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Case Report

Long-Term Survival after Stereotactic Radiotherapy Combined with Immunotherapy in a Patient with Recurrent Oral Cancer

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Keywords
Squamous cell carcinoma · Stereotactic radiotherapy · Immunotherapy · Head and neck cancer

Abstract
Introduction: Recurrent oral squamous cell carcinoma (SCC) poses significant challenges in treatment, requiring a multifaceted approach for effective management. ***Case Presentation:*** We present the case of a 68-year-old patient with a history of keratonizing SCC of the mandibular gingiva, treated with surgical resection, adjuvant radiotherapy (RT) to a total dose of 60 Gy in 30 fractions and 6 cycles of concurrent chemotherapy. After 6 years of follow-up, the patient experienced a local late recurrence in clinical stage rT4N0M0 requiring palliative chemotherapy (6 cycles of PF regimen). Due to progression, nivolumab-based immunotherapy was administered. After the 11th cycle of immunotherapy, high-dose re-irradiation (18 Gy in 3 fractions) was applied due to subsequent progression. The addition of stereotactic RT to the immunotherapy allowed nivolumab to be continued until cycle 64, ensuring long-term disease stabilization with acceptable tolerability. Consecutive palliative chemotherapy included paclitaxel and methotrexate. ***Conclusion:*** This case highlights the complex management of recurrent oral SCC, emphasizing the role of combining stereotactic RT with nivolumab in prolonging the administration of immunotherapy.

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Introduction

Among the leading global neoplasms, head and neck cancer (HNC) ranks in the top ten, with a prominent concentration in the oral cavity [1]. Squamous cell carcinoma (SCC) located on the floor of the mouth accounts for the majority of cases in this area. Primary risk factors include tobacco smoking, alcohol consumption, and human papillomavirus infection. The primary treatment option is surgical resection of the tumor with adequate margins. Adjuvant management in advanced cases includes radiotherapy (RT) or chemoradiotherapy (CRT) [2]. In cases of unresectable recurrence, palliative immunotherapy or chemotherapy can be applied. Schemes based on pembrolizumab or nivolumab are preferred immunotherapy regimens [3–5]. Moreover, personalizing treatment by adding stereotactic RT to immunotherapy after progression on immunotherapy alone may be an effective option for maintaining long-term local control. In this paper, we present a patient with oral cancer who received radical treatment and, after the diagnosis of unresectable local late recurrence, underwent immunotherapy with a stereotactic body radiation therapy (SBRT) was implemented with good results.

Case Report

A 68-year-old patient presented with several weeks of oral pain and a tumor on the left side of the mandibular gingiva. The biopsy revealed keratonizing SCC. The surgical resection of the tumor with reconstruction with free fibular flap and left-side lymphadenectomy including Ia–III groups was performed. Histopathological examination showed complete resection of SCC G2 with two close 2 mm margins and one metastatic lymph node without extracapsular extension. The pathological stage was determined as pT2N1. Due to the close margins and intermediate grade presented in the histopathological report, the patient was qualified for adjuvant CRT. Conventional RT was given to the tumor bed and ipsilateral regional lymph nodes (Ia–IV groups on the left side of the neck) with a total dose of 60 Gy in 30 fractions, using the IMRT technique. Radiotherapy was performed using a linear accelerator (Artista, Siemens, Pinnacle planning system) with a nominal photon energy of 6 MV. The dose analysis of conventional RT is presented in Table 1, and the dose distribution is shown in Figure 1. Concurrently, 6 cycles of cisplatin (40 mg/m^2 every 7 days) were given due to close margins.

