

Case Report

Large cell neuroendocrine carcinoma of the submandibular gland: a case report and literature review

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Summary

Neuroendocrine tumors (NET) are a heterogeneous group of malignancies with a broad spectrum of histomorphologies, tissue origins, and clinical outcomes, which arise from neural crest cells with neuroendocrine differentiation. Salivary gland tumors account for 3-6% of all head and neck neoplasms, while large cell neuroendocrine carcinomas (LCNEC) of the salivary gland are extremely rare, with few cases reported in literature, and only 5 cases involving submandibular gland. The rarity of these tumors in salivary glands is probably related to the scarcity of neuroendocrine cells in this tissue, whose presence is still a matter of debate. Regardless of their low frequency, it is imperative to differentiate these tumors from the much more common squamous cell carcinomas and metastatic NETs, due to different therapeutic approach and prognosis. In this paper, we report the case of a 21-year-old man, with a LCNEC involving a submandibular gland followed by several recurrences over the years. In addition, we include a comprehensive review of the available literature on this topic.

Key words

Neuroendocrine tumors • Salivary gland • Submandibular gland • LCNEC

Introduction

Neuroendocrine tumors (NET) are a group of malignant neoplasms characterized by a wide histological and clinical heterogeneity. NETs originate from the diffuse neuroendocrine system cells, and although they can occur in different organs and tissues, they appear more frequently in digestive and respiratory tracts. Primary NETs of the salivary glands are uncommon, accounting for up to 1-3% of major salivary gland malignancies, and originate almost exclusively in parotid and submandibular glands¹. Sublingual and minor salivary gland NETs rarely occur and are difficult to distinguish from morphologically identical NETs derived from the surface mucosa of the upper aerodigestive tract. The 4th Edition of the World Health Organization (WHO) Classification of Head and Neck Tumors describes two histotypes of salivary gland NET within the group of poorly differentiated carcinomas: small neuroendocrine carcinomas cells (SmCC), which account for most of

the salivary gland NET, and large-cell neuroendocrine carcinomas (LCNEC), which are extremely rare: indeed, the SmCC to LCNEC ratio is about 5:1^{1,2}. The rarity of NETs in the salivary glands is probably related to the scarcity of neuroendocrine cells in this tissue. Indeed, the presence and distribution of neuroendocrine cells in human salivary glands is still a matter of debate.

Case report

In August of 2005, a 21-year-old Caucasian man was referred to the Department of Maxillofacial Surgery, "Ospedali Riuniti" General Hospital, Ancona, Italy, by his general practitioner for a painful swelling in left submandibular region for 2 months. Past medical history was unremarkable. On palpation, a firm and painful small nodule was detected in that region. There were no intraoral lesions and the facial nerve was preserved. CT revealed a nodular, well-enhanced tumor,

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about 2.5 cm in maximum diameter, in the left submandibular gland, with a moderate swelling of some homolateral cervical lymph nodes. The fine-needle aspiration cytology (FNAC) of the nodule was non-diagnostic. The patient underwent total left submandibular gland and lymph node removal and the material was sent to the Institute of Pathology, Marche Polytechnic University, Ancona, for histological examination.

On gross examination, the submandibular gland showed a grayish-white, firm and solid nodule, measuring 2.5 x 1.8 cm. This lesion had well-defined margins, with a margin distance of 0.1 cm.

On microscopic examination, the submandibular lesion was characterized by organoid growth with minimal differentiation and high mitotic rates, showing tumor invasion into muscular tissue (Fig. 1A). The tumor growth

pattern consisted of sheets and trabeculae, with a tendency for coagulative necrosis (Fig. 1B). Furthermore, occasional intravascular and perivascular extension of tumor tissue was observed (Fig. 1C). The tumor was composed of large, pleomorphic ($> 30 \mu\text{m}$) and poorly differentiated neoplastic cells, with scarce eosinophilic or clear cytoplasm. The tumor cell nuclei had angulated molded shape, prominent nucleoli, arranged in solid nests, coarse and thickened chromatin with a vesicular distribution, and smudgy basophilic material surrounding intra-tumoral blood vessels (Fig. 1D). The cell borders were well-defined and occasional bizarre giant tumor cells were present.

