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Radiographic-anatomy, natural history and extension pathways of parotid and submandibular gland cancers

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Running title: Natural history of parotid and submandibular gland cancers

Abstract

Intensity-modulated radiotherapy has been widely used routinely in recent past years for post-operative radiotherapy of salivary gland cancers. Because of the sharp dose fall off outside of target volumes with IMRT, each volume must be strictly and rigorously defined, as the areas not specifically included in the target volume will not be treated to a therapeutic dose. The selection and delineation of these volumes is complex and requires extensive knowledge of parotid and submandibular gland cancer radiographic-anatomy, natural history and extension pathways (including local tumor spread, PNI risks and regional spread), which are detailed in the present article.

Keywords

Extension pathways; Radiotherapy; Salivary gland cancers; Submandibular gland; Parotid gland

1 Introduction

Salivary gland cancers account for approximately 3-4% of head and neck cancers [1–3]. They originate in the parotid gland in 65-80% and in the submandibular gland in 10%, respectively. They are characterized by a very wide histological variety of epithelial tumors [4], with the most frequent being mucoepidermoid carcinomas, adenoid cystic carcinomas and adenocarcinomas. Perineural invasion (PNI; microscopic and/or macroscopic) is a common finding in salivary gland cancers, given the rich network of small and large nerves within this anatomical region [5–7]. Some histologies, such as adenoid cystic carcinoma, are of particular risk of PNI [6–11]. The incidence of PNI has been reported as 31–96% of cases of adenoid cystic carcinoma [12]. Considerable variation in the rates of PNI may be attributed to different detection methods for both the pathological diagnosis of PNI [13] and the radiological interpretation of macroscopic PNI [14].

Surgery, when feasible, is the cornerstone of curative treatment for the vast majority of these cancers [2,15]. Surgery alone is generally sufficient in localized, low-grade tumors, with complete resection (R0) and without recurrence risk factors. Risk factors for locoregional recurrence include T3-T4 tumors, positive (R1) or close (< 5 mm) resection margins, high histological grade, PNI, lymphovascular invasion and lymph node involvement [8,16–18]. In these high-risk patients, post-operative radiotherapy (PORT) is usually recommended [2,9,18–23].

Despite the negative results of the recently published COSTAR trial evaluating cochlear-sparing intensity modulated radiotherapy (IMRT) vs. conventional three-dimensional radiotherapy (3DRT) in parotid gland cancers [24], IMRT has been widely used routinely in recent past years for PORT of salivary gland cancers [25–30]. Because of the sharp dose fall off outside of target volumes with IMRT, each volume must be strictly and rigorously defined, as the areas not specifically included in the target volume will not be treated to a therapeutic dose. The selection and delineation of these volumes is complex and requires extensive knowledge of parotid and submandibular gland cancer radiographic-anatomy, natural history and extension pathways (including local tumor spread, PNI risks and regional spread), which are detailed in the present article. Data are mainly derived from

retrospective studies of surgical and clinical experience, as there are almost no prospective data in this setting

2 Radiographic-anatomy and extension pathways of parotid gland cancers

Radiographic-anatomy of the parotid gland region and of regions of interest for possible extension pathways are presented on a planning CT-scan in Figure 1.

The parotid gland is a bilateral lateralized structure that displays a lobular and irregular morphology. It is bordered superiorly by the zygomatic arch and the temporomandibular joint, anteriorly and medially by the masseter muscle, and posteriorly by the sternocleidomastoid muscle, and the mastoid process of the lateral temporal bone [31–35]. Anatomically, it is divided into deep (or endofacial) and superficial (or exofacial) lobes, which are separated by the facial nerve (VII). The superficial lobe lies lateral to the facial nerve and overlies the lateral surface of the masseter muscle. The deep lobe lies medial to the facial nerve and is situated between the mastoid process of the temporal bone and the mandibular ramus [31–34]. The secretions of the parotid gland are transported to the oral cavity by the parotid (or Stensen's) duct, which runs along the masseter muscle, passes through the buccinator muscle, and opens upon the oral surface of the cheek by a small orifice, opposite the second upper molar tooth [36].

