maximum) rectal toxicity was diagnosed in nine patients. For 51 male patients that received SBRT boost, 3- and 5-year BRFS was 76.5% and 67.7%. Late grade-II (maximum) genitourinary toxicity was detected in five cases, late grade-II rectal toxicity in four cases. Other three patients developed late grade-III–IV rectal toxicity that required diverting colostomy. SBRT boost was associated with higher maximum dose to 2 cm³ of anterior rectal wall (D2cm³rectum) compared to HDRB: 92% versus 55% of dose to prostate. Severe rectal toxicity was negligible at EQD, D2cm³rectum <85 Gy and EQD, D5cm³ rectum <75 Gy.

Conclusion: Our results indicate similar 3- and 5-year BRFS in patients with high very high-risk prostate cancer who received HDRB or SBRT boost, but SBRT boost is associated with higher rate of severe late rectal toxicity.

Keywords: Prostate cancer, Stereotactic body radiotherapy, Brachytherapy, Multimodal treatment, Boost
Brachytherapy versus SBRT prostate boost

As it allows delivery of highest total equivalent dose (EQD₂ > 100 Gy) without a significant increase of radiation burden for normal tissues [5,6,8].

Accumulated clinical experience confirms that stereotactic ablative body radiotherapy (SBRT) as well as brachytherapy is characterized by highly accurate irradiation of the prostate with sharp dose gradient and efficient sparing of surrounding normal tissues [3,10]. This makes it possible to consider SBRT as a promising non-invasive method of boost delivery to the prostate. However, there are no clinical data with direct comparison of the efficacy and safety of HDRB versus SBRT boost in treatment of high and very high-risk prostate cancer. Therefore, in this single center retrospective study we analyzed our personal experience of using HDRB and SBRT for delivery of the boost to the prostate after elective pelvic nodal irradiation.

Materials and Methods

In the practice of the Institute, HDRB has been used since 2012 for monotherapy of low and intermediate risk prostate cancer, and as a routine technique for boost delivery after pelvic nodal irradiation in high and very high-risk groups. SBRT has been used since 2013 for monotherapy of patients with low and intermediate risk prostate cancer. Unfortunately, our brachytherapy equipment was out of order twice for periods of 145 and 55 days. At this time SBRT was the only modality for "boosting" the prostate (33 cases). In addition, since 2016 in patients with contraindications for spinal anesthesia and/or severe comorbidities we also have used SBRT for "boost" delivery (18 cases).

Finally, 149 patients with high/very high-risk prostate cancer (clinical stage T3–4, Gleason >7, prostate specific antigen [PSA] >20 ng/mL) treated at N.N. Petrov National Medical Research Center of Oncology between June 2012 and April 2018 were included in the analysis approved by the local Ethical Committee (No. 09/2020). Written informed consent was obtained from all participants before the start of the treatment. One-third (31.7%) of the patients had instrumental signs (MRI, PET-CT) of pelvic lymph node involvement. Staging was performed according to the American Joint Committee on Cancer (AJCC) 7th edition. All male patients had androgen deprivation therapy with subsequent pelvic lymph node irradiation initiated 1–3 months after the start of hormonal treatment: in 93 patients as 3D conformal 4-field technique; in the remaining 56 male patients using volumetric modulated arc therapy (VMAT)—the prescribed dose varied from 43 Gy to 50 Gy (Table 1).

1. Brachytherapy boost

From June 2012 to June 2017, 98 patients (average age, 65.1 years; range, 49 to 82 years) received brachytherapy boost delivered as 2 fractions (2 implantations) of 10 Gy (81 males) or 1 fraction of 15 Gy (17 males) 3–4 weeks after the end of pelvic irradiation. The mean intervals between fractions was 18.4 days (range, 14 to 24 days) and never exceed 24 days. Total equivalent dose in 2 Gy fractions (EQD₂) of the boost were 66–71 Gy (EQD₂ for α/β = 1.5) and 52–71 Gy (EQD₂ for α/β = 3).

Implantation of the needles was performed under spinal anesthesia with transrectal ultrasound (TRUS) guidance. Pre- and post-implantation automatic 3D TRUS image acquisition was performed for real-time intraoperative treatment planning with inverse and/or volumetric optimization algorithms using Oncentra Prostate planning system (Elekta, Stockholm, Sweden). The organ-at-risk defined in every case were as follows: anterior rectal wall, urethra (catheter), bladder neck (catheter balloon). Gross tumour volume (GTV) was defined as the prostate and proximal 1/2–2/3 of seminal vesicles; clinical target volume (CTV) was created by 2–3 mm expansion of GTV in all directions except posterior and in the direction of the bladder. The dose was prescribed to CTV with the
following objectives: CTV V<sub>100</sub> > 93%; CTV D<sub>90</sub> > 100%; urethra maximum dose < 115% and urethra D<sub>100</sub> < 110%. A 2 cm<sup>2</sup> maximum dose to the bladder neck and anterior rectal wall should be kept below 75% (D<sub>2cm²</sub> < 75%).

