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Rare Malignant Tumors of the Parotid Glands: Oncocytic Neoplasms

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1. Introduction

Salivary gland neoplasms are a rare group of tumors; the annual incidence rate is 1 in 100,000 individual, comprising about 3% of all head and neck neoplasms [4]. The mean age of patients with salivary gland tumors is 45 years, peaking in the sixth and seventh decades of life. Benign salivary gland tumors occur more frequently in females, while malignant tumors are slightly more frequent in males. The parotid gland is the most frequent site - about 70% of cases. About 80% of parotid tumors are benign and 64 to 80% of all primary salivary gland epithelial tumors involve the parotid gland, mostly located in the superficial lobe [5].

Oncocytic neoplasms comprise a group of rare tumours of the parotid glands, and their incidence represents approximately 1% of parotid neoplasms [1]. Histologically they are classified according to the new World Health Organization classification in three distinct types, namely oncocytosis, oncocytoma and oncocytic carcinoma [2]. Oncocytomas usually occur in the elderly and affect the parotid glands in 80% [3]. Pathologically, oncocytoma is described as a well circumscribed mass, composed of layers of oncocytes (small round nucleus, micro-granular, eosinophilic cytoplasm). Oncocytes are large, granular, eosinophilic epithelial cells mainly found in glandular tissue, including that of the salivary glands and thyroid. Oncocytomas that originate from oncocytes are very rare neoplasms that account for less than 1% of all salivary gland tumors [4].

Oncocytic carcinomas are even more uncommon; they represent 11% of all oncocytic salivary gland neoplasms, 0.5% of all epithelial salivary gland malignancies and 0.18% of all epithelial salivary gland tumors [5, 10]. The terms oncocytic carcinoma, oncocytic adenocarcinoma, malignant oncocytoma and malignant oxyphilic adenoma are synonymous [6]. Besides these defined neoplasms, there are other entities that are not well identified oncocytic changes of the parotid gland, such as oncocytic metaplasia, diffuse oncocytosis, nodular oncocytosis and multifocal nodular oncocytic hyperplasia and also oncocytic metaplasia within other salivary gland tumors such as the Warthin's tumor [7].

While the diagnosis of these lesions is usually straightforward, the histologic distinction between nodular oncocytosis and oncocytoma is admittedly rather arbitrary in certain cases.

Many pathologists believe the presence of a single, well-circumscribed and at least partially encapsulated nodule favors the diagnosis of oncocytoma while multiple, unencapsulated nodules distributed in a lobular configuration favors nodular oncocytosis [25]. Even more confusing is the designation of oncocytoma arising in oncocytosis to describe a dominant often encapsulated nodule in the background of oncocytosis. This distinction, however, is academic and of little to no clinical or prognostic significance. More important is the distinction of these lesions from their malignant counterparts, oncocytic carcinomas, as well as the oncocytic variants of other salivary gland carcinomas and metastatic lesions with oncocytic morphology. Also, oncocytic cells have been reported to occur in mucoepidermoid carcinoma (MEC); in addition, a rare variant of MEC known as oncocytic MEC has been described in the last decade [16-19]. These tumors are composed exclusively of oncocytic cells arranged in nests and sheets in sclerotic stroma with variable number of chronic inflammatory cells [19]. The majority of the oncocytic MEC described in the literature as lack of or containing minimal squamous /epidermoid cells. On re-review we believe, based on the criteria described by Weinreb et.al, 5 of 10 cases represent MEC containing oncocytic cells as one the cellular components while 5 of 10 cases represent true oncocytic variant of MEC [19]. We believe that the most helpful features in differentiating MEC containing oncocytic cells from other salivary gland lesions in FNA specimens is the presence of extracellular mucin, mucous cells and pseudo-goblet/clear cells.

Many types of benign and malignant salivary gland tumors can have foci of oncocytic cells. If the oncocytic component comprises a small portion of the lesion the differential diagnosis is not a challenge. Oncocytomas may be unencapsulated and exhibit atypical nuclear changes which may make a distinction from oncocytic carcinoma complicated. In comparison with those two entities oncocytic carcinomas usually have considerably greater mitotic figures, cellular pleomorphism (fig. 1) and most importantly unequivocal evidence infiltration into surrounding tissues (fig. 2). Etit et al [20] showed that a tumor titled as oncocytic Carcinoma ex pleomorphic adenoma composed exclusively of malignant oncocytic cells with extensive infiltration into the surrounding tissues including muscle, vascular and perineural invasion with 23 metastatic cervical lymph nodes. A total parotidectomy with a functional neck dissection was performed. Macroscopically, two distinct tumors were identified; one located in the superficial lobe and the other located in the deep lobe. Microscopically the tumor in the superficial lobe exhibited a tumor composed of large, round, polyhedral cells arranged in small clusters, with isolated individual cells, and occasionally, solid sheets. On hematoxylin and eosin slides, cells had abundant, finely granular, eosinophilic cytoplasm (fig. 3). Many of the oncocytic cells had pleomorphic, medium or large nuclei with an eosinophilic irregular, macronucleoli. Necrosis and extensive lymphovascular tumoral thrombi were noted, but no comedonecrosis, tubular, cribriform or papillary areas were seen. Focally, oncocytic changes were noted in residual normal salivary gland parenchyma. In the deep lobe, in addition to the neoplastic oncocytes, there was close association of various epithelial cell types some forming ductal structures and myxoid mesenchymal-like stroma of a typical pleomorphic adenoma. In their case, 50% of the tumor in the deep lobe was histologically compatible with pleomorphic adenoma with oncocytic carcinoma, while 100% of the tumor in the superficial lobe was oncocytic carcinoma. The clinical significance of oncocytic carcinoma to the prognosis of oncocytic Carcinoma ex pleomorphic adenoma has not known. The tumour may show positive immunoreactivity for AE-1/AE-3, CK-7, CEA, EMA and p63.