The parotid gland is surrounded by a fascial capsule [37] in continuity with the deep cervical fascia. Most benign tumors and low-grade early-stage malignant tumors are retained within the parotid region by this capsule. However, extracapsular spread can occur and tumors can invade nearby structures and spaces, classifying these tumors as at least T3 (8th edition UICC/AJCC TNM) [38]. Furthermore, parotid gland cancers are often at risk of PNI (mostly along the facial nerve VII and to a lesser extent other *named* nerves; see below) [7,9,39–46]. The main extension pathways of advanced parotid gland cancers are detailed below.

2.1 Parapharyngeal and retrostyloid spaces

The fascia separating the parotid gland from the parapharyngeal space constitutes a weakness zone and thus a possible extension pathway, especially for deep lobe tumors [47–52]. Kuet et al.

reviewed a series of 1293 cases of primary tumors arising from the parapharyngeal space [50]. Forty-five percent of these tumors were salivary gland tumors, of which 22% were malignant tumors. Surgery with PORT remains the mainstay of treatment, with a higher risk of complications, especially concerning cranial nerve injury [50]. More posteriorly, advanced tumors can also invade the retrostyloid (or poststyloid) space, which represents the posterior part of the parapharyngeal space. It corresponds to the so-called 'carotid space'. The retrostyloid space contains neurovascular structures: the internal carotid artery, internal jugular vein, sympathetic chain, and cranial nerves IX, X, XI and XII along with paraganglionic tissue/sympathetic chain. Thus, it constitutes a possible vertical extension pathway from deep neck spaces to the skull base [47–52]. If the tumor encases the carotid artery, it is classified as T4b [38].

The pterygomandibular space (the medial part of the masticator space) is situated at the anterior vicinity of the parapharyngeal space [47], thereby representing a possible extension pathway, up to the infra-temporal fossa. It contains the medial and lateral pterygoid muscles, the internal maxillary vessels and the mandibular nerve (V3), which is thus at risk of PNI. Therefore the pterygomandibular space acts as a conduit for neurovascular structures.

2.2 External acoustic meatus

At the superior part of the parotid gland, the fascia separating the parotid gland from the cartilages of the concha and tragus constitutes a weakness zone and thus a possible extension pathway to the external acoustic meatus [47,53]. Invasion of the external acoustic meatus classifies the tumor as at least T4a [38].

2.3 Other nearby structures

In certain cases, other nearby structures (non-exhaustive list below) can be invaded by advanced parotid gland cancers. Analysis of preoperative imaging, pathological, and operative reports as well as clinical examination is crucial.

Skin. The subcutaneous adipose tissue and the skin can be invaded by advanced parotid gland cancers [52,53]. Invasion of the skin classifies the tumor as at least T4a [38].

Masseter muscle. The superficial lobe of the parotid gland overlies the lateral surface of the masseter muscle, which can be invaded [52].

Bone structures. The parotid gland is surrounded by different bone structures that can be invaded: the zygomatic arch, lateral temporal bone [54], mastoid bone, and mandibular ramus. Invasion of the mandible classifies the tumor as at least T4a, and invasion of the skull base as T4b [38].

Parotid duct. Anteriorly to the superficial lobe, there is often an accessory parotid gland [55], which may be separated from the main gland. This accessory parotid gland is lying over the parotid duct, which can thus constitute an anterior extension pathway [56].

Submandibular space. The parotid space is separated from the submandibular space by a fibrous septum. Thus, although the two spaces are in close contact, they do not communicate directly. However, the submandibular space communicates more directly with the parapharyngeal space.

