Adjuvant radiotherapy and survival of patients with squamous cell carcinoma involving the entire tongue: The SEER database analysis

Zhenyu Ding
Central South University
Run Yao
Central South University
Jun Zuo
Central South University
Ning Li (liningxy@csu.edu.cn)
Central South University

Research Article

Keywords:

Posted Date: March 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1406293/v1

Abstract

We examined the benefits of adjuvant radiotherapy (aRT) for patients with tongue squamous cell carcinoma (SCC). The Surveillance, Epidemiology, and End Results database was applied to identify patients treated with or without aRT for tongue SCC. The Kaplan–Meier method and log-rank test assessed survival curves for SCC stages stratified by aRT. Hazard ratios were estimated for stage and aRT concerning overall survival (OS) and disease-specific survival (DSS). Propensity-score matching was performed to assess differences in baseline characteristics. We included 3322 cases. The total number of deaths and disease-specific deaths were 1234 (37.15%) and 938 (28.24%), respectively. The Kaplan–Meier curves for 5-year OS and DSS showed that patients receiving aRT had lower and higher survival probabilities during Stages I and IV, respectively ($P<0.0001$). On Cox regression analysis, aRT and 5-year OS and DSS were positively and negatively associated with Stage I and Stage IV patients, respectively. Sensitivity analysis results were consistent before and after PSM. OS and DSS of Stage II and III patients in the aRT and non-aRT groups were not significantly different ($P<0.05$). aRT WAS significantly associated with survival benefits and worse survival for Stage IV and I tongue SCC cases, respectively.

Introduction

Annually, squamous cell carcinoma (SCC) affects more than 650,000 people worldwide, and 330,000 people die from the disease each year [1–3]. Several factors may contribute to the development of oral and oropharyngeal SCC, including tobacco use, alcohol consumption, and human papillomavirus infection [4–6]. In response to the national health campaign and public health awareness, the incidence of oral cancer has declined in general [5, 7]. However, several studies have reported that head and neck cancer is becoming more common among young people and women, indicating an epidemiological shift from older adults and men to younger adults and women [5, 8–10]. Moreover, public health concerns remain significant because of the disease burden. Cancers affecting the anterior two-thirds of the tongue are referred to as carcinomas of the tongue, whereas those affecting the posterior one-third are referred to as base of tongue cancers [6]. In SCC of the body of the tongue, the malignant clinical characteristics include rapid local invasion and lymph node metastasis, which can result in impaired speech and chewing and, ultimately, affect the patients' quality of life [11, 12]. Although diagnostic techniques and modalities have advanced dramatically in recent years, the overall survival (OS) rate for tongue SCC has been reduced owing to its clinicopathological features [13–16].

Over the past few decades, the therapeutic regimen for SCC has not changed significantly. Various treatments are currently used, including radiotherapy alone or in combination with adjuvant chemotherapy, resection of the primary tumor with or without adjuvant radiotherapy (aRT), and neck dissection [1, 17]. Previous studies have found that head and neck cancer patients with high-risk features benefit from postoperative chemotherapy in terms of local-regional control and disease-free survival [18, 19]. In contrast, short- and long-term radiation therapies are frequently associated with toxic side effects, including dysgeusia, dysphagia, aspiration, mucositis, soft tissue necrosis, carotid atherosclerosis, stroke, radiation fibrosis, osteoradionecrosis, and cranial neuropathy [4, 20]. Radiation therapy regimens are currently topics of controversy. According to some evidence, aRT does not appear have considerable benefits for oral SCC at the early stage [21–24]. Other reports have suggested that aRT is effective, even during the early stages of head and neck SCC [25–29]. However, these studies have limitations. Sandhya et al. and Shim et al. conducted their studies with a limited number of patients [21, 22] and Luryi et al. and Sowder et al. did not evaluate the benefits of radiotherapy for each subsite [23, 24]. Therefore, there is a need to investigate appropriate groups for postoperative radiotherapy, which can alleviate the side effects of therapeutic regimens and provide patients with a better quality of life.

The National Comprehensive Cancer Network treatment guidelines recommend a combination of surgery and radiotherapy as the primary treatment for early-stage oral SCC; however, reports on its effectiveness are limited [30]. Therefore, we extracted data from the Surveillance, Epidemiology, and End Results (SEER) database, funded by the National Cancer Institute, to address this knowledge gap regarding the effect of radiotherapy on survival in patients with entire tongue SCC. This study was designed to examine the effects of aRT on patients by using the SEER database with different stages of SCC involving the

entire tongue body (including the frontal two-thirds of the tongue and base of the tongue), identify the most suitable group of patients for aRT, and reduce unnecessary therapeutic procedures.

