



HAL
open science

Therapeutic strategy for advanced stages salivary carcinomas of the tongue: A multicenter REFCOR study

Valentine Poissonnet, Emilien Chabrillac, Emmanuelle Uro-Coste, Virginie Woisard, Antoine Moya-Plana, Florent Espitalier, Joel Castelli, Thibault Dedieu, Sébastien Salas, Renaud Garrel, et al.

► To cite this version:

Valentine Poissonnet, Emilien Chabrillac, Emmanuelle Uro-Coste, Virginie Woisard, Antoine Moya-Plana, et al.. Therapeutic strategy for advanced stages salivary carcinomas of the tongue: A multicenter REFCOR study. *Oral Oncology*, 2024, 159, pp.107072. 10.1016/j.oraloncology.2024.107072 . hal-04824410

HAL Id: hal-04824410

<https://hal.science/hal-04824410v1>

Submitted on 6 Dec 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License



Therapeutic strategy for advanced stages salivary carcinomas of the tongue: A multicenter REFCOR study

Valentine Poissonnet^{a,*}, Emilien Chabrilac^a, Emmanuelle Uro-Coste^b, Virginie Woisard^a, Antoine Moya-Plana^c, Florent Espitalier^d, Joel Castelli^e, Thibault Dedieu^f, Sébastien Salas^g, Renaud Garrel^h, Robin Baudouinⁱ, Gilles Poissonnet^j, Claire Castain^k, Jonathan Barbut^l, Haitham Mirghani^m, Diane Evrardⁿ, Olivier Bouchain^o, Jean Paul Marie^p, Hélène Orliac^q, Philippe Ceruse^r, Xavier Dufour^s, Esteban Brenet^t, Audrey Rambeau^u, Philippe Herman^v, Yazan Abu Shama^w, Chloé Bertolus^x, Sarah Atallah^y, Sylvain Morinière^z, Christian Righini^{aa}, François Mouawad^{ab}, Suzy Duflo^{ac}, Bertille Segier^{ad}, Sébastien Vergez^a

^a Otolaryngology, Head and Neck Surgery Department, University Cancer Institute Toulouse and Toulouse University Hospital, Larrey Hospital, Toulouse, France

^b Department of Anatomical Pathology, University Cancer Institute Toulouse, Toulouse France

^c Head and Neck Oncology Department, Gustave-Roussy Institute, Villejuif, France

^d Otolaryngology, Head and Neck Surgery Department, University Hospital of Nantes, France

^e Department of Radiation Oncology, Centre Eugene Marquis, Rennes, France

^f Otolaryngology, Head and Neck Surgery Department, University Hospital of Strasbourg, France

^g AP-HM, Aix-Marseille University, Department of Medical Oncology, Marseille, France

^h Otolaryngology, Head and Neck Surgery Department, University Hospital of Montpellier, France

ⁱ Otolaryngology, Head and Neck Surgery Department, Foch Hospital, Paris, France

^j Otolaryngology, Head and Neck Surgery Department, Head and Neck University Institute, Nice, France

^k Department of Anatomical Pathology, Bordeaux University Hospital-CHU, F-33000, Bordeaux, France

^l Otolaryngology, Head and Neck Surgery Department, Hospital of Toulon, France

^m Otolaryngology, Head and Neck Surgery Department, George Pompidou European Hospital, Paris, France

ⁿ Otolaryngology, Head and Neck Surgery Department, Bichat Hospital, Paris, France

^o Head and Neck Surgery Department, CHU Sart Tilman, University Liege, Belgium

^p Otolaryngology, Head and Neck Surgery Department, University Hospital of Rouen, France

^q Department of Radiation Therapy, University Hospital of Limoges, France

^r Otolaryngology, Head and Neck Surgery Department, University Hospital of Lyon, France

^s Otolaryngology, Head and Neck Surgery Department, University Hospital of Poitiers, France

^t Otolaryngology, Head and Neck Surgery Department, University Hospital of Reims, France

^u Oncology Department, François Baclesse Centre, Caen, France

^v Otolaryngology, Head and Neck Surgery Department, Lariboisière Hospital, 2 rue Ambroise Paré, 75010 Paris, France

^w Otolaryngology, Head and Neck Surgery Department, University Hospital of Nancy, France

^x Department of Oral and Maxillo-Facial Surgery, Pitié-Salpêtrière Hospital, APHP, Sorbonne Université, France

^y Head and Neck Surgery Department, Tenon Hospital, APHP, Sorbonne University, Paris, France

^z Otolaryngology, Head and Neck Surgery Department, University Hospital of Tours, France

^{aa} Otolaryngology, Head and Neck Surgery Department, University Hospital of Grenoble, France

^{ab} Otolaryngology, Head and Neck Surgery Department, University Hospital of Lille, France

^{ac} Otolaryngology, Head and Neck Surgery Department, University Hospital of Point-à-Pitre, France

^{ad} Statistical Department, Institut Claudius Regaud, University Institute of Cancer, Toulouse, France

ARTICLE INFO

Keywords:

Minor salivary gland
Salivary gland carcinoma
Tongue

ABSTRACT

Introduction: Salivary carcinomas of the tongue represent a therapeutic challenge as their radical excision is particularly mutilating. We aimed to study the oncologic and functional outcomes of advanced stages salivary carcinomas of the tongue.

* Corresponding author.

E-mail address: valentine.poissonnet@gmail.com (V. Poissonnet).

<https://doi.org/10.1016/j.oraloncology.2024.107072>

Received 6 May 2024; Received in revised form 30 September 2024; Accepted 4 October 2024

Available online 20 October 2024

1368-8375/© 2024 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Locally-advanced stage
Totalglossectomy

Materials and methods: This retrospective multicentric study, based on the French national network on rare head and neck cancers (REFCOR), included all patients with a T3-T4 salivary carcinoma of the tongue, diagnosed between January 2009 and December 2018.

Results: In total, 47 patients were included, of which 44.7 % underwent surgery. Histologies were mostly adenoid cystic carcinomas (61.7 %), followed by other adenocarcinomas (27.7 %) and mucoepidermoid carcinomas (10.6 %). Median follow-up duration was 63.9 months. In multivariable analysis, surgery was significantly associated with better Recurrence-Free Survival (HR = 0.23, 95 %CI [0.09;0.55]) and Local/Regional Recurrence-Free Survival (HR = 0.31, 95 %CI [0.10;0.95]). The rate of distant metastasis at the end of follow-up was 61.9 % in the surgical group and 57.7 % in the non-surgical group. The Distant Metastasis Free Survival was 54.9 % [38.3;68.7], without statistical difference between both groups. There were similar rates of definitive gastrostomies but the rate of normal oral diet at the last follow-up seemed higher in the surgery group (38.1 % vs 15.4 %).

