Case Report

Radiation-Induced Undifferentiated Spindle Cell Sarcoma Following High-Dose-Rate Interstitial Brachytherapy for Tongue Squamous Cell Carcinoma

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Abstract: High-dose-rate interstitial brachytherapy (HDR-ISBT) has recently come to be considered one of the most effective treatments for oral cancer. On the other hand, it is important to note that radiation therapy has some side effects. Especially, radiation-induced malignancy is probably the most serious complication affecting long-term survivors. We report a case of a radiation-induced undifferentiated spindle cell sarcoma that developed following HDR-ISBT for tongue squamous cell carcinoma (SCC). A 39-year-old woman with right tongue SCC underwent HDR-ISBT (60 Gy, 10 fractions, 8 days) treatment. Five years and one month later, a tumor had developed at the primary site. Surgery was performed for the tumor, which was histopathologically diagnosed as an undifferentiated spindle cell sarcoma. That was distinct from the squamous cell origin of the primary cancer. According to recently established criteria for radiation-induced malignancy, this case was classified as a radiation-induced sarcoma. A search of the literature revealed no previous report of radiation-induced malignancy following HDR-ISBT for tongue cancer.

Keywords: radiation-induced; sarcoma; brachytherapy; tongue

1. Introduction

Among oral cancers, tongue cancer is most prevalent, with histopathological findings showing squamous cell carcinoma (SCC) to be responsible for 90% of these cancers. While surgical resection is considered to be the standard treatment for tongue cancer [1], radiotherapy may be utilized in some cases because of its advantages regarding the preservation of function and morphology. Previous studies have noted three-year local control

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rates following interstitial brachytherapy (ISBT) for tongue cancer of 82–84% [2,3]. Both low-dose-rate ISBT (LDR-ISBT) and high-dose-rate ISBT (HDR-ISBT) are available. The advantages of LDR-ISBT include its simplicity, the low level of anesthesia required, and the low cost of the apparatus. Among its disadvantages are the fact that the operator cannot avoid being exposed to radiation, a shielded room is required for long-term patient irradiation, and the dose distribution cannot be changed. HDR-ISBT overcomes these disadvantages, with an irradiation time of only a few minutes, and it has recently come to be considered one of the most effective treatments for oral cancer [3]. It is important to note that radiation therapy has some side effects. Those occurring early during irradiation for oral cancer treatment include stomatitis and taste disorders, while the later side effects include soft-tissue ulcers and osteonecrosis [4]. However, radiation-induced malignancy is probably the most serious complication affecting long-term survivors [5]. There is no consensus definition of radiation-induced malignancy, but the most important point is to distinguish it from recurrence. Therefore, the minimum requirement for diagnosis is a long period between the initial treatment and the occurrence of a new malignancy, and recently presented criteria include a latency period of several years [6,7]. Furthermore, if a histopathological finding of a new malignancy is different from the previous initial cancer, it is considered to be a radiation-induced malignancy [8]. Several reports of radiation-induced malignancy due to external beam radiation have been presented [9], while there are few reported cases following brachytherapy [10]. A search of the literature revealed no previous report of radiation-induced malignancy following HDR-ISBT for tongue cancer. The purpose of this study is to document information of a patient with tongue SCC who was successfully treated with radiation therapy, but developed a radiation-induced undifferentiated spindle cell sarcoma of the tongue five years and one month later. Furthermore, a pseudotumor developed between the time of radiation exposure and the development of the undifferentiated spindle cell sarcoma.

2. Case

A 39-year-old woman visited our hospital with pain on the right side of her tongue. A clinical photograph showing a reddish irregular mass lesion in the right lateral border of tongue is presented in Figure 1, while T2-weighted MRI results showing a tumor sized 24 × 14 × 22 mm at the right lateral border of tongue (yellow arrows) are presented in Figure 2. Based on the biopsy and imaging results, the patient was diagnosed with SCC (cT3N0M0, Stage III). The patient underwent HDR-ISBT (60 Gy, 10 fractions, 10 flexible applicator tubes, double-plane) for 8 days, performed on the right side of the tongue (Figure 3).

