Salvage Re-irradiation with Intensity-modulated Radiotherapy, Chemotherapy Combined with Hyperthermia for Local Recurrence of Nasopharyngeal Carcinoma After Chemoradiotherapy

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Abstract: A sufficient dose of radiation is difficult to administer in re-irradiation for local recurrence of cancer after radiotherapy because of the dose limitation to organs at risk. Re-irradiation cases also include radioresistant tumors that are difficult to control locally, and their prognosis is poor in general. The effect of re-irradiation using intensity-modulated radiotherapy (IMRT) has recently been reported to significantly reduce the dose to organs at risk, and the efficacy of hyperthermia has been reported for radioresistant tumors. We report a case of local recurrence after concurrent chemoradiotherapy treated with salvage re-irradiation using IMRT and chemotherapy combined with hyperthermia in a patient with nasopharyngeal carcinoma, and include a discussion of the literature.

Keywords: nasopharyngeal cancer, radiotherapy, re-irradiation, hyperthermia, IMRT.

Introduction

Local recurrence of nasopharyngeal carcinoma after concurrent chemoradiotherapy (CCRT) occurs in 10–20% of cases and is often unresectable, although salvage resection is sometimes considered [1, 2]. Re-irradiation using high-precision irradiation such as intensity-modulated radiation therapy (IMRT) and stereotactic irradiation has been demonstrated to achieve salvage in recent years [3, 4], but a sufficient dose is usually difficult to administer in re-irradiation owing to dose constraints in organs at risk, and local control is difficult to achieve owing to the radioresistant nature of some tumors [5].

Hyperthermia has a cell-killing effect by denaturing proteins and altering intracellular metabolism. Many biological studies have shown that hyperthermia sensitizes the antitumor effects of radiotherapy and anticancer drugs [6]. The higher thermosensitivity of cancer cells has been shown in radioresistant cellular environments. Its therapeutic effect is highly temperature dependent, and synergistic effects can be obtained by combining heating of at least 41°C with radiotherapy [6].

In this report, we describe a patient with local recurrence after CCRT for nasopharyngeal carcinoma who was treated with a combined therapy of salvage re-irradiation with IMRT, chemotherapy, and local hyperthermia.
Case

Our case was a man in his forties who had visited a neurosurgeon with a complaint of diplopia that he had been experiencing for 2 years and 3 months before he was referred to us for salvage re-irradiation therapy. Left abducens nerve palsy was observed. A tumor on the left side of the nasopharynx and single lymph node metastasis in the left level IIb region were found in endoscopic and contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) examinations. The initial size of the metastatic lymph node was 1.8 cm. Non-keratinizing squamous cell carcinoma was detected in an endoscopic biopsy. The patient was diagnosed as having a cT4N1M0 stage IV nasopharyngeal carcinoma (Union for International Cancer Control TNM Classification of Malignant Tumours, 8th Edition [7]).

Three cycles of TPS therapy (docetaxel: 70 mg/m², cisplatin: 70 mg/m², and S-1: 100 mg/body) were administered as induction chemotherapy. Minor tumor shrinkage (stable disease [SD]) was observed in contrast-enhanced MRI (Figure 1), and CCRT had been performed 1 year and 10 months previously. We performed radiotherapy using the simultaneous integrated boost (SIB) method of IMRT. The primary and metastatic lymph nodes were treated with 70 Gy/35 Fr, and levels Ib to VI, including the retropharyngeal region, were treated with 56 Gy/35 Fr. For chemotherapy, cisplatin 80 mg was administered every 3 weeks for 3 cycles (Figure 2). The acute toxicities assessed by Common terminology criteria for adverse events (CTCAE) version 5.0 [8] were pharyngeal mucositis (grade 2) and dermatitis (grade 1), which improved in about 3 weeks. A Response evaluation criteria in solid tumours (RECIST) evaluation of the contrast-enhanced CT 1 year and 8 months before salvage re-irradiation therapy had revealed tumor reduction (partial response [PR]), and [18F]-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography 1 year and 6 months prior had revealed no increase or sign of FDG uptake (Figure 3), which was judged to be equivalent to complete response [CR].

