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Review

The keys to conservative treatment of early-stage squamous cell carcinoma of the tonsillar region

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ABSTRACT

To analyze the medical literature devoted to work-up, epidemiology, local control, survival, complications and sequelae after conservative treatment for early-stage squamous cell carcinoma of the tonsillar region. An analysis of the PubMed (1975–2016) database was performed using the following keywords and associations: “tonsil/tonsillar region/oropharynx” AND “squamous cell carcinoma” AND “early-stage (I–II; T1–2N0M0)” AND “radiation therapy/radiotherapy” OR “conservative surgery/oropharyngectomy/transoral surgery/radical tonsillectomy”. The search retrieved 10 retrospective series documenting local control and/or survival in series with more than 50 cases and a minimum 2 years' follow-up after conservative treatment; no prospective studies, meta-analyses and/or Cochrane analyses were found. Magnetic resonance imaging is the key radiological exam for local extension assessment. Human papilloma virus infection (HPV) is a risk factor that must be screened for systematically, since it induces tumoral radio-sensitivity and increases the risk of specific synchronous and metachronous second primaries. Whatever conservative treatment used, local control and survival rates higher than 85% were achieved. Implementing intensity-modulated radiation therapy reduced the incidence and severity of radiation-related complications and sequelae. Transoral surgery yielded very low morbidity/mortality rates, enabled association to ipsilateral neck dissection, and allowed radiation therapy to be reserved for the management of metachronous second primaries. Transoral surgery appeared to be the first-line option in the majority of cases. Lifetime follow-up adapted to HPV status is mandatory. The development of HPV vaccination does not mean that campaigns against smoking and alcohol abuse are of diminished importance.

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1. Introduction

Based on a literature review, the authors detail the radiologic anatomic particularities, assessment and epidemiological specificities of early-stage (I–II; T1–T2N0M0) squamous cell carcinoma (SCC) of the tonsillar region, and treatment outcome in terms of survival, local failure, toxicity and complications following radiation therapy versus “conservative” mandible-sparing surgery. The PubMed database for the period 1975–2016 was searched using the following search-terms and associations: “tonsil/tonsillar region/oropharynx” and “squamous cell carcinoma” and “early-stage (I–II; T1–2N0M0)” and “radiation therapy/radiotherapy” or “conservative surgery/

oropharyngectomy/transoral surgery/radical tonsillectomy”. Exclusion criteria comprised: articles focusing on cancer other than SCC or on advanced stages (III–IV), series of early-stage SCC with fewer than 50 patients and/or less than 2 years' follow-up, series undergoing mandibular sectioning and/or resection, and case reports. Ten retrospective studies (several of which from one center) were retrieved specifically analyzing oncologic results in terms of local control and survival in series of > 50 patients at ≥ 2 year's follow-up following conservative treatment; no prospective studies, meta-analyses or Cochrane analyses were found [1–10].

2. Radiological anatomic particularities, assessment and epidemiology of early-stage squamous cell carcinoma of the tonsillar region

The tonsillar region has a roughly isosceles shape, with a superior apex [11]. The anterior tonsillar pillar, describing the

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anterior side of the triangle, consists of the palatoglossus muscle, which has the anatomic particularity of extending forward in three bundles joining the lateral side of the mobile tongue up to the tip and running upward into the ipsilateral soft palate [11]. The posterior tonsillar pillar, consisting of the palatopharyngeus muscle, extends from the skull base to the oesophageal bundle and is the posterior limit of the triangle [11]. The superior and middle pharyngeal constrictor muscles set within two aponeuroses (intra- and peri-pharyngeal) separate the tonsil from the parapharyngeal space [11]. This lateral wall has the anatomic particularity of being crossed by the styloglossus muscle (which ramifies into the base of the tongue) and glossopharyngeal nerve while the stylopharyngeus muscle joins the inferior constrictor muscle [11]. The apex of the tonsillar region is formed by the junction of the two pillars resulting in an ogive within the lateral soft palate. The base of the triangle corresponds to the tonsilloglossal groove. The tonsillar region includes the palatine tonsil above and, below, the subtonsillar region, which may contain lymphoid tissue connecting the palatine and lingual tonsils [11]. Ohtsuka et al. [12], in an anatomic study of 107 subjects, stressed that regional muscle anatomy does not vary with age and that in 55% of cases the muscle covering of the lateral wall is discontinuous.

The site of origin (anterior pillar, posterior pillar, tonsil) of the SCC within the tonsillar region determines its local extension, which proceeds by invasion of underlying muscle fibers. In early-stages (I–II), SCC diameter does not exceed 4 cm, and the parapharyngeal space, mandible, styloglossus, stylopharyngeus and medial pterygoid and/or mylohyoid muscles remain uninvolved [13]. Local extension at this stage is along the constrictor, palatoglossus and palatopharyngeus muscle fibers. Involvement of muscle fibers adjacent to the tumor increases with T stage ($T_2 > T_1$), with incidence ranging between 27% and 77% [13,14]. Microscopically, cancer cells extend beyond the macroscopic limits of the tumor by a mean 0.5 ± 0.4 mm into the muscle and 0.8 ± 0.6 mm into the mucosa [13]. Ipsilateral lymph-node involvement in levels II and III is frequent; in ipsilateral neck dissection of levels II–IV in T1–2N0 tonsillar region SCC, Laccourreye et al. [9] noted nodal involvement in 26.2% of cases on histology. On the other hand, in these early-stages, level I, contralateral level II–IV and/or retropharyngeal involvement is exceptional [9].