Conclusion: Radical surgery in that population mainly aims to improve local/regional control, which may result in better long-term swallowing functions. About half of these tumors may be associated with occult distant metastasis at initial presentation. More studies are warranted to establish the role of postoperative RT and non-surgical treatment with concurrent CRT.

Introduction

The tongue is a key organ for speech and swallowing, and its use is essential for human interaction [1]. During the oral phase, it allows perception of the bolus (size, consistency, flavor), then its position and propulsion through the pharynx into the esophagus [2]. Bolus transit is dependent upon the tongue and pharyngeal pressure, allowing the integrity of the swallowing process [3]. Malignant tongue tumors constitute a therapeutic challenge, because the functional aspects must be weighed against the expected oncological outcomes. Radical excision, which consists of partial or total glossectomy, sometimes associated with total laryngectomy, may lead to significant morbidity and loss of function, associated with troublesome psychological and social disability [4–6]. Some authors reported a better control of the disease with radical excision followed by radiotherapy (RT), but this strategy is based on few retrospective and biased studies [7,8].

When treating a tongue squamous cell carcinomas, if the surgery is considered too disabling, a conservative treatment with chemoradiotherapy (CRT) is a satisfactory option for both functional and oncological outcomes [9,10]. However, salivary carcinomas are less radiosensitive and chemosensitive [11,12], making the therapeutic decision less obvious. Moreover, almost half of salivary carcinomas of the tongue are diagnosed at an advanced stage (mostly mucoepidermoid carcinomas, adenoid cystic carcinomas and adenocarcinomas) [13,14], involving extensive lingual resections. Due to the high incidence of distant metastasis and recurrences during the clinical course of these tumors, surgeons and oncologists must be aware of both oncological and functional outcomes to expect when contemplating a radical and mutilating surgery [15].

Since salivary tumors of the tongue are often diagnosed at a late stage, and mainly arise from the base of tongue, the functional outcomes are a common concern in the therapeutic decision-making of locally advanced tumors i.e., T3-T4 status according to the 2009 (7th edition) American Joint Committee on Cancer (AJCC) classification [8,12,13]. To this date, no study addressed that specific question. Therefore, we aimed to study the oncologic and functional outcomes of patients with locally advanced (T3-T4) salivary carcinomas of the tongue, using the multicentric database of the French National Network on rare head and neck cancers (REFCOR).

Materials and methods

This was a multicentric retrospective study, collecting data using the French National Network on rare head and neck cancers (REFCOR), a French prospective enrolment multicentric cohort, in 33 French reference centers for head and neck cancer treatment (listed in [Table A of Supplementary Data](#)). Inclusion was performed by each center with a standardized questionnaire after an informed consent form was

delivered, followed by data anonymization. Patients were treated according to national guidelines from the REFCOR, after discussion in a multidisciplinary board [16,17]. A recourse to a specific national multidisciplinary meeting was sought in case of complex situations. Dubious slides were reviewed by expert pathologists from the REFCORpath group to ensure diagnostic accuracy. This study has been approved in December 2020 by the REFCOR Scientific Board.

We included all patients with a locally advanced (T3-T4) salivary gland carcinoma arising from the tongue (oral tongue or base of tongue) between January 2009 and December 2018. The exclusion criteria were as follows: distant metastasis at initial presentation, treatment without curative intent, history of head and neck RT for another disease, lack of clinical or follow-up data.

All data were collected within each center by the same senior investigator (first author). Patient's characteristics that were recorded included demographics, body mass index (BMI), comorbidities according to the Charlson Comorbidity Index (CCI) [18], tobacco and alcohol use, Performance Status (PS), clinical signs at presentation. Tumor grade was reported according to the WHO 2005 Classification [19], and TNM status according to the 2009 (7th edition) AJCC staging system. We collected data regarding the therapeutic strategy (type of resection, neck dissection, reconstruction, RT, systemic therapy) as well as oncological and functional outcomes i.e., use of tracheostomy, nasogastric tube, gastrostomy, quality of speech and swallowing at the last follow-up visit. Speech and swallowing outcomes were assessed by the physician or the speech therapist, when available.

Kruskal-Wallis and Chi-2 or exact Fisher tests were assessed to compare groups for quantitative and qualitative variables, respectively. Overall Survival (OS), Recurrence-Free survival (RFS), LocoRegional Recurrence-Free Survival (LRRFS) and Distant Metastasis-Free Survival (DMFS) were calculated from initial diagnosis to the first event (death from any cause for OS, recurrence or death for RFS, local or regional recurrence for LRRFS, distant metastasis recurrence for DMFS). Univariable and multivariable survival analyses were performed using the Logrank test and Cox proportional hazards model, respectively. The variables selection for multivariable analysis was made using a 10 % significance level in univariable analysis. To compare survival outcomes according to surgery, Cox proportional hazards with time-dependent variable (TD Cox model) and a 6-month Landmark analysis were used to address the immortal time bias introduced by the time between diagnosis and surgery. TD Cox model was used to perform univariable and multivariable analyses, including surgery as a time-varying variable, allowing patients to move from non-surgical group to the surgical group over time. The Landmark approach was used, in addition, to represent survival outcomes graphically, by surgery group, using Kaplan-Meier method. For the 6-month Landmark analysis, patients who were treated with surgery 6 months after diagnosis or who did not have surgical procedure at all were classified in the non-surgical group and

patients who died, recurred or were lost to follow-up before 6 months were excluded. All statistical tests were two-sided and a p-value strictly lower than 5 % was considered statistically significant. All statistical analyses were carried out using STATA software version 16.

Results

A total of 152 patients from 33 centers (Supplementary data, Table A) were screened using the French National Network on rare head and neck cancers with the key-words “tongue” and “base of tongue”. Among them, 47 patients met the inclusion criteria and were considered for final analysis. Reasons for exclusion were T1-T2 tumors (n = 51), non-salivary histology upon expert pathologic review (n = 24), location other than tongue (n = 3), duplicate (n = 2), insufficient data (n = 20) and distant metastasis at initial presentation/palliative treatment (n = 5).