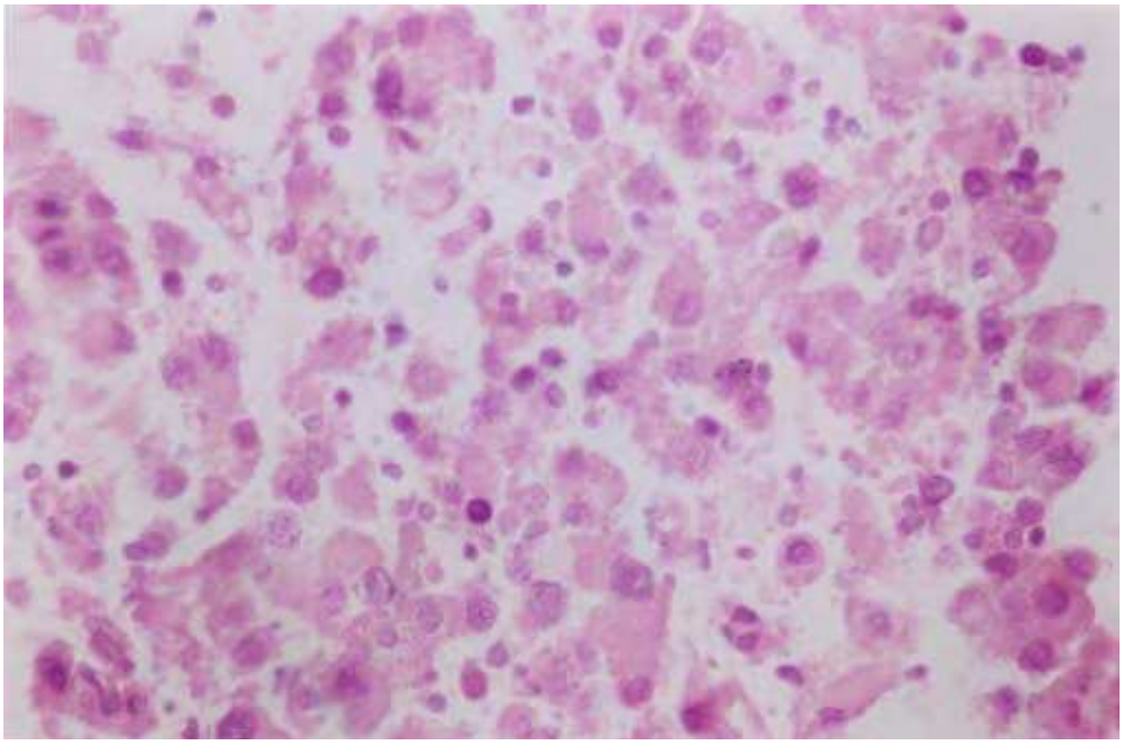


Fig. 1. The tumor consists of oncocytes only (H&E, original magnification, x200)