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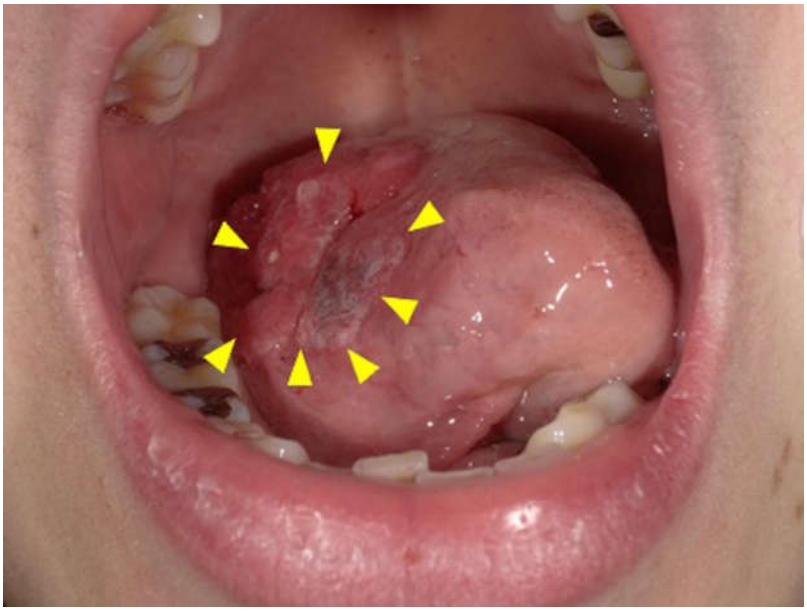

Figure 1. Pretreatment clinical photograph.

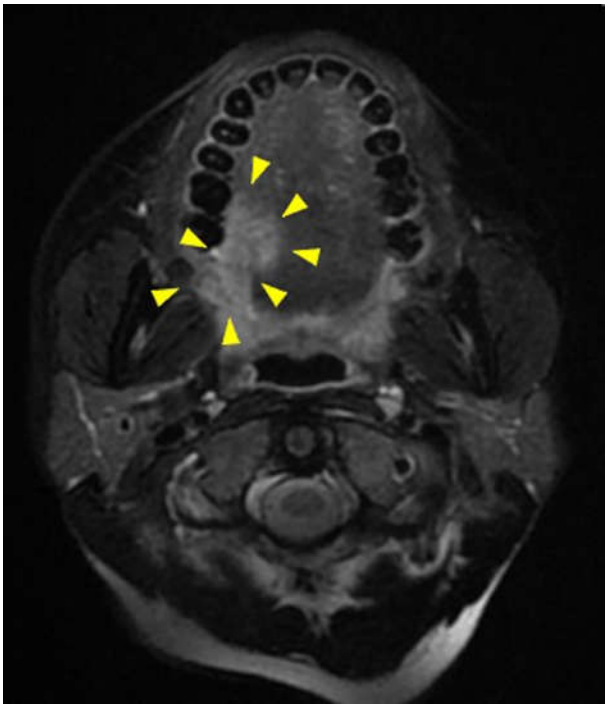

Figure 2. Pretreatment T2-weighted MR image.