Magnetic resonance imaging (MRI) of the head and neck showed no evidence of locoregional recurrence 5 months after the treatment. The patient was followed for 5 years without any symptoms of cancer. In the sixth year of observation, the patient reported pain in the mouth. An exophytic tumor with ulceration was diagnosed over the transplanted flap on the left side of the oral cavity. Positron emission tomography and MRI of the head and neck revealed a 36 × 25 × 26 mm infiltration involving the left cheek and masticator space with two metastatic lymph nodes on the right side in group IB. The biopsy of the tumor showed the late recurrence of SCC G2. Based on imaging tests and flexible nasal endoscopy, the clinical stage was determined to be rT4N2cM0. The patient was presented to the Head and Neck Unit and was disqualified from surgical treatment due to a partial infiltration of the tumor into the masseter muscle and pterygoid muscle and the inability to reconstruct tissues. He was qualified for six cycles of palliative chemotherapy according to the PF regimen (cisplatin 100 mg/m^2 on day 1 and 5-fluorouracil 1,000 mg/m^2 continuous infusion over 24 h for 4 days, repeated every 21 days). Based on an MRI scan performed after three cycles, the infiltration and metastatic lymph nodes response were defined as stagnation and partial regression, respectively. One month after completion of the 6th cycle of chemotherapy, MRI revealed progression of the tumor to a size of 46 × 28 mm, and the patient was qualified for immunotherapy based on nivolumab-240 mg i.v. in 100 mL 0.9% NaCl every 2 weeks. After 6

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Table 1. Conventional RT – dose analysis

	D_{min}, Gy	D_{max}, Gy	D_{mean}, Gy
Brainstem	1.1	18.5	3.6
Spinal canal	0.6	41.3	18.7
Optic nerve left	1.1	1.3	1.2
Lens left	1.0	1.4	1.2
Optic nerve right	1.1	1.4	1.3
Lens right	1.2	1.5	1.3
Chiasm	1.3	1.5	1.4
Mandible	2.0	61.1	27.7
Parotid gland right	2.8	25.5	13.5
Parotid gland left	2.9	62.7	22.8
Thyroid	12.3	61.2	36.2
Eye right	0.6	1.9	1.3
Eye left	0.4	1.8	1.3
Larynx	12.3	60.8	34.9
CTV 60	32.0	65.4	60.5
Planning target volume 60	11.8	65.8	59.9

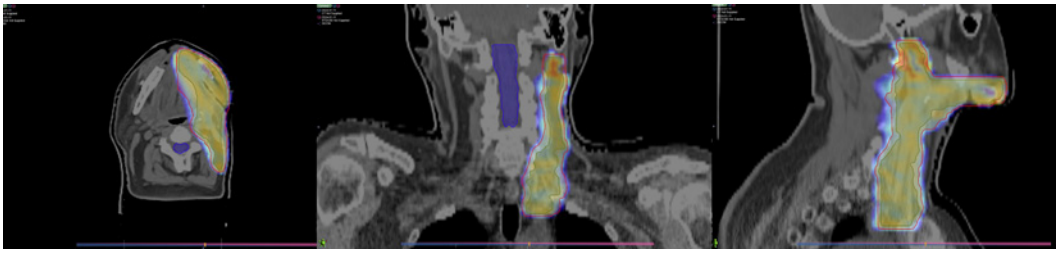

Fig. 1. Conventional RT. Dose distribution is shown on the CT scan.

cycles of immunotherapy, MRI revealed a 24% regression of the tumor (35 × 28 mm) and an increase in the apparent diffusion coefficient indicating a good response to the treatment. Enlarged lymph nodes in the neck were not visualized. After 11 cycles of immunotherapy, a further MRI showed the progression of tumor, measuring 63 × 39 mm with limited apparent diffusion coefficient. Additionally, the patient suffered from tumor bleeding and progressive trismus. In order to avoid discontinuation of immunotherapy, the patient was eligible for re-irradiation combined with immunotherapy, given the stimulation of the immune system and the antitumor response after high-dose stereotactic RT. SBRT was delivered to the gross tumor volume with a 3 mm margin to create a planning target volume. The treatment was provided over 6 days to a total dose of 18 Gy in 3 fractions with the use of a C-arm accelerator (Edge, Varian Medical Systems, Palo Alto, CA, USA). SBRT was based on a treatment plan made for three 6FFF arcs using the VMAT technique. The dose analysis of the stereotactic RT is presented in Table 2, and the dose distribution is shown in Figure 2.