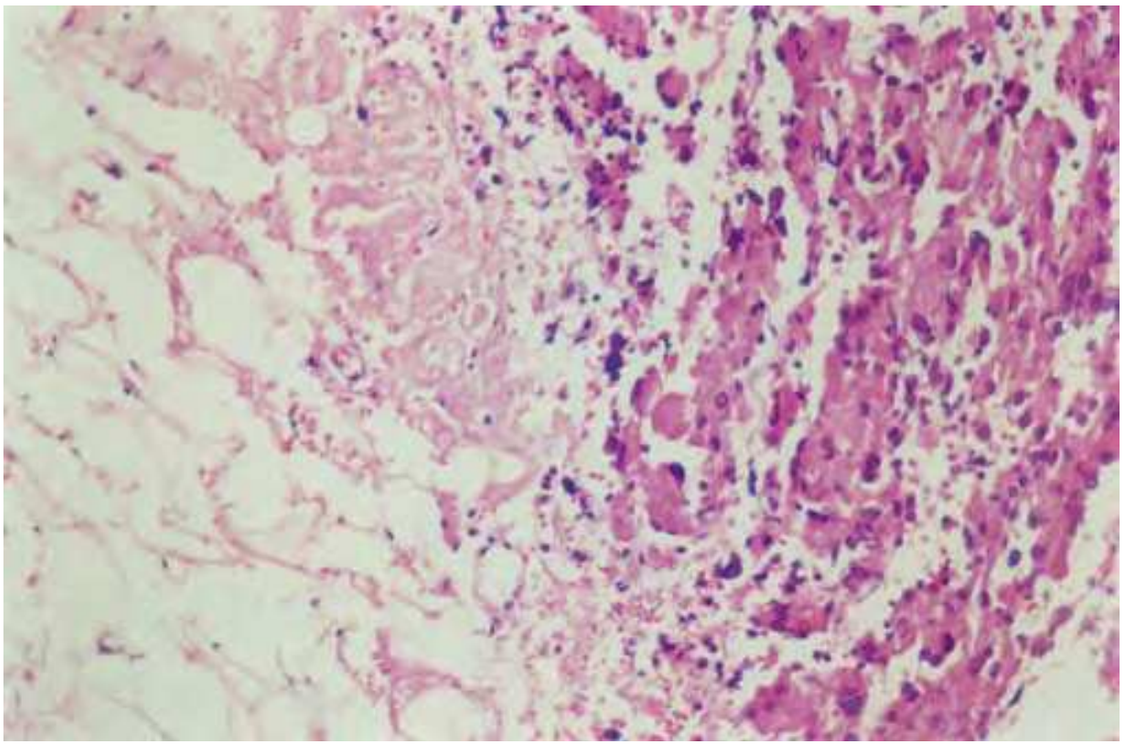
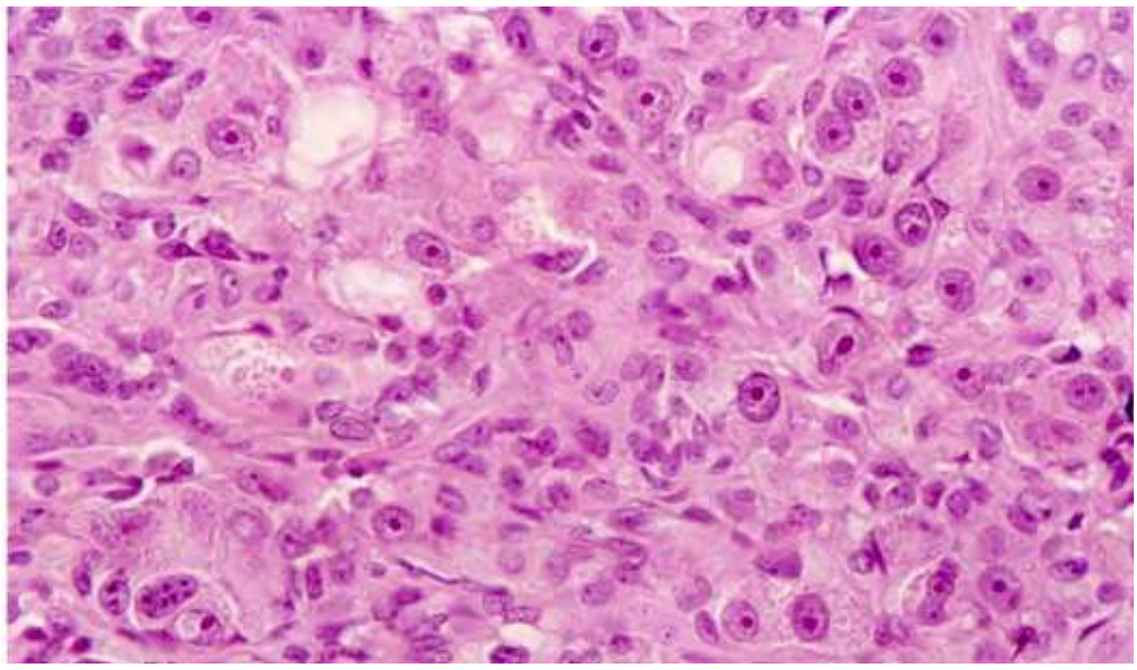


Fig. 2. Tumor cells infiltrating the surrounding adipose tissue are seen (H&E, original magnification, x100)



(*Figure 3 is from Prof. Dr Yan Gao, permission was taken)

Fig. 3. The tumor cells having eosinophilic granular cytoplasm and round vesicular nuclei (sometimes double nuclei), often with big and red nucleoli. (H&E)

Epithelial-myoepithelial carcinoma (EMCa) is an uncommon, biphasic salivary gland malignancy composed of ductal epithelial cells and myoepithelial cells with a broad morphologic spectrum. Among these variants was the oncocytic or oncocytic-sebaceous EMCa (OEMCa), which was initially described by Savera and Salama in 2005 [21]. This variant that was defined by prominent oncocytic change in the ductal and/or myoepithelial component and sebaceous elements populated 8% of all EMCa [22]. The cells in this variant are true oncocytes because the prominent granular, eosinophilic cytoplasm is constituted by abundant mitochondria. However, unlike the oncocytes in OEMCa, apocrine epithelial-myoepithelial carcinoma cells could only be considered ''oncocytoid'' because they did not quite show the same degree of granularity or abundant mitochondria by histochemical or immunohistochemical stains. Their eosinophilia is likely a result of a combination of factors: protein content, secretory vacuoles, with perhaps a minor contribution from mitochondria. These cells showed periapical snouts, vacuolated cytoplasm, and nuclei with prominent central nucleoli and were also positive for androgen receptor (AR), which is typically expressed in salivary duct carcinoma.

