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REVIEW

# Oral Malignant Peripheral Nerve Sheath Tumors: A Systematic Review of the Case Reports

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## Abstract

Malignant peripheral nerve sheath tumors (MPNST) originated from cells of the peripheral nerve sheath. These tumors account for 5% of all soft tissue sarcomas. MPNST are extemely rare in the oral and maxillofacial region. Oral Malignant peripheral nerve sheath tumors (OMPNST) arise denovo or from neurofibromatosis type I. d. OMPNST usually presents with a progressive swelling which may be painful.The mean age in patients is about 40 to 46 years. The most common sites OMPNST is the mandible, lips, and buccal mucosa. Radiographic examination of intraosseous tumors reveal irregular destruction of the surrounding bone. Definitive diagnosis of OMPNST is confirmed on the basis of findings histopathological and immunohistochemical evaluation. The prognosis OMPNSTS is poor and to treat by radical surgical excision, radiation therapy and chemotherapy. This systematic review aimed to determine the most significant influential factors in OMPNSTS and evaluate the diagnostic and therapeutic methods in this regard.

**Keywords:** Peripheral nerve sheath- sarcomas- maxillofacial- neurofibromatosis

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## Introduction

MPNST, also known as malignant schwannma, neurofibrosarcoma and neurogenic sarcoma are rare soft tissue sarcoma that account about 3% to 10% of all sarcomas [1-4]. Almost 50% of MPNSTs occurs in patients with neurofibromatosis type 1 (von recklinghausen's disease) but it can arise denovo or be associated with radiation exposure [5, 6]. MPNST originate from schwann cells and nerve sheath cell that are very rare in the maxillofacial region [7-9]. Its incidence in the oral region is extremely rare, about 0,001%. Oral malignant peripheral nerve sheath tumor (OMPNST) are very rare and usually presents with progressive swelling which may be painful [10-12]. OMPNST may occur anywhere, but the most common sites are the mandible, lips, and buccal mucosa [13-14]. The mean age in patients with MPNST is between 40 and 46 years for sporadic cases and 29–36 years for NF1 associated cases. No gender predilection there is not for this disease [15-18].

Radiographically, intraosseous tumors of the mandible reveal widening of the mandibular canal or the mental foramen, with or without irregular destruction of the surrounding bone [2, 3, 19-21].

Microscopically, OMPNST shows proliferation of malignant spindle-shaped cells arranged in the form of fascicles, which often resemble the cells of fibrosarcomaan [5, 6-8]. These cells are irregular in shape with wavy or comma-shaped nuclei. also fascicles may be present in less cellular myxoid areas [2, 6-22]. In some of the tumors may formed heterologous elements such as skeletal muscle differentiation (malignant Triton tumor), cartilage, bone, or glandular structures [1, 3, 4, 23, 24].

Immunohistochemical examinations are usually performed to confirmed final diagnosis of the lesion. Anti-S100 protein is the most important antibody identifying OMPNST [7, 9, 10, 25]. These lesions have a poor prognosis, and the first- treatment line involves Surgical resection of the tumor [10, 11, 26]. Radiotherapy and chemotherapy is also recommended as an adjuvant treatment [27-28]. MPNST tendency to recurrance and metastasize, especially to the lungs [25-27]. This systematic review aimed to address the following questions:

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• What are the most influential factors in the occurrence of intraoral OMPNST?

• What are the most common symptoms and complications associated with OMPNST?