Clinical characteristics

Table 1 shows the main characteristics of patients and tumors. Tumors were 29 adenoid cystic carcinomas (ACC), 5 mucoepidermoid carcinomas (MEC), and 13 other adenocarcinomas (OA). In details, the latter comprised adenocarcinomas not otherwise specified (n = 6), polymorphous (n = 1), cribriform (n = 2), mucinous (n = 2), clear cell (n = 1) and acinous (n = 1) adenocarcinomas. Patients were mainly females (57.4 %, gender ratio F/M = 1.35). The median age at diagnosis was 66 years (range 36 – 82). Most of them had a PS Score of 0 (85.1 %). There was no significant difference in the patient and tumor characteristics between the surgical and the non-surgical groups, except for midline-crossing tumor (more common in the non-surgical group, p = 0.006). There was a statistical trend for a younger age in the surgical group (p = 0.085).

Treatment characteristics

Table 2 shows surgery-related data. The surgical group comprises 21 patients (44.7 %) who underwent primary surgery. Of note, one third of them (33.3 %) underwent total or subtotal glossectomy. A postoperative treatment was administered in 95.2 % of cases. In the non-surgical group, 10 patients underwent RT alone (38.5 %) and 16 received CRT (61.5 %).

Functional outcomes

Table 3 displays the functional outcomes at the last follow-up visit. A tracheostomy was performed in 22 patients (46.8 %), mainly in the surgical group (85.7 %). All patients were decannulated at the last follow-up visit, except 1 in the non-surgical group. A total of 23 patients (48.9 %) required a gastrostomy during or after treatment i.e., 13 in the surgical group (50.0 %), and 10 in the non-surgical group (47.6 %). At last follow-up visit, the rate of gastrostomy-tube dependency was equivalent between surgical and non-surgical groups (28.6 % vs 26.9 %). Speech impairment was mild (48.9 %) or moderate (48.9 %), without difference between surgical and non-surgical approach. The chances to resume normal oral diet were more than 2.5 times higher in the surgical group (38.1 % vs 15.4 %), though this did not reach statistical significance (p = 0.147).

Survival outcomes

After a median follow-up of 63.9 months (95 %CI [39.1;93.9]), 36 patients (76.6 %) presented with a recurrence of the disease and 11 patients (23.4 %) died. All patients who died had a progressive disease at the time of death. The median RFS was 23.9 months (95 %CI [17.1;37.2]). The 3-year OS, RFS, LRRFS and DMFS were 2.3 % [77.7; 97.5], 38.8 % [24.2; 53.1], 70.5 % [54.5; 81.8] and 54.9 % [38.3; 68.7],

Table 1

Main characteristics of patients and tumors.

Clinical characteristics	All patients n = 47 (%)	Non-surgical group n = 26 (%)	Surgical group n = 21 (%)	p-value
Age: median age [range]	66.0 [36.0–82.0]	68.0 [37.0–82.0]	60.0 [36.0–79.0]	0.085
BMI: median BMI (n = 45) [range]	23 [16.4–35.5]	23.2 [16.4–35.5]	22.9 [17.6–32.7]	0.818
Missing	2	0	2	
CCI:				0.285
0	2 (4.3)	1 (3.8)	1 (4.8)	
1	3 (6.4)	0 (0.0)	3 (14.3)	
2	7 (14.9)	3 (11.5)	4 (19.0)	
3	20 (42.6)	12 (46.2)	8 (38.1)	
≥ 4	15 (31.9)	10 (38.5)	5 (23.8)	
Alcohol consumption:				0.437
Yes	8 (17.0)	3 (11.5)	5 (23.8)	
Occasionally/No	39 (83.0)	23 (88.5)	16 (76.2)	
Tobacco consumption:				0.237
Yes	18 (38.3)	8 (30.8)	10 (47.6)	
Pre-treatment PS Score:				1
0	40 (85.1)	22 (84.6)	18 (85.7)	
≥ 1	7 (14.9)	4 (15.4)	3 (14.3)	
Histology:				0.516
ACC	29 (61.7)	16 (61.5)	13 (61.9)	
MEC	5 (10.6)	4 (15.4)	1 (4.8)	
OA	13 (27.7)	6 (23.1)	7 (33.3)	
Tumor site:				0.158
Base of tongue	42 (89.4)	25 (96.2)	17 (81.0)	
Oral tongue	5 (10.6)	1 (3.8)	4 (19.0)	
Midline-crossing tumor:				0.006
Yes	36 (76.6)	24 (92.3)	12 (57.1)	
Tumor extension:				
–Vallecula	14 (29.8)	10 (38.5)	4 (19.0)	0.148
–Glossotonsillar sulcus	18 (38.3)	9 (34.6)	9 (42.9)	0.563
–Tonsil	10 (21.3)	7 (26.9)	3 (14.3)	0.475
–Floor of the mouth	20 (42.6)	10 (38.5)	10 (47.6)	0.528
T-status:				0.579
T3	22 (46.8)	11 (42.3)	11 (52.4)	
T4a	22 (46.8)	14 (53.8)	8 (38.1)	
T4b	3 (6.4)	1 (3.8)	2 (9.5)	
N-status:				0.34
N0	26 (55.3)	16 (61.5)	10 (47.6)	
N+	21 (44.7)	10 (38.5)	11 (52.4)	
Grade (n = 39)				0.443
Low	5 (12.8)	4 (20.0)	1 (5.3)	
Intermediate	26 (66.7)	13 (65.0)	13 (68.4)	
High	8 (20.5)	3 (15.0)	5 (26.3)	
Missing	8	6	2	

BMI: Body Mass Index; PS: performance status score. CCI: Comorbidity Charlson Index; MEC: mucoepidermoid carcinoma; ACC: adenoid cystic carcinoma; OA: other adenocarcinomas; p-value: determined by Kruskal-Wallis test for quantitative variables and Chi-2 or exact Fisher for qualitative variables.

respectively.

In univariable analyses, OS did not differ between the surgical and non-surgical groups (HR 0.56 [0.16;1.93], p = 0.357 in TD Cox model and HR 0.56 [0.16; 1.92], p = 0.349 in 6-month Landmark approach). However, RFS was significantly better in the surgical group (HR 0.20 [0.09; 0.48], p < 0.001 and HR 0.21 [0.09; 0.49], p < 0.001 in TD Cox model and 6-month Landmark approach respectively). LRRFS was also significantly better in the surgical group with the 6-month landmark approach (HR 0.25 [0.09; 0.72], p = 0.005) and the TD Cox-model (HR 0.26 [0.09; 0.73], p = 0.011). Most patients had distant metastasis at the end of follow-up (61.9 % in the surgical group versus 57.7 % in the non-surgical group). The 3-year DMFS was 64.3 % [39.0; 81.3] and 47.5 % [24.0; 67.8] (p = 0.219). No difference was observed in the DMFS between both groups with the 6-month landmark approach (HR 0.61 [0.28; 1.35], p = 0.219) and the TD Cox-model (HR 0.58 [0.27;1.27], p = 0.172). Fig. 1 shows OS, RFS, LRRFS and DMFS in the surgical and non-surgical groups using a 6-month Landmark approach.