Oncocytic carcinoma may occur in many sites in addition to the salivary glands, including the nasal and thoracic cavities, ovary, kidney, thyroid gland, breast and parathyroid.

Oncocytic salivary gland carcinoma is uncommon representing only 0.05–0.4% of salivary gland neoplasms and about 5% of oncocytic neoplasms [3]. Similar to their benign counterparts, nearly 80% occur in the parotid gland. Interestingly, the majority is presumed to arise in a preexisting oncocytoma but they also may occur de novo [14,15]. Diagnostic criteria for salivary gland oncocytic carcinoma include destructive invasion of adjacent salivary or non-salivary tissue, perineural and/or vascular invasion, and metastases. Oncocytic carcinoma is an unusual proliferation of cytomorphologically malignant

oncocytes and adenocarcinomatous architecture phenotypes mainly found in glandular tissue [8]. The terms oncocytic carcinoma, oncocytic adenocarcinoma, malignant oncocytoma and malignant oxyphilic adenoma are synonymous. Its malignant nature is distinguished from oncocytoma by abnormal morphological features and infiltrative growth [3]. The majority of oncocytic carcinoma cases have occurred in the parotid glands, but tumors that involved the submandibular gland and minor glands of the palate have also been described [11]. Also, oncocytic carcinoma of the submandibular gland has only been reported in 11 cases [23]. Fine needle aspiration is the procedure of choice for making a diagnosis in the majority of cases, although its sensitivity is reported to be only 29%, in the oncocytic carcinoma. Rarity of the disease, sampling error and lack of interpreter experience are account for the majority of pitfalls. The oncocytic nature of the tumor cells is confirmed with special methods, such as histochemical or immunohistochemical stains [8]. Necrosis, peri-neural spread, pleomorphism, intravascular invasion, and distant metastasis to the cervical lymph nodes, kidneys, lungs, and mediastinum are the main features of this high-grade malignant tumor [8].

Surgical management with radical or superficial parotidectomy represents the cornerstone of therapy [3]. Probably, there is no need for chemotherapy and/or irradiation, given the benign nature and slow growth rate of the tumour; recurrence is less than 20%, mainly because of incomplete surgical resection. Criteria for the diagnosis of malignancy in salivary oncocytic tumors include: (1) local lymph node metastasis; (2) distant metastasis; (3) peri-neural, vascular or lymphatic invasion; (4) frequent mitoses and cellular pleomorphism with extensive invasion and destruction of adjacent structures [12]. Distant metastasis is very rare. For instance, only one case of oncocytic carcinoma arising in the submandibular gland with disseminated bone metastases was reported in the literature [24]. Local recurrence was also considered as one of the characteristics of oncocytic carcinoma. According to the WHO Histological Typing of Salivary Gland Tumors (2005) [29], two criteria are necessary to establish the diagnosis of oncocytic carcinoma. Firstly, the tumor cells must be identified as oncocytes. Secondly, the diagnosis of malignancy should be based not only on cellular and nuclear pleomorphism, but also on local infiltration and metastasis. Oncocytic carcinoma can be differentiated from benign oncocytoma by the presence of a connective tissue capsule in the latter. Moreover, compared to oncocytoma, oncocytic carcinoma usually shows a greater mitotic activity and more nuclear pleomorphism.

This tumor is predominantly composed of round or polyhedral cells arranged in small clusters and occasional solid sheets. Cells have abundant eosinophilic cytoplasm, a result of excessive numbers of mitochondria [8]. Histochemical and immunohistochemical procedures are also essential for the differential diagnosis [11]. Although not commonly used, it has been reported that anti-mitochondrial antibody is highly specific and sensitive to confirm the oncocytic nature of the granular cytoplasm [13]. FNAC is less sensitive for oncocytic neoplasms, perhaps due to the rarity of these tumors and diagnostic pitfalls previously associated with FNAC (for example, sampling errors and overinterpretation of paucicellular specimens) [3]. Approximately one-third of patients with oncocytic carcinoma of the parotid develop a painful mass or experience facial paralysis. The skin overlying the gland is occasionally discolored or wrinkled [8]. Diagnosis is usually made 1 to 2 years after the onset of disease [4]. For clinicians, the differentiation of oncocytic carcinomas from benign oncocytic neoplasms is quite important. Histologically, oncocytic carcinomas have an infiltrative and at times vascular- or neuroinvasive growth pattern. Histochemically,

PTAH staining distinctly illustrate positive, small, dark-blue cytoplasmic granules, which represent mitochondria. Brandwein and Huvos especially recommended the use of prolonged (48 h) PTAH staining [30]. It has also been reported that immunohistochemistry using an anti-mitochondrial antibody is a highly sensitive and specific method for identifying the mitochondria by light microscopy [13]. This procedure is easy to perform and readily available for the specimens embedded in paraffin which would otherwise not be appropriate for analysis by electron microscopy.