• What are the most effective methods in diagnosing and treating OMPNST

## Materials and Methods

This systematic review aimed to investigate the published articles focusing on oral malignant peripheral nerve sheath tumor through searching in databases such as PubMed and Google Scholar. Initially, all the published articles during 1961–2018 with related abstracts were assessed by one researcher. Literature search was conducted using keywords such as oral, malignant schwannoma, malignant peripheral nerve sheath tumor and neurofibrosarcoma. Selected articles were published in English and Persian, and duplicate reports were excluded from the study. In this study, we only reviewed case reports of OMPNST. Among other excluded studies were articles published in other language, previous reviews, meta-analyses, expert opinions, consensus statements, original articles, editorials, letters, and qualitative studies. Furthermore, studies performed on other types of OMPNST were eliminated from this review. Initially, 826 articles were identified based on the title, 94 of which were selected after the close screening of the abstract. In total, 34articles were selected out of 94 related studies, and other excluded articles were as follows: 17 reviews articles, 43 head and neck MPNST articles and 4qualitative research. Eventually, 30case reports were systematically reviewed by the researchers. Required data were extracted by one researcher, and all the selected articles were reviewed in full text after screening. Moreover, the results obtained by each case report were studied in detail and evaluated based on the objectives of this study. In the present review, we focused on different variables including age, gender, location, and size of OMPNST, duration of disease, associated complications, and type of treatment and diagnosis. Among the reviewed cases of OMPNST, 13 patients were males and 19 were females. In addition, the mean age of the patients with OMPNST in different countries was 37.5 years (age range: 8 - 76 years). Out of 32articles, 8 were published in India, 2 cases were in Iran,3 cases were in Brazil , 3cases were in American and 5cases were reported in Japan. In general, several cases of OMPNST were reported in regions of Asia and Europe. With regard to the location of the tumor, 6 cases of OMPNST were reported to be on Tangue, 5were reported to be on maxilla , 7were reported to be on maxilla, 4were reported to be on parotid and 4were reported to be on inferior alveolar nerve . Other cases have been reported in other area such as palate , gingival, lower lip , mental and lingual nerve.

## Discussion

MPNSTs are a rare spindle cell sarcoma that originate from nerve sheath cells, Schwann cells, neurofibroma and neurilemmoma [29-30]. MPNST is an aggressive sarcoma that may arise denovo or about 5% to 42% in association with neurofibromatosis type I [25, 27, 31, 32]. The etiology of spontaneous MPNST is still unknown [4, 7, 8]. MPNST may occur anywhere in the body but only 8% to 16% of cases presenting in the maxillofacial region [10, 11, 13]. MPNST in the head and neck region typically involves eight cranial nerves and trigeminal nerve [15-19]. MPNST in the oral cavity is very rare and only a few cases have been reported in the literature. In OMPNST the mandible, lips and buccal mucosa is the most common locatin [12-15, 16-18-23]. While OMPNST is normally an enlarging mass that sometimes exhibits rapid growth and often produced symptoms of pain and paresthesia [5-7, 14]. If present in sof tissue the lesion present as firm elevation with indistinct margins and ulceration of the mucosa may or may not be occur [24-25-32-33]. When bone is involved , tumors present as radiolucencies with indistinct margins and may appear as a widening of the mandibular canal and dilatation of the mental foramen [22, 23, 25].

*Assessment of age, tumor size, and gender in patients with OMPNST*

The first case of OMPNST in the maxilla was reported by Shotton in 1988 [21], 10 previously reported cases of MPNST occurred in other location of body. Oral MPNST most frequently appear during the third to sixth decades of life, with no sex prediction [3, 4, 6, 9, 10]. According to the literature, the majority of the patients with oral MPNST were female and only 13 cases were male [12, 13, 15]. According to the results of the present review, patients with OMPNST were within the age range of 8–76 years [17, 19, 20, 28]. Generally, age distribution of patients OMPNST is variable [30, 32, 33]. Furthermore, findings of the current review indicated that mean age of the patients with OMPNST was 37.5 years, which could be affected by different variables such as the location of OMPNST [27, 28, 30-33]. The mean age in patients with neurofibromatosis type I (29 to 36 years) is about one decade younger than in those without his condition (40 to 46 years) [7, 8, 11, 13, 17]. In terms of tumor size, oral MPNST are normally smaller compared to MPNST despite their repid growth rate [18, 20, 22-24]. Size of OMPNST is approximately 1–4 cm, while they might be larger if located in the mediastinal and retroperitoneal regions in the reviewed cases, size of OMPNST ranged between 9 mm and 8 cm [25-27, 33]. In the current study, duration of the disease was found to be variable, ranging between 1 weeks and 45 months. As such, reported cases by K.W.Grdtz, et al. had the longest duration (45 months) compared to other studies [19]. The most diameter of the tumors was reported to be 9cm in the study bySoumyajiet al. and7cm × 6 cm × 4 cm in the study by Ozmen et al [8-9].