2.4 Perineural invasion risk in parotid gland cancers

PNI constitutes a frequent extension pathway of parotid gland cancers that typically propagates in retrograde fashion along the nerve paths toward the skull base [7,43–46]. Recent articles have focused on the risk of PNI in head and neck cancers, including parotid gland cancers, and its importance in radiation therapy [39–42]. PNI is a clinicopathological entity generally defined as tumor-cell invasion in, around, and through the nerves [57,58]. Adenoid cystic carcinoma is the most frequent neoplasm to exhibit this behavior, with 31-96% of PNI reported [12]. There are two distinct PNI categories [58]. The most common is “microscopic PNI” when PNI is identified in a resection specimen as a histological finding of small, microscopically identified peripheral nerves in the immediate proximity of the neoplasm. In that case, the extent of microscopic PNI may vary from focal to multiple (extensive). The second category is “macroscopic PNI”, a clinical and/or radiological finding of larger nerves. The AJCC has suggested the use of the term *named nerve* for this circumstance, though only in the context of oral cancer but surprisingly did not extend the concept to salivary gland cancer where it restricted the language to identify the facial nerve alone in the TNM classification [38,59]. Obviously, the facial nerve (VII) is the main nerve at risk, with other

nerves being less frequently affected. Invasion of the facial nerve (VII) classifies the tumor as at least T4a [38]. Chen et al. showed, in a series of 140 patients with pathological evidence of PNI at the time of initial surgery, that inclusion of nerve paths up to the skull base in PORT reduced the actual probability of tumor recurrence in the skull base from 15% to 5% ($p = 0.03$). This was even more significant for T4 stages. The 5-year overall survival for patients who experienced a skull base recurrence was 19% compared with 91% for those who did not ($P < 0.001$) [9]. Therefore, the paths of the main cranial nerves nearby must be known in order to be included in the target volumes when needed (see below).

The facial nerve (VII) penetrates the base of the skull through the internal acoustic canal and runs through the petrous bones and the facial canal in 3 different portions: the labyrinthine (between the cochlea and the vestibule, to the geniculate ganglion), tympanic (to the horizontal semicircular canal), and mastoid segments (vertical portion) (Figure 2). The facial nerve (VII) then exits the skull through the stylomastoid foramen. From the stylomastoid foramen, the facial nerve runs between the digastric and stylohyoid muscles, enters the parotid gland and then splits into several branches.

The mandibular nerve (V3) can be also be affected i) by advanced tumors infiltrating the pterygomandibular/masticator space (see above); ii) through the auriculotemporal nerve (a branch of the mandibular nerve) which provides the secretory-motor innervation of the parotid gland; iii) or through communicating interconnections with the facial nerve (VII) via the chorda tympani [41]. The mandibular nerve (V3) runs laterally from the floor of Meckel's cave and exits the skull base via the foramen ovale into the masticator space. The mandibular nerve then divides into an anterior and a posterior division. The lingual nerve issues from this posterior division and joins the chorda tympani, a branch of the facial nerve (VII). The auriculotemporal nerve also issues from this posterior division and travels through the parotid gland.

Thompson et al. recently published a study concerning a series of 547 patients with parotid malignancy, of which 23 patients exhibited radiographic findings suggestive of auriculotemporal nerve involvement [60]. Auriculotemporal nerve involvement was commonly associated with periauricular pain and coexisting facial weakness.

3 Radiographic-anatomy and extension pathways of submandibular gland tumors

Radiographic-anatomy of the submandibular gland region and of regions of interest for possible extension pathways are presented on a planning CT-scan in Figure 1. Data regarding submandibular gland cancers and their natural history and extension pathways are much less abundant than for parotid gland cancers.

The submandibular gland is located within the anterior part of the submandibular triangle [35]. The limits of this triangle are, superiorly, the inferior border of the body of the mandible; anteriorly, the anterior belly of the digastric muscle; and posteriorly, the posterior belly of the digastric muscle. The submandibular gland is indented by the posterior border of the mylohyoid muscle which divides the gland into a superficial and a deep part. It has three surfaces: inferior (covered by skin and platysma), lateral (related to the medial surface of the mandible), and medial (related to the mylohyoid, hyoglossus, and digastric muscles). Secretions from the submandibular gland travel into the oral cavity via the submandibular duct (or Wharton's duct).