Immuno-phenotypically, tumour shows intense immunoreactivity for mitochondria, CK5/6, CK8/18 (fig. 4), CK10/13, CK19, and EMA, whereas there is no reactivity documented for SMA or S-100 (fig. 5-7) [28]. In addition, there is an increased expression of MIB-1 antibody against Ki-67 antigen in contrast to benign oncocytomas (fig. 8). This finding helps in the differentiation of oncocytic carcinomas from both benign oncocytomas and highly malignant oncocytic carcinomas [7]. Oncocytic lesions are characterized by cells with an atypical accumulation of mitochondria (fig. 9). This accumulation has been recognized as a compensatory mechanism to intrinsic functional defects of these organelles, resulting in energy production impairment and increased generation of reactive oxygen species (ROS), including hydrogen peroxide (H2O2). Peroxiredoxin I (Prx I) is a H2O2 scavenging protein and the expression of its yeast homolog was reported to be influenced by mitochondrial function. Demasi et a showed that Prx I is over-expressed in oncocytes regardless of the salivary gland lesion where they appear. Their results suggested that Prx I expression in oncocytes is related to its ability to decompose mitochondrial-derived H2O2 and that it could provide to the cells a protective role in an environment that, by continuously producing potential DNA-damaging ROS, predisposes to genome instability and cellular transformation [31].