The 12th cycle of nivolumab and the first fraction of RTH were administered on the same day. A percutaneous endoscopic gastrostomy was set on the last day of SBRT to ensure adequate nutrition. After the 14th cycle of nivolumab, an MRI revealed a partial response of the tumor

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Table 2. Stereotactic RT – dose analysis

	D_{min}, Gy	D_{max}, Gy	D_{mean}, Gy
Brainstem	0.1	3.5	0.8
Spinal canal	0.0	3.4	0.6
Optic nerve left	0.1	0.3	0.1
Lens left	0.0	0.2	0.1
Optic nerve right	0.1	0.2	0.2
Lens right	0.1	0.2	0.1
Chiasm	0.1	0.2	0.2
Mandible	0.4	19.6	8.7
Parotid gland right	0.8	4.5	1.9
Parotid gland left	5.6	19.1	11.7
Eye right	0.1	0.2	0.1
Eye left	0.0	0.3	0.1
Cochlea left	0.3	4.4	1.3
Cochlea right	0.3	3.3	1.4
Larynx	0.0	0.7	0.1
Brain	0.0	4.1	0.2
Planning target volume	14.0	20.2	18.6
Gross tumor volume	16.1	20.2	18.7

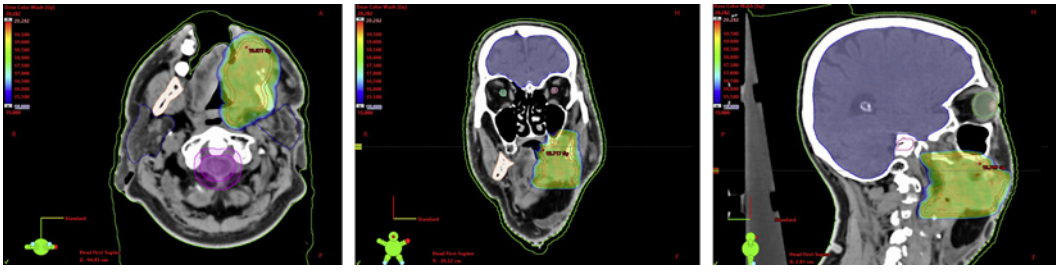

Fig. 2. Stereotactic RT. Dose distribution is shown on the CT scan.

(42 × 22 mm). Before the 15th cycle of immunotherapy, the laboratory tests revealed an increase in TSH level up to 18 mIU/L (0.35–4.94). Grade 2 hypothyroidism according to Common Terminology Criteria for Adverse Events (CTCAE v5.0) was diagnosed and after consultation with an endocrinologist, and levothyroxine (50 μg once daily) was administered. At the time of the 23rd cycle of nivolumab, the patient reported grade 2 (CTCAE v5.0) arthritis symptoms (interphalangeal joints of the right hand and both knees). Immunotherapy was withheld. After consultation with the rheumatologist, implementation of glucocorticosteroids (prednisolone 20 mg once daily initially) and the reduction of adverse events to grade 1, immunotherapy was resumed after the 8-week break. MRI performed after the 25th cycle of nivolumab showed a further reduction in infiltration to 17 × 10 mm. After the 64th cycle of immunotherapy, the patient developed a Clostridium Difficile infection, which was treated with vancomycin-based antibiotic therapy. One month later, an MRI showed progression. After consultation with the Head and Neck Unit, immunotherapy was stopped and the patient was qualified for paclitaxel-based chemotherapy (80 mg/m^2 every 7 days). After 21 cycles of paclitaxel, MRI showed further

