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CASE REPORT

Clinicopathological study of malignant peripheral nerve sheath tumors in the head and neck: Case reports and review of literature

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Abstract

BACKGROUND

Malignant peripheral nerve sheath tumor (MPNST) is a rare and aggressive soft tissue sarcoma that poses a major diagnostic and therapeutic challenge.

CASE SUMMARY

We retrospectively reviewed patients with head and neck MPNSTs treated in our hospital from 2000 to 2021. The clinical features, pathological manifestations, treatments, and prognoses were summarized. We also reviewed the literature, focusing on MPNST in the mandible and maxilla. The study population consisted of five women and five men aged 22–75 years (mean age, 49 years). Of the 10

patients, 7 were initial cases and 3 were recurrent cases. All lesions were sporadic. The most common site was the mandible. The most frequently encountered symptoms were a progressive mass and local swelling. Complete or partial loss of trimethylation at lysine 27 of histone H3 (H3K27me3) was evident on staining in four of nine cases (one case was excluded due to lack of tissue for evaluation of loss of H3K27me3). The 2- and 5-year disease-specific survival rates were 86% and 43%, respectively. The average survival time was 64 mo.

CONCLUSION
MPNST is a highly malignant tumor with a poor prognosis, prone to a high risk of recurrence and distant metastasis. Complete surgical resection is the main treatment.

Key Words: Malignant peripheral nerve sheath tumor; Head and neck; Treatment; Intraosseous; Surgery; Case report

Core Tip: We retrospectively reviewed patients with head and neck malignant peripheral nerve sheath tumors treated in our hospital from 2000 to 2021. The study population consisted of five women and five men aged 22–75 years (mean age, 49 years). The 2- and 5-year disease-specific survival rates were 86% and 43%, respectively. The average survival time was 64 mo. Complete or partial loss of trimethylation at lysine 27 of histone H3 (H3K27me3) was evident on staining in four of nine cases (one case was excluded due to lack of tissue for evaluation of loss of H3K27me3).

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INTRODUCTION

Malignant peripheral nerve sheath tumor (MPNST) is an uncommon and aggressive tumor that arises from the cells of peripheral nerve sheaths. The most common anatomical sites are the trunk, extremities, and retroperitoneum. The head and neck region accounts for only 2%–9% of cases[1,2]. The clinical presentation of head and neck MPNST includes a rapidly enlarging mass, radicular pain or paresthesia, and neurological defects that depend on the anatomical sites involved[1]. Almost half of all cases are caused by defects in the neurofibromatosis type 1 gene located on chromosome 17; fewer than 10% of cases are radiation-induced (post-radiation sarcomas); the rest are sporadic cases of unknown etiology[3,4]. Histologically, MPNST is a spindle cell sarcoma arising from peripheral nerves, and varies in terms of nerve sheath differentiation; MPNST has been considered as a neurogenic sarcoma, neurofibrosarcoma, malignant schwannoma [1,5]. Most MPNSTs exhibit a tightly packed, stripe-like proliferation of spindle cells, which often complicate the diagnosis for pathologists. It is difficult to differentiate MPNSTs from other spindle cell sarcomas. The level of S-100 expression ranges from 50% to 70%, and is usually focal. In general, more primitive tumors are also more malignant, and are associated with low levels of S-100. Recent studies found that various components of polycomb repressive complex 2 (PRC2) are inactivated in most MPNSTs. Homozygous PRC2 inactivation leads to loss of H3K27me3 (as revealed by immunohistochemical analysis), which may be a new immunohistochemistry marker for MPNST[6-9].

MPNST is a high-grade malignant tumor with a high recurrence rate. The local recurrence rate is almost 50%, and 33% of patients develop bone and lung metastases[1,10]. Similar to most soft tissue sarcomas, wide excision is the main treatment; the utility of adjuvant radiotherapy and chemotherapy remains controversial[1]. In line with the high malignancy, the 5-year overall survival rate is only 20%-51%[3,11,12].