The proliferative index, evaluated with Mib1/Ki-67, was about 30-35% (Fig. 2A). The tumor cells expressed immunoreactivity for CD56, synaptophysin, AE1/AE3,

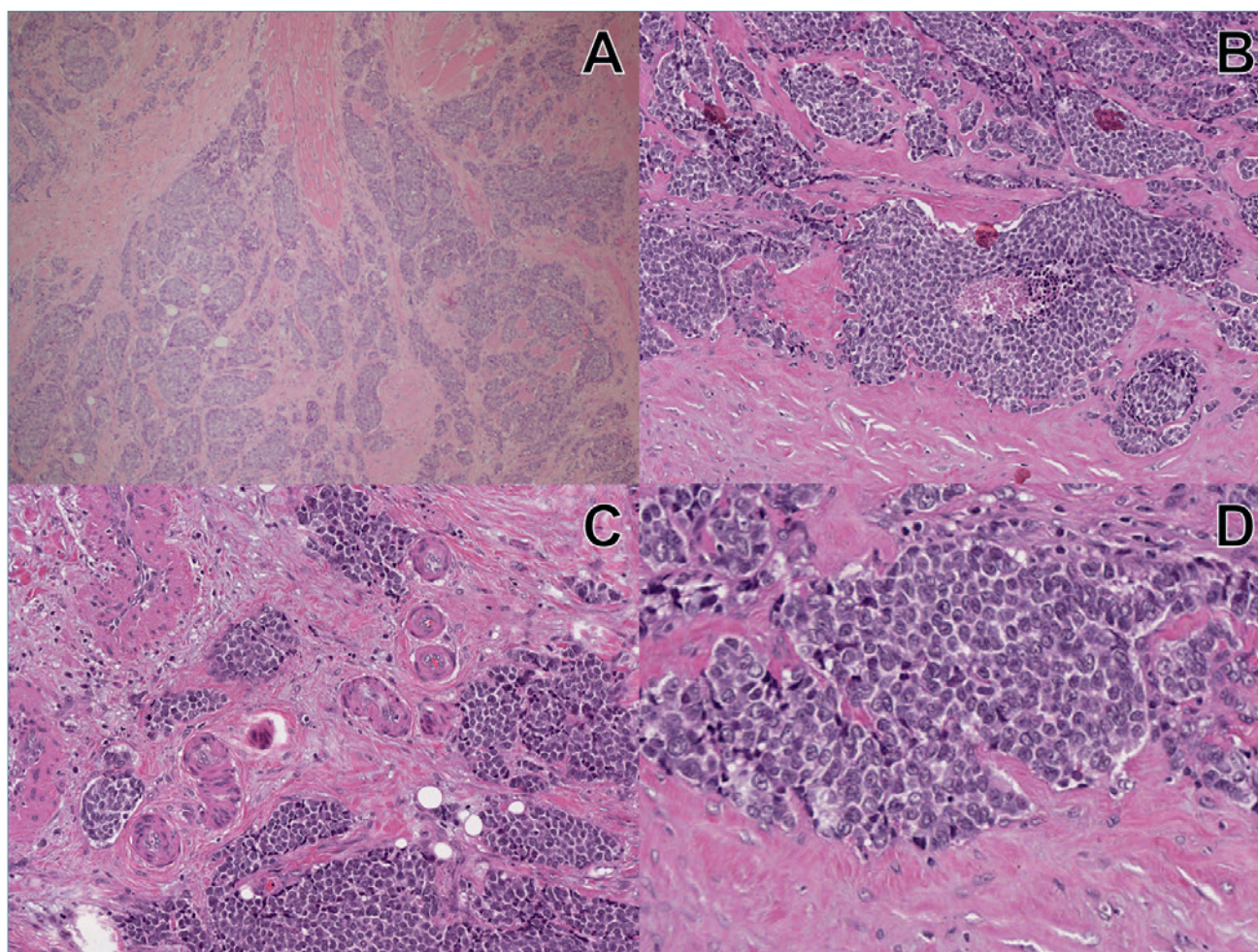


Fig. 1. Microscopic overview of LCNEC shows tumor invading muscular tissue (A). The tumor growth pattern consisted of sheets and trabeculae, with small necrotic areas (B) and occasional intravascular and perivascular invasion (C). The lesion is composed of poorly differentiated neoplastic cells with scarce cytoplasm, polymorphic nuclei, thickened chromatin, and small nucleoli (D) (H&E stain, 20X).