Results

Patient characteristics

Initially, the data of 13379 SCC patients were retrieved from the SEER database between 2004 and 2015. After excluding 6659 cases coded with surg prim site code 0 (none, no surgery of primary site; autopsy only), 446 patients with Tx, 29 patients with Nx, 36 patients with Mx, 17 patients with surg prim site code 99 (unknown if surgery was performed; death certificate only), 2749 patients with a follow-up duration < 5 years, and 121 cases recorded with missing data, a total of 3322 patients were enrolled for the final analysis (Fig. 1). Among them, 3322 cases had 5-year OS data and 3026 cases had 5-year disease-free survival (DSS) data. These patients were predominantly men (63.73%); 36.27% of the patients were women. The total number of deaths and disease-specific deaths (DSDs) were 1234 (37.15%) and 938 (28.24%), respectively.

Based on the therapeutic regimens, we classified the included patients into two groups, surgery with and without aRT, and compared the baseline characteristics of the two groups. The differences in age, sex, race, primary site, grade, chemotherapy, stage, and TN classification were significant ($P < 0.05$) of aRT and non-aRT receivers, but not M classification ($P > 0.05$), in the initial data (Table 1).

Table 1
Baseline characteristics of aRT receivers and non-aRT receivers (2004–2015)

	aRT		P-value
	No (n = 1709)	Yes (n = 1613)	
Age			< 0.001
30–49 years	373 (21.83%)	352 (21.82%)	
50–59 years	446 (26.10%)	570 (35.34%)	
60–69 years	420 (24.58%)	446 (27.65%)	
≥ 70 years	470 (27.50%)	245 (15.19%)	
Sex			< 0.001
Female	717 (41.95%)	488 (30.25%)	
Male	992 (58.05%)	1125 (69.75%)	
Race			0.004
White	1468 (85.90%)	1370 (84.93%)	
Black	74 (4.33%)	109 (6.76%)	
others	167 (9.77%)	134 (8.31%)	
Primary site			< 0.001
Base of tongue	266 (15.56%)	708 (43.89%)	
Dorsal surface of tongue	108 (6.32%)	68 (4.22%)	
Border of tongue	544 (31.83%)	338 (20.95%)	
Ventral surface of tongue	325 (19.02%)	164 (10.17%)	
Anterior 2/3 of tongue	466 (27.27%)	335 (20.77%)	
Grade			< 0.001
I-Well differentiated	543 (31.77%)	134 (8.31%)	
II-Moderately differentiated	887 (51.90%)	847 (52.51%)	
III-Poorly differentiated	271 (15.86%)	613 (38.00%)	
IV-Undifferentiated	8 (0.47%)	19 (1.18%)	
Chemotherapy			< 0.001
Yes	42 (2.46%)	855 (53.01%)	
No/Unknown	1667 (97.54%)	758 (46.99%)	
Stage			< 0.001
I	1096 (64.13%)	181 (11.22%)	
II	272 (15.92%)	212 (13.14%)	
III	174 (10.18%)	393 (24.36%)	

aRT, adjuvant radiotherapy; NOS, not otherwise specified

	aRT		P-value
	No (n = 1709)	Yes (n = 1613)	
IV	167 (9.78%)	827 (51.27%)	
T-classification			< 0.001
T1	1203 (70.39%)	508 (31.49%)	
T2	355 (20.77%)	691 (42.84%)	
T3	95 (5.56%)	208 (12.90%)	
T4a	52 (3.04%)	189 (11.72%)	
T4b	4 (0.23%)	15 (0.93%)	
T4NOS	0 (0.00%)	2 (0.12%)	
N-classification			< 0.001
N0	1442 (84.38%)	492 (30.50%)	
N1	144 (8.43%)	380 (23.56%)	
N2a	24 (1.40%)	108 (6.70%)	
N2b	71 (4.15%)	465 (28.83%)	
N2c	18 (1.05%)	120 (7.44%)	
N2NOS	3 (0.18%)	12 (0.74%)	
N3	7 (0.41%)	36 (2.23%)	
M-classification			0.138
M0	1694 (99.12%)	1590 (98.57%)	
M1	15 (0.88%)	23 (1.43%)	
aRT, adjuvant radiotherapy; NOS, not otherwise specified			

Kaplan–Meier survival curves for 5-year OS and DSS

Kaplan–Meier survival analysis revealed that among Stage I patients, 14.27% received aRT, while 85.83% did not, compared with 16.8% non-aRT receivers and 83.2% aRT receivers among those with Stage IV disease (Table 1). Stage I patients undergoing aRT had a lower 5-year survival probability for both OS and DSS than non-aRT receivers. ($P < 0.0001$) (Fig. 2a, e) In contrast, aRT showed significant benefits for the treatment of Stage IV tumors, with a 10–20% improvement in the OS and DSS survival probabilities ($P < 0.0001$) (Fig. 2d, h). In addition, there were no significant survival benefits of aRT for aRT and non-aRT receivers with Stage II and III tumors (Fig. 2b, c, f, g) ($P > 0.05$).

