Int. J. Oral Maxillofac. Surg. 2018; xxx: xxx–xxx
https://doi.org/10.1016/j.ijom.2018.01.017, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Research Paper
Head and Neck Oncology

Base of tongue cancer—is it tongue cancer located at the base of the tongue, or is it a type of lingual tonsil cancer? The perspective from a genomic analysis

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K. Kim, K. Y. Choi, J. H. Kim, I. S. Park, Y. S. Rho, D. J. Lee: Base of tongue cancer—is it tongue cancer located at the base of the tongue, or is it a type of lingual tonsil cancer? The perspective from a genomic analysis. Int. J. Oral Maxillofac. Surg. 2018; xxx: xxx–xxx.

Abstract. The aim of this study was to determine whether base of tongue (BOT) cancer is tongue cancer located at the base of the tongue or lingual tonsil cancer originating from tonsil tissue. This was a retrospective study using data from The Cancer Genome Atlas (TCGA). The genomic patterns of three primary cancers (BOT, oral tongue, and tonsil) were compared to determine their similarities and differences. Gene expression data (n = 193; 26 BOT, 125 oral tongue, and 42 tonsil cases), copy number alteration data (n = 142; 19 BOT, 96 oral tongue, and 27 tonsil cases), and somatic mutation data (n = 187; 25 BOT, 122 oral tongue, and 40 tonsil cases) were analyzed using the t-test, heatmap analysis, and OncoPrint, respectively. Clinical information for the three tumour groups was included in the analyses. When using multiplatform analysis, BOT cancer showed nearly the same genomic pattern as tonsil cancer, but not oral tongue cancer. The χ^2 test and survival analysis revealed that BOT cancer had the same clinical and survival patterns as tonsil cancer. In conclusion, BOT cancer showed a genomic pattern similar to that of tonsil cancer, but different to that of oral tongue cancer. Further prospective studies are warranted before the results of this study can be applied in a clinical setting.

Key words: BOT cancer; tongue cancer; tonsil cancer; gene expression; copy number alteration; somatic mutation.

Accepted for publication 26 January 2018

0901-5027/000001+08

Oropharyngeal cancer includes cancers arising from the palatine tonsil, walls of the pharynx, base of the tongue (BOT), and soft palate. In contrast to other head and neck squamous cell carcinomas (HNSCCs), which are usually associated with smoking and alcohol consumption, approximately 60–70% of oropharyngeal cancers are associated with human papillomavirus (HPV) infection[1]. There has been a significant surge in the rate of oropharyngeal cancer in the last few decades, due to an epidemic of HPV[2].

HNSCCs generally have poor treatment outcomes, and as a result, treatment strategies have been intensified, which has unfortunately led to increased treatment-related morbidity[3]. However, for oropharyngeal cancer, particularly for HPV-positive cases, such aggressive treatment may not be needed because there are effective but less morbid treatment modalities, such as chemoradiotherapy. It is well known that tonsil and BOT cancer patients who are positive for HPV have a better prognosis than those who are not. Many studies have reported that patients with HPV-positive tonsil and BOT cancer have a better 3-year disease-specific survival (DSS) compared to corresponding patients with HPV-negative tumours and other HNSCCs (80% vs. 40%, 3-year DSS)[4,5].

However, HPV-positive tumours do not always show a superior prognosis with less morbid treatment modalities. There are several factors that should be considered when selecting patients for de-intensification therapy. Chau et al. reported that a history of smoking and bulky nodal disease have a negative impact on the favourable prognosis associated with HPV[6]. Ljokjel et al. found that a previous history of smoking and age at diagnosis predicted DSS among HPV-positive patients[7]. In this respect, patient selection is critical, especially when considering de-intensification treatment regimens for HPV-positive patients.