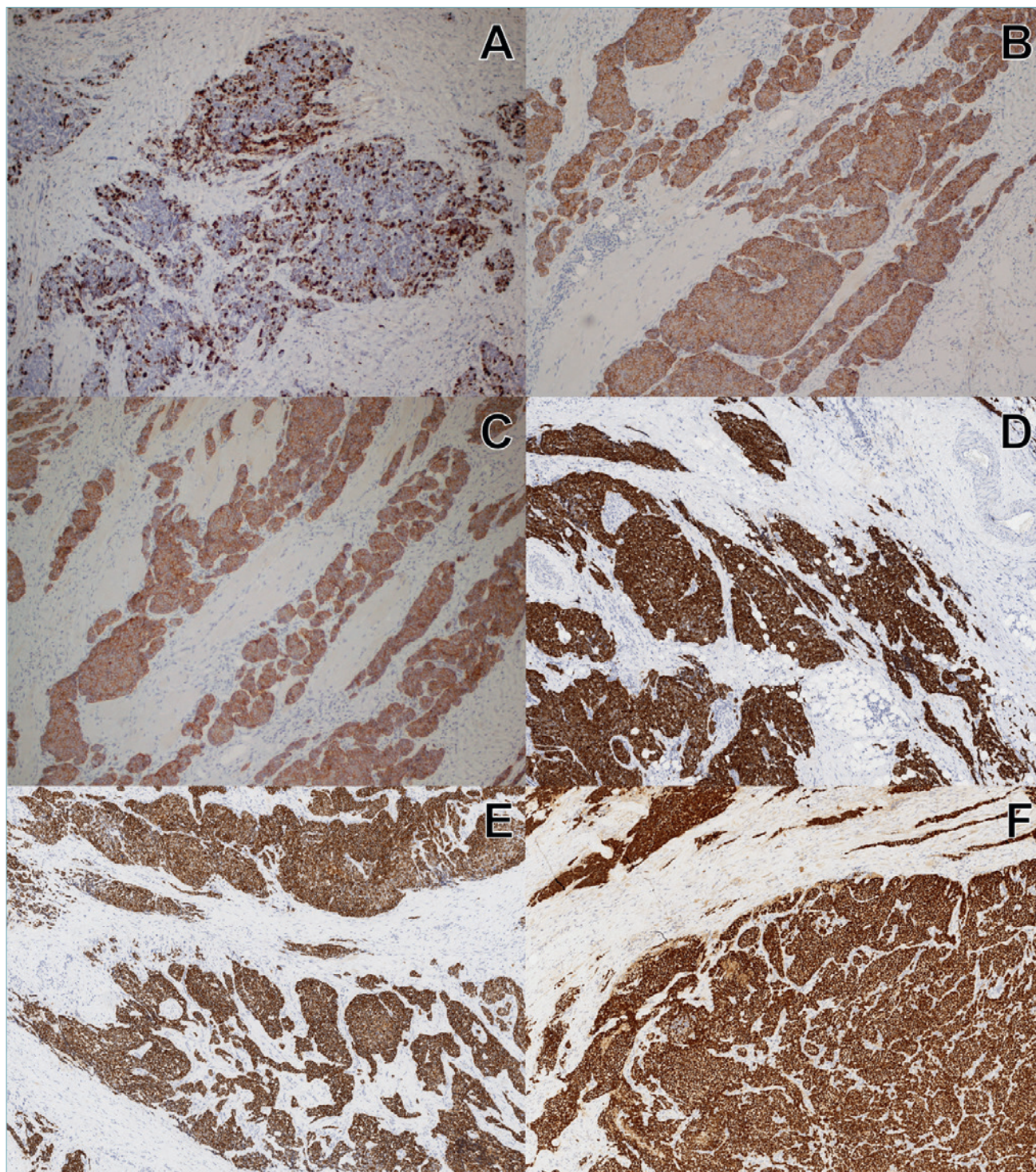


Fig. 2. Immunohistochemical staining for MIB1/Ki-67, showing high proliferative index (30-35%) (A). Immunohistochemical expression of synaptophysin (B), CD56 (C), AE1/AE3 (D), CAM 5.2 (E), and p63 (F) (20X).

CAM 5.2, and p63 (Fig. 2B-F). No immunostaining for CK7, CK20, chromogranin A, S100, and HMB45, was observed.

Excluding some metastatic and primary tumor entities (i.e Merkel cell carcinoma, Ewing family tumors, solid adenoïd cystic carcinoma, metastatic neuroblastoma,

lymphomas and melanoma), based on the cell morphology, growth pattern, proliferative index, and immunophenotype, the lesion was classified as primary poorly differentiated LCNEC of the left submandibular gland.

In February 2009, the tumor recurred in the lower pole of the left parotid gland as a grayish-white capsulated nodule measuring 1.7 cm in diameter. Subsequently, in December 2015, a small nodule of the left sublingual gland was detected; it consisted of a neoplastic nodule measuring 3 x 1.5 cm with neoplastic infiltration of the left lingual nerve, morphologically similar to the previously diagnosed neoplasm. In February 2016, a third recurrence was observed on the left floor of the mouth. On gross examination, the lesion showed an ill-defined grayish-white nodule measuring 1.2 cm in the oral soft tissue, with muscle and perineural infiltration. Histological and immunohistochemical examinations confirmed the neuroendocrine nature of the tumor. In February 2018 another recurrence was diagnosed, showing multiple laterocervical white nodules up to 1 cm in diameter within fibroadipose tissues. Furthermore, diffuse lymph node involvement and distant metastases (e.g. liver, spinal column) were found.