Here, we report on 10 MPNST cases, including 4 in the mandible and one in the maxilla, treated at our institution over a 20-year period. Immunohistochemical evaluation of H3K27me3 was conducted. We also review the literature with a focus on intraosseous MPNST in mandible and maxilla.

CASE PRESENTATION

Chief complaints

Case 1: A 62-year-old woman was referred to our hospital with a chief complaint of pigmented gingival lesions of the left anterior maxilla.

Case 2: A 28-year-old woman had a 6-mo history of a left mandibular gingival mass.

History of present illness

Case 1: The pathological diagnosis was an oral melanotic macule with increased melanocyte activity (Figure 1A). Two years later, clinical examination revealed a mild asymptomatic swelling on the anterior maxilla and two swollen lymph nodes on each side of the neck.

Case 2: The mandibular mass was located in the region of the 1st premolar to 1st molar teeth. The cortex of the buccal side was not continuous and the soft tissues of the cheek and tongue side were thickened.

Personal and family history

Case 1 and Case 2: Personal *and* family history denies the family history of genetic disease.

Laboratory examinations

Case 1 and Cases 2: Laboratory examinations reveal nothing abnormal.

Imaging examinations

Case 1: Computed tomography (CT) revealed a soft tissue mass in the anterior maxilla involving the surgical defect in the incisor region (Figure 1B).

Case 2: CT revealed a poorly-defined lytic lesion in the left mandible.

Clinicopathological characteristics

The clinical characteristics of the 10 patients are presented in Table 1; there were 7 *de novo* cases and 3 recurrences. No patient had a history of NF1 syndrome or radiotherapy before the first consultation. There were five male and five female patients, ranging in age from 22 to 75 years (mean age = 49 years). The mandible was the most common anatomical site. Other locations included the maxilla, gingiva, infratemporal fossa, and palate. The tumor size ranged from 1.5 to 4.5 cm (mean size = 2.9 cm). The most common initial symptoms were a progressive mass and local swelling (10/10 cases), sometimes accompanied by peripheral nerve symptoms including local pain or numbness (4/10 cases).

Morphologically, the tumors were composed predominantly of relatively monomorphic spindle cells arranged in intersecting long fascicles. The lesional cells exhibited hyperchromatic ovoid nuclei, with inconspicuous nucleoli and scant cytoplasm. MPNST is generally considered to be a high-grade sarcoma; in line with this, the mitosis score was relatively high in the current study. Large cells exhibiting obvious pleomorphism, or multinucleated giant cells, were found in three cases. Three other cases had areas of epithelial differentiation (Figure 2A-C). All cases evaluated with S100 staining were positive or focal positive, and melanotic markers such as HMB-45 and Melan-A were negative. H3K27me3 staining was evaluated immunohistochemically in the nine surgical cases; one of these (11.1%) exhibited complete H3K27me3 loss, while three (33.3%) showed partial loss (Figure 2D-F).

Nine of the ten patients were initially treated *via* wide excision; the other patient was prescribed chemotherapy because the tumor was too large to excise. Follow-up information was available for seven patients, who were followed-up for 13–216 mo (mean follow-up = 64 mo). Of these patients, four received both adjuvant radiotherapy and chemotherapy; the remaining patient received radiotherapy only after surgery. Two patients developed local recurrence, and four distant metastasis, within 2 years. Four patients died, while three patients remain under follow-up and are free from disease after 24, 28 and 74 mo, respectively. The 2 and 5-year disease-specific survival (DSS) rates were 86% and 43%, respectively.

FINAL DIAGNOSIS

Case 1 and Cases 2: Biopsies were used to diagnose MPNST.

TREATMENT

Case 1: The patient then underwent partial maxillectomy and radical neck dissection.

Case 2: The patient underwent wide mandibular resection and radical neck dissection, followed by adjuvant radiotherapy and chemotherapy.