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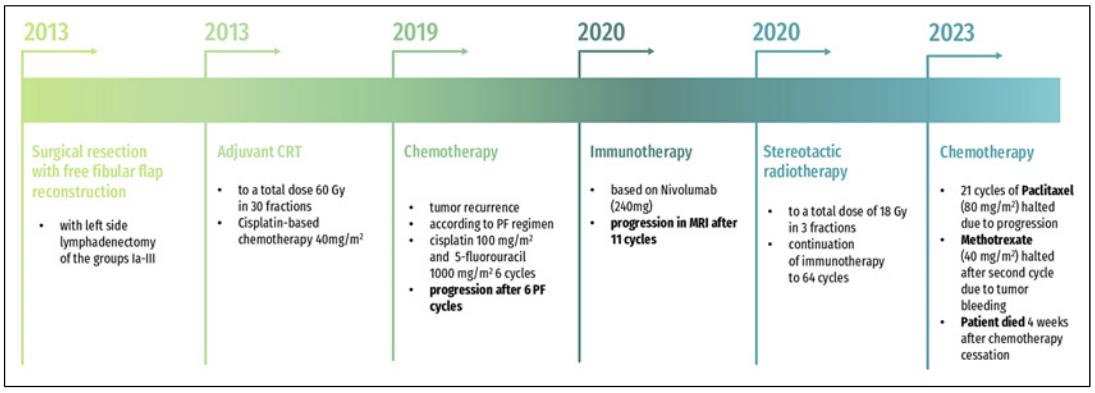

Fig. 3. Graphical timeline of the patient's treatment history.

progression. During this treatment, pneumonia developed and was successfully treated with a broad-spectrum antibiotic therapy. The case was readmitted at the Head and Neck Unit with recommendation for chemotherapy based on methotrexate (40 mg/m^2 every 7 days). The treatment was stopped after the second cycle due to bleeding from the tumor and the patient's deterioration. The patient died 4 weeks after the chemotherapy cessation. Figure 3 shows a graphical timeline of the patient's treatment history. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000542321).

Discussion

The primary treatment of oral cancer is surgery. Wide surgical excision followed by appropriate reconstruction should be the standard procedure. In advanced cases, adjuvant RT or CRT is indicated depending on the pathological report [6]. Numerous studies have confirmed the efficacy of applying a multimodal approach in oral cancer patients. Surgery followed by CRT not only improves treatment response rate but also prolongs overall survival [7, 8]. Due to the narrow surgical margin, our patient was treated with postoperative CRT which allowed him to survive for 5 years without cancer recurrence. More than half of patients with oral squamous cell carcinoma (OSCC) experience a recurrence. Tumor resection with adequate margins is the primary treatment option with the best survival outcomes after recurrence. However, prior surgery and RT can disrupt tumor barrier planes and alter anatomical orientation, making recurrent tumors potentially inoperable [9]. In this case, the inclusion of palliative chemotherapy, according to the PF regimen, is applicable. Andreasis et al. conducted a study to demonstrate the efficacy of chemotherapy, specifically the combination of cisplatin and 5-fluorouracil, in the treatment of advanced OSCC. The study included 44 patients aged between 33 and 75 years (with a median age of 60 years). Among them, 7 patients had stage III disease, and 37 had stage IV of the disease. Responders had a median survival of 15 months, while nonresponders had a median survival of 9 months [10]. Our patient received 6 cycles of palliative PF chemotherapy with good tolerability. Unfortunately, an MRI scan 1 month later showed progression. In patients who experience disease progression after platinum-based chemotherapy, the use of programmed death 1 antibody therapy may improve overall survival rates and induce durable responses in some patients [11]. Monoclonal antibodies – nivolumab and pembrolizumab – are commonly used in HNC patients. These anti-PD-1 immune checkpoint inhibitors are responsible for blocking the suppressive signaling pathway and