Discussion

One of the main problems in the management of patients with NET is the lack of universally accepted standards, both for nomenclature and for disease staging. Recently, the WHO recommended a new classification system for pancreatic neuroendocrine neoplasms, while the other organs still refer to the 2010 WHO classification³. The grading evaluation is performed on the basis of morphological criteria and the evaluation of the proliferation fraction according to the European Neuroendocrine Tumor Society (ENETS) scheme⁴. This classification distinguishes differentiated NET and poorly differentiated neuroendocrine carcinoma (NEC): (a) NET G1 (mitotic counting < 2 for 10 high power fields (HPF) and/or Ki67 index < 3%); (b) NET G2 (mitotic counting 2-20 for 10 HPF and/or Ki67 index 3-20%); (c) NET G3 (mitotic counting > 20 for 10 HPF and/or > 20% Ki67 index); (d) NEC (mitotic counting > 20 for 10 HPF and/or > 20% Ki-67 index). G3 NET and NEC are characterized by high mitotic and/or proliferative index values, and the only difference is the presence of well-differentiated or poorly differentiated morphology, respectively.

The clinical, histological, and immunohistochemical features of the present case are consistent with LCNEC, according to the WHO Classification of Head and Neck Tumors, and with NET G3, according to the

ENETS scheme for pancreatic neuroendocrine neoplasms^{3,4}.

Salivary gland NETs usually affect adults with only exceedingly rare examples occurring in the pediatric population⁵. The most common clinical presentation is a rapidly growing neck mass occurring in parotid gland region or less commonly in the submandibular region. The diagnosis of salivary gland NET may be difficult due to the low incidence of these tumors. The diagnosis is based on histological, ultrastructural, and immunohistochemical criteria and on a comprehensive work-up to rule out the metastatic origin of the tumor^{6,7}. Both SmCCs and LCNECs are high-grade carcinomas characterized by organoid cellular growth with minimal differentiation, rapid mitotic activity, and frequent presence of coagulative necrosis. Palisading at the periphery of tumor nests, trabeculae, and rosettes can be encountered. The LCNEC cells have relatively abundant cytoplasm, larger nuclei with more coarse chromatin and prominent nucleoli⁸.

Salivary gland LCNEC is an exceedingly rare entity: to our knowledge, there are only 15 cases reported in literature from 1990 (Tab. I). This tumor mainly affects male patients and seems to occur exclusively in adults, ranging between 21 and 88 years old (mean age 66.7 ± 23.4 years); noteworthy, this is the youngest salivary gland LCNEC reported in literature.

The LCNECs usually involve the parotid gland with just 6 cases affecting the submandibular gland. The most common clinical presentation is a rapidly growing neck mass occurring in the parotid gland region or less commonly in the submandibular region. On the contrary, some patients may complain of a painful mass with facial nerve paralysis. LCNEC usually presents as a poorly defined firm mass, showing a mean size of 5.17 ± 3.29 cm, but in some cases, they are smaller, probably owing to their superficial location, which are easier to detect.

The most common diagnostic procedure used to investigate these tumors is FNAC, even if a large core needle biopsy must be preferred because small biopsy samples may be overlooked or misdiagnosed⁹. Clinical examination and imaging techniques (ultrasounds, X-rays, CT, PET-CT, and MRI) are required to diagnose LCNEC and may help rule out the metastatic origin of the NET.

Regarding immunohistochemical findings, the most studies markers were chromogranin A and synaptophysin, showing positivity in 46.2% and 78.6% of cases, respectively. Other immunohistochemical markers were evaluated in some cases of salivary gland LCNEC, such as CD 56, CK AE1/AE3, and synaptophysin, showing positivity in all of them (Tab. I). Tumor cells may express synaptophysin, chromogranin

Tab. I. Cases of salivary gland LCNECs reported in the literature.