2. SBRT boost

From May 2015 to April 2018, 51 patients (mean age, 68.4 years; range, 51 to 76 years) received SBRT boost to the prostate; in 33 cases as the substitute of HDRB because brachytherapy equipment was out of order, and in the remaining 18 patients because of contraindication for spinal anesthesia. Patient characteristics are presented in Table 1. The boost was delivered as 3 fractions of 7 Gy each (51 Gy EQD<sub>2</sub> for α/β = 1.5 and 42 Gy EQD<sub>2</sub> for α/β = 3). Gold fiducial markers (3 per patient) were transperineally inserted into the prostate under the TRUS guidance. Planning MRI and simulation CT were performed with an empty rectum and a full (200–400 mL) bladder 3–7 days after fiducial markers placement. GTV and CTV were the same as described earlier for HDRB boost, and planning target volume (PTV) was 3–5 mm in all directions and 1–3 mm posteriorly. The dose was prescribed to 90% PTV. A total dose of 21 Gy in 3 daily fractions was delivered with TrueBeam or Novalis (Varian Medical Systems, Palo Alto, CA, USA) linear accelerators. Cone-beam CT was used for treatment guidance before and after each VMAT session. In male with full rectum and/or empty bladder SBRT session was delayed and performed after adequate preparation of the patient. Spacers or rectal balloons were not used in patients included in the analysis.

3. Patient follow-up and toxicity assessment

According to our standard follow-up strategy, patients were evaluated every 3 months for the first year and every 6 months thereafter. The primary endpoints of this analysis were biochemical disease-free survival and late toxicity. Acute toxicity and late toxicity were determined using Common Terminology Criteria for Adverse Events (CTCAE) version 5 [11]. For each person the highest CTCAE score recorded 6 and more months after the end of treatment was defined as maximum late toxicity.

PSA was obtained at baseline, every 3 months for the first 2 years and every 6 months thereafter. The PSA relapse was diagnosed as nadir after the end of treatment plus 2 ng/mL (Phoenix definition). PSA bounce was characterized by PSA raised above nadir with a subsequent decline to nadir level.

The correlations of treatment (HDRB vs. SBRT) and dosimetric variables with the probability of severe late rectal complications were analyzed with χ² test and t-test for independent variables. Biochemical relapse-free survival was evaluated using Kaplan–Meier curves. A p-values below 0.05 were considered significant.

Results

The median follow-up in the group of HDRB boost was 87.7 months (range, 42.1 to 102.0 months). The 3-year and 5-year BRFS were 75.6% and 66.8%, respectively (Fig. 1).

During the follow-up period, one patient died of prostate cancer; three patients died of other reasons (cardiovascular decompensation, second tumor). Local recurrences in the prostate were detected in 3 (10.3%) of 29 patients with biochemical relapse. Pelvic nodes involvements were detected in 8 (27.6%) cases, retroperitoneal lymph nodes above the bifurcation of aorta in other 11 (37.9%) observations. Bone metastases were diagnosed in 11 (37.9%) of 29 patients with biochemical relapse.

Late grade III urinary toxicity was detected in 1 (1.1%) of 98 patients. It manifested by urethra stricture surgically treated with a good functional result. Grade II toxicity was mentioned in 28 (28.6%) cases and in most observations (24 male) manifested by frequency and/or urgency that were successfully treated by anti-inflammatory therapy and α-blockers. Grade II rectal toxicity was detected in 8 (8.2%) cases and manifested by episodes of rectal bleeding and/or painful defecation that were the cause of conservative treatment. In one man, we diagnosed a subcompensated rectal stenosis treated conservatively and also estimated as grade II toxicity.

In 51 patients who received SBRT boost, the median follow-up was 55.1 months (range, 31.1 to 69.1 months); two patients were lost for follow-up 38 and 43 months after the end of treatment. The 3-year biochemical relapse-free survival was 82.3%, 5-year
was 67.7%. Biochemical relapses were diagnosed in 12 patients: in 8 of 12 cases they manifested by bone metastases and were subclinical in the remained four observations.

Late grade II urinary complications (two cases of urinary urgency and/or frequency and three cases of retention treated by α-blockers) were detected in five patients (9.8%). We explained lower incidents of grade II urinary toxicity after SBRT by non-invasive character of this technique that does not require catheterization of urethra and needle insertion. Late grade II rectal toxicity was detected in four cases (8.6%) and in all observations was represented by rectal bleedings (2 males) that did not recur, and/or painful defecation (2 males) that were the cause of conservative treatment.

Late grade III–IV rectal toxicity was revealed in three cases (5.9%). In three patients with proctitis and clinically significant bleedings the conservative treatment by argon plasma coagulation and hemotransfusions was ineffective. In all three cases the patients underwent colostomy, one male patient that was on oral anticoagulant after the coronary surgery, manifested by severe bleeding and was treated in the intensive care unit (grade IV toxicity).