Table 2
Initial treatment modalities for the surgical group.

	T3-T4 status Surgical group n = 21 (%)
Approach	
– Partial glossectomy	15 (71.4)
– (S)TG	6 (28.6)
– Neck dissection	21 (100.0)
Reconstruction	
No flap	3 (15.0)
Pedicled flap	3 (15.0)
Free flap	14 (70.0)
Missing	1
Pathology	
<i>Tumor size (mm) (n = 20)</i>	
Median [range]	41.0 [7.5;60.0]
Missing	1
<i>Surgical margins (n = 17)</i>	
< 1 mm	9 (52.9)
1–5 mm	8 (47.1)
Missing	4
<i>ECE (if neck dissection) (n = 20)</i>	
Yes	8 (40.0)
Missing	1
<i>LVI (n = 13)</i>	
Yes	5 (38.5)
Missing	8
<i>PNI (n = 19)</i>	
Yes	15 (78.9)
Missing	
Post-operative therapy (n = 20)	
–RT alone	15 (71.4)
–CRT	5 (23.8)

ECE: extracapsular extension; LVI: lymphovascular embolism;

PNI: perineural invasion

PG: partial glossectomy; (S)TG: (sub)total glossectomy.

RT: radiotherapy; CRT: chemoradiotherapy.

Table 3
Functional outcomes at the last follow up-visit.

Functional outcomes	All treatments n = 47 (%)	Non-surgical strategy (n = 26)	Surgical strategy (n = 21)
Tracheostomy:			
– Temporary	21 (44.7)	3 (11.5)	18 (85.7)
– Definitive	1 (2.1)	1 (3.8)	0 (0.0)
Feeding during treatment:			
– No enteral support	15 (31.9)	13 (50.0)	2 (9.5)
– Nasogastric tube only	9 (19.1)	0 (0.0)	9 (42.9)
– Gastrostomy after nasogastric feeding tube	8 (17.0)	3 (11.5)	5 (23.8)
– Upfront gastrostomy	15 (31.9)	10 (38.5)	5 (23.8)
Definitive gastrostomy:			
Yes	13 (27.6)	7 (26.9)	6 (28.6)
Speech quality impairment:			
–Mild	23 (48.9)	13 (50.0)	10 (47.6)
–Moderate	23 (48.9)	13 (50.0)	10 (47.6)
–Severe	1 (2.1)	0 (0.0)	1 (4.8)
Food intake:			
– Oral, all textures	12 (25.5)	4 (15.4)	8 (38.1)
– Oral, restricted textures	22 (46.8)	15 (57.7)	7 (33.3)
– Oral and enteral	3 (6.4)	2 (7.7)	1 (4.8)
– Mainly enteral, oral intake for pleasure only	7 (14.9)	4 (15.4)	3 (14.3)
– Enteral only	3 (6.4)	1 (3.8)	2 (9.5)

Results of univariable analysis of RFS and OS are shown in Table 4. Glossotonsillar sulcus involvement and N + status were associated with poorer OS while midline crossing tumors had a tendency for poorer RFS ($p = 0.061$). In multivariable analysis, surgery remained significantly associated with better RFS (HR 0.23 [0.09; 0.55], $p = 0.001$) and better

LRRFS (HR 0.31 [0.10; 0.95], $p = 0.041$) after adjustment for midline-crossing feature of the tumor. Multivariable analysis was not performed for OS and DMFS due to the small number of events.

Description of recurrences

The presence and site of recurrence are presented in Fig. 2. Recurrence occurred in 36 patients (76.6 %). Out of the 14 patients who received primary surgery and experienced a disease recurrence, 4 underwent salvage surgery of the recurrence (28.6 %, all of them being distant metastasis of ACC), 2 underwent radiation therapy (14.3 %), 4 received chemotherapy (28.6 %), 2 underwent immunotherapy (14.3 %), and 2 received palliative care (14.3 %). Of the 22 patients in the non-surgical group who presented with a recurrence, 4 underwent salvage surgery (3 for local and 1 for regional recurrence), 4 received RT (18.2 %), 5 underwent chemotherapy alone (22.7 %), 4 received immunotherapy (18.2 %), and 5 received palliative care (22.7 %, only ACC).

Discussion

Salivary carcinomas of the tongue are uncommon, but carry a dismal prognosis with a high risk of recurrence. More than half of them are diagnosed at an advanced stage (T3-T4) [12,13] because of their un-specific clinical presentation, with a slowly growing submucosal mass, frequently located deep in the base of tongue, leading to a significant diagnostic delay [20]. Indeed, tumors of the mobile tongue are diagnosed more easily.

In this national cohort of T3-T4 salivary carcinomas of the tongue, most patients from the cohort (76.9 %) presented with a recurrence during their follow-up, with a median follow-up exceeding 5 years (63.9 months [39.1;93.9]). Surgery was significantly associated with better RFS (HR 0.23 [0.09; 0.55], $p = 0.001$) and better LRRFS (HR 0.31 [0.10; 0.95], $p = 0.041$). Interestingly, the rate of distant metastasis at the end of follow-up was similar between surgical and non-surgical groups (61.9 % vs 57.7 %, respectively), and so was the 3-year DMFS. This high rate of distant metastasis occurring without local/regional failure in the surgery group suggests that about half of T3-T4 salivary carcinomas of the tongue may be associated with occult distant metastasis at initial presentation. This is partly explained by the long follow-up duration (>5 years) and the high rate of ACC (61.7 %), known for their propensity to develop distant metastasis [21]. Altogether, our study shows that radical surgery in that population mainly aims to improve local/regional control. A better local control may in turn improve the long-term swallowing functions, as the chances to resume normal oral diet were 2.5 times higher in the surgical group (38.1 % vs 15.4 %), though this did not reach statistical significance.

Given the rarity of these tumors, little is known regarding the optimal treatment regimen, making their management particularly challenging. Upfront surgery with en-bloc surgical excision is considered the mainstay of treatment [17]. However, it should be performed only when clear margins are achievable, as this is a significant predictor of OS [22–24]. Similarly to the N + status of the disease, glossotonsillar sulcus involvement was predictive for poor OS in our series. This could be explained by its close anatomical relation to the carotid artery, which limits the deep excisional margins. Postoperative RT indications are still controversial [20]. Some recommend it in case of advanced stage and positive margins [25,26], but others reported a consistently increased local control rate at 5 and 10 years and recommend it for all patients [27].