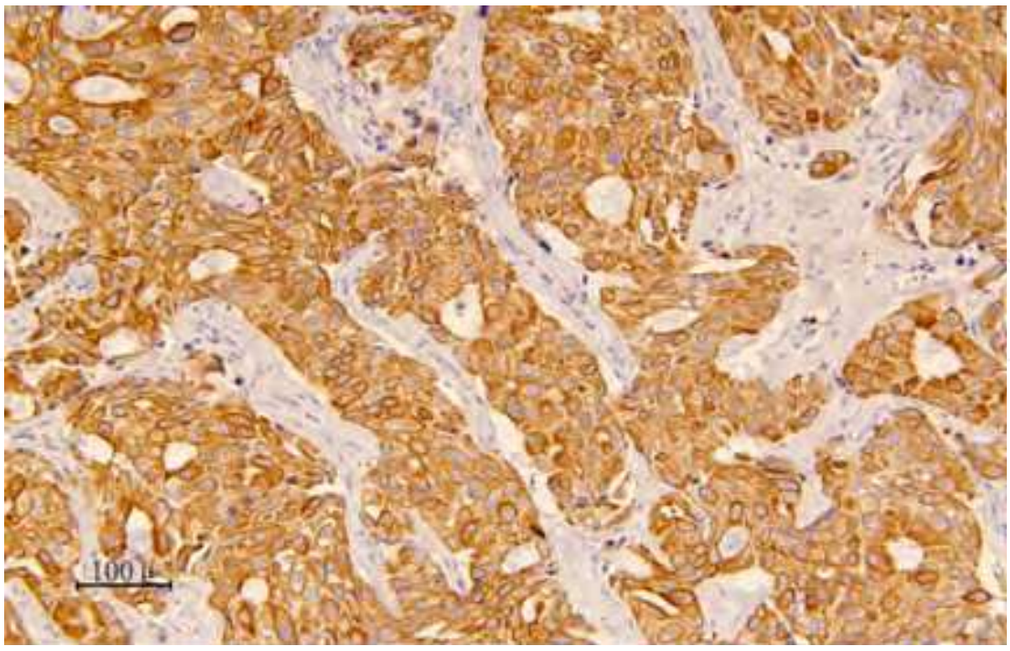


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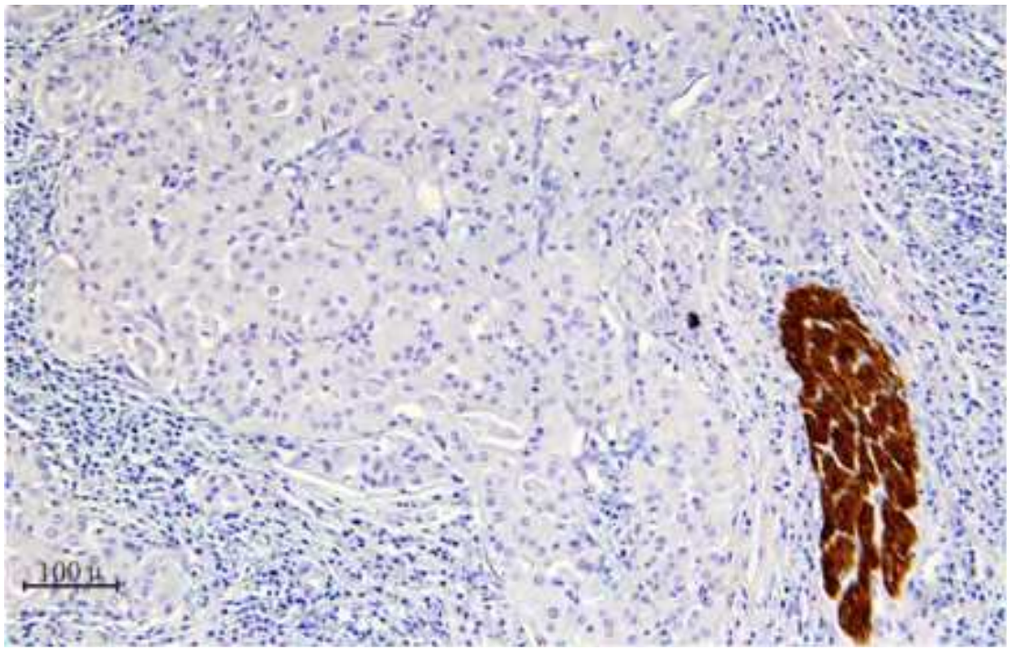
Fig. 4. Immunohistochemical reactivity of the tumor cells for CK8/18.



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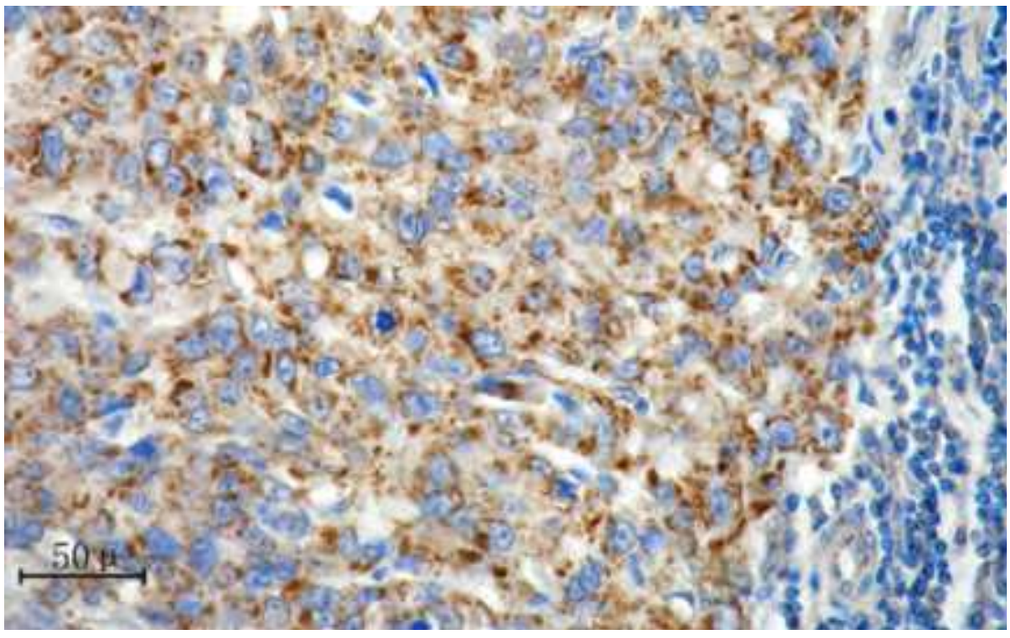

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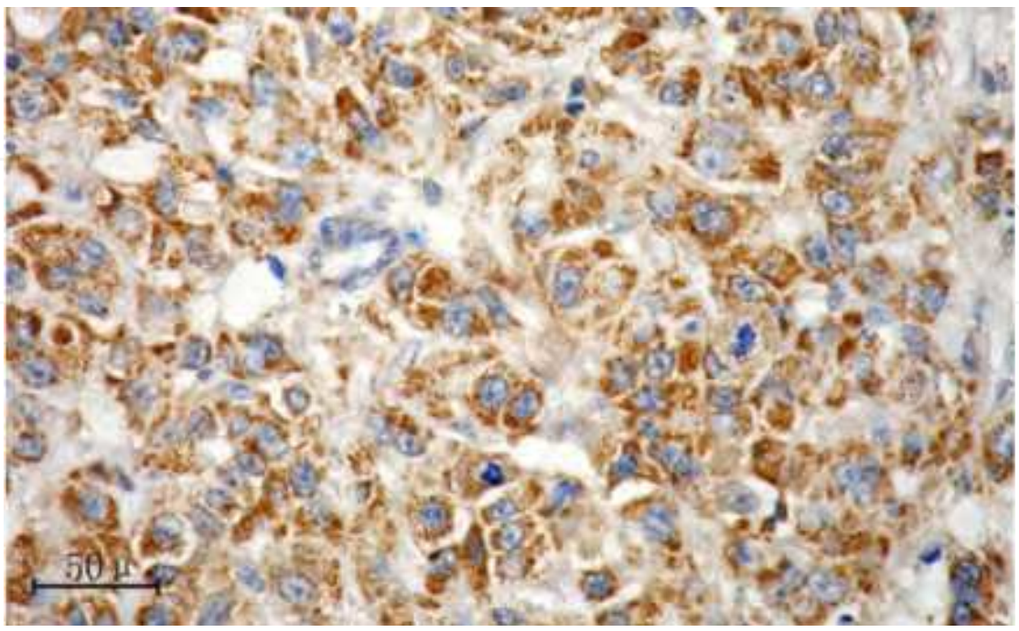