OUTCOME AND FOLLOW-UP

Case 1: Two years later, CT performed during regular follow-up revealed multiple pulmonary nodules; further examination confirmed lung and bone metastases.

Cases 2: The patient has remained disease-free for 2 years.

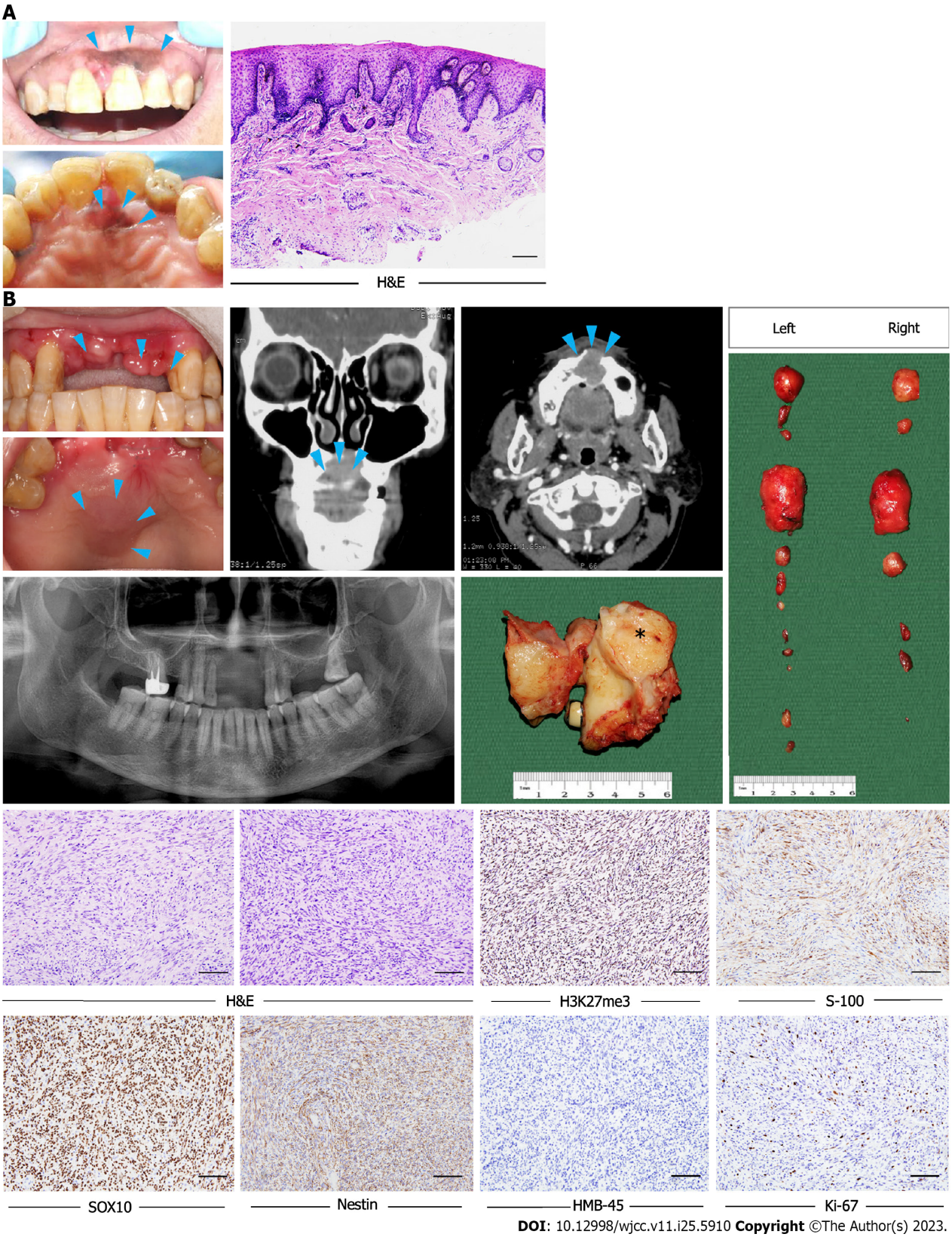

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Figure 1 Clinicopathological characteristics of the patient in case 1. A: Clinical and pathological presentations of the patient during the first visit to our hospital. A macular brown to black lesion was on the anterior maxillary gingiva and incisive foramen region (arrows). Histopathological image revealed the lesion was black macule; B: Clinicopathological presentations of the patient during the second visit to our hospital. A multinodular mass was noted on the anterior maxillary gingiva, and a local swelling was on the anterior to median portion of the palate. Coronal head computed tomography scan shows soft tissue masses in the front of the upper jaw with unclear boundary. The masses involved the post-surgical defect in the incisor region and there was lytic destruction of the underlying bone (arrows). Enlarged lymph nodes and the gross specimen of the lesion after the surgery. H&E characteristics of the case confirmed the diagnosis was malignant peripheral nerve sheath tumor. Tumor cells show partial loss of H3K27me3 and positive stain for S-100, SOX10, nestin, and negative stain for HMB-45. The Ki-67

index is about 10%. Scale bar: 250 μm (A), 50 μm (B).

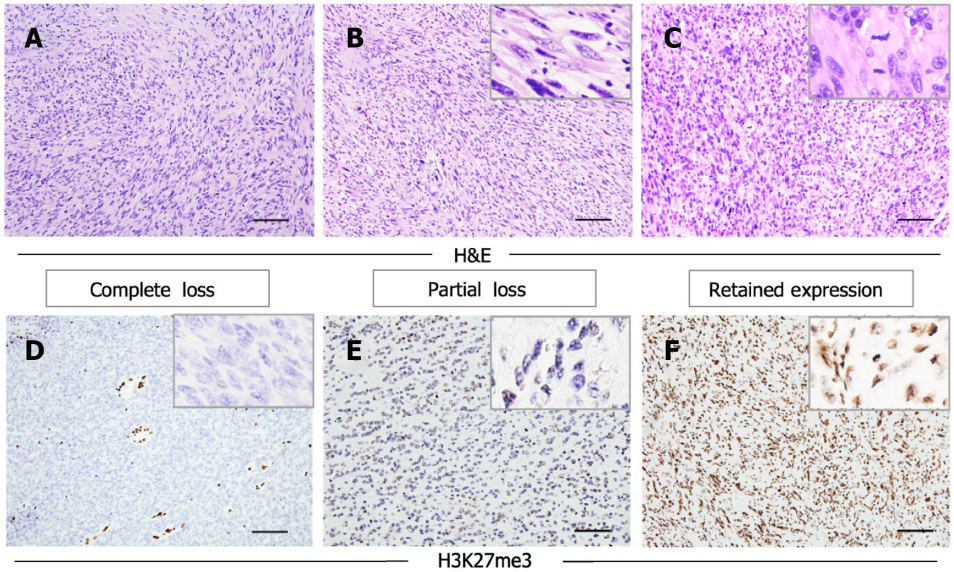

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Figure 2 Histological characteristics of malignant peripheral nerve sheath tumor (MPNST) and immunohistochemical analysis of H3K27me3 in MPNST sections. A: The lesion cells display predominantly spindle in an architectural pattern; B: The cells are enlongated and tends to be hyperchromatic with scant cytoplasm; C: There is severe cytologic atypia and nuclear pleomorphism, with focally brisk mitotic activity; D: Complete loss of H3K27me3 expression on sections. Staining of blood vessels and inflammatory cells is the internal positive controls; E: Partial loss of H3K27me3 expression on the section; F: Strong expression of H3K27me3 is retained in some MPNST cases. Scale bars: 50 μm.

