Preliminary Results of Radiation Therapy for Locally Advanced or Recurrent Adenoid Cystic Carcinomas of the Head and Neck using Combined Conventional Radiation Therapy and Hypofractionated Inverse Planned Stereotactic Radiation Therapy

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Preliminary Results of Radiation Therapy for Locally Advanced or Recurrent Adenoid Cystic Carcinomas of the Head and Neck using Combined Conventional Radiation Therapy and Hypofractionated Inverse Planned Stereotactic Radiation Therapy

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Abstract  Purpose. To investigate the clinical outcomes and feasibility of combined conventional radiation therapy (RT) and hypofractionated inverse planned stereotactic radiation therapy (SRT) for locally advanced or recurrent adenoid cystic carcinomas (ACCs) of the head and neck. Patients and methods. Five patients with ACCs of the head and neck were treated with combined conventional RT and inverse planned SRT. Radiation doses of 40 to 50 Gy were delivered with 20 to 25 fractions using conventional RT, and then an additional 20 to 25 Gy was delivered by 4 to 5 fractions of SRT. Results. Median follow-up was 12 months. Local control was obtained in all 5 patients, PR in 2 patients and SD in 3 patients. According to the Radiation Therapy Oncology Group (RTOG) late-radiation morbidity scoring criteria, adverse effects included Grade 2 xerostomia in 1 patient, Grade 2 trismus in 1 patient, and Grade 4 mucosal ulceration in 1 patient. Conclusion. Combined treatment with conventional RT and hypofractionated inverse planned SRT may be effective for short-term local control in patients with locally advanced or recurrent ACCs. Further evaluation is needed for long-term follow-up.

Key words : adenoid cystic carcinoma, head and neck, SRT, Cyberknife

Introduction

Adenoid cystic carcinomas (ACCs) of the salivary glands in the head and neck are rare malignancies, accounting for 2-5% of all head and neck malignancies1). Generally, ACCs show slow-growth and little incidence of cervical lymph node metastases, and actuarial overall survival rates are 70-80% at 3 years after treatment2). However, these diseases are difficult to treat because of infiltrative and aggressive growth patterns, perineural spread patterns, persistent recurrence patterns and distant metastases3). Retrospective studies have shown that favorable outcomes are expected with surgery followed by postoperative radiation therapy (RT), and this treatment approach has been generally
patients, mesopharynx gland. The location of the tumors histopathologically proven ACCs before the RT. Tarting time of RT. From pulmonary and hepatic metastases at the patients presented patients presented. T respective analysis of combined conventional RT and determining whether this treatment could serve as an alternative to high-LET or proton RT.

Patients and Methods

Patient characteristics
Between December 2006 and September 2007, 5 patients with ACCs of the head and neck were treated with combined conventional RT and inverse planned SRT for the primary or recurrent tumor site. There were 2 male and 3 female patients. The median age at the time of RT was 61.4 years (range 53 to 73 years). All patients had histopathologically proven ACCs before the RT. The location of the tumors was maxillary sinus in 2 patients, nasopharynx in 2 patients and parotid gland in 1 patient. All patients were staged in accordance with 2002 UICC TNM classification. Detailed information on the tumor location and T-stage of the tumors is shown in Table 1. Two patients presented with primary tumors, and 3 patients presented with recurrent tumors after surgery. Two patients had already suffered from pulmonary and hepatic metastases at the time of RT.

Conventional RT treatment plans
Conventional RT treatment planning was accomplished using version 7.3.10 of the Eclipse treatment planning system (Varian, Palo Alto, USA). Treatment planning was performed using computed tomographic scans (slice thickness, 3 mm). The head and neck of all patients were immobilized with a thermoplastic head mask. The clinical target volume (CTV) was defined as the gross tumor volume (GTV) plus a variable margin added for microscopic perineural spreads and regional lymph nodes. The CTVs of most cases were set up for the GTV plus 2 to 3 cm margin. The planning target volume (PTV) contained an automated 0.5 to 1 cm expansion of the CTV to account for immobilization and repositioning accuracy. The covering doses for the PTV would be 40 to 50 Gy. The daily fraction size was 2 Gy. The photon energy of 6MV was used in all patients.