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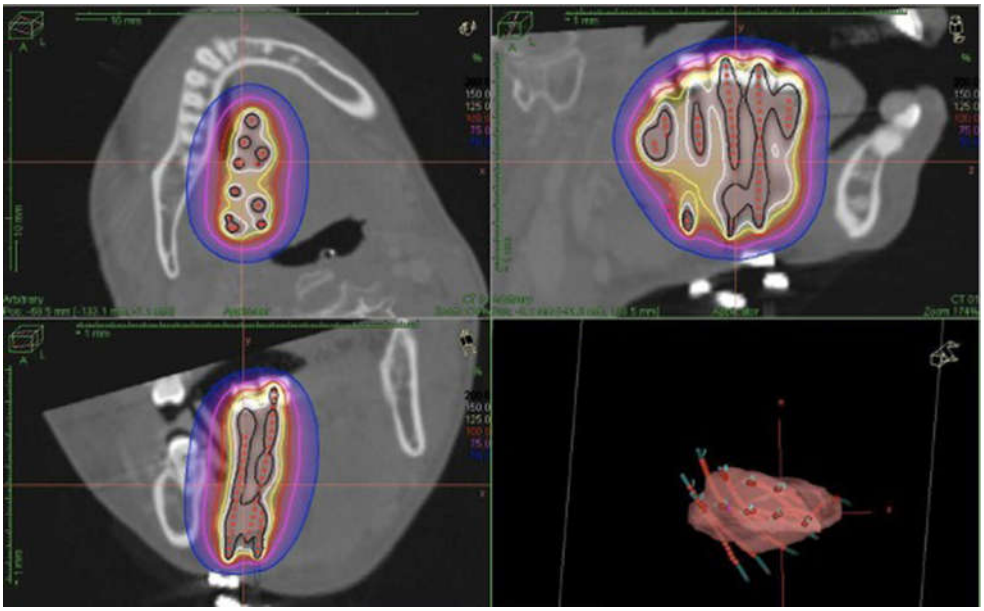

Figure 3. Dose-distribution diagram for high-dose-rate interstitial brachytherapy. Axial (top left), sagittal (top right) and coronal (bottom left) sections showing the dose distribution profile. A three-dimensional rendering image showing position of 10 flexible applicator tubes in relation to planning target volume (bottom right).

During follow-up, the patient noticed a mass lesion in the right side of the floor of the mouth three years and one month after the completion of therapy (Figure 4). An elevated lesion on the right side of the floor of the mouth was resected five months later, and based on the surgical specimen, it was histopathologically diagnosed as high-grade dysplasia of the mucosa with suspicion of reactive hyperplasia. The tumor consisted of spindle-shaped atypical cells without malignancy (Figure 5). It was thought that the tumor was a reactive granulation containing atypical stromal cells caused by radiation, since the patient had a history of radiation. The lesion was small and superficial, with no apparent invasion into deeper muscle layers, and the shape was outwardly protruding.

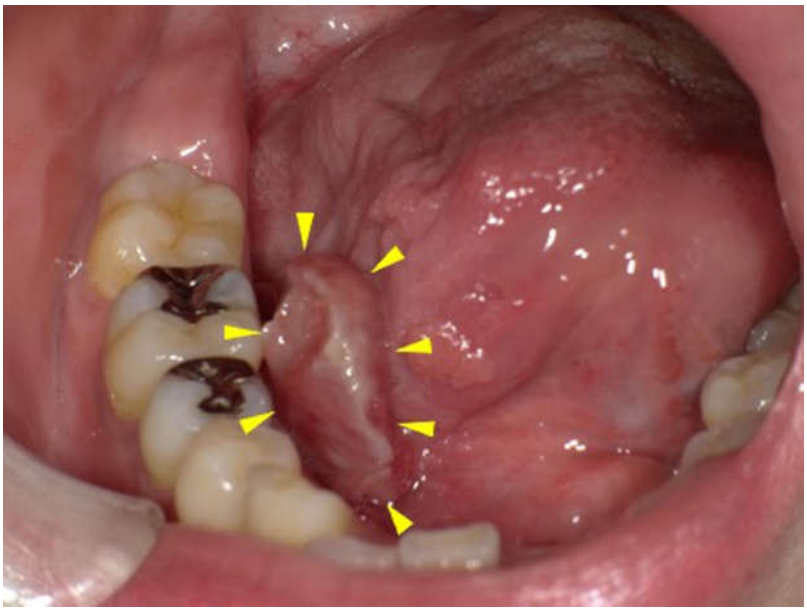

Figure 4. Clinical photograph three years one month after completion of radiation therapy.