Author (year)	Age	Sex	Symptoms (months)	Instrumental investigation	Site (cm)	Gland type	Treatment	Immunohistochemical markers					Follow-up (months)	Recurrence (months)	Death (months)
								Chr	Syn	CD56	p63	SNE			
Hui et al. (1990)	-	-	-	-	-	-	-						-	-	-
Larsson and Donner (1999)	88	F	Painless swelling	FNAC	2	Par.	Surgery, RxT	-	+			+	36	No	
Nagao et al. (2000)	72	M	Painless swelling (4)	FNAC, CT	7	Par.	Surgery, RxT, ChmT	-	+			+	5	Yes (4)	Yes (1)
	73	M	Painless swelling (4)		0.33	Par.	Surgery, RxT	+	-			+	48	Yes (24)	Yes (24)
Casas et al. (2005)	74	M	Painless swelling (18) facial paralysis (< 1)	FNAC, CT	9	Par.	Surgery, RxT	+	+				8	No	
Ueo et al. (2005)	72	M	Painless swelling (3)	CT	4.5	Par.	Surgery, RxT	+	+			+	1	Yes (1)	Yes (8)
Sowerby et al. (2007)	81	M	Facial paralysis	FNAC	6	Subm.	RxT, ChmT	-	+				27	No	Yes (6)
Chernock et al. (2011)	68	M	-	-	-	Par.	-	+	+				6	Yes (-)	
	73	M	-	-	-	Par.	-	+	-				36	No	
Petrone et al. (2013)	72	F	Painless swelling	FNAC, X-ray	1.4	Subm.	Surgery	+	+				-	-	
Yamamoto et al. (2013)	58	M	Painless swelling (4)	MRI, PET	2	Subm.	Surgery	-	+	+			14	No	
Kawaratani et al. (2013)	68	M	Painless swelling	FNAC, CT	5	Subm.	Autopsy	-	+	+	-		No	Death	
Andreassen et al. (2016)	69	F	Rapid grow swelling (<1)	US, FNAC, PET-CT	5.5	Subm.	Surgery, RxT, ChmT	-	+	+	+		19	No	
Faisal et al. (2016)	45	M	Painfull swelling (5), facial weakness (3)	X-ray, FNAC, MRI, PET-CT	9.5	Par.	Surgery, RxT		-	+			12	No	
Present case (2019)	21	M	Painfull swelling (2)	FNAC, CT, PET	2.5	Subm.	Surgery	-	+		+		125	Yes (41)	

FNAC = Fine-Needle Aspiration Cytology; CT = Computed Tomography; MRI = Magnetic Resonance Imaging; PET = Positron Emission Tomography; Par. = Parotid; Subm. = Submandibular; RxT = Radiotherapy; ChmT = Chemotherapy; Chr = Chromogranin; Syn = Synaptophysin.

A and/or CD56; indeed, the NETs stain for at least one of these known neuroendocrine markers ^{6,9}. Electron microscopy could facilitate the diagnosis showing some neuroendocrine features such as 100-275 nm sized dense-core granules within the cytoplasm of tumor cells ¹⁰. Immunohistochemical staining is helpful to distinguish other malignant large cell neoplasms, such as melanoma and Merkel cell carcinoma arising in parotid or submandibular regions. Surgical resection of the affected gland is the treatment of choice; however, in two cases it was not performed. Three patients received only surgical resection, while radiotherapy and chemotherapy were associated in 8 and 3 cases, respectively. Only in two cases a combination of surgery, radiotherapy, and chemotherapy was used. The mean follow-up time was 28.1 ± 32.2 months and recurrences were reported in 5 patients, showing a disease-free survival time of 17.5 ± 11.8 months. Currently, there are no guidelines to treat salivary gland NETs and the main therapeutic strategies generally derive from other tumor types, such as cutaneous Merkel cell carcinoma ¹¹. Surgery is the gold standard for well differentiated NETs with most patients undergoing local resection and neck dissection, even though there is a lack of agreement about the need of elective neck dissection in these cases. The majority of patients receive adjuvant radiotherapy, although its effectiveness has not been demonstrated ¹². Chemotherapy seems to be ineffective as well, although the responsiveness of these lesions to different types of chemotherapeutic drugs has not been well documented ¹³.

In conclusion, LCNEC of the salivary glands represents a diagnostic and therapeutic challenge due to its extreme rarity. The definitive diagnosis is based on histological evaluation, demonstrating the presence of typical neuroendocrine architecture with positivity to neuroendocrine markers. Imaging is necessary to exclude metastatic origin of the tumor, since NETs occur more frequently in other body regions ⁹, or to differentiate these tumors from the much more common squamous cell carcinomas, because the therapeutic approach and prognosis are significantly different. For localized tumors, surgery seems to be the first therapeutic option, supplemented by radiotherapy and/or

chemotherapy, but studies with larger sample size are advised to establish guidelines.

CONFLICT OF INTEREST STATEMENT

None declared.

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