DISCUSSION

MPNST is an infiltrating and aggressive tumor of neural origin[13]. Although head and neck MPNSTs are histologically similar to MPNSTs in other regions, there are important clinical differences. Patel *et al*[3] performed a comparative analysis based on the SEER database. The mean age of head and neck MPNST patients was 49.1 years, compared to 46.1 years for patients with MPNSTs in other regions. The former group showed a male predilection (60.2%) while a sex predilection for females (54.2%) in the latter group. Also, the average tumor size of the former group was smaller than in the latter group. The mean age and average tumor size of our patients are consistent with these observations, but we observed no gender differences. This may reflect regional differences among our relatively small sample. MPNSTs develop sporadically, rather than in association with NF-1, in the head and neck region. Ma *et al*[2] reported that 69.8% (30/43) of MPNSTs were sporadic[14]. None of our cases had a history of NF1 syndrome or malignant transformation after radiotherapy, suggesting that they were all sporadic.

Previous studies found that primary intraosseous MPNST was rare[15]. We report four cases in the mandible and one case in the maxilla in this study; our review of the English language literature revealed 48 cases of primary intraosseous MPNST including 27 such cases in the mandible and 21 such cases in the maxilla. In the mandible, Ma *et al*[2] reported five patients, of whom three suffered recurrences. The other 22 cases were single cases; the clinical data of these cases, and our four cases, are shown in Supplementary Table 1[15-26]. Among the 26 patients, there were 19 women and 7 men, ranging in age from 4.5 to 76 years [mean age = 33 years (data were unavailable for three patients)]. One patient had a history of NF1 syndrome, and seventeen did not (data were unavailable for five patients). In the maxilla, Ma *et al*[2] reported 12 patients, of whom seven suffered recurrences. The other 9 cases were single cases; the clinical data of these cases, and our case, are shown in Table 2[19,27-34]. Among the 10 patients, there were 5 women and 5 men, ranging in age from 12 to 65 years (mean age = 44 years). Two patients had a history of NF1 syndrome, and six did not (data were unavailable for two patients). These datas revealed that MPNST in the mandible was more common in women than men, and there were no differences in the maxilla. Most of the patients had no history of NF1 syndrome in both mandible and maxilliary.

Given the lack of unique histological criteria and a specific immunoprofile, diagnosing MPNST can be very challenging. Some tumors have morphological features that overlap with those of MPNST, including fibrosarcomas and leiomyosarcomas; differential diagnosis is therefore essential. Fibrosarcomas have a simple structure, and are rich in collagen and S-100-negative onimmunohistochemistry. Leiomyosarcoma cells exhibit vacuoles around nuclei; the lesions develop in tissues and organs rich in smooth muscle, and stain positively for desmin and smooth muscle actin. When epithelioid cells predominate, MPSNT must be distinguished from malignant melanoma and epithelioid sarcoma. The lesion site of malignant melanoma is more superficial than that of MPSNT; moreover, the cell morphology is more irregular, and the nucleus is larger and more intenselystained. Melanomas stain positively for HMB45 and Melan-A.

Table 2 A review of malignant peripheral nerve sheath tumor cases arising in the maxilla

Ref.	Patients (*n*)	Sex	Age	Treatment	Follow-up (mon)	Recurrence	NF association
Kameyama *et al*[27], 1987	1	F	61	/	/	/	No
Urade *et al*[28], 1990	1	F	47	S+R+C	22	Died of disease	No
Che *et al*[19], 2006	1	F	13	R	/	/	No
Patil *et al*[29], 2007	1	M	45	/	/	/	No
Janardhanan *et al*[30], 2011	1	M	40	S	/	Died of disease	Yes
Ali *et al*[31], 2011	1	M	50	R	8	No	/
Tamgadge *et al*[32], 2014	1	M	65	/	/	/	No
Neetha *et al*[33], 2004	1	F	12	R	/	/	/
Muraki *et al*[34], 1999	1	M	43	R+C	20	Died of disease	Yes
Present study	1	F	62	S+R+C	28	Yes	No

S: Surgery; R: Radiotherapy; C: Chemotherapy; NF: Nuclear factor.

Epithelioid sarcomas are typical granulomas with many collagen fibers, and stain negatively for neuron-specific enolase.