The submandibular gland is surrounded by a fascial capsule [35]. Most benign tumors and low-grade early-stage malignant tumors are contained within the submandibular region by this fascial capsule. However, for advanced tumors, extracapsular spread can occur and tumors can invade nearby structures and spaces, classifying these tumors as at least T3 (8th edition UICC/AJCC TNM) [38]. Furthermore, submandibular gland cancers are often at risk of PNI, mostly along the hypoglossal nerve (XII) and the lingual nerve (a branch of the mandibular nerve [V3]) (see below) [7,9,43–46]. The main extension pathways of advanced submandibular gland cancers are detailed below.

3.1 Local invasion risk in submandibular gland cancers

Anteriorly: tumors can invade the anterior belly of the digastric muscle and thus the floor of mouth and the tongue

Laterally: tumors can invade the body of the mandible, even if the periosteum constitutes a strong anatomic barrier. More posteriorly, the platysma also constitutes a resistant anatomic barrier,

which can still be invaded with possible extension to the skin. Invasion of the mandible and/or the skin classifies the tumor as at least T4a [38].

Medially: tumors can invade the muscles of the tongue (especially extrinsic muscles such as the hyoglossus or styloglossus) and the floor of the mouth (posterior belly of the digastric muscle or the mylohyoid muscle)

Posteriorly: the stylohyoid ligament separating the submandibular triangle from the parotid gland constitutes a resistant anatomic barrier

Superiorly: tumors can invade the parapharyngeal space and, more laterally, the medial pterygoid muscle in its inferior part

Inferiorly: tumors can invade the subhyoid region

3.2 Perineural invasion risk in submandibular gland cancers

The submandibular gland shares an intimate anatomical relationship with the hypoglossal nerve (XII) and the lingual nerve (branch of the mandibular nerve [V3]), with the risk of PNI especially for high neurotropism histology such as adenoid cystic carcinoma [8–11]. Recent articles have focused on the risk of PNI in head and neck cancers, including submandibular gland cancers, and its importance in radiation therapy [39–42]. Tumors can propagate mostly in a retrograde manner along the nerve pathways towards the skull base [7,43–46]. Although skull base recurrences for submandibular gland cancers are rarely reported [61], recurrences near the cranial foramina can develop if coverage up to the base of the skull is not included [9]. Recurrence at the base of the skull constitutes an extremely adverse prognostic factor, with survival at 5 years less than 20% [9]. PORT significantly reduced the risk of recurrence at the base of the skull, whose main risk factors are a T4-stage tumor and the presence of PNI [9]. Therefore, the paths of the main cranial nerves evolving nearby must be known in order to be included in the target volumes when needed (see below).

The hypoglossal nerve (XII) exits the skull base via the hypoglossal canal. It then moves laterally and downward to lie between the internal carotid artery and the internal jugular vein. All of these structures are deep into the posterior belly of the digastric muscle. The nerve then loops anteriorly (passing laterally to the bifurcation of the common carotid artery) to run along the lateral

surface of the hyoglossus muscle, deep into the mylohyoid muscle where it lies deep within the submandibular gland. The fibers of the hypoglossal nerve (XII) then divide to supply the different muscles of the tongue.

The lingual nerve is a branch of the posterior division of the mandibular nerve (V3). The mandibular nerve (V3) runs laterally from the floor of the Meckel cave and exits the skull base via the foramen ovale into the masticator space. The mandibular nerve then divides into an anterior and a posterior branch, from which the lingual nerve originates, at the level of the mandibular foramen, in the infratemporal fossa. At this level, the lingual nerve joins the chorda tympani, a branch of the facial nerve (VII). The lingual nerve then descends to the medial aspect of the lateral pterygoid muscle and passes downward between the ramus of the mandible and the medial pterygoid muscle. The lingual nerve makes a turn in an anteromedial direction in the submandibular triangle, at the upper border of the submandibular gland. It then descends to the medial border of the submandibular gland, and loops around the submandibular duct to reach the tongue.