In contrast to tonsil cancers, BOT cancers are usually found late because the tumour remains asymptomatic until it reaches an advanced stage and the anatomical location is not easily accessible without an endoscopic system. Another factor contributing to the poor prognosis is that it is difficult to achieve adequate surgical margins, especially when the BOT cancer invades most of the tongue and surrounding structures. In the past, the majority of BOT cancers were resected via an invasive approach method including mandibulotomy or mandibulectomy with a lip-splitting incision[8]. Recently, with the development of surgical procedures, the pull-through (or mandibular lingual release approach) and transoral robotic surgery (TORS) have mostly replaced the conventional aggressive method[9]. Nevertheless, BOT cancer surgery is still usually associated with a much higher morbidity than tonsil cancer surgery.

BOT cancer appears to develop from lingual tonsillar tissue, because most BOT cancers show tumour growth and a metastasis pattern similar to tonsil cancer, especially in HPV-positive cases. However, some BOT cancers are aggressive, invading most of the tongue and surrounding structures, thus needing wide surgical excision including total glossectomy. To effectively combat this disease, there is a need to evaluate the biology of BOT cancer using clinical and genomic data and to compare the data with those of tongue cancer and tonsil cancer.

The aim of this study was to determine whether BOT cancer is tongue cancer located at the base of the tongue or lingual tonsil cancer originating from tonsillar tissue, through the use of multiplatform genomic analysis.

Materials and methods

Genomic and clinical datasets

All genomic data for HNSCCs from three primary sites (BOT, oral tongue, and tonsil) were obtained from The Cancer Genome Atlas (TCGA) Data Portal (https://tcga-data.nci.nih.gov) and the University of California Santa Cruz Cancer Browser (https://genome-cancer.ucsc.edu). Gene-level gene expression data from mRNA sequencing ($n = 193$; 26 BOT, 125 oral tongue, and 42 tonsil cases), copy number (CPN) alteration data ($n = 142$; 19 BOT, 96 oral tongue, and 27 tonsil cases), and somatic mutation data ($n = 187$; 25 BOT, 122 oral tongue, and 40 tonsil cases) were included in the analyses. Clinical data included survival data, sex, age, and stage and primary site of HNSCC (Table 1; Supplementary Material, Data 1).

Analysis of the gene expression data and unsupervised clustering

BRB-ArrayTools (http://linus.nci.nih.gov/BRB-ArrayTools.html) software was used to analyze the gene expression data[10]. ConsensusClusterPlus (Bioconductor) was used to perform unsupervised clustering of gene expression data (6856 genes, two-fold difference in at least 19 cases relative to the median value across tissues) from 193 primary tumours and to find the optimal number of clusters[11]. A heatmap was generated using the Cluster and TreeView programs[12]. Other statistical analyses were performed using the R language environment (http://www.r-project.org).

Selection of specific gene signatures in each cluster

To select genes that were differentially expressed between the three primary sites, multiple two-sample *t*-tests were performed for all possible combinations of the three primary tumour groups. A stringent significance cut-off of $P < 0.001$ was used and there had to be an at least 1.5-fold difference.

Analysis of copy number alterations and somatic mutation data

A heatmap was generated using the Cluster and TreeView programs, as mentioned above[12]. Somatic mutation data were analyzed using OncoPrint at the cBioPortal website (http://www.cbioportal.org/). For the mutational analysis, 125 significantly mutated genes from well-known and emerging cellular processes in cancer were used, based on previously reported data[13].

Survival analysis

The association of each primary tumour (BOT, oral tongue, and tonsil) with overall survival was estimated using Kaplan–Meier plots and the log rank test. Overall survival was defined as the time from surgery to death. Data were censored when a patient was alive without recurrence at last follow-up. A *P*-value of <0.05 was considered to indicate a significant difference. All statistical analyses were conducted in the R language environment (http://www.r-project.org).

Results

Clinical characteristics and survival in relation to the primary site of HNSCC

Table 1 shows the clinical characteristics for each primary site (BOT, oral tongue, and tonsil, $n = 193$) and the results of the statistical analysis. There was no significant difference in mean age between the three groups (Supplementary Material, Fig. S1). In the analysis of the sex distribution, the χ^2 test showed a statistically significant difference between BOT and tonsil cancer versus oral tongue cancer ($P = 0.009$), with both BOT and tonsil cancer having a much higher male to female ratio than oral tongue cancer