Local recurrence in the nasopharyngeal mucosa was detected on endoscopy three months before the patient visited us (Figure 4). Endoscopic resection of the tumor was performed as a salvage procedure, and grade 2 hearing loss in the left ear occurred because the left Eustachian tube also had to be resected. Pathological examination of the resected specimen revealed a non-keratinized squamous cell carcinoma that was positive for deep surgical margins, negative for p16, and posi-

Figure 1. Magnetic resonance images (gadolinium contrast-enhanced fat-saturated T1-weighted images). A: at initial diagnosis B: After 2 cycles of induction chemotherapy (gadolinium contrast-enhanced threedimensional spoiled gradient-recalled echo image). These were showing the primary tumor (yellow arrows)
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A recurrent tumor invasion of the clivus was detected on contrast-enhanced MRI and FDG-PET 3 months after the endoscopic resection (Figure 5). No other recurrence or distant metastasis was found, and the patient was diagnosed as having rT3 N0 M0 carcinoma. Concurrent CCRT with re-irradiation and hyperthermia were performed as a salvage treatment. Re-irradiation was performed with IMRT using the SIB method, with irradiation of the recurrent tumor at the clivus with 60 Gy/30 Fr, and with 45 Gy/30 Fr at the tumor bed where the endoscopic resection had been performed (Figure 6). Chemotherapy consisted of weekly administration of 40-mg carboplatin during the re-irradiation period. Hyperthermia was administered a total of 7 times during the re-irradiation period by external heating using an 8-MHz capacitively coupled device immediately after the IMRT, for 50 minutes each time, maintaining the oral temperature in the 42°C range and administering at the highest power possible (600–700 W, 0.4–0.5 A).

Tumor response (PR) was observed in the MRI 2 months after the completion of re-irradiation (Figure 5). Tumor shrinkage was still detected in the CT images obtained 8 months after the completion of the re-irradiation, and no side effects were observed. A feeling of obstruction in the left ear was observed 1 year after the re-irradiation. A tumor growth on the left side of the nasopharynx that was revealed in endoscopy and CT was biopsied and diagnosed as a local re-

Figure 2. Dose distribution of the primary tumor for initial intensity-modulated radiation therapy. The prescribed target dose and doses to the organs at risk were as follows: planning target volume (PTV)-primary: D95 70 Gy, Dmean 74 Gy; PTV-prophylactic area: D95 51 Gy, Dmean 59 Gy; parotid gland: Dmean 29 Gy; optic nerve: Dmax 50 Gy; brainstem: Dmax 70 Gy, Dmean 39 Gy; jawbone: Dmax 64 Gy, Dmean 41 Gy; inner ear: Dmean 42 Gy. Isodose lines: magenta, 70 Gy; yellow, 60 Gy; purple, 50 Gy; dark green, 40 Gy.

Figure 4. Endoscopic image at the time of local recurrence. It was showing a recurrent tumor on the left wall of the nasopharynx.
The patient was treated with nivolumab, but a CT scan taken after 15 courses (7 months) of the nivolumab therapy showed progression of the disease. Administration of S-1 (tegafur, gimeracil, oteracil, and potassium) was started, but was terminated after one cycle owing to the appearance of drug rash. The anti-cancer drug was changed to docetaxel, and the patient is still currently undergoing treatment. Twenty-six months have passed since the completion of re-irradiation, and no late effects of the re-irradiation have been observed.

**Figure 5. Magnetic resonance images.** (A: T1-weighted image, B: gadolinium contrast-enhanced fat-saturated T1-weighted image) 2 months after endoscopic mucosal resection, showing a recurrent lesion infiltrating the clivus (yellow arrows). (C: T1-weighted image, D: gadolinium contrast-enhanced fat-saturated T1-weighted image) At 2 months after completion of re-irradiation, showing partial response.

**Discussion**

To the best of our knowledge, this is the first report on the combined treatment of salvage re-irradiation using IMRT, chemotherapy, and hyperthermia for local recurrence of nasopharyngeal carcinoma after CCRT. In local recurrence of nasopharyngeal carcinoma after CCRT, local re-recurrence occurs in approximately 60% of patients after salvage resection [1]. Although chemotherapy improves the prognosis, it is still worse than that with local treatments such as salvage surgery and re-irradiation [9, 10]. A retrospective study of
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319 cases of nasopharyngeal carcinoma with local recurrence showed that the 3-year overall survival rate of patients with localized recurrence was 74%, which was better than that of patients with other head and neck cancers [9]. That study also revealed that, even with the addition of salvage treatment such as resection and re-irradiation, the overall survival rate improved only in the patients with rT1-T2, and did not improve in the patients with rT3 or higher because of the possibility of difficulty in administering a curative radiation dose and the high incidence of adverse events. According to other reports, 5-year local control and overall survival rate of re-irradiation therapy for locally advanced (rT3-4) nasopharyngeal cancer remain poor, at 23–40% and 28–37%, respectively [11–13]. A report of 239 locally recurrent nasopharyngeal carcinoma patients treated with re-irradiation showed that the patients with rT3-4 had significantly more late toxicities than patients with rT1-2 [14]. These previous reports indicate that rT3 cases require improved treatment outcomes, and we suggest that local control is difficult to achieve with re-irradiation therapy alone; that is why we performed a combined treatment of IMRT-based re-irradiation with hyperthermia and chemotherapy. The feasibility of this combined treatment was demonstrated in this case report.