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Fig. 5-7. No S-100 reactivity in tumor cells. Oncocytes in both lymph nodes with metastasis (5) and primary foci (6) have intense granular cytoplasmic immunoreactivity for anti-mitochondria immunostaining (7).

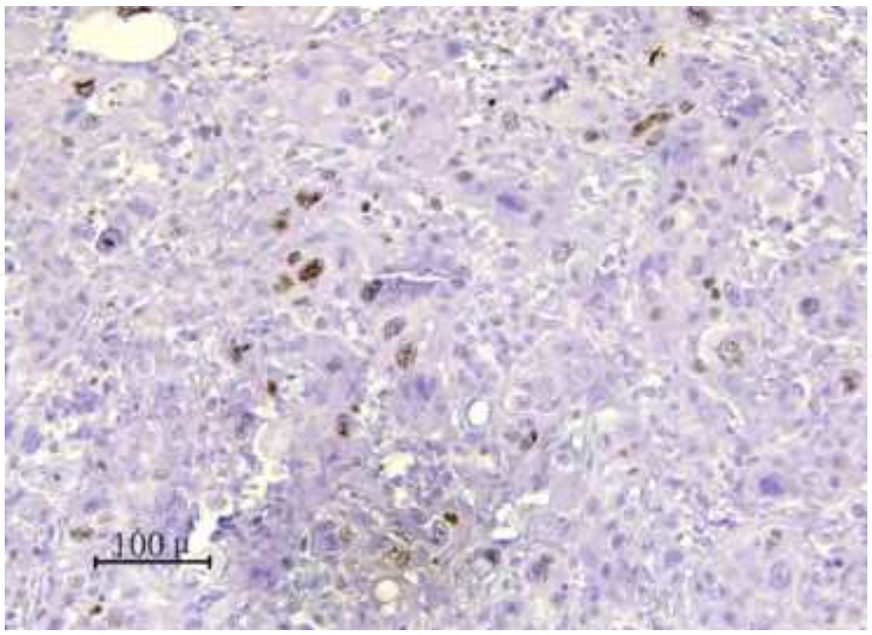

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Fig. 8. Ki-67 positive nuclear staining in malignant oncocytes.

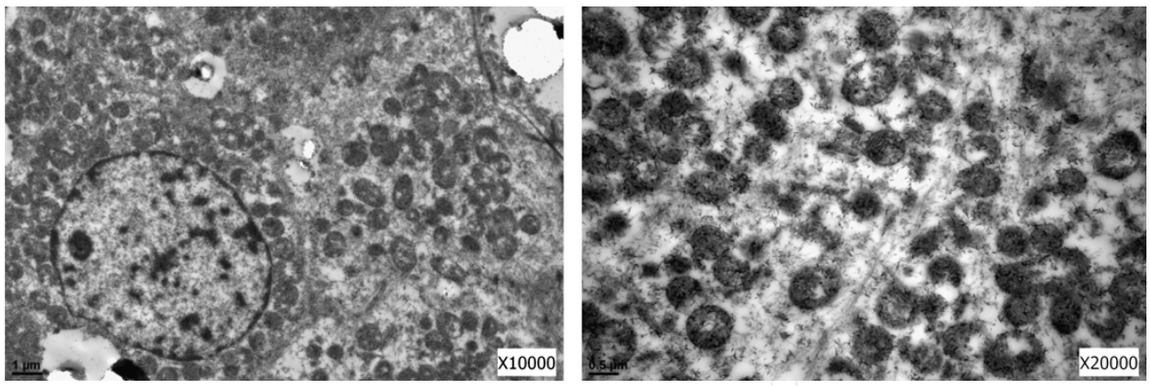

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Fig. 9. Electron microscopy demonstrating numerous mitochondria in the cytoplasm of the tumor cells. (left, x10,000; right, x20,000).