Even if many of these tumors respond to RT, remission is rarely obtained by definitive RT [28]. Particle therapy (protons and carbon ions) are not easily accessible but represent a promising option to treat salivary gland cancer, thanks to their better dose distribution and a better radiobiological effectiveness [29,30]. In a series of locally advanced ACC of the tongue base, carbon-ion RT provided a 92 %-rate of 5-year local control rate, with little toxicity [31].

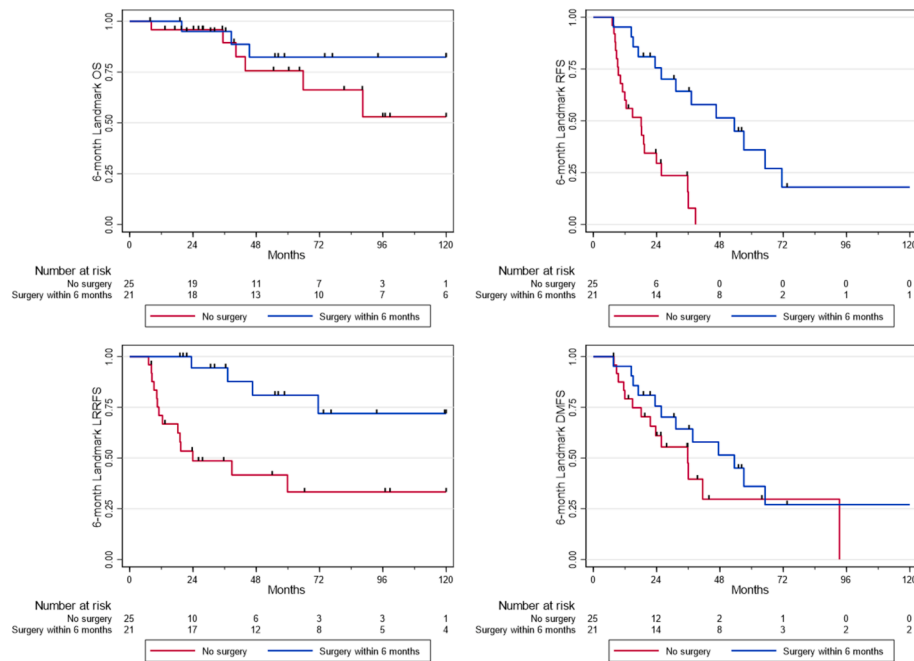


Fig. 1. Overall Survival (OS), Recurrence-Free Survival (RFS), LocoRegional Recurrence-Free Survival (LRRFS) and Distant Metastasis-Free Survival (DMFS) using a Landmark approach at 6 months.

Table 4

Univariable analysis of OS and RFS in patients treated for a T3-T4 tongue salivary gland carcinoma.

Factors	OS		RFS		LRRFS	
	HR [95 %CI]	p-value	HR [95 %CI]	p-value	HR [95 %CI]	p-value
Age at diagnosis:	1.03 [0.97;1.10]	0.295	1.02 [0.99;1.05]	0.245	1.03 [0.98;1.07]	0.26
BMI:	0.93 [0.81;1.08]	0.36	1.04 [0.96;1.12]	0.34	0.94 [0.83; 1.06]	0.298
Alcohol consumption: Yes versus No/Occasionally	2.07 [0.60;7.17]	0.239	1.1 [0.45;2.68]	0.841	0.82 [0.24; 2.86]	0.759
Smoker: Yes versus No	1.1 [0.33;3.61]	0.877	0.95 [0.47;1.90]	0.875	0.64 [0.24; 1.72]	0.373
PS score: 1–2 versus 0	3.39 [0.79;14.48]	0.081	1.67 [0.67;4.16]	0.266	1.07 [0.31; 3.72]	0.919
Tumor site: Oral tongue versus base of tongue	2.01 [0.43;9.42]	0.368	0.95 [0.33;2.71]	0.919	0.96 [0.22; 4.24]	0.957
Midline-crossing tumor Yes versus No	2.17 [0.46;10.24]	0.317	2.19 [0.94;5.09]	0.061	3.28 [0.75; 14.30]	0.095
Tumor extension:						
– Vallecule: Yes versus No	0.67 [0.14;3.18]	0.613	1.54 [0.74;3.22]	0.247	1.35 [0.50; 3.63]	0.546
– Glossotonsillar sulcus: Yes versus No	3.61 [1.00;13.06]	0.037	1.5 [0.76;2.96]	0.243	0.69 [0.25; 1.95]	0.487
– Tonsil: Yes versus No	2.18 [0.54;8.73]	0.261	1.28 [0.58;2.85]	0.544	2.21 [0.77; 6.30]	0.129
– Floor of the mouth: Yes versus No	0.69 [0.18;2.61]	0.582	0.68 [0.33;1.41]	0.297	0.65 [0.25; 1.70]	0.373
N-status: N + versus N0	6.03 [1.58;23.08]	0.003	1.25 [0.64;2.46]	0.512	1.5 [0.60; 3.73]	0.38

BMI: Body Mass Index; PS: performance status; MEC: mucoepidermoid carcinoma; ACC: adenoid cystic carcinoma; OA: other adenocarcinoma; OS: overall survival; RFS: recurrence-free survival. Significant p-values are highlighted in bold, statistical trends are highlighted in italic.