Table. 1 New Researches Base on RAS and BRAF in MPNST

| Authors/ Publication Year (Reference) | Country | Age | Gender | Location of Schwannoma | Size | Duration of Disease | Reported Complications | Type of Treatment | Follow-up | Diagnostic modalities (histopathological findings) |
|---|---|---|---|---|---|---|---|---|---|---|
| Monika Probstet al. 2018 [1] | Berlin, Germany | 58 | male | Inferior alveolar nerve | 1 cm | 1 year | Pain in the lower jaw and in the right lower lip and chin region. With numness, pain, and mild swelling | Radical surgical manage-ment is the treatment of choice | 1year | The latter especially exhibited an inhomogeneous expression of S-100, which can be found in nerve sheath tumors but also in malignant melanomas. Analysis for CD45, CKpan, HMB45,melan-A, and tyrosinase as well as for BRAF mutation was negative. |
| Soumyajit Roy MDa, et al. 2017 [2] | India | 30 year | male | MPNST of the tongue | 9-10 cm | 24 months | hypoglossal nerve palsy (the tongue was deviated to right side and fasciculation was noted over the right half of the tongue) | He underwent surgery followed by adjuvant chemotherapy with ifosfamide and epirubicin | | Incisional biopsy showed a malignant spindle cell tumor in the sub-epithelial connective tissue. The tumor cells were immune-positive for S-100 |
| José Alcides Arruda, et al. 2016 [3] | Brazil | 16 years | female | peripheral nerve sheath tumor of the maxilla | 2 . 5 × 1.0 cm | A few months | pain involving the upper left incisors region | surgical excision of the upper left lateral incisor as well as the total removal of the remaining lesion and adjuvant chemotherapy. | years 9 | positive for S-100 protein and glialfibrillary acidic protein showed that the lesion was an intraosseous malignant peripheral nerve sheath tumor of the maxilla. malignant neoplasm fragments consisting of fusiform cells with comma-shaped nuclei. |
| Sumit Majumdar, et al. 201 [4] | India | 25 year | female | MPNST of the mandible | 3× 3 cm | 3 months | pain in her lower right back tooth | a minor surgical procedure during which extraction of involved tooth and incisional biopsy from the lesional site were performed | still under follow-up | Immunohistological (IHC) studies were conducted to confirm the neural origin by S-100 and Neuron Sp cific Enolase (NSE). The section was strongly positive for S-100 and NSE [Table/Fig-7,8]. Wide excision of the lesion with negative margins was done. The excision biopsy also suggested MPNST |
| Thiago Lucena do Amaral, DDS, et al 2016 [5] | Brazil | 67 year | male | Malignant peripheral nerve sheath tumor of the lower labial Mucosa. MPNST | 2× 1 cm | 4 months | painful swelling | SurgeryRadiotherapy Chemotherapy | 4 years | Immunohistochemical analysis of tumor cells revealed positivity for S-100 prtein, CD56, CD34, and neuron-specific enolase but was negative for neurofilament protein, glut-1, claudin-1, desmin, and smooth muscle actin. |
| Shilpa Patel, et al. 2015 [6] | India | 3 0 years | female | Malignant perip eral nerve sheath tumour (MPNST) of mandible | 8× 4 cm | 2 months | A tender swelling on the rightside of the mandible | Posterior segmental mandibule tomy was performed under general anaesthesia.Chemotherapy and radiotherapy. | The patient was then lost to follow-up. | a partially encapsulated lesion having a fasciculated growth pattern with alternate hypocellular and hypercellular areas. Immunohistochemical analysis showed intense and diffuse positivity for vimentin, S-100 and Bcl-2 |
| Sandhya Tamgadge et al.2014 [7] | Iran (Isfahan) | 65 year | male | Intraosseous malignant peripheral nerve sheath tumor of maxilla | 3× 5 cm | 9-10 months | a swelling and partial numbness of the upper left side of the jaw. mild, intermittent, dull aching pain along with a discomfort during the mastication | Surgery . | short term and long-term follow-up | Immunohistochemistry (IHC), Mesenchymal malignant spindle cellsshowing diffuse and intense positivitywith S-100, glial fibrillar acidic protein, Leu-7, myelin basic protein, neuron specific enolaseand neurofilament |