reactivating the antitumor response. Treatment based on immunotherapy creates a chance to improve overall survival; however, it can cause some adverse effects, including gastrointestinal, neurological, cutaneous, and endocrine toxicities [12–14]. Currently, in Poland, the standard of care for metastatic HNC patients with CPS (Combined Positive Score) >1 is immune therapy +/− chemotherapy or cetuximab with chemotherapy [3, 4, 15]. Ferris et al. [4] investigated the use of nivolumab in the treatment of advanced HNC in a randomized trial. 361 patients were randomized 2:1 to receive nivolumab (3 mg/kg every 2 weeks) or systemic therapy (methotrexate, docetaxel, or cetuximab). Median overall survival was 7.5 months in the nivolumab group compared with 5.1 months in the other group. Moreover, Japanese researchers evaluated the efficacy and safety of nivolumab (3 mg/kg every 2 weeks) versus investigator-selected therapy in 34 patients with platinum-resistant recurrent or metastatic head and neck SCC. Median survival was 9.5 months with nivolumab and 6.2 months with the other therapies. nivolumab showed better outcomes and treatment tolerability [16]. Furthermore, a limited number of clinical cases have been reported in the literature detailing complete responses to nivolumab therapy in OSCC [17]. Progression during immunotherapy is usually the final cause of treatment discontinuation. Implementation of high-dose re-irradiation may be an effective therapeutic option and enable continuation of the treatment with immunotherapy. Our patient received 64 cycles of immunotherapy with acceptable tolerability. The long-term efficacy of immunotherapy was made possible by the use of high-dose SBRT after the 11th treatment cycle. This advanced approach is supported by numerous studies. According to Runnels et al. [18], SBRT can enhance the efficacy of treatment through an immunomodulatory or immunostimulatory effect. Radiation therapy, especially when using higher fractional doses, enables the release of tumor-specific antigens that activate T lymphocytes and natural killer cells to identify and attack cancer cells throughout the body. Turkish researchers conducted a retrospective assessment of 15 patients diagnosed with metastatic or recurrent head and neck SCC. Each patient underwent SBRT at a dose of 3 × 8 Gy to all lesions concurrently with immunotherapy (nivolumab at 3 mg/kg every 14 days). After a 6-month follow-up, the overall survival rate reached 93%, with a progression-free survival rate of 86%. Remarkably, the local control rate at the SBRT-treated site was 96%. The superior survival and local control outcomes indicate a synergistic effect of SBRT combined with immunotherapy [19]. Moreover, a recent review by Australian researchers concludes that there is growing evidence, mostly retrospective, to support the use of SBRT in patients with metastatic SCC of the head and neck. However, no prospective, randomized trials have yet been conducted [20]. As a new therapeutic approach, particle therapy is a promising alternative to conventional photon RT. By using protons, it is possible to significantly reduce the physical dose delivered to surrounding healthy tissues during irradiation. Recent studies have demonstrated dosimetric benefits, mainly in terms of minimizing the total dose to organs at risk and noncritical normal tissues. However, it is crucial to determine whether the theoretical advantages of proton beam RT can be translated into quantifiable clinical benefits [21]. So far, there is a lack of specific studies in the literature. After 64 cycles of nivolumab, chemotherapy based initially on paclitaxel and then methotrexate was administered due to progression. Based on literature data, single-agent therapy has limited and short-term efficacy, which is undoubtedly due to tumor chemoresistance after the longstanding treatment process and poorer patient performance status [22, 23]. Oncological treatment should be a research-based approach in every situation. Nonetheless, individualization of treatment and combined therapy is beneficial in selected cases. Our experience on the grounds of presented oral cavity cancer and previously published laryngeal cancer [24] let us draw inferences that stereotactic RT should be considered to prolong the treatment time of immunotherapy. A simultaneous application of stereotactic RT with immunotherapy should be supported by a clinical trial comparing the tolerance and effectiveness of this method with alone immunotherapy.

Conclusions

The use of surgery followed by adjuvant CRT as primary treatment and chemotherapy in different regimens and immunotherapy especially combined with SBRT as a palliative approach can provide an increase in overall survival. Stereotactic RT can further enhance the therapeutic effect of nivolumab and allow continuation of immunotherapy with acceptable treatment-related toxicities.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization: P.P. and M.H.; methodology: P.P., M.H., and A.N.; resources: A.K., A.P., K.D.-R., and K.P.; writing – original draft preparation: P.P. and A.N.; writing – review and editing: M.H., A.K., A.P., K.D.-R., and K.P.; and supervision: K.S.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author. The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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