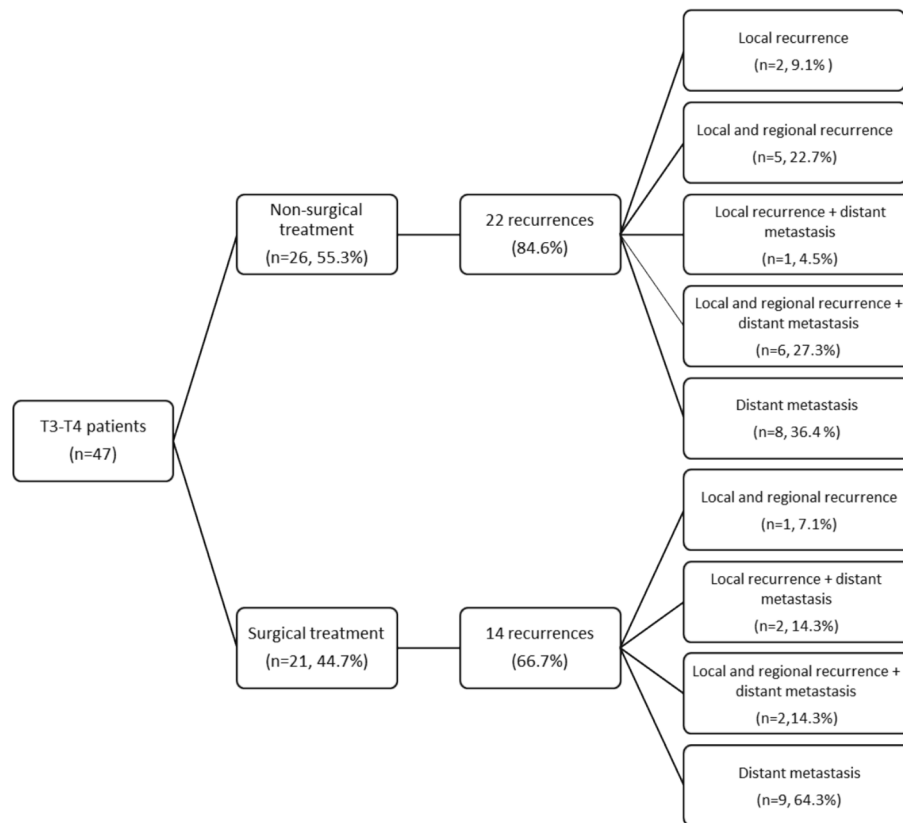


Fig. 2. Pattern of recurrence according to the primary treatment.

Concurrent CRT is an alternative for organ preservation or when the tumor is unresectable, but no series in the literature exceeded 15 patients, and all of them focused on ACC, mixed different tumor locations and/or used atypical treatment regimens [30–34]. In other words, the outcomes of CRT as primary treatment of salivary cancers of the tongue are widely unknown [20]. The potential efficacy of primary CRT has been extrapolated from the experience with squamous cell carcinoma of the head and neck [9,10], despite the fact that chemotherapy is poorly effective in the treatment of salivary cancers, with uncommon objective responses, but a frequent stabilization of the disease [32,35,36]. While CRT may avoid a mutilating surgery, it is also associated with a significant toxicity and poor functional outcomes, especially in the cases of locoregional failure [37,38]. In our series, the rates of definitive gastrostomy and tracheostomy were identical in the surgical and non-surgical groups. However, resuming a normal oral diet seemed more than twice as likely in the surgical group (38.1 % vs 15.4 %). This can be attributed to the high rate of local/regional failure in the non-surgical group as well as the performance of current reconstruction techniques, allowing to restore the tongue volume and its contact with the palate.

In our series, there was no significant difference in the distribution of histologies, PS score, T status between the surgical and the non-surgical groups, which demonstrates that selection bias was limited. Indeed, it shows that an impaired patient's general condition and a larger tumor size were not the reasons for choosing a non-surgical treatment. The only significant clinical difference between the two groups was the midline-crossing feature of the tumor, which was significantly more common in the non-surgical group ($p = 0.006$), and also associated with a statistical trend for poorer RFS ($p = 0.061$). As excising these tumors usually requires a total glossectomy, we can assume that the mutilating nature of the procedure led the surgeon to prefer a conservative treatment, or led to the patient's refusal of surgery.

Total glossectomy has been reported to be associated with a social isolation and psychological distress, and a major alteration of the quality

of life [6]. However, the quality of life of patients without local/regional control of the disease is also reported to be poor, with impaired general condition, pain, bleeding risk, swallowing and breathing difficulties, leading to repeated hospitalizations [39]. Therefore, radical surgery and concurrent CRT should always be considered.

The staging with MRI is paramount for decision-making. ACC, which are frequently found at the base of the tongue and are the main histology in our series, present with perineural invasion in almost half of the cases [40], which can lead to unexpectedly extended resections or microscopically positive surgical margins.

Weaknesses of this study are the small number of patients/events, the heterogeneity of histologies and its retrospective nature. Though we were not able to find out precisely the reason why patients from the non-surgical group did not undergo surgery, the selection bias was probably limited i.e., PS scores and T-status were similar in both groups. The functional assessments were not comprehensive and lacked evaluation of the quality of life. Finally, a longer follow-up may highlight more recurrences, especially as late recurrences may occur decades after the primary treatment [41].

The strengths of our study are the expert pathologist review upon inclusion, the homogeneity of patient management thanks to national REFCOR guidelines and national multidisciplinary boards [16], and the homogeneity of tumor location.

Conclusion

In this national cohort of T3-T4 salivary carcinomas of the tongue, surgery was significantly associated with better RFS and LRRFS, but did not improve OS. About half of these tumors may be associated with occult distant metastasis at initial presentation. Altogether, our study shows that radical surgery in that population mainly aims to improve local/regional control and long-term swallowing functions. More studies are warranted to establish the role of postoperative RT and non-surgical

treatment with concurrent CRT.

CRedit authorship contribution statement

Valentine Poissonnet: Writing – original draft, Methodology, Investigation, Data curation. **Emilien Chabrilac:** Writing – review & editing, Supervision, Formal analysis. **Emmanuelle Uro-Coste:** Writing – review & editing. **Virginie Woisard:** Writing – review & editing, Conceptualization. **Antoine Moya-Plana:** Writing – review & editing. **Florent Espitalier:** Writing – review & editing. **Joel Castelli:** Writing – review & editing. **Thibault Dedieu:** Writing – review & editing. **Sébastien Salas:** Writing – review & editing. **Renaud Garrel:** Writing – review & editing. **Robin Baudouin:** Writing – review & editing. **Gilles Poissonnet:** Writing – review & editing. **Claire Castain:** Writing – review & editing, Conceptualization. **Jonathan Barbut:** Writing – review & editing. **Haitham Mirghani:** Writing – review & editing. **Diane Evrard:** Writing – review & editing. **Olivier Bouchain:** Writing – review & editing. **Jean Paul Marie:** Writing – review & editing. **Hélène Orliac:** Writing – review & editing. **Philippe Ceruse:** Writing – review & editing. **Xavier Dufour:** Writing – review & editing. **Esteban Brenet:** Writing – review & editing. **Audrey Rambeau:** Writing – review & editing. **Philippe Herman:** Writing – review & editing. **Yazan Abu Shama:** Writing – review & editing. **Chloé Bertolus:** Writing – review & editing. **Sarah Atallah:** Writing – review & editing. **Sylvain Morinière:** Writing – review & editing. **Christian Righini:** Writing – review & editing. **François Mouawad:** Writing – review & editing. **Suzy Duflo:** Writing – review & editing. **Bertille Segier:** Software, Methodology, Formal analysis, Data curation. **Sébastien Vergez:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the French National Cancer Institute (INCa) for funding the REFCOR, and all REFCOR members for their collaboration.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.oraloncology.2024.107072>.