Continued Table 1. New Researches Base on RAS and BRAF in MPNST

| Authors/ Publication Year (Reference) | Country | Age | Gender | Location of Schwannoma | Size | Duration of Disease | Reported Complications | Type of Treatment | Follow-up | Diagnostic modalities (histopathological findings) |
|---|---|---|---|---|---|---|---|---|---|---|
| Ozmen ¨ Ozt¨urk1, et al. 2012 [8] | Turkey | 16 year | male | MPNST ,aMalignant Peripheral NerveSheath Tumor ofthe Oral Cavity | 7 × 6 × 4 cm | weeks 6 | a rapidly enlarging mass in the mouth causing severe dysphagia, mandibular and temporomandibular pain, and respiratory difficulty | Surgery | 8 months | A CT scanning showed a mass. Histopathology reveals malignant tissue composed of spindle cells arranges in cellular fascicles and a mixture of poorly defined cellular and cystic components expressing vimentin and S-100. Its features reveal a fusiformor globoidmass with necrosis, pseudocystic change, or hemorrhage |
| W. V. B. S. Ramalingam, MS et al. 2012 [9] | India | 22 year | male | MPNSTMalignant Peripheral Nerve Sheath Tumor of the Oral Cavity | 6×7 cm | 2 Months | a painless swelling on the right un-dersurface of tongue and diffuse swelling in the right submandibular. mild difficulty in swallowing, with no complaints of difficulty in breath-ing or a change in voice | surgery and was treated with 6 cycles of chemotherapy with gemcitabine and docetaxel as a palliative measure. | 3 month | Indirect laryngoscopy showed a smooth swelling in the right base of the tongue and vallecula pushing the epiglottis posteriorly. tomographic (CT) scan showed a large, soft tissue density mass in the oropharynx. Immunohistochemistry of the specimen was positive for S100. vimentin and negative for creatine kinase, Epithelial Membrane Antigen (EMA), desmin, and CD34 |
| MJ Ashraf et al. 2010 [10] | Iran Shiraz | 67 year | female | Malignant peripheral nerve sheath tumor of the tongue | 4 × 3 cm | 1 week | complaining of swelling in the tongue | The patient underwent hemiglossectomy. surgery | 8 months | Among these markers, only positive vimentin and weakly focal positivity for S100 and NSE were observed, which was in favor of the neurogenic origin of this tumor. |
| Venkatesh G. Naikmasur, MDS, et al. 2009 [11] | India | 2 8 - year | female | anterior mandible | 8×10 cm | 1 month | swelling in the anterior mandibular | Radical surgery. Surgical removal remains the mainstay of treatment. Adjuvant radiation therapy may improve local control | 1 year | Histologic evaluation of the biopsy specimen under light microscopy showed a highly cellular neoplastic tissue composed of large compactly arranged spindleand fusiform-shaped cells. The tumor was focally reactive to S-100 Immunohistochemistry is useful in confirming neural differentiation. 10 S-100 immunoreactivity is seen in 50%- 90% of MPNSTs |
| Hemalatha AL et al 2006 [12] | India | 3 5 year | female | MPNST Malignant peripheral nerve sheath tumor in oral cavity | 4× 5 × 5 mm | one year | Swelling in tongue | . surgery | 1 year | Histopathological examination of the excised mass showed features of spindle cell sarcoma following which a provisional diagnosis of MPNST was offered Immunohistochemistry confirmed neural origin of the tumour |
| Neetha MC et al 2004 [13] | India | 12 year | female | Malignant peripheral nerve sheath tumor of the maxilla | | 2 months | with a swelling of left cheek region Intraorally, the swelling extended buccally and palatally from premolar to tuberosity region. Swelling was fixed and firm to hard in consistency. | Surgery. | 8 months | histological features were suggestive of malignant peripheral nerve sheath tumor of the maxilla. |
| Jacqueline A. James et al. 2003 [14] | Manchester, United Kingdom | 2 8 year | female | MPNSTLow-grade malignant Triton tumor of the oral cavity.in the buccal vestibule adjacent to the maxillary left premolars | 1.5× 5 ×5 mm | Month 2 | an enlarging, painless swelling in the premolar region of the left maxillary vestibule. | surgery | 5 months | Immunohistochemistry demonstrated diffuse positivity of the spindle cells for S100 protein. The large pleomorphic cells showed weak positivity for -sarcomeric actin and myoglobin .The same cells were variably but strongly positive for desmin |