Inverse planned SRT treatment plans
Inverse planned SRT treatment planning was accomplished using the CyberKnife II treatment planning system (Accuray, Sunnyvale, USA). Treatment planning was performed using enhanced-contrast computed tomographic (CT) scans and gadolinium-enhanced magnetic resonance images (MRI) (slice thickness, 1.3 mm). The head and neck of all patients were re-immobilized with a thermoplastic head mask on the planning CT. The re-planning was performed after 40 Gy of conventional RT was delivered, or earlier. The planning CT images were integrated to MRI by the Accufusion of CyberKnife II treatment system. The PTV was defined as the GTV with no added margin. Other structures considered to be critically at risk included the optic nerve, optic chiasm, eye balls, brainstem, the temporal lobe and cerebellum. The major risk organs for each patient were delineated and taken into account. Twenty to 25 Gy was prescribed to the isodose line of D95%, which completely surrounded the PTV, and 6 MV photons were used. The collimator size depended on the geometry of the treated tumor. During SRT, tumor tracking was performed using the 6-D
Fig. 1 Dose distribution on axial, sagittal and coronal axes of case 4 in conventional RT (a) and inverse planned SRT (b). The dose coverage of tumor is favorable and the dose of neighboring organs at risk decreases drastically. (Figure 1-b)
skull tracking. The total treatment time was approximately 1 hour. The daily fraction size was 4 to 5 Gy. The dose distribution of conventional RT and hypofractionated SRT is shown in Figure 1. The total delivery dose and biological effective dose (BED) of combined with conventional RT and SRT are shown in Table 1.

Follow-up and evaluation of the local control and late toxicity

Gadolinium-enhanced MRI was performed every 2–3 months after RT. Local control was evaluated to have been attained if there was no evidence of tumor growth at the primary or recurrent sites based on clinical and MRI findings at follow-up. The late toxicities were graded according to the Radiation Therapy Oncology Group (RTOG) late radiation morbidity scoring criteria10a.

Results

Treatment outcomes

Median follow-up for surviving patients was 12 months (range, 8–18 months). Local control for the treated sites was achieved in all patients. Of these 5 patients, 3 patients experienced a minor decrease and 2 patients experienced a major decrease in the tumor size. The initial response in accordance with the RECIST guideline was stable disease (SD) in 3 patients and partial response (PR) in 2 patients (Table 1). MRIs of case 4 before and after RT are shown in Figure 2. Case 4 was treated by systemic chemotherapy for pulmonary and hepatic metastases sequentially after RT. Another patient (case 1) experienced orbital recurrence outside the radiation field at 10 months after RT. Additional RT was performed for this site and tumor was controlled. Local control rate at 1 year was 4/4(100%).

<table>
<thead>
<tr>
<th>Case</th>
<th>T-stage</th>
<th>Tumor Location</th>
<th>CRT (Gy)</th>
<th>SRT (Gy)</th>
<th>BED (α/β = 10)</th>
<th>Local control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>T3</td>
<td>Parotid</td>
<td>40</td>
<td>25</td>
<td>85.5</td>
<td>SD</td>
</tr>
<tr>
<td>Case 2</td>
<td>T3</td>
<td>Mesopharynx</td>
<td>40</td>
<td>25</td>
<td>85.5</td>
<td>PR</td>
</tr>
<tr>
<td>Case 3</td>
<td>T2b</td>
<td>Mesopharynx</td>
<td>40</td>
<td>25</td>
<td>85.5</td>
<td>SD</td>
</tr>
<tr>
<td>Case 4</td>
<td>T4b</td>
<td>Maxillary sinus</td>
<td>40</td>
<td>20</td>
<td>78.0</td>
<td>PR</td>
</tr>
<tr>
<td>Case 5</td>
<td>T4b</td>
<td>Maxillary sinus</td>
<td>50</td>
<td>25</td>
<td>97.5</td>
<td>SD</td>
</tr>
</tbody>
</table>

CRT, conventional radiation therapy PR, partial response SRT, stereotactic radiation therapy SD, stable disease

Fig. 2 Case 4: Clinical course of ACC in maxillary sinus before (a) and 10 months after RT (b) The contrast stain of tumor in maxillary sinus to middle cranial fossa decreased and the tumor reduction of PR was observed in accordance with the RECIST guideline after radiation therapy.
Late toxicity

The case 2 patient experienced grade 2 xerostomia, and the case 5 patient experienced grade 2 trismus of the ipsilateral mandibular joint. The late toxicities of 4 patients were Grade 0 to 2. However, one patient (case 3) experienced mucosal ulceration by necrosis of the irradiated site; the late toxicity of this case was evaluated as grade 4 (Table 2).