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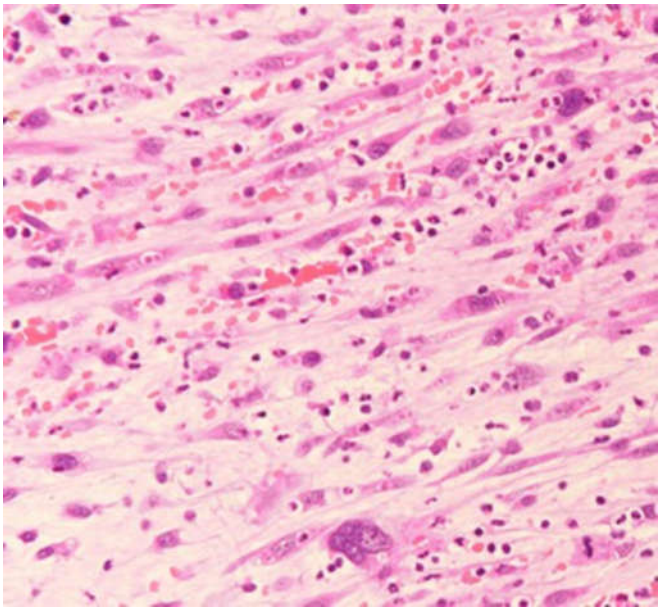

Figure 5. Histologic image. The mass shows spindle-shaped atypical cells with enlarged and densely stained nucleus proliferation, accompanied by neutrophil-dominated inflammatory cell infiltration (HE stain, x200).

After five years and one month of follow-up after the radiation therapy, regrowth of a lesion with induration on the right lateral border of tongue was observed (Figures 6 and 7). A total glossectomy, rectus abdominis muscle flap reconstruction, partial mandibulectomy, scapular reconstruction, and bilateral radical neck dissection were performed. The histopathological diagnosis was an undifferentiated spindle cell sarcoma (T4aN0M0) (Figure 8). One year and ten months after the surgery, there has been no obvious recurrence or metastasis (Figure 9).

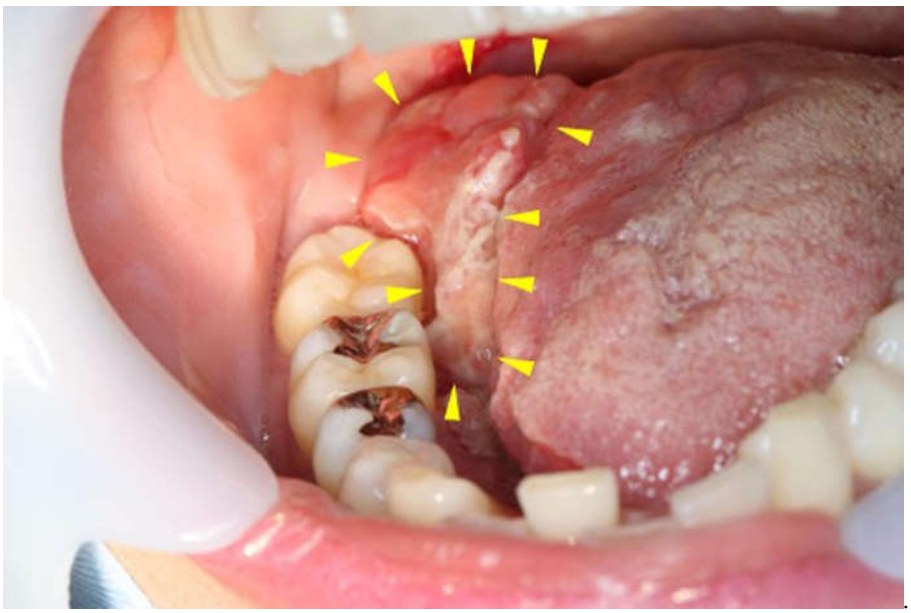

Figure 6. Clinical photograph obtained prior to second operation.