Taking into account significantly higher risk of grade III–IV rectal toxicity in patients who received SBRT boost to the prostate (p = 0.038), we performed dosimetric comparison of HDRB and SBRT treatment plans (Table 2, Fig. 2). The presented data demonstrated two important dosimetric differences between HDRB and SBRT boost: significantly lower dose to the anterior rectum wall (p < 0.0001) and higher mean prostate dose (p < 0.001) in patients who received SBRT boost. In patients who received SBRT boost, we separately analyzed the correlation between doses absorbed by anterior rectum wall (D2cm1 and D5cm1) and probability of severe rectal toxicity (Tables 3, 4). According to our data, the risk of severe late rectal toxicity is negligible when D2cm1 and D5cm1 (α/β = 3) are below 85 Gy and 75 Gy, respectively. The probability of late rectal complication becomes unacceptable when D2cm1 and D5cm1 (α/β = 3) are above 90 Gy and 81 Gy.

Table 2. Dosimetric parameter comparison

<table>
<thead>
<tr>
<th>Organ</th>
<th>Target (prostate)</th>
<th>Rectum</th>
<th>Urethra</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HDRB</td>
<td>SBRT</td>
<td>HDRB</td>
</tr>
<tr>
<td>V100% (%)</td>
<td>94.9 ± 3.6</td>
<td>97.9 ± 2.1</td>
<td>103.6 ± 4.0</td>
</tr>
<tr>
<td>D90% (%)</td>
<td>60.8 ± 4.5</td>
<td>88.8 ± 6.9</td>
<td>60.8 ± 4.5</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. Doses represented as the percent of the prescription dose. HDRB, high dose rate brachytherapy; SBRT, stereotactic body radiotherapy; V100%, volume of the prostate (gross tumor volume) receiving 100% of the prescription dose; D90%, radiation dose delivered to 90% of the prostate (gross tumor volume); D2cm1, maximum dose received by 0.1 cm² of the anterior rectal wall; D5cm1, maximum dose received by 2 cm² of the anterior rectal wall; D30%, dose received by 10% of the urethra volume.

Discussion and Conclusion

The performed retrospective analysis demonstrates a similar efficacy of HDRB and SBRT when used as a prostate boost after regional lymph node irradiation in combination with hormonal therapy: 3-year and 5-year biochemical relapse-free survival was 74.6% versus 76.5% and 66.8% versus 67.7%, respectively. Literature data demonstrated a substantial variability of BRFS rates for patients with high and/or very high-risk prostate cancer. Some authors re-
ported that it was in the range of 81%–91% even after the monotherapy with HDRB or SBRT [12, 13]. These data corresponded to our previous findings of 78% of BRFS after HDRB of patients with high-risk prostate cancer [14]. On the other hand, the prospective multicenter trials and some retrospective reports pointed out that 5-year BRFS in mixed population of high and very high-risk prostate cancer patients varied from 47% to 67% [6, 15, 16]. Taking into account the predominance of very high-risk patients in both HDRB and SBRT boost groups of our study and considering that most of relapses were represented by generalization with bone and/or “out of fields” lymph node metastases, the presented rates of BRFS seem acceptable. It is also important to mention very high rates of a 5-year locoregional control that exceeded 90% in HDRB group, and was equal to 100% after a 3-year follow-up in male who underwent SBRT boost.

The biggest surprise of this study was the high level of severe late rectal toxicity after SBRT boost. Our previous experience with HDRB, SBRT monotherapy and HDRB boost in more than 900 patients with prostate cancer indicates excellent safety profile for both procedures with grade III rectal toxicity below 1%. In patients who received HDRB boost, we did not mentioned grade III rectal toxicity, and late grade II toxicity was detected only in 8.2% cases. The dosimetric analysis gives some explanations to the observed differences: D_{\text{2cm}^3} and D_{\text{5cm}^3} for anterior rectal wall was about 22%–28% higher with SBRT boost. These dosimetric differences in the dose to the anterior rectal wall were already mentioned in the literature [17-19]. In particular, in the study of Frohlich et al. [19], D_{\text{2cm}^3} to the rectum was 1.8 higher with SBRT compared to HDRB. Literature analysis clearly demonstrated that these differences transformed into important clinical consequences. For instance, it was shown that low and high dose rate brachytherapy was associated with significant reduction of grade III rectal toxicity when compared to external beam radiotherapy [4, 20, 21]. SBRT [22] as monotherapy treatment and SBRT as a boost [18, 23]. It is interesting that in all of these studies brachytherapy manifested by maximum grade II rectal toxicity that matches our data. Conversely, grade III rectal late toxicity varied in most of these studies around 2.5%–5% [4, 18, 22, 23]. Parzen et al. [21] analyzed rectal toxicity in 2,863 patients with prostate cancer and mentioned that compared to external beam radiotherapy HDRB was associated with the decreased rates of chronic rectal grade ≥ II bleeding (1.3% vs. 8.7%).