<table>
<thead>
<tr>
<th>Case</th>
<th>Toxicity</th>
<th>RTOG</th>
<th>Late radiation morbidity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>none</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 2</td>
<td>xerostomia</td>
<td>Grade 2</td>
<td></td>
</tr>
<tr>
<td>Case 3</td>
<td>ulceration</td>
<td>Grade 4</td>
<td></td>
</tr>
<tr>
<td>Case 4</td>
<td>none</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 5</td>
<td>trismus</td>
<td>Grade 2</td>
<td></td>
</tr>
</tbody>
</table>

RTOG, Radiation Therapy Oncology Group

Table 2 Late toxicity after treatment

Discussion

Several retrospective studies have shown favorable outcomes in patients of postoperative RT using photons. The presence of a positive surgical margin seems to be an important prognostic factor, however, several reports have been unable to demonstrate a significant correlation between a positive margin and the clinical outcome. The local failure rate with surgery alone for ACCs of the parotid gland was 50% (15). Therefore, a combined approach with surgery and RT is generally accepted in the initial treatment for ACCs. In this study, all cases presented inoperable status for reasons of locally advanced tumors or recurrent ACCs after surgery. An efficient treatment strategy for locally advanced or recurrent ACCs has not been confirmed. Douglas et al. reported that the 5-year loco-regional control rate of either inoperable, gross residual postoperatively, or recurrent ACCs after neutron RT was 47% (16).

Gomez et al. studied 59 patients with primary ACCs who received intensity-modulated RT (IMRT), three-dimensional conformal RT and conventional RT using photons, and found a good 5-year local control rate of 91%. The median total dose was 63 Gy (range, 50 to 70 Gy) (12). The hyperfractionated photon radiation therapy for a total dose of 65 to 70 Gy had a 5-year locoregional control rate of 78% (17). However, hyperfractionation photon RT may not be the preferred fractionation scheme for this histology from the radiobiologic point of view because ACCs are relatively slow-growing tumors (18). Photon RT for primary ACCs is favorable, however, it may be suboptimal in patients with locally advanced or recurrent ACCs in terms of long-term control (19,17). Munter et al. reviewed 25 patients treated with inverse planned stereotactic IMRT using photons and reported a 3-year local control rate of 38% with a median total dose of 66 Gy (5). Several other reports of IMRT for head and neck tumors showed good target coverage and the low incidence of complications by sparing organs-at-risk (19,20). However, the daily delivery dose of 2 Gy may be small and unfavorable for ACCs.

For patients with ACCs which generally have been considered resistant to photons because of slow growth, a low population of mitotic cells and high population of hypoxic cells, high-LET RT such as neutrons and carbon ions may be effective. In fact, several reports presented favorable outcomes in the local control of ACCs (20,18). Especially, Schulz-Ertner et al. showed that locoregional control rates at 2 years and 4 years for locally advanced ACCs were 77.5% and 77.5% with combined modern photon RT (SRT or IMRT) and a carbon ion boost, and 77.2% and 24.6% with modern photon RT alone (18). Proton RT, which is characterized by low-LET, also resulted excellent local control rates for locally advanced ACCs. Pommier et al. reported that the local control rate after 5 years of RT by protons was 93% for skull base ACCs, and Resto reported that the local control rate after 5 years was 86 to 100% (21). The median total doses in the latter study were 75.9 Gy cobalt-gray equivalent (CGE) (range, 70.0 to 76.8 CGE) with protons alone and 71.6 Gy (range, 55.4 to 79.4 Gy)
with a combination of proton beams and photon radiation. The adequate dose for local control of locally advanced ACCs may be more than 70 Gy.