Impact of aRT on 5-year overall death and disease-specific death in patients with different tumor stages

Cox regression analysis showed that among Stage I patients, the 5-year overall death (OD) risk in aRT receivers increased by 105% (Hazard ratio [HR], 2.05; 95% confidence interval [CI], 1.57–2.67) and the 5-year DSD risk in aRT receivers increased by 171% (HR, 2.71, 95% CI, 1.97–3.72) in contrast with those in non-aRT receivers in the non-adjusted model. Among Stage IV patients, the 5-year OD risk in aRT receivers decreased by 48% (HR, 0.52; 95% CI, 0.42–0.6), and the 5-year DSD risk in aRT receivers decreased by 49% (HR, 0.51; 95% CI, 0.41–0.6) compared to those in non-aRT receivers in the non-adjusted model. Stage II and III patients receiving aRT and those not receiving aRT did not differ significantly. Similar results were observed for the adjusted model (Table 2).

Table 2
Impact of aRT on OD and DSD in patients with different tumor stages

		Stage I		Stage II		Stage III		Stage IV	
		HR (95%CI)		HR (95%CI)		HR (95%CI)		HR (95%CI)	
		OD (305/1277)	DSD (187/1159)	OD (181/484)	DSD (121/424)	OD (235/567)	DSD (187/519)	OD (513/994)	DSD (443/924)
Non-adjusted									
aRT	No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	Yes	2.05 (1.57, 2.67) *	2.71 (1.97, 3.72) *	1.21 (0.90, 1.61)	1.22 (0.85, 1.74)	0.84 (0.64, 1.09)	0.84 (0.62, 1.15)	0.52 (0.42, 0.64) *	0.51 (0.41, 0.64) *
Adjusted [a]									
aRT	No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	Yes	1.72 (1.28, 2.33) *	2.07 (1.43, 2.98) *	1.18 (0.85, 1.63)	1.13 (0.75, 1.68)	1.00 (0.74, 1.36)	1.01 (0.72, 1.42)	0.58 (0.45, 0.74) *	0.59 (0.45, 0.77) *

*indicates P < 0.05

[a]adjusted for age, sex, race, primary site, grade, and chemotherapy.

aRT, adjuvant radiotherapy; CI, confidence interval; DSD, disease-specific death; HR, hazard ratio; OD, overall death

Sensitivity analysis

We matched 1502 cases in the aRT (n = 751) and non-aRT (n = 751) groups by propensity-score matching (PSM) totally. We failed to detect significant differences in age, sex, race, grade, and chemotherapy for these matched cases, except for the primary site (P < 0.05) (Table 3). In the Kaplan–Meier survival analysis, we obtained the same results as those before PSM; aRT showed a benefit for both 5-year OS and DSS in patients diagnosed with Stage IV tumors but a negative effect in those with Stage I tumors (P < 0.001) (Fig. 3a, e, d, h). The difference between Stage II and III disease was not significant (P > 0.05) (Fig. 3b, c, f, g).

Table 3
Baseline characteristics of aRT receivers and non-aRT receivers after propensity score matching

Variables	aRT		Standardized diff.	P value
	Yes(n = 751)	No (n = 751)		
Age				0.0517
30–49 years	164 (21.8)	170 (22.6)	0.02	
50–59 years	230 (30.6)	221 (29.4)	0.03	
60–69 years	199 (26.5)	164 (21.8)	0.11	
≥ 70 years	158 (21)	196 (26.1)	0.12	
Sex			0.02	0.7486
Female	275 (36.6)	282 (37.5)		
Male	476 (63.4)	469 (62.5)		
Race				0.8567
White	626 (83.4)	633 (84.3)	0.03	
Black	53 (7.1)	52 (6.9)	0.01	
Others	72 (9.6)	66 (8.8)	0.03	
Primary site				< 0.0001
Base of tongue	222 (29.6)	172 (22.9)	0.15	
Dorsal surface of tongue	36 (4.8)	69 (9.2)	0.17	
Border of tongue	190 (25.3)	296 (39.4)	0.31	
Ventral surface of tongue	103 (13.7)	94 (12.5)	0.04	
Anterior 2/3 of tongue	200 (26.6)	120 (16)	0.26	
Grade				0.4739
I-Well differentiated	90 (12)	107 (14.2)	0.07	
II-Moderately differentiated	451 (60.1)	434 (57.8)	0.05	
III-Poorly differentiated	202 (26.9)	205 (27.3)	0.01	
IV-Undifferentiated	8 (1.1)	5 (0.7)	0.04	
Chemotherapy			0	1.0000
Yes	42 (5.6)	42 (5.6)		
No/Unknown	709 (94.4)	709 (94.4)		