Dose escalation to the primary tumor in high/very high-risk prostate cancer is an important factor associated with high rates of long-term relapse free and overall survival [24, 25]. On the other hand, reduction of radiation dose to the anterior rectal wall below its tolerance minimized the risk of severe functional impairments [26, 27]. When choosing the technique of SBRT boost (total dose and fractionation scheme), we were guided by numerous reports on maximum tolerant doses to the anterior rectal wall that correspond to acceptable (≤ 1%–2%) severe (grade ≥ III) rectal toxicity in monotherapy [27-29] or boost [30-32] trials. In SBRT studies it was shown that the EQD_{3} for α/β = 3 to 2 cm^3 of anterior rectal wall in the range of 83.5–92.5 Gy was associated with minimal severe toxicity [22, 23, 28-30]. A comprehensive analysis of rectal toxicity in dose escalation study was performed by Kim et al. [26], and the authors concluded that delayed severe rectal injury occurs when > 3 cm^3 of continues rectal wall received 50 Gy (EQD_{3} for α/β = 3 ≥ 130 Gy). The authors also postulated three main mechanisms of rectal toxicity: direct stem cell inactivation, disrupted stem cell migration and vascular/stroma damage which is closely correlated with the delayed rectal wall tolerance [26].

Our practice with SBRT boost indicated a significantly lower threshold dose in terms of late rectal toxicity. In particular, we found out that it is possible to minimize the probability of severe late rectal toxicity when D_{\text{2cm}^3} and D_{\text{5cm}^3} (α/β = 3) are below 85 Gy and 75 Gy. Probably, such differences in tolerance doses can be explained by a more aggressive treatment of our patients—they received a combination of pelvic lymph node irradiation with SBRT. In this case, the whole circumference of the rectum received 46–50 Gy with additional dose to the anterior rectal wall during the delivery of the boost. Another possible explanation is the aggressive local treatment of the rectal bleeding—all three males with grade III
rectal toxicity underwent endoscopic invasive local interventions in non-oncologic outpatient clinics.

To our knowledge, this is the first study that directly compares HDRB and SBRT when used as a boost in combination with a standard elective pelvic nodal irradiation, but our results have several important limitations. The main two are a relatively short follow-up period, especially in SBRT boost group, and the absence of the true randomization. It is well known that even in patients with high and very high prostate cancer many biochemical and clinical relapses can manifest after 5–10 years of follow-up. On the other hand, most events related to late toxicity become evident during the first 3 years after the treatment, and it can be proposed that the observation time was sufficient to capture most of the late treatment complications. The retrospective nature of this analysis compromises the comparison of two boost techniques. On the other hand, taking into account that indications for combined treatment in both groups were identical, and the choice of boost technique was driven only by the availability of HDRB equipment, it seems that the presented results objectively reflect the differences in efficacy and safety of both boost strategies.

In conclusion, our results indicate similar 3-year and 5-year biochemical control in patients with high/very high-risk prostate cancer who received elective pelvic irradiation with HDRB or SBRT boost. We also found out that SBRT boost was associated with higher late rectal toxicity than HDRB boost. The dosimetric comparison of SBRT and HDRB demonstrates that HDRB can deliver the prescribed dose to the prostate with a significantly lower exposure (28% lower D2cm3 (α/β = 3) > 75 Gy) to the anterior rectal wall. Our data show that in patients who received SBRT boost, the risk of severe late toxicity occurs when the dose absorbed by anterior rectal wall exceeds D2cm3 (α/β = 3) > 85 Gy and/or D2cm3 (α/β = 3) > 75 Gy.

Statement of Ethics

This study was approved by the local Ethical Committee (No. 09/2020).

Conflict of Interest

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

Funding

None.

Author Contributions

Conceptualization: SNN, SVK; Funding acquisition: SNN, RVN; Investigation and methodology: SNN, RVN, YOM, MYG, NDJ, YSM; Project administration: SNN, RVN; Resources: SNN, SVK; Supervision: SNN, RVN; Writing of the original draft: SNN, RVN, YOM, MYG, NDJ, YSM; Writing of the review and editing: SNN; Software: RVN, YOM; Validation: SNN; Formal analysis: SNN, RVN, SVK; Data curation: SNN, RVN, YOM, MYG, NDJ, YSM; Visualization: SNN, RVN, YOM. All the authors have proofread the final version.