Continued Table 1. New Researches Base on RAS and BRAF in MPNST

| Authors/ Publication Year (Reference) | Country | Age | Gender | Location of Schwannoma | Size | Duration of Disease | Reported Complications | Type of Treatment | Follow-up | Diagnostic modalities (histopathological findings). |
|---|---|---|---|---|---|---|---|---|---|---|
| Marianne Dcerbo,et al 1992 [18] | American | 13 year | female | Malignant Schwannoma of the Palate: | 1.5 cm | 3 months | with a chief complaint of a sore in the roof of her mouth | Surgery radiotherapy. | 7 Years | been shown to be positive for the S- 100 marker, fibrosarcoma, leiomyosarcoma, and sarcomatoid undifferentiated carcinoma do not contain this protein |
| M.ohnishi et al 1992 [19] | Japan | 8 year | male | Extensive malignant schwannoma of the mandibular nerve | 2×3 × 1 cm | a few days | with limited upward movement of his upper left eyelid | Surgery Chemotherapy | Years 5 | The radiographs showed an expanded mandibular canal and expanded foramen ovale Immunoperoxidase staining for the neural crest marker S-100 protein was positive, whereas NSE was negative. The tumor was diagnosed as malignant schwannoma. |
| Skorek A et al. 2000 [20] | korea | 12 year | female | Malignant parotid salivary gland peripheral nerve sheath tu-mour in a | 2× 2 × 1 cm | 1 months | painless swelling | Chemotherapy | 2 year | Immunohistochemical studies showed positive staining of tumour cells for vimentin and focally for S-100 protein. |
| K. W. Grdtz, et al. 1991 [21] | Switzerland | 62 year | male | Malignant melanotic schwannoma of the oral cavity | 4 × 3 cm | 3 years and 9 months | The right submandibular lymph nodes were enlarged on palpation. There were no sensory deficits. to feel weak and complained about constipation | surgery The patient died 2 months later. | 1 year | Iron stains for hemosiderin and alcian blue and PAS were negative. There was only focal but intense nuclear cytopla min reactibility of tumor cells (pigmented and not pigmented) for S-100 protein. This was particularly marked in the "low-grade" parts of the neoplasm. Staining for vimentin was not very strong but diffusely positive |
| Kardos TB et al. 1990 [22] | New Zealand | 32 years | | aggressive, peripheral nerve-sheath tumour that presented as a lump on the alveolar mucosa near the mental foramen | 2 × 3 cm | 4 months | Painful swelling | surgery. | 8 months | Immunohistochemical studies showed positive staining of tumour cells for vimentin and focally for S-100 protein |
| J. C. SHOTTON, et al 1988 [23] | British Asian woman, | 26 years | female | The malignant Triton tu-mour maxilla | 6×4 cm | 3 months | pain in that area | Radiotherapy Chemotherapy Surgery | 1 year | .Immunocytochemistry was also used to confirm coexistant neural and muscular tissue. An SlOO test which is used to confirm the presence of neural or neural crest origin protein was positive and a stain for desmin, a muscle protein |
| M. B. Guglielmotti, et al 1987 [25] | Argentina | 18 years | male | Malignant schwannoma of the gingiva | 2× 1.6 cm | 6 months | painless swelling | Surgery under local anesthesia | 2 years | The tumoral mass was highly cellular, comprising plump spindle-shaped cells usually with elongated cytoplasmatic processes, with nuclear hyperchromatism, pleomorpbism and a large number of mitosis.The final histologic diagnosis was malignant peripheral neurogenic tumor. |
| Kanemitsu Siiirasuna ,et al. 1986 [26] | Japan | 76 years | female | in the mandible extending from the left 2nd molar to the right premolar region | 5.0 × 3.3 × 4.5 cm | 3 months | painless swelling on the mandible | treatment, the ptient was observed periodically.The surgical wound healed without evdence of residual of recurent lesion in the area of excision 12 months after the operation. | 8 months | radiographic findings, a provisional diagnosis of odontogenic tumor was made. the cells were significantly positive for S-IOO protein. Intermediate sized filaments, including keratin, virnentin,and desmin were not detected in the tumor immunohistochemicall |