References

- [1] Naqvi Y, Gupta V. Functional Voice Disorders. *Functional Impairment: Management, Types and Challenges* 2022;43–80. doi: 10.1017/s0022215100096122.
- [2] Shaw SM, Martino R. The normal swallow: Muscular and neurophysiological control. *Otolaryngol Clin North Am* 2013;46:937–56. <https://doi.org/10.1016/j.otc.2013.09.006>.
- [3] McConnel FMS. Analysis of pressure generation and bolus transit during pharyngeal swallowing. *Laryngoscope* 1988;98:71–8. <https://doi.org/10.1288/00005537-198801000-00015>.
- [4] Wang J, Luo H, Liu F, Fu K, Zhang M. Quality of life in oral cancer patients-effects of tongue resection and sociocultural aspects. *J Craniofac Surg* 2013;24:e493–6. <https://doi.org/10.1097/SCS.0B013E31829429AA>.
- [5] Li W, Yang Y, Xu Z, Liu F, Cheng Y, Xu L, et al. Assessment of quality of life of patients with oral cavity cancer who have had defects reconstructed with free anterolateral thigh perforator flaps. *Br J Oral Maxillofac Surg* 2013;51:497–501. <https://doi.org/10.1016/j.bjoms.2012.09.005>.
- [6] Suzuki K, Nishio N, Kimura H, Tokura T, Kishi S, Ozaki N, et al. Comparison of quality of life and psychological distress in patients with tongue cancer undergoing a total/subtotal glossectomy or extended hemiglossectomy and free flap transfer: A prospective evaluation. *Int J Oral Maxillofac Surg* 2022. <https://doi.org/10.1016/j.ijom.2022.11.010>.
- [7] Bradley PJ. Adenoid cystic carcinoma of the head and neck: A review. *Curr Opin Otolaryngol Head Neck Surg* 2004;12:127–32. <https://doi.org/10.1097/00020840-200404000-00013>.
- [8] Goldblatt LI, Ellis GL. Salivary gland tumors of the tongue. Analysis of 55 new cases and review of the literature. *Cancer* 1987;60:74–81. [https://doi.org/10.1002/1097-0142\(19870701\)60:1<74::aid-cnrcr2820600113>3.0.co;2-b](https://doi.org/10.1002/1097-0142(19870701)60:1<74::aid-cnrcr2820600113>3.0.co;2-b).
- [9] J P Pignon, J Bourhis, C Dromex LD. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. *Meta-Analysis of Chemotherapy on Head and Neck Cancer*. *Lancet* 2000;355:949–55.
- [10] Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, et al. Final results of the 94–01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol* 2004;22:69–76. <https://doi.org/10.1200/JCO.2004.08.021>.
- [11] Ferrell JK, Mace JC, Clayburgh D. Contemporary treatment patterns and outcomes of salivary gland carcinoma: A National Cancer Database review. *European Archives of Oto-Rhino-Laryngology : Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): Affiliated with the German Society for Oto-Rhino-Laryngology - Head Neck Surg* 2019;276:1135–46. <https://doi.org/10.1007/s00405-019-05282-2>.
- [12] Kessler DJ, Mickel RA, Calcaterra TC. Malignant salivary gland tumors of the base of the tongue. *Archives of Otolaryngology (Chicago, Ill : 1960)* 1985;111:664–6. doi: 10.1001/ARCHOTOL.1985.00800120058006.
- [13] De Vries EJ, Johnson JT, Myers EN, Barnes EL, Mandell-Brown M. Base of tongue salivary gland tumors. *Head Neck Surg* 1987;9:329–31. <https://doi.org/10.1002/HED.2890090604>.
- [14] Goepfert H, Giraldo AA, Byers RM, Luna MA. Salivary gland tumors of the base of the tongue. *Archives of Otolaryngology (Chicago, Ill : 1960)* 1976;102:391–5. doi: 10.1001/ARCHOTOL.1976.00780120039002.
- [15] Matsuba HM, Simpson JR, Mauney M, Thawley SE. Adenoid cystic salivary gland carcinoma: A clinicopathologic correlation. *Head Neck Surg* 1986;8:200–4. <https://doi.org/10.1002/hed.2890080312>.
- [16] Vergez S, Chabrilac E, Fakhry N. Salivary gland cancer: Recommendations by formal consensus, for the French Network of Rare Head and Neck Tumors (REFCOR). *Eur Ann Otorhinolaryngol Head Neck Dis* 2023;S1879-7296(23)00164-3. doi: 10.1016/j.anorl.2023.11.012.
- [17] Pham Dang N, Jegoux F, Barry B, Verillaud B, Baujat B, Fakhry N, et al. Surgery of sublingual and minor salivary gland cancer: REFCOR recommendations by the formal consensus method. *Eur Ann Otorhinolaryngol Head Neck Dis* 2023;S1879-7296(23)00163-1. doi: 10.1016/j.anorl.2023.11.011.
- [18] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 1987;40:373–83. [https://doi.org/10.1016/0021-9681\(87\)90171-8](https://doi.org/10.1016/0021-9681(87)90171-8).
- [19] Barnes L, Eveson JW, Reichart P, Sidransky D. Editors. “Salivary glands” in World Health Organization classification of tumours. Pathology and genetics of head and neck tumours. Lyon: IARC Press; 2005.
- [20] Luna-Ortiz K, Carmona-Luna T, Cano-Valdez AM, Mosqueda-Taylor A, Herrera-Gómez A, Villavicencio-Valencia V. Adenoid cystic carcinoma of the tongue—clinicopathological study and survival analysis. *Head Neck Oncol* 2009;1:15. <https://doi.org/10.1186/1758-3284-1-15>.
- [21] Han N, Ong H, Liu Z, Ruan M, Yang W, Zhang C. Lymph node involvement predicts poor prognosis in primary tongue adenoid cystic carcinoma: A preliminary study of 54 cases. *J Craniofac Surg* 2017;45:589–94. <https://doi.org/10.1016/j.jcms.2017.01.012>.
- [22] Iyer NG, Kim L, Nixon IJ, Palmer F, Kraus D, Shaha AR, et al. Factors predicting outcome in malignant minor salivary gland tumors of the oropharynx. *Arch Otolaryngol-Head Neck Surg* 2010;136:1240–7. <https://doi.org/10.1001/ARCHOTO.2010.213>.
- [23] Vander Poorten VLM, Balm AJM, Hilgers FJM, Tan IB, Keus RB, Hart AAM. Stage as major long term outcome predictor in minor salivary gland carcinoma. *Cancer* 2000;89:1195–204. [https://doi.org/10.1002/1097-0142\(20000915\)89:6<1195::aid-cnrcr2>3.3.co;2-a](https://doi.org/10.1002/1097-0142(20000915)89:6<1195::aid-cnrcr2>3.3.co;2-a).
- [24] Goel AN, Badran KW, Braun APG, Garrett AM, Long JL. Minor Salivary Gland Carcinoma of the Oropharynx: A Population-Based Analysis of 1426 Patients. *Otolaryngology–Head and Neck Surgery : Official Journal of American Academy of Otolaryngology-Head and Neck Surgery* 2018;158:287–94. doi: 10.1177/0194599817735309.
- [25] Silverman DA, Carlson TP, Khuntia D, Bergstrom RT, Saxton J, Esclamado RM. Role for postoperative radiation therapy in adenoid cystic carcinoma of the head and neck. *Laryngoscope* 2004;114:1194–9. <https://doi.org/10.1097/00005537-200407000-00012>.
- [26] Thariat J, Ferrand F-R, Fakhry N, Even C, Vergez S, Chabrilac E, et al. Radiotherapy for salivary gland cancer: REFCOR recommendations by the formal consensus method. *Eur Ann Otorhinolaryngol Head Neck Dis* 2023;S1879-7296(23)00158-8. doi: 10.1016/j.anorl.2023.11.006.
- [27] Mendenhall WM, Morris CG, Amdur RJ, Werning JW, Hinerman RW, Villaret DB. Radiotherapy alone or combined with surgery for adenoid cystic carcinoma of the head and neck. *Head Neck* 2004;26:154–62. <https://doi.org/10.1002/HED.10380>.
- [28] Spiro RH, Huvos AG, Strong EW. Adenoid cystic carcinoma of salivary origin. A clinicopathologic study of 242 cases. *Am J Surg* 1974;128:512–20. [https://doi.org/10.1016/0002-9610\(74\)90265-7](https://doi.org/10.1016/0002-9610(74)90265-7).
- [29] Orlandi E, Iacovelli NA, Bonora M, Cavallo A, Fossati P. Salivary Gland. Photon beam and particle radiotherapy: Present and future. *Oral Oncol* 2016;60:146–56. <https://doi.org/10.1016/j.oraloncology.2016.06.019>.