References


Mucoepidermoid carcinoma of the trachea in a 9-year-old male child: case report and review of literature

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Received: May 11, 2021
Revised: August 25, 2021
Accepted: September 1, 2021

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Mucoepidermoid carcinoma (MEC) is the most common malignancy of minor salivary glands in adults. Pulmonary MEC is extremely uncommon, comprising only 0.1–0.2% of the primary lung malignancies and <1% of primary bronchial tumors. It is even rarer in children, and literature is limited to a few case reports only. Here we present a case report of a 9-year-old boy diagnosed with primary MEC of the trachea along with a review of the literature. A 9-year-old male child presented with complaint of dry cough for two years which was later associated with shortness of breath after one year. Bronchoscopic examination revealed a growth arising from right lateral wall of carina occluding 50% of the lumen and detailed histopathological examination revealed it to be a MEC of the trachea. The patient underwent local excision of the tumor with primary anastomosis. Because of positive margin, adjuvant radiotherapy of 60 Gy in 30 fractions was given to the tumor bed. The patient tolerated the treatment well and is disease free at 6 months follow-up. Experience with MEC of the trachea in children is limited, and optimal treatment protocols have not been defined, with current treatment mainly extrapolated from MEC of the salivary glands.

Keywords: Mucoepidermoid carcinoma, Trachea, Child

Introduction

Primary malignancies of the lung are very rare in the pediatric population, accounting for < 1% of all pediatric malignancies [1]. Even rarer are the primary malignancies of the trachea-bronchial tree in this population. Mucoepidermoid carcinoma (MEC) is uncommon in lungs constituting only 0.1%–0.2% of the primary lung malignancies [2]. In the pediatric age group, it represents 9%–10% of all malignant primary lung tumors [1]. MEC is mainly the tumor of salivary glands and was initially described by Smetana et al. [3] in 1952. Pediatric cases of MEC of the trachea are mainly limited to fewer than 10 cases reported in literature so far and are often clubbed with MEC of the whole tracheobronchial tree.

Here, we report a case of 9-year-old male with MEC of the trachea treated with surgery and postoperative radiotherapy. Till now, only fewer than ten cases of primary MEC of trachea has been reported in children. Rarity of the disease may often lead to delayed diagnosis or misdiagnosis.

Case Report

A 9-year-old male child presented with complaint of dry cough for 2 years which was later associated with shortness of breath after 1 year. There was no seasonal variation. In view of overlapping specific symptoms patient was earlier diagnosed as case of asthma and took treatment for the same but to no relief [4].

A bronchoscopy was done which revealed growth from right lateral wall of carina occluding 50% of the lumen. Positron emission
tomography (PET) scan showed a heterogeneous enhancing non fluorodeoxyglucose (FDG) avid lesion in right lateral wall of trachea 2.5 cm above the carina. Patient underwent excision of the mass and primary anastomosis. On pathological examination of the specimen, grossly the tumor showed both exophytic and endophytic growth which was extending and eroding tracheal ring cartilage.

Microscopically (Fig. 1A–1F) it revealed ill-defined tumor within the sub-epithelium giving polypoidal appearance to overlying mucosa. It seemed to be arising from the submucosal glands and eroding hyaline cartilage at places. Tumor cells were predominantly composed of intermediate cells and were arranged in the form of nests, islands, trabeculae and at places solid sheets. Mitosis was infrequent. There were no areas showing cystic degeneration, significant nuclear atypia or necrosis. Circumferential resection margin was close and distal and proximal resection margins were involved by the tumor. In consideration of the above findings final diagnosis was of tracheal MEC of intermediate grade.

In view of positive margins he was given adjuvant radiotherapy with a dose of 60 Gy in 30 fractions in 6 weeks with volumetric modulated arc therapy (VMAT) on a 6-MV linear accelerator. The VMAT was planned using two arcs. A 95% of the prescribed dose was delivered to 98% of the PTV. The dose constraints to the organs-at-risk were well respected. The $D_{max}$ of the spinal cord was 44 Gy. $V_{25}$ of B/L lungs was 25.6%, $V_{13}$ was 13.3% and $V_{30}$ was 4.7%. $D_{mean}$ received by heart was 0.89 Gy. Esophagus received a $D_{mean}$ of 22 Gy and $D_{mean}$ of thyroid gland was 45 Gy.

During the course of radiotherapy, the patient developed grade 1 skin reactions and grade 2 esophagitis which were managed conservatively without requiring any treatment gap. The patient tolerated the treatment well and is presently asymptomatic and is disease free both clinically and radiologically at 6 months of follow-up. Dose distribution of the final plan of radiotherapy is shown in Fig. 2.

**Discussion**

MECs of tracheobronchial tree is extremely rare neoplasm in pediatric population. MEC represents 0.2% of all lung tumors [2,5]. So far fewer than ten patients have been reported in literature in children less than 10 years of age. Table 1 summarizes the cases of MEC of trachea in children less than 10 years of age. All the patients mentioned in the table were managed with surgical resec-

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Fig. 1. (A) Squamous cells (black arrow, large cells having round pyknotic nuclei and abundant cytoplasm) and intermediate cells (blue arrow, small cells with high nuclear to cytoplasmic ratio and less cytoplasm). (B) Intermediate cells (blue arrow). (C) Mucus/vacuolated cells (red arrow, cells with abundant intracytoplasmic mucinous vacuoles) and respiratory lining (black arrow). (D) Higher power of previous image to appreciate mucus/vacuolated cells. (E) Periodic Acid-Schiff (PAS) stain and Alcian blue stain highlighting the intracytoplasmic mucin in the mucus/vacuolated cells in blue color (black arrow). (F) P63 nuclear positivity in squamous and intermediate cells.
Fig. 2. Dose distribution of the final radiotherapy plan.