Recent studies have shown that loss of H3K27me3, as revealed by immunohistochemical staining, was described in MPNST.The complete loss rate ranges from 34% to 84%[9,35-42]. Among our patients, 11.1% (n = 1) of the MPNST cases showed complete loss of H3K27me3, while 33.3% (n = 3) showed partial loss. Thus, the H3K27me3 Loss rate was lower than reported previously, perhaps reflecting differences among histological subgroups. Lyskjaer *et al*[43] found that 76% of MPNSTs with classical histological features had lost H3K27me3, compared to only 23% of MPNSTs with heterologous elements or low-grade components. The complete loss rate of the epithelioid MPNST subtype was 0%.

Patel *et al*[3] reported that the 5-year head and neck MPNST DSS rate was 65.1%, based on analysis of the SEER database. Similar studies from single institutions reported 5-year DSS rates of 30% and 20%, and a 2-year DSS rate of 21% [14,44]. In our study, the 2- and 5-year DSS rates were 86% and 43%, respectively. Local recurrence and distant metastasis exerted a major influence on DSS. In our study, 43% (3/7) of patients developed local recurrence; two of these patients died and the other one was lost to follow-up. In total, 57% (4/7) of the patients developed distant metastases and 75% died. Both of the patients without local recurrence or distant metastasis are still alive. Other studies revealed that tumor size, stage, and surgical resection significantly influenced DSS[1,2].

Radical surgical resection is the mainstay of MPNST treatment[44,45]. In our study, 9 of 10 patients underwent wide excision; in the remaining case, the tumor was too large to excise. Adjuvant therapies, such as radiotherapy and chemotherapy, are now prescribed for MPNST patients. Some studies have suggested that radiation should be routine to improve survival and decrease the risk of recurrence[44,46]. Chemotherapy has been prescribed for those with large or recurrent tumors, but any role for chemotherapy as an MPNST treatment remains controversial[2]. In our study, both radiation and chemotherapy were prescribed for four patients, and radiation only for one. As our study included a relatively small number of cases, larger series are needed to validate the results.

CONCLUSION

In summary, MPNST is an uncommon and aggressive soft tissue sarcomas and the head and neck MPNST is extremely rare. Clinical and pathological characteristics of MPNST are not significant. The patients are with poor prognoses and associated with a high risk of recurrence and distant metastasis. Complete surgical resection is the main treatment.

Table 1 Clinicopathological characteristics of malignant peripheral nerve sheath tumor arising in the head and neck

Case	Sex/age	Location	Size (cm)	Treatment	Recurrence (site)	Survival	Follow-up (months)	H3K27Me3
1	F/62	Anterior maxilla	2.5	S+R+C	DR (lung, bone)	Yes	28	Positive
2	F/28	Left mandible	3	S+R+C	NR	Yes	24	Positive
3	M/22	Right submandibular region	2.5	S	/	/	/	Complete loss
4	M/74	Gingival and the left cheek and left temporal	2.5	S	/	/	/	Positive
5	F/48	Mandible	3	S+R+C	LR, DR (lung)	No	70	Positive
6	M/40	Left facial and upper left gingiva	3	S+R	LR, DR (trunk, brain)	No	216	Partial loss
7	F/40	Right mandible	3	S	/	/	/	Partial loss
8	F/44	The left inferior temporal fossa	4.5	R+C	NR	No	13	Partial loss
9	M/58	Right palat	1.5	S	NR	Yes	74	/
10	M/75	Mandibular gingival	3	S	DR (lung, lymph node)	No	24	Positive

S: Surgery; R: Radiotherapy; C: Chemotherapy; LR: Local recurrence; DR: Distant recurrence; NR: No recurrence.

FOOTNOTES

Author contributions: Li L and Ma XK contributed equally to this work; Zhang R, Li L, Ma XK, Wang DC, Gao Y designed the research study; Jing Y, Dong RF performed the research; Li L, Ma XK, Zhang R analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

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