- [30] Bhattasali O, Holliday E, Kies MS, Hanna EY, Garden AS, Rosenthal DI, et al. Definitive proton radiation therapy and concurrent cisplatin for unresectable head and neck adenoid cystic carcinoma: A series of 9 cases and a critical review of the literature. *Head Neck* 2016;38(Suppl 1):E1472–80. <https://doi.org/10.1002/hed.24262>.
- [31] Koto M, Hasegawa A, Takagi R, Ikawa H, Naganawa K, Mizoe J-E, et al. Evaluation of the safety and efficacy of carbon ion radiotherapy for locally advanced adenoid cystic carcinoma of the tongue base. *Head Neck* 2016;38(Suppl 1):E2122–6. <https://doi.org/10.1002/hed.24397>.
- [32] Haddad RI, Posner MR, Busse PM, Norris CM, Goguen LA, Wirth LJ, et al. Chemoradiotherapy for adenoid cystic carcinoma: preliminary results of an organ sparing approach. *Am J Clin Oncol* 2006;29:153–7. <https://doi.org/10.1097/01.COC.0000203756.36866.17>.
- [33] Homma A, Sakashita T, Hatakeyama H, Kano S, Mizumachi T, Nakamaru Y, et al. The efficacy of superselective intra-arterial infusion with concomitant radiotherapy for adenoid cystic carcinoma of the head and neck. *Acta Otolaryngol* 2015;135:950–4. <https://doi.org/10.3109/00016489.2015.1040171>.
- [34] Takayama K, Kato T, Nakamura T, Azami Y, Ono T, Suzuki M, et al. Proton beam therapy combined with intra-arterial infusion chemotherapy for stage IV adenoid cystic carcinoma of the base of the tongue. *Cancers (Basel)* 2019;11:1413. <https://doi.org/10.3390/cancers11101413>.
- [35] Laurie SA, Licitra L. Systemic therapy in the palliative management of advanced salivary gland cancers. *J Clin Oncol* 2006;24:2673–8. <https://doi.org/10.1200/JCO.2005.05.3025>.
- [36] Atallah S, Marc M, Schernberg A, Huguet F, Wagner I, Mäkitie A, et al. Beyond surgical treatment in adenoid cystic carcinoma of the head and neck: A literature review. *Cancer Manag Res* 2022;14:1879–90. <https://doi.org/10.2147/CMAR.S355663>.
- [37] Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre J-L, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004;350:1945–52. <https://doi.org/10.1056/NEJMOA032641>.
- [38] Gebre-Medhin M, Brun E, Engström P, Cange HH, Hammarstedt-Nordenvall L, Reizenstein J, et al. ARTSCAN III: A randomized phase III study comparing chemoradiotherapy with cisplatin versus cetuximab in patients with locoregionally advanced head and neck squamous cell cancer. *J Clin Oncol* 2021;39:38–47. <https://doi.org/10.1200/JCO.20.02072>.
- [39] Mayland CR, Ho QM, Doughty HC, Rogers SN, Peddinti P, Chada P, et al. The palliative care needs and experiences of people with advanced head and neck cancer: A scoping review. *Palliat Med* 2021;35:27–44. <https://doi.org/10.1177/0269216320963892>.
- [40] Barrett AW, Speight PM. Perineural invasion in adenoid cystic carcinoma of the salivary glands: A valid prognostic indicator? *Oral Oncol* 2009;45:936–40. <https://doi.org/10.1016/j.ORALONCOLOGY.2009.07.001>.
- [41] Chabrilac E, Vergez S, Barry B, Jegoux F, Verillaud B, Pham Dang N, et al. Post-treatment monitoring of salivary gland cancer: REFCOR recommendations by the formal consensus method. *Eur Ann Otorhinolaryngol Head Neck Dis* 2023;S1879-7296(23)00155-2. doi: 10.1016/j.anorl.2023.11.003.