Continued Table 1. New Researches Base on RAS and BRAF in MPNST

| Authors/ Publication Year (Reference) | Country | Age | Gender | Location of Schwan-noma | Size | Duration of Disease | Reported Complications | Type of Treatment | Follow -up | Diagnostic modalities (histopathological findings) |
|---|---|---|---|---|---|---|---|---|---|---|
| Hammond HL 1969 [32] | United States | 58 years | female | Malignant peripheral nerve sheath tumors of the oral cavity | 4 × 3 × 7 cm | 8 months | pain in the right shoulder, a biopsy of a mass in the right scapular area cough, lowgrade fever, and pharyngitis | thyroidectomy was performed Treatment with radioactive Iodine treated with cobalt-60 irradiation The discharge diagnoses mere (1 j metastntie malignant schwannoma and (2) metastatir.follicular carcinoma of the thyroid. | 2 weeks | The overlying spithelium exhibited some hyperkeratosis, spongiosis, and moderate irregularity and hyperplasia of the basal-cell layer Reticulum stains (Wilder's) revealed a pattern of nodular and fascicle-like formations which, on cross section, somewhat simulated the appearance of nerve fasciculi. The reticulum fibers in some areas were arranged in a parallel fashion; in others, they surrounded individual cells or cell clusters |
| Shun-Ichi Imamura et al.2002 [34] | JAPAN | 64 year | male | in his right subauricular space. tumor was a parotid gland neoplasm invading the parapharyngeal space. | 4× 5 cm | 2 weeks | first noticed rapid swelling and pain in his right. right facial palsy | a combination of chemotherapy and a total ra-diation was given instead of surgical treatment | Three months the patient died | Immunohistochemical staining for vimentin showed strong intracytoplasmic staining of the tumor cells. Nerve cell adhesion molecule was moderately positive in many tumor cells. Immunostaining for Leu7, CD68,and epithelial membrane antigen was partially positive in the tumor cells. Only very weak . No staining was noted for desmin, cytokeratin cocktail CK22, S-lOO protein, glial fibrillary acidic protein, or CD34. Strong expression of p53 protein was noted in the tumor cells. We counted Ki67 labeling indices in more than half of the tumor cells.. |
| M. S. Kenali,* ,et al. 1999 [35] | Australia | 29 years | male | MPNSTof the tongue M LIGNANT PERIPHERAL NERVE SHEATH TUMOUR OF THE TONGUE | 8.5 ×5 × 6 cm | 12 months | a rightsided painless tongue mass which had slowly grown over the previous 12 months. He had no other symptoms. | Radiotherapy surgery | 1 year | tumours are strongly and diffusely positive for S-100 protein |
| Anace´lia Mendes Fernandes,et al. 2005 [36] | Brazil | 37 year | male | MPNST of the tongue | 2 × 2 cm | 5 months | complaining of swelling in the tongue with an evolution of one week. The intraoral physical exam showed a painful, ulcerated, exophitic | surgery | seventeen months | Immunohistochemical reactions were performed with streptavidine–biotin protocol. The neoplasic cells were S-100 positive Ki-67 showed to be positive in a few cells |
| Zhongmin Che, ,et al. 2006 [37] | Korea | 10 years | female | in the Jaws | 3× 3× 3 cm | 3 months | Facial disfigurement due to the bulging of the right lower face was also noted. A physical examination revealed multiple cafe-au-lait spots in her neck, back, and axilla | After an incisional biopsy, surgical enucleations of the mandibular and maxillary lesion via intraoral approach were performed | 2 year | immunostaining for S-100 protein was negative on the follicle stroma. |