4 Risk of nodal metastases of parotid gland and submandibular gland cancers

Overall, the percentage of positive neck nodes for parotid and submandibular gland cancers at presentation amounts to approximately 20% [3]. These patients are usually treated with a therapeutic neck dissection of the involved areas and echelons at higher risk followed by PORT in most cases.

The management of cN0 patients is more controversial. The risk of occult node metastases for cN0 patients has been reported as between 12% and 45% [23,62–65]. However, the risk of occult neck disease, and consequently, the indication to treat the neck electively, varies widely depending on different factors. This risk can be estimated on histological type, histological grade, T category, and tumor localization [3,63,66]. Concerning the histological type, the greatest risk (lymph node involvement >50%) is seen for squamous cell carcinoma, adenocarcinoma, undifferentiated cancer, and salivary duct cancer. An intermediate risk is seen for mucoepidermoid cancer (especially in grade 2 or higher) and a lower risk for acinic cell cancer, adenoid cystic carcinoma, and carcinoma ex pleomorphic adenoma [3,19,62,66–68]. Min et al. reported a general incidence of lymph node metastasis of 10% in a study of 616 patients with salivary gland adenoid cystic carcinoma [68].

Concerning histological grade, Frankenthaler et al. reported in a series of 99 parotid gland cancers a 18% risk of occult lymph node metastases for high and intermediate grades vs. 3% for low grades [69]. However, the definition of the histological grades of salivary gland cancers has evolved considerably over time, which could represent a bias in the interpretation of the literature. Concerning T categories, the risk was estimated at 15%, 26%, and 33% for T1, T2, and T3-T4 category tumors, respectively [3,66]. Terhaard et al. proposed a score to estimate the risk of positive neck nodes according to T stage (T: T1=1; T2=2; T3-4=3), histological type (acinic, adenoid cystic, carcinoma ex pleomorphic adenoma =1; mucoepidermoid carcinoma=2; squamous cell, undifferentiated carcinoma=3) and site [66]. For parotid gland cancers, the risk was estimated to 4%, 12%, 25%, 33% and 38%, for a total score of 2, 3, 4, 5 and 6, respectively. For submandibular gland cancers, the risk was estimated to 0%, 33%, 57%, 60% and 50%, for a total score of 2, 3, 4, 5 and 6, respectively. Furthermore, for parotid gland cancers, positive neck nodes are frequently seen in the case of facial nerve paralysis [3,66,67]. Based upon these data, some experts recommend elective neck dissection for all patients with malignant salivary gland tumors [70,71]; however others reserve elective neck dissection for patients with features suggestive of high-risk for occult nodal disease: high-grade tumors, large tumors (T3 and T4), and facial nerve paralysis/weakness [72]. In any case, close collaboration between surgery and radiation therapy teams seems essential for the management of cN0 patients. Elective dissection of levels II and III can easily be performed with minimal additional morbidity at the time of parotidectomy or submandibulectomy and should be considered for high-grade salivary gland tumors where PORT is not planned. If PORT is to be used, elective neck dissection seems of less importance, given the data suggesting equivalence of surgery and RT in the treatment of the cN0 neck [62,73]. In analogy with mucosal head and neck cancers, an adequate neck dissection should include a minimal number of lymph nodes (18 for mucosal head and neck cancers), even if this number is not clearly identified in parotid and submandibular cancers [74].

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Figure Legends

Figure 1. Radiographic-anatomy of the submandibular and parotid gland region and of regions of interest for possible extension pathways.

Figure 2. Radio-anatomy of the skull base path of the facial nerve (VII).