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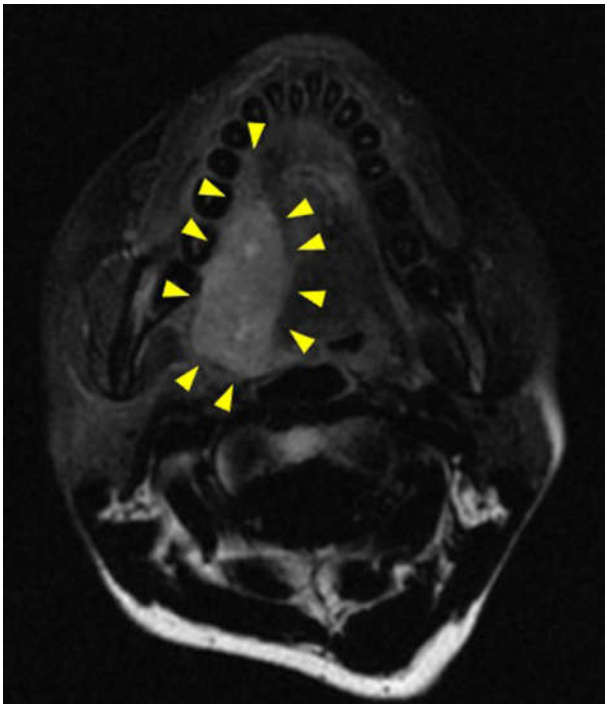

Figure 7. T2-weighted MR image obtained prior to second operation. The image results show lesion at the right lateral border of tongue measuring approximately 36 × 18 mm in diameter (yellow arrow). Comparisons with preoperative T2-weighted images show that the location of the current tumor was nearly the same as that of the primary tumor.

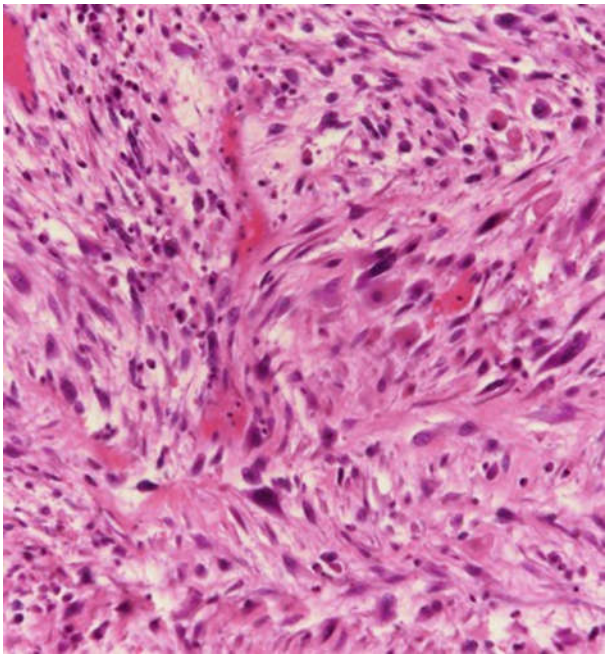

Figure 8. Histologic image. Cell density and dysplasia are high. The cells are spindle-shaped, though the sizes are different. Some cell nuclei are strongly stained and show differences in shape (HE stain, x200).