Continued Table 1. New Researches Base on RAS and BRAF in MPNST

| Authors/ Publication Year (Reference) | Country | Age | Gender | Location of Schwannoma | Size | Duration of Disease | Reported Complications | Type of Treatment | Follow-up | Diagnostic modalities (histopathological findings) |
|---|---|---|---|---|---|---|---|---|---|---|
| M. M. Elias ,et al. 2007 [38] | india | 41 years | female | Malignant schwannoma of the para-pharyngeal space in von Recklinghausen's disease | 4× 3× 3 cm | 2 months | with a massive malignant schwannoma in the parapharyngeal space | surgery | 1 year | Immunohistochemical studies showed positive staining of tumour cells for vimentin and focally for S-100 protein |
| Hiroshi Yamazaki ,et al. 2005 [39] | Japan | 24 years | male | tongue | 3 0 × 1 5 mm | about 3 weeks | painless swelling in the left side of the tongue | Biopsy. Partial glossectomy was performed under general anesthesia | 2 years. | The tumor cells were S-100-negative, SMA-negative, and focally type IV collagen-positive. Strong immunoreactivity for EMA was demonstrated by many of the tumor cells |
| Kanemitsu Siirasu-na, et al. 1986 [40] | Japan | 76 years | female | Malignant schwannoma of the mandible | 5 . 0 × 3 . 3 × 4 . 5 cm | 3 months | a painless swelling on the mandible of | partial resection of the mandible was performed under general anesthesia following tracheotomy. The surgical wound healed without evidence | 12 months | the cells were significantly positive for S-IOO protein. Intermediate sized filaments, including keratin, virnentin,and desmin were not detected in the tumor. |
| Shyama Prem Sa, ,et al. 2011 [41] | India | 43 years | female | Mandible | 8 × 5 cm | 3 months | swelling | A postoperative wound infection with MRSA was treated successfully with a twenty one day course of vancomycin. Surgery RT | 12 months | immune- histochemistry, the tissue was strongly and diffusely positive for Vimentin, S100 and Neuron-specific enolase and negative for Cytokeratin, Factor V111 and CD34.. |
| T. Sabesan ,et al. 2008 [42] | UK | 38 years | female | tumour of the parapharyngeal space in a patient with neurofi-bromatosis type 1 | 7×2 cm | sixmonth | a gradually-enlarging right-sided neck mass and a three-week history of husky voice, dysphagia, and breathing difficulty. | She was treated with adjuvant ra-diotherapy. | 3 year | staining for vimentin and GFAP was present. The tumour failed to stain for smooth muscle actin, desmin, S100, CD34 or HMB45. |
| Salehinejad et al 2013 [43] | Iran | 24 year | man | maxilla | 3× 2 ×1 cm | 3 months | Facial disfigurement due to the bulging of the right lower face was also noted. A physical examination revealed multiple cafe-au-lait spots in her neck, back, and axilla | After an incisional biopsy, surgical enucleations of the mandibular and maxillary lesion via intraoral approach were performed | 2 year | immunostaining for S-100 protein was negative on the follicle stroma. |

*Location and complications of OMPNST*

OMPNST can originated sporadically from a neurofibroma or very extremely as metastasis [22-24].

Oral MPNSTs are often located on the mandible, lips. and buccal mucosa [15, 16, 18, 20]. According to the findings of the present review, the majority of the reported cases of intraoral MPNST were identified on the tongue and mandible. OMPNST rarely occur in the gingival area in this regard, M.B.Guglielmotti, et al. reported a case of MPNST in gingival with painless swelling in a 18-year –old which was the first reported case of OMPNST on the gingival [22]. Some of the cases intraosseous OMPNST to imitate of inflammatory periapical lesions with radiography appearance from unilocular to multilocular [19, 25, 26, 28, 29]. The clinical symptoms of OMPNST are usually a local mass with severe pain and paresthesia, dysphagia,trismus and dysarthria are observed in cases with large tumors, depending on the anatomy of the affected region [7, 8, 12, 14, 17, 29]. Swelling, and pain are the most common complications caused by intraoral MPNST [29-33]. In the present review, 50% cases of painless OMPNST was verified in the literature. Moreover, 90% cases had discomfort associated with the swelling of region [2, 5-7, 18].

*Diagnosis and treatment*

Diagnosis of OMPNST can be very difficult clinically, radiographically and histopathology especially in sporadic cases [1, 2, 6-10, 15]. Clinically, no differences have been reported between intraoral MPNST and ordinary oral soft tissue sarcoma [16, 19, 23, 26, 28]. Therefore, it is not possible to distinguish between OMPNST and other types of these oral sarcoma. A diagnosis of OMPNST must be detected on the basis of criteria such as arising from a nerve and Schwann cell [15, 18, 20, 31, 33, 34]. Histopathologically, this tumor cause shows fascicles of atypical spindle -shaped cells and heterogeneous components such as glandular structures, cartilage and skeletal muscle in the hyper – hypo cellular (myxoid zone) areas can be distinguished with other types of spindle sarcomas such as fibromatosis, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, malignant fibrous histiocytoma, synovial sarcoma, osteosarcoma, angiosarcoma and melanoma. Therefore, immunohistochemistry evaluation is necessary for definitive diagnosis [4, 5, 7, 8, 10, 16, 19, 21, 28-30]. The tumor cells showed positive immunostaininig for S-100, Vimentin , neuron specific enolase (NSE), GFAP, Leu-7, myelin basic protein and BCL-2 that confirmed neurogenic origin [25, 27, 28, 32]. The results some of researches indicated expression of P53 and Ki67 are 2 reasons for the diagnosis MPNST [32, 33]. In the present study, predominant histopathological findings on OMPNST that observed in all the reported cases included a encapsulated tumors consisting of a fascicular pattern in hypo and hyper cellular areas with proliferatio of atypical of spindle cells with bizarre and wavy or comma-shaped hyperchromatic to vesicular nuclei and elongated eosinophilic cytoplasm. In most cases necrosis, hemorage and mitotic activity are frequent. One of the method to diagnosis and detected of OMPPNST is electron microscopic examination that including of elongated cells with interwining cytoplasmic processes [20, 22, 23, 25]. Cytoplasm contained densely cord granules, mitochondria and pinocytotic vesicles [16, 17, 19-20]. Radiological approaches, such as magnetic resonance imaging (MRI) and computed tomography (CT) and could be used for reveals the nerve origin and show the erosion of the mandible and widening of the mandibular canal respectively [17, 19, 24, 27, 28, 29]. Positron emission tomography (PET) with the glucose analogue 18- fluorodeoxyglucose is benefit in cases of metastasis and recurrent disease [29, 30-33].