The 2018 Edition of the Japanese Clinical Practice Guidelines for Head and Neck Cancer recommends irradiation with ≥60 Gy for salvage re-irradiation in cases of recurrence as a treatment option [3, 15]. Severe late toxicity of grade 3 or higher has been reported in approximately 20% of patients [5, 9]. Adverse events related to the optic chiasm, optic nerve, brainstem, carotid artery, parotid gland, pharyngeal mucosa, temporomandibular joint, and retina are problematic because of the anatomical location of the nasopharyngeal carcinoma. Careful patient selection and dose reduction by IMRT for these risk organs are important. Although the recurrent lesion in this case was rT3 with skull invasion, the dose to the optic nerve, brainstem, and parotid gland could be reduced by using IMRT, and a curative dose of 60 Gy/30 fractions could be administered without serious side effects.

In general, cases of recurrence in the irradiation field after CCRT are likely to be biologically resistant to treatment. An irradiation dose of 60 Gy/30 fractions alone is therefore unlikely to be sufficient for head and neck cancer [5]. In a meta-analysis of randomized controlled trials on head and neck cancer, the addition of hyperthermia to radiotherapy was shown to significantly improve the local control rate by approximately 20% [16]. As mentioned in the Introduction, hyperthermia has a therapeutic potential for treatment-refractory cases. A meta-analysis of five randomized controlled trials for local recurrence of breast cancer revealed that the addition of hyperthermia to re-irradiation significantly improved the CR rate from 31% to 57% [17]. In the present case, although the prognosis was expected to be poor because of the lesion extending to the base of the skull (rT3), local control was achieved for 1 year after re-irradiation with IMRT combined with hyperthermia. No late adverse events due to the radiotherapy were observed for 26 months after the treatment.

Figure 6. Dose distribution in the recurrent tumor for re-irradiation using intensity-modulated radiotherapy. The prescribed target dose and doses to organs at risk for the initial IMRT were as follows: PTV-recurrent tumor, D95 49 Gy, Dmean 61 Gy; PTV-tumor bed where endoscopic resection was performed, D95 40 Gy, Dmean 47 Gy; left optic nerve, Dmax 2 Gy; brain stem, Dmax 27 Gy; parotid gland, Dmean 5 Gy; jawbone, Dmax 24 Gy, Dmean 11 Gy. Isodose lines: magenta, 60 Gy; yellow, 50 Gy; purple, 40 Gy. IMRT: Intensity-modulated radiation therapy, PTV: Planning target volume.
combined treatment, including the re-irradiation. The performance of hyperthermia at a favorable temperature of 42°C may have contributed to the improvement of the treatment outcome. Although sufficient follow-up for late effects is necessary, further accumulation of therapeutic results is expected to show the benefit of the combined treatment of CCRT with hyperthermia and re-irradiation using IMRT in cases of recurrence after CCRT for nasopharyngeal cancer.

Since the pathology of the biopsied recurrent specimen in our case showed a high expression of PD-L1 (>95%), immune checkpoint inhibitors of the nivolumab were administrated for 7 months after the relapse from the combined treatment. In a multinational phase II study to evaluate the antitumor activity of nivolumab in patients with multiply pretreated recurrent or metastatic nasopharyngeal carcinoma, the 1-year overall survival rate was 59% and 1-year progression-free survival rate was 19.3% [18]. There was no statistical difference between patients with PD-L1-negative versus PD-L1-positive tumors in terms of overall survival or progression-free survival [18]. The activation of anti-tumor immunity by radiotherapy has become well known recently, and synergistic use of immune checkpoint inhibitors and radiotherapy has the potential to improve survival [19]. Activation of anti-tumor immunity via heat shock proteins by hyperthermia has also been suggested in recent preclinical data [20]. The development of the combination therapy of re-irradiation therapy, hyperthermia, and immune checkpoint inhibitors is expected to be useful in the treatment of recurrent nasopharyngeal carcinoma.

In conclusion, we report a case of local recurrence of nasopharyngeal carcinoma that responded to combined CCRT and hyperthermia with re-irradiation using IMRT, and demonstrated the feasibility of hyperthermia in combination with re-irradiation using IMRT and chemotherapy in a case of rT3. Further accumulation of cases is expected to evaluate the efficacy and safety of this combined treatment.

Conflict of Interest

Author Takayuki OHGURI received a scholarship donation from Yamamoto Vinita Co., Ltd., Osaka, Japan.

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