Table 1. Summary of the cases of mucoepidermoid carcinoma trachea

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Site and grade of tumor</th>
<th>Treatment</th>
<th>Adjuvant treatment</th>
<th>Survival</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papiashvilli et al. [5]</td>
<td>2012</td>
<td>9</td>
<td>Male</td>
<td>Trachea</td>
<td>Surgery</td>
<td>No</td>
<td>24 months</td>
<td>Tumor free</td>
</tr>
<tr>
<td>Noda et al. [15]</td>
<td>1998</td>
<td>7</td>
<td>Male</td>
<td>Trachea, intermediate grade</td>
<td>Surgery</td>
<td>No</td>
<td>16 months</td>
<td>Tumor free</td>
</tr>
<tr>
<td>Desai et al. [14]</td>
<td>1998</td>
<td>4</td>
<td>Female</td>
<td>Trachea, low grade</td>
<td>Surgery</td>
<td>No</td>
<td>8 weeks</td>
<td>Tumor free</td>
</tr>
<tr>
<td>Romao et al. [12]</td>
<td>2009</td>
<td>8</td>
<td>Female</td>
<td>Trachea, low grade</td>
<td>Surgery</td>
<td>No</td>
<td>3 years</td>
<td>Tumor free</td>
</tr>
<tr>
<td>Romao et al. [12]</td>
<td>2009</td>
<td>9</td>
<td>Female</td>
<td>Trachea</td>
<td>Surgery</td>
<td>No</td>
<td>1 year</td>
<td>Tumor free</td>
</tr>
<tr>
<td>Kim et al. [16]</td>
<td>1998</td>
<td>9</td>
<td>Male</td>
<td>Trachea, low grade</td>
<td>Surgery</td>
<td>No</td>
<td>15 months</td>
<td>Tumor free</td>
</tr>
<tr>
<td>Chan et al. [13]</td>
<td>2005</td>
<td>4</td>
<td>Male</td>
<td>Trachea</td>
<td>Surgery</td>
<td>No</td>
<td>1 year</td>
<td>Tumor free</td>
</tr>
<tr>
<td>Lin et al. [4]</td>
<td>2016</td>
<td>12</td>
<td>Male</td>
<td>Trachea</td>
<td>Surgery</td>
<td>No</td>
<td>12 months</td>
<td>Tumor free</td>
</tr>
</tbody>
</table>

In the lung, MEC presents in a wide age range, however, younger patients are rare. In a cohort of 18 patients age range from 29–86 years was reported by Rapidis et al. [6]. Ozawa et al. [7] reported...
age range of 22–86 years in a cohort of 43 patients and an age range of 33–70 years in a cohort of 30 patients. Reports in involving pediatric age group of less than 10 years is very rare.

Due to its rarity and overlapping symptoms with bronchial asthma the diagnosis is often delayed in a child presenting with recurrent upper respiratory tract symptoms. Diagnosis delay for up to 20 months has been reported in literature. Children with MEC of the tracheobronchial tree presents most commonly with coughing, wheezing, bronchitis, fever, chest pain and dyspnoea due later stage of the disease. Coughing, haemoptysis, fever, wheezing and recurrent pneumonia were the most common signs in patients in studies by Tsuchiya et al. [8] and Dinopoulos et al. [9]. In the present report the patient developed dry cough for about 2 years duration which was later accompanied by shortness of breath due to tracheal luminal compromise. During the course the patient was initially diagnosed as a case of bronchial asthma and thus there was a diagnosis delay of approximately 2 years.

The investigation often begins with chest X-ray and CT-scan of the chest. The tumors usually present as a lobulated exophytic luminal mass. Bronchoscopy is indicated for better visualisation of the tumors and to take biopsy for confirmatory diagnosis.

MEC of the tracheobronchial tree is histologically similar to MEC of salivary glands and these are categorised into low-, intermediate-, and high-grade tumors based on nuclear pleomorphism, necrosis, type of cell (mucous, intermediate, and epidermoid), and degree of mitotic activity [10]. Low-grade tumors are slow growing and are generally managed by surgery alone whereas high-grade tumors have poor prognosis due to greater chance of recurrences and metastasis and often require multimodality treatment [10]. In a study by Heitmiller et al. [11] on 18 patients, patients with high-grade tumors did much worse with all of them dying within one and half years. However, all patients with low-grade tumors were reportedly alive at 4.7 years.