Assessment of early-stage oropharyngeal SCC locoregional extension relied on the tryptic clinical examination-panendoscopy-imaging. In 2010, the American Joint Committee on Cancer and the Union for International Cancer Control included imaging data in their classification, defining early-stages as showing maximum diameter ≤ 4 cm ($T_1: T \leq 2$ cm; $T_2: 2$ cm $< T \leq 4$ cm) without lymph-node involvement (N0) or remote metastasis (M0) [15]. Radiologic involvement of the parapharyngeal spaces and/or extrinsic muscles of the tongue (notably, palatoglossus and styloglossus) defined stage T4a (advanced: IV) [13]. In 2012, the French Society of ORL considered cervical CT as the gold standard for local extension assessment in oropharyngeal cancer [16]. In the tonsillar region, however, Gadolinium-enhanced T1-weighted MRI sequences provide more precise evaluation of invasion of oropharyngeal tissue, both mucosal and muscular, with fine analysis of the parapharyngeal space and styloglossus muscle [17], while T2-weighted sequences allow lymph-node assessment [17]. MRI has thus become the main imaging technique in locoregional extension assessment of early-stage tonsillar region cancer, even, though the intramuscular exploration is less precise than in the tongue-base or oral cavity [18]. This two-fold evolution in classification and in imaging will result in an increase the number of patients staged T4a appearing clinically as T1–2, which will consequently improved oncologic results for radiation therapy in advanced T4 cases. Clinicians must therefore pay great attention when comparing series prior to and

after the spread of MRI for early-stage tonsillar region cancer assessment.

In early-stage SCC, the risk of remote metastasis is very low, and PET-scan is in principle inappropriate for initial work-up [19,20]; nevertheless, given the rate of synchronous second primaries (which may be outside of the upper aerodigestive tract in case of HPV infection) and patients' frequent demand, this radiological examination is becoming increasingly widespread, replacing the classical association of esophageal endoscopy and thoracoabdominal CT scan.

Smoking and alcohol abuse are the classic risk factors for tonsillar region squamous cell carcinoma; non-cessation further reduces long-term survival by increasing the risk of metachronous second primaries of the upper aerodigestive tract [21–24]. However, as incidence of tonsillar region SCC has been increasing over the last 20 years in under 45-year-old non-smokers without alcohol intoxication, other risk factors have come to be suspected. Cannabis consumption and gastroesophageal reflux were for a while incriminated, but have in fact shown no scientific evidence of involvement. HPV, on the other hand, was detected in 65% of oropharyngeal SCC patients in the USA in 2010 and in almost 7% of the general population in 2016, and is now recognized as a real risk factor [24,25]. There remains great uncertainty as to the factors for persistence or resolution of oropharyngeal HPV infection: 80% of cases resolve spontaneously within 6 to 12 months, and persistence is associated with male gender, advanced age and smoking; uncertainty also prevails as to the HPV-induced mechanisms underlying malignant transformation in the oropharyngeal epithelium. It is, however, well established that HPV subtypes 16, 18, 33 and 35 induce oropharyngeal SCC [24]. In the USA, subtype 16 was detected in almost 90% of oropharyngeal SCCs, and was associated with sexual transmission factors (early sexual relations, large number of partners, and oral and anal sexual relations), nicotine and alcohol intoxication, immune deficiency (notably with HIV infection), elevated rate of basaloid SCC, decreased rate of metachronous upper aerodigestive tract second primaries, increased of rate of metachronous second primaries specifically in the anal canal, cervix, vagina, penis and vulva, and good prognosis [24–30]. There have been no assessments of the prognostic impact of HPV-16 on early-stage oropharyngeal SCC but, in advanced stages, it correlates with almost 15% improvement in local control, 2 year disease-free survival and 2 year overall survival [28,29]. In a retrospective study of 5500 cases of tonsillar region SCC treated between 1974 and 2003, the North American Surveillance Epidemiology and End Results (SEER) program noted a 40% reduction in the cancer-related death risk in under 50-year-old patients (more liable to be HPV positive than their elders) [30]. Given the significantly greater survival (due to enhanced chemo- and radio-sensitivity) in HPV+ oropharyngeal SCC, it was recommended to include HPV status in initial assessment, so as to optimize treatment [31]. And, in its 2012 guidelines, the French Society of ORL recommended screening for HPV-16 in diagnostic endoscopy samples taken for suspected oropharyngeal SCC [32].

3. Radiation therapy for early-stage squamous cell carcinoma of the tonsillar region

In 1996, Moose et al. [3] reported an 81% 3-year local control estimate and a 77% 3-year survival estimate after radiation therapy (dosage ≥ 63 Gy) for early-stage tonsillar region SCC. In this series, survival varied significantly with the site of origin of the cancer; 84% in tonsillar carcinoma versus 54% in pillar locations [3]. The same year, Fein et al. [4] reported an 87% 2-year local control estimate in T1 squamous cell carcinoma and a 79% estimate in T2, following radiation therapy (non-fractionated with 68 Gy median dose,

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