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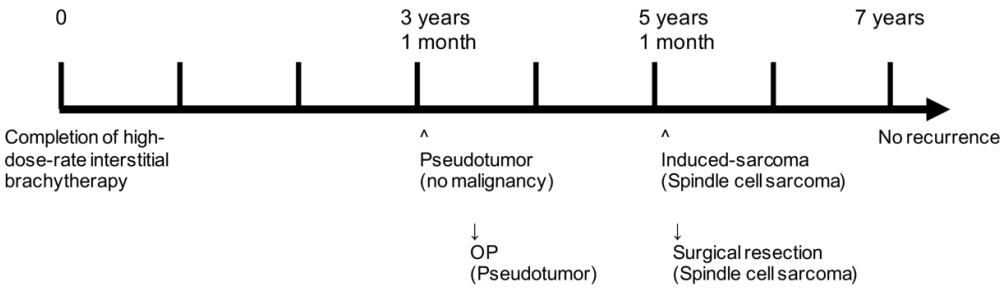

Figure 9. Summary of therapeutic course.

3. Discussions

According to criteria for radiation-induced malignancy presented by Sakai et al. [8], such induced cancer can be classified into three groups (A, B, and C) based on the histopathology, organ of origin, latency period, and irradiation field (Table 1). This classification is based on the definition of multiple primary malignancies presented by Warren and Gates [11].

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Table 1. Diagnostic reliability of radiation-induced malignancies according to Sakai et al. [8].

Confidence Factor		Criteria (Except for Leukemia)			
		Histopathological Type	Organ of Origin	Latency Period	Site of Origin
A (high)	1	Different	Different	>5 years	Within irradiated area
	2		Same		
B (medium)	1	Same	Different (non-continuous)		
	2		Different (continuous)		
C (low)	1	Same	Same (non-continuous)		
	2		Same (continuous)		

This definition is considered to be very reliable, as it includes histopathological findings. The present case was classified as having an A2 reliability level, with a latency period of five years, which is consistent with the definition put forward by Sakai et al. Other studies have adopted the criteria for osteosarcoma presented by Cahan et al. [12] (widely used for the diagnosis of a radiation-induced sarcoma) and described a latency period of two years [6,7]. In the present case, the latent period was five years and one month, which is also consistent with the definition. The patient's initial malignancy was a SCC. Following radiation therapy, a pseudotumor was detected with no evidence of malignancy. Considering that undifferentiated spindle cell sarcoma is a rare disease, it seems appropriate to conclude that it was induced by radiotherapy in the present patient.

A radiation-induced pseudotumor develops earlier than sarcoma, with a median latent period of 79 months [13]. Although both sarcoma and a pseudotumor can be induced by radiation, it remains unclear whether a pseudotumor represents the precursor stage of a sarcoma [14]. A literature review of radiation-induced sarcoma showed that the median age at diagnosis of radiation-induced sarcomas of the head and neck was 52 years (interquartile range: 21.5 years), with a mean latency between the initial RT treatment and diagnosis of 11.1 years (range: 1.3–38 years) noted in one study [5] and 11.5 years (range: 6–17 years) noted in another [9].

The rates of occurrence of radiation-induced sarcomas in the head and neck range from 0.14% to 1.8% in the analyzed cases, including reports of external beam radiation therapy and low-dose-rate interstitial brachytherapy [9,10,15]. The present case is the first reported instance of malignancy induced after HDR-ISBT in a patient treated at our hospital, and a search of the literature revealed no other report of radiation-induced malignancy development following that procedure. According to a retrospective study of radiation therapy for oral SCC, a radiation-induced pseudotumor is considered to be a rare complication, with a prevalence of only 0.02% [13].

4. Conclusions

We report here a case of a suspected radiation-induced malignancy occurring at the site of HDR-ISBT performed for tongue SCC.

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Institutional Review Board Statement: The local Ethics Committee of the Osaka University Graduate School of Dentistry does not require ethical approval for reporting this type of case, in view of the retrospective nature of the study and the fact that all of the procedures were performed as part of routine care. This study followed the principles of the Declaration of Helsinki.

Informed Consent Statement: Written informed consent was obtained from the patient for her anonymized information to be published in this article.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare that there is no conflict of interest.

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