MRI is gold standard for diagnosis MPNST especially in cases with enlarged tumors or uncertain diagnostic biopsy [4, 6, 17, 28]. Through methods such as CT-scan and MRI, valuable data could be obtained for the appropriate diagnosis of OMPNST, while biopsy and histopathological evaluation are necessary to the definitive diagnosis of these lesions [9, 11, 16, 25, 33].

The optimum treatment of OMPNST still remain obscure. Wide surgical excision is considered the first-line treatment for OMPNST [16, 26, 28, 29, 32]. Local recurrence is common about 40%. Adjuvant RT is being used for all OMPNSTs although its role remains unknown and usually the dose is 60-70 GY [11, 18, 22, 26, 29].The role of adjuvant chemotherapy for OMPNST remain unclear and chemotherapy is generally limited to the management of locally advanced and metastatic lesions [17, 27, 28, 30, 31]. Despite management and control of OMPNST about 44% of patients shows metastasis [1, 4, 5, 16, 17]. The most common metastatic location for MPNST is lung, bone, pleura, liver and spine [21, 26, 28, 33]. Metastasis to lymph node and brain is uncommon. Almost in 50% of cases, hematogenous metastasis is created [10, 16, 18, 19, 23, 25, 26, 32].

Prognosis of OMPNST is poor. Tumor prognosis depends to size of lesion, location, stage and grade [14, 15, 18, 22]. Prognosis MPNST in the extremities is better than maxillofacial lesions [16, 19, 20, 22]. Overall survival rate for patients with sporadic OMPNST patients is 40 – 70% and in patients with NF1-associated is 10% at 5 years for this reasion NF1 patient must be monitored for malignanct changes so early identification [6, 7, 8, 11, 15, 17, 20]. Findings of research DiCerbo et al. demonstrated that patients with MPNST in maxillofacial area had a worse prognosis in compared with patients with MPNST in the extremities [17].

Recently, new researches shows targeted therapies originated of activation of RAS pathway and successful treatment of BRAF V6ooE mutated in MPNST [18]. Oral MPNST is considered a highly aggressive neoplasm [1-2-6-9-11-16-20-25]. However, malignant schwannomas have been observed in some patients, along with ancient schwannomas in other regions. Surgical excision is considered the first-line treatment for these lesions with preservation of the neighboring structures (Table 1).

*Limitations*

In the review of the literature, some studies lacked the

key information regarding the reported cases, diagnostic methods, and proposed interventions. Therefore, many studies were excluded due to the lack of plausibility of case presentations or accurate and sufficient data. Furthermore, reporting of the included studies could not be performed based on the CARE statement for the same reason.

In conclusion, according to the results of this study, OMPNST is very rare in patients without NF1 syndrome. Considering OMPNST is without severe pain and paresthesia in some of cases and this malignant neoplasm can mimic of any benign tumor therefore dentists should be careful in the final diagnosis and treatment. Depending on the histopathological nature and extent of the lesion, surgical procedures are normally performed on patients with OMPNST. Evaluation of differential diagnoses of MPNST is importance since these lesions might be indistinguishable from other malignant tumors. In conclusion, histopathological examinations and immunohistochemical analysis are essential to the accurate diagnosis of MPNST. As for the treatment of these lesions, surgical excision of the tumor. Radiotherapy and chemotherapy is considered effective.

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*Conflict of interest*

The authors declare that they have no conflict of interest.

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