Occasionally, separation of primary salivary oncocytic lesions can be problematic as other salivary gland tumors can demonstrate both oncocytic and clear cell change. Clear cell and/or oncocytic change is either characteristic or present as a common variant in clear cell carcinoma, sebaceous adenoma/carcinoma, pleomorphic adenoma, myoepithelioma, myoepithelial carcinoma, acinic cell carcinoma, epithelial-myoepithelial carcinoma and mucoepidermoid carcinoma. To add to the diagnostic dilemma, metastases to the head and neck region can manifest as oncocytic and/or clear cell lesions. The prototypical metastasis that can masquerade as oncocytoma/oncocytosis is metastatic renal cell carcinoma (RCC). Both lesions can be composed of oncocytic and/or clear cells and both can have similar architectural grown patterns, lumen formation, and vascularized stroma. Although immunohistochemistry panels have been used to aid with this differential, significant overlap in staining limits their usefulness [26]. McHugh et al anecdotally noted that p63 immunohistochemical expression occurs in oncocytomas but not in metastatic RCC to the head and neck [27]. Besides oncocytomas, other tumors are also considered to distinguish from OC. Acinic cell adenocarcinoma can be differentiated from OC since the cytoplasmic granules in acinic cell adenocarcinoma are amphophilic or basophilic and the patterns of growth can be microcystic or papillary. Salivary duct carcinoma, in contrast to OC, usually forms duct-like spaces with papillary and cribriform growth and often shows comedo- like necrosis. In the meantime, the presence of numerous mitochondria in the cytoplasm of the oncocytes that is confirmed on ultrastructural examination is not found in the neoplastic cells from other malignancies mentioned above, which can be considered for adjuvant diagnosis. However, the processes of fixation or embedding of specimens for light microscopy often destroy the fine structure of organelle in the cytoplasm so that it is difficult to observe mitochondria clearly.

Management and treatment of oncocytic carcinomas is not well established due to the low incidence of this tumor type. It consists of surgical intervention and radiotherapy, although the efficacy of radiotherapy is unclear. Surgery especially radical resection is the widely accepted treatment for OC. When the tumor invades the facial nerve, the nerve should be sacrificed in principle. Immediate nerve grafting for reconstruction of facial nerve defect could be performed. Goode and Corio [14] reported 4 cases treated only by conservative surgery all recurred after the operation, three of which metastasized. Furthermore, many cases described in the literature were treated with surgery including neck dissection.

Radiation does not appear to alter favorably the biological behavior of this tumor. Prophylactic neck dissection may be indicated for tumors that are larger than 2 cm in diameter [14]. The prognosis of oncocytic carcinomas is not well known because of their low incidence. Further investigation of the prognosis of patients with oncocytic carcinoma of the parotid gland is warranted as more cases are reported. Nakada et al. reported 23 cases of OC with cervical lymph node metastasis in a review of 42 cases [15]. The patients ranged in age from 30 to 91 years (mean: 58). The analysis of 31 reported cases with information regarding local lymph node and distant metastases and clinical course revealed that nine of ten patients who died of disease had distant metastases, while seven of these ten patients had local lymph node involvement. In contrast, none of 21 living patients had distant metastases, and 11 of these had only local lymph node involvement. Therefore, they concluded that distant metastasis appeared to be the most important prognostic feature of oncocytic carcinoma; local lymph node metastasis was not necessarily a critical factor in the overall prognosis.

Goode and Corio [14] reported that tumors smaller than 2 cm in diameter appeared to be associated with a better prognosis than those that were larger. It has been suggested that elected neck dissection be indicated when the tumor size is larger than 2 cm or the histopathologic features suggest the tumor spreads to the cervical lymph nodes. Adjuvant radiotherapy has also been used for the treatment of oncocytic carcinoma [6, 14, 15, 23]. In Zhou et al [28] study, 5 of 12 patients received radiotherapy, of whom two had multiple metastases and died of disease about 1 year after initial treatment, 2 patients are alive with disease 6 and 42 months after treatment but both with recurrence occurred, and only one is alive without evidence of disease 77 months after treatment. Altogether, for the extensive tumors, radical resection combined with elective neck dissection may be the first choice for treatment, while the role of radiotherapy or chemotherapy is still controversial. It seems clear from these studies that patients who undergo more aggressive initial surgery have a significantly better overall prognosis. I preferred a close follow-up to an elective neck dissection, and reserved the neck dissection for a recurrence.

In summary, oncocytic carcinomas of salivary gland origin are high-grade tumors with local recurrences, regional or distant metastases, diagnosis of which based on a combination of clinical and histopathological features. Immunohistochemistry for mitochondria is considered helpful for the adjuvant diagnosis. Complete surgical excision is the treatment of choice while the role of radiotherapy or chemotherapy is still controversial, and careful long-term follow-up is necessary.

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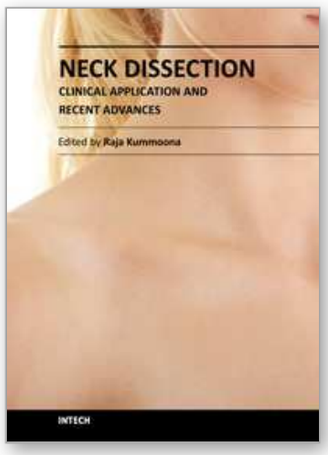

Neck Dissection - Clinical Application and Recent Advances

Edited by Prof. Raja Kummoona

ISBN 978-953-51-0104-8

Hard cover, 164 pages

Publisher InTech

Published online 22, February, 2012

Published in print edition February, 2012

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