MEC of the tracheobronchial tree in children should be considered potentially malignant. However due to slow growing nature of these tumors a prompt diagnosis and early surgical treatment is necessary. Complete surgical resection with en-bloc removal of tracheal rings and reconstruction of the trachea is the primary treatment [12-16]. Long-term cure has been achieved with complete resection in low grade MEC patients in most of the studies. However, due to scarcity of the literature available, the role of adjuvant treatment is still unclear especially in intermediate grade histology.

MECs of the salivary glands have been treated successfully with radiotherapy in the adjuvant setting. Studies have shown benefit of postoperative radiotherapy in patients with positive surgical margins, high-grade histology and recurrences in MECs of salivary glands [6]. Adequate local control in salivary gland MECs with positive margins have been achieved with dose of 55 Gy or more of adjuvant radiotherapy [17]. With the scarcity of literature available for adjuvant treatment in tracheobronchial MECs and extrapolating the role of radiotherapy in salivary gland MECs, adjuvant radiotherapy with a dose of 60 Gy was delivered to the patient in our report. Adjuvant treatment have been used in cases of R2 resection or in case of high-grade tumors or a recurrence. Fauroux et al. [18] reported a child who had recurrence after 3 years of initial resection. Benefit of combined chemotherapy and radiotherapy has been shown in few studies in high grade MEC and in recurrences. Risk/benefit ratio of adjuvant treatment should be explained to patients and guardians. In the index case, as the mean dose to thyroid gland was 45 Gy, parents have been counselled regarding the potential risk of hypothyroidism in long term and frequent monitoring with thyroid function test. Patient should also be counselled and monitored for any possible risk of radiation induced cancers especially in pediatric population.

There have been few reports studying the role of targeted therapy in treatment of MEC of tracheobronchial tree. MECs of the salivary gland are known to frequently overexpress epidermal growth factor receptor (EGFR). Specimens of pulmonary origin MECs were also tested for EGFR mutations by Han et al. [19], EGFR overexpression has been reported in few cases of high-grade MEC. Tyrosine kinase inhibitors (TKIs) are a known treatment option in adjuvant setting in EGFR mutation positive non-small-cell lung cancer. Partial response has been seen in some of the patients with high grade MECs with the use of EGFR tyrosine kinase [19]. Prospective randomized studies are needed to further investigate the role of EGFR TKIs in tracheal MEC.

Childhood MECs of the tracheobronchial tree tend to do better compared to those in adults. In a study of Chin et al. [10], 1-year survival of only 20% in high-grade MEC in adult patients and 80% for low- and intermediate-grade MEC was found. However, in pediatric patients of MEC the 5-year and 10-year overall survival and disease-free survival was found to be 100% in study done by Neville et al. [20].

MEC of the tracheobronchial tree is extremely rare in pediatric and is often overlooked while considering in the differential diagnosis for patients with signs of upper respiratory tract obstruction. Complete surgical resection is the primary treatment modality for low-grade MEC. However, high-grade and recurrent MECs of tracheobronchial tree in adults have been managed with radiotherapy and chemotherapy in the adjuvant setting [18]. Role of radiotherapy is also important in tracheal tumors where symptomatic control from luminal compromise by the tumors is required. Prospective studies are required for better defining treatment strategies of this
malignancy.

**Statement of Ethics**

Written informed consent was obtained from the parents and ethical clearance was exempted by institutes ethics committee.

**Conflict of Interest**

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

**Author Contribution**

Conceptualization, RM. Investigation and methodology, DKU. Project administration, RM, DKU. Supervision, RM. Writing of the original draft, DKU. Writing of the review and editing, RM, NJP, AB, SG, NB, DK. Formal analysis, RM, DKU. Data curation, DKU, RM. All the authors have proofread the final version.

**Data Availability Statement**

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

**References**


https://doi.org/10.3857/roj.2021.00500
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The Research Ethics Committee of the Korean Society for Radiation Oncology covers ethical issues involved with research and publication. This committee is composed of one chairperson and the members of the committee. The director of the ethics committee acts as the chairperson of this committee. The members of the Research Ethics Committee include the vice president, the auditor, the directors of general affairs, research, and publication committees, and two directors without a portfolio of the society become ex officio. The members of this committee serve for a term of two years, and they may be reappointed.

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

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

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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 or Korean-English Medical Terminology, published by the Korean Medical Association. The use of acronyms and abbreviations is discouraged and should be kept to a minimum. When used, they are to be defined where first used, followed by the acronym or abbreviation in parentheses. Drug and chemical names should be stated in standard chemical or generic nomenclature. Units of measure should be presented according to the SI units (e.g., Gy, Sv, Bq, m, kg, L).

(3) Reporting Guidelines for Specific Study Designs
For the specific study design, such as randomized control studies, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, it is recommended that the authors follow the reporting guidelines listed in the following table.