This study was aimed to evaluate the treatment outcomes by integrated boost hypofractionated inverse planned SRT using photons. This treatment strategy enables higher target doses, good target coverage and sparing of neighboring organs at risk. Tumor doses of photons more than 70 Gy are recommended for macroscopic ACCs using photons, but most cases are impossible because of the tolerance doses of neighboring organs at risk, such as the brainstem, optic chiasm and nerve. The techniques of SRT or IMRT are suitable for enabling higher radiation doses in low–LET radiation. Additionally, the hypofractionated RT increased daily single dose could be effective for tumors resistant low–LET radiation. In the present study, the BED of combined conventional RT and inverse planned SRT was 78 to 97.5 Gy as $a/\beta = 10$. When converted a daily single dose as 2 Gy, total delivery doses in this study were equivalent to 65 to 81 Gy. The treatment modality using hypofractionated SRT made it possible to irradiate more than 70 Gy or equivalent doses for macroscopic ACCs. Our data showed good local control at 1 year after RT. The tumor size of all cases was observed to decrease. Munter et al. also concluded that inverse planned stereotactic IMRT was feasible in the treatment of ACCs due to its high control rates and low rate of side effects. However, further evaluation is needed for long–term local control and late toxicities.

There is no standard regimen of chemotherapy for ACCs. Patients with locally advanced and unresectable ACCs have been treated with a cisplatin–based regimen, carboplatin and paclitaxel and doxorubicin hydrochloride. Terashima et al. reported long–term local control of recurrent ACC with combined RT of 60 Gy using photons and intraarterial infusion chemotherapy with carboplatin. In several reports, the most common late toxicity was xerostomia. Gomez et al. reported Grade 3 or higher toxicity in 6 of 56 patients receiving photon IMRT, three–dimensional conformal RT and conventional techniques. Munter et al. reported no patients suffering from Grade 3 or higher toxicities after photon IMRT. Neutron RT presented higher late toxicity of Grade 3 or higher than other treatment modalities such as photons and protons. Schulz–Ertner et al. reported that rates of severe late toxicity were < 5% in patients treated with combination photon RT and a carbon–ion boost. In the aspect of late toxicities, the effective RT modality, such as SRT, IMRT and high–LET RT may be suitable in using the integrated boost radiation. In the present study, 1 patient developed grade 4 ulceration, and other patients developed less than grade 2 xerostomia and trismus as late toxicities. However, among hypofractionated SRT cases, careful attention may be needed in the treatment planning and follow–up for those with tumor localization in the oral or pharyngeal mucosa.

In our current study, good short–term local control was observed. The present treatment modality combining conventional RT and hypofractionated inverse planned SRT may be useful. However, further evaluation is needed for long–term follow–up.

References


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局所進行性あるいは再発性の頭頸部腺様囊胞癌に対する通常分割照射＋インバースプランによる低分割定位照射追加の治療成績

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目的　放射線抵抗性である頭頸部領域の腺様囊胞癌に対する通常分割照射＋サイバーナイフによるインバースプラン低分割定位照射追加の治療成績を検討する。

対象と方法　九州大学病院放射線科にて 2006 年 12 月から 2007 年 9 月までに放射線治療を施行した頭頸部領域の腺様囊胞癌5例を対象とした。平均年齢61.4歳（53-73歳）、男性2例、女性3例。部位は上顎洞2例、中咽頭2例、耳下腺1例、初発2例、再発3例であった。放射線治療通常分割照射を先行し、腫瘍遠隔部にサイバーナイフによる低分割定位照射を追加した。通常分割照射線量は40-50 Gy（20-25分割）、低分割定位照射追加線量は20-25 Gy（4-5分割）で、総線量は a / β = 10として Biological effective dose は78.0〜97.5 Gy（86.4±6.3）であった。観察期間中央値は12ケ月（8〜18ケ月）であった。

結果　腫瘍縮小は全例にみられ、局所制御は100%であった（PR 2例、SD 3例）。1例で照射野外に再発を認め追加放射線治療が施行され、肺・肝転移の1例は放射線治療後に全身化学療法が施行された。有害事象は RTOG Grade 2 の唾液分泌障害1例、Grade 2 の顱蓋板症1例、Grade 4 の粘膜潰瘍を認めた。

考察　放射線抵抗性腫瘍である腺様囊胞癌に対する放射線治療は、通常分割照射のみでは局所制御が充分に得られない可能性があるが、本次報告ではサイバーナイフによる低分割定位照射の併用により良好な局所一次効果が確認され、有害事象も許容できると考えられた。今後は長期の腫瘍制御および晩期有害事象の評価が必要と考えられた。