aRT, adjuvant radiotherapy

To eliminate bias from the primary site, we adjusted this variable in the HR analysis (Table 4). The Cox regression analysis showed that aRT was positively correlated with both 5-year OD (HR, 2.51; 95% CI, 1.77–3.55) and DSD (HR, 2.76l 95% CI, 1.82–4.19) in Stage I patients. aRT was negatively associated with both 5-year OD (HR, 0.55; 95% CI, 0.41–0.74) and DSD (HR, 0.55; 95% CI, 0.40–0.76) in Stage IV patients (Table 4). Similar results were observed for the adjusted model. The results before and after PSM were consistent.

Table 4
Impact of aRT on OD and DSD in patients with different tumor stages in the matched cohort

		Stage I		Stage II		Stage III		Stage IV	
		HR (95%CI)		HR (95%CI)		HR (95%CI)		HR (95%CI)	
		OD (130/585)	DSD (90/545)	OD (105/280)	DSD (77/252)	OD (113/300)	DSD (95/282)	OD (190/337)	DSD (164/311)
Non-adjusted									
aRT	**No**	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	Yes	2.51 (1.77, 3.55) *	2.76 (1.82, 4.19) *	1.34 (0.90, 1.99)	1.08 (0.69, 1.70)	1.29 (0.85, 1.97)	1.23 (0.78, 1.93)	0.55 (0.41, 0.74) *	0.55 (0.40, 0.76) *
Adjusted [a]									
aRT	**No**	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
	Yes	2.55 (1.78, 3.67) *	2.86 (1.85, 4.42) *	1.28 (0.85, 1.92)	1.01 (0.63, 1.60)	1.24 (0.81, 1.90)	1.17 (0.74, 1.84)	0.52 (0.39, 0.70) *	0.53 (0.38, 0.72) *

*indicates P < 0.05

[a]adjusted for primary site.

aRT, adjuvant radiotherapy; CI, confidence interval; DSD, disease-specific death; HR, hazard ratio; OD, overall death

Ethical approval

The SEER research data files were downloaded using the account number 20161-Nov2020. The account is approved to access to the 1975-2018 SEER Research Plus Data (November 2020 Submission). The data released by the SEER database do not require informed patient consent. All experiments were performed in accordance with relevant guidelines and regulations.

Discussion

This study revealed that aRT is significantly associated with survival benefits in patients with Stage IV SCC of the tongue. aRT is commonly used after surgery in cases of unfavorable histological findings. For large tumors, several oncologists recommend aRT if the surgical margins are close to the tumor or involved or if several positive nodes persist after neck dissection. Previous studies have indicated that early tongue cancers are associated with 5-year survival rates of at least 80% [21,31,32], although cancers of the tongue have a worse prognosis than those affecting other oral areas. Rusthoven et al. revealed that Stage I and II tongue cancers have 60.9% and 83.5% 5-year OS and cause-specific survival rates, respectively; other oral subsites had rates of 64.7% and 94.1%, respectively, according to the SEER database [33]. Shim et al. attributed the high survival rate of tongue cancer to appropriate radiotherapy [21]. Thus, feasible and reasonable radiation therapy regimens are important for the survival status of patients. In this study, we analyzed the survival of patients with SCC of the tongue and sought to determine the impact of aRT use on survival. We discovered that aRT confers advanced survival in Stage IV SCC of the tongue, whereas it failed to improve survival status in Stage I to Stage III SCC patients. Furthermore, aRT for Stage I cancers has a negative impact on patient survival. To unequivocally establish the association between the tumor stage and aRT, we verified the results in the original and PSM cohorts and obtained the same conclusion. Our results contribute to the growing body of knowledge related to tongue SCC-related outcomes and reveal that survival and response to aRT vary with tumor stage. In this article, we report a number of observational associations that can provide motivation and set the stage for future mechanistic studies investigating the biological mechanisms that may underlie the observed differences in tongue body SCC prognosis and response to treatment.

In our original data analysis, aRT served as a risk factor for patients with Stage I tumors in 5-year OS and DSS. In addition, it is worth noting that we could not detect any significant benefits of aRT for Stage II and Stage III patients. These results suggest that these early-stage patients do not benefit from aRT. There are reports [21–24] of findings similar to those of our study. Sandhya et al. analyzed a cohort of 103 cases and suggested that postoperative radiation therapy had no significant impact on the survival of patients with Stage I and II deep tongue cancers, with no less than a 4-mm tumor invasion depth [22]. According to Shim et al., 86 patients with early-stage tongue cancer were enrolled in the study, but no significant differences were observed in the OS rate