<table>
<thead>
<tr>
<th>Initiative</th>
<th>Type of study</th>
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<td>STARD</td>
<td>Studies of diagnostic accuracy</td>
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<tr>
<td>PRISMA</td>
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<tr>
<td>STROBE</td>
<td>Observational studies in epidemiology</td>
<td><a href="http://www.strobe-statement.org">http://www.strobe-statement.org</a></td>
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Original articles are reports of basic or clinical investigations. The manuscript for an original article should be organized on a separate page in the following sequence: title page, abstract and keywords, text (introduction, materials and methods, results, discussion, and conclusion), statements, references, tables, and figure legends.

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· Each author’s name (first name, middle name, and surname) followed by the highest academic degree (e.g., Gil Dong Hong, MD).
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· Source(s) of support in the form of grants, equipment, drugs, or all of these.
· Complete mailing address, telephone, and E-mail for correspondence and reprints.

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

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Text should be arranged in the following order: Introduction, Materials and Methods, Results, Discussion, and Conclusion.
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Introduction section should contain 1) the background and rationale of the study and 2) the objective of the study. The former part should state background information and references that inform the reader as to why the study was performed. Please avoid an extensive review of the literature. The final paragraph of the introduction should clearly state the hypothesis and the objective of the study.

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__________________________________________________________________________

xii
점착성투명창상피복재, 화상, 건조 피부 등 피부 장벽이 파괴된 부위에 보호를 위해 사용하는 창상피복재

TO PROTECT
THE SKIN BARRIER

점착성투명창상피복재, 화상, 건조 피부 등 피부 장벽이 파괴된 부위에 보호를 위해 사용하는 창상피복재
등가량 하루 10 mg 이하로 감량할 수 없는 중증 (3등급) 면역 매개 이상사례의 경우 이 약의 투여를 중단한다. 면역 매개 이상사례가 다음 표에 요약되어 있다. [이 약의 용법 조절 및 관리 권장 사항]

(3등급) 면역 매개 이상사례의 경우 이약의 투여를 보류한다. 생명을 위협하는 (4등급) 면역 매개 이상사례와, 전신 면역 억제 치료가 필요하거나 코르티코스테로이드 시작 12주 이내에 프레드니손 또는 투여한 뒤, 이 약 1500 mg 단독요법을 4주 간격으로 투여하는 것이며, 질환이 진행되거나 허용 불가능한 독성 발생 전까지 투여한다. 체중 30 kg 이하의 환자는 체중에 따라 이 약 20 mg/kg을

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

UPDAD 5-YEARS OVERALL SURVIVAL IN THE ITT POPULATION

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months since Randomization</th>
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<tr>
<td>Durvalumab</td>
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<th>Probability of OS</th>
<th>Durvalumab</th>
<th>Placebo</th>
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<td>283</td>
</tr>
</tbody>
</table>

28% REDUCTION in risk of death (vs. 29.1 months with placebo)
MEDIAN OS 47.5 months (vs. 36.3 months with placebo)

PD-L1 발현 양성(발현 비율 > 1%)이면서 백금 기반 동시적 항암화학 방사선요법 2주기 이상 투여 후 질병진전이 없는 만성폐쇄환기 불량이 있는 국소 진행성(stage III NSCLC, nonsmall-cell lung cancer; cCRT, concurrent chemoradiation therapy; OS, overall survival; ITT, intent-to-treat; HR, hazard ratio; CI, confidence interval; PD-L1, programmed cell death-ligand 1; PI, programmed cell death protein 1; N, number; 42% 5-year OS rate with durvalumab vs. 32% with placebo; 95% CI, 36% to 48%)

임핀지™의 용법 조절 및 관리 권장 사항

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

STUDY DESIGN The PACIFIC study design, eligibility criteria and assessments have been fully described previously. Eligible patients had histologically and/or cytologically documented Stage IIA, 1b, IIIa, IIIb, IIIc or III IV (any N) stage non-small-cell lung cancer (NSCLC), with a WHO performance status of 0 or 1. Patients had to have received at least 4 cycles of platinum-based chemotherapy or a combination of chemotherapy and ipilimumab, and there had to be no evidence of disease progression, initiation of alternative cancer therapy, unacceptable toxicity, or consent withdrawal. Patients were randomized 2:1 to durvalumab 10 mg/kg intravenously or placebo every 2 weeks for up to 12 months or until confirmed disease progression, initiation of alternative cancer therapy, unacceptable toxicity, or consent withdrawal. The prerequisite for inclusion in PACIFIC and enrollment was not restricted to any threshold levels for PD-L1 expression. Patients were randomized 2:1 to durvalumab 10 mg/kg intravenously or placebo every 2 weeks for up to 12 months or until confirmed disease progression, initiation of alternative cancer therapy, unacceptable toxicity, or consent withdrawal. The prerequisite for inclusion in PACIFIC and enrollment was not restricted to any threshold levels for PD-L1 expression. Patients were randomized 2:1 to durvalumab 10 mg/kg intravenously or placebo every 2 weeks for up to 12 months or until confirmed disease progression, initiation of alternative cancer therapy, unacceptable toxicity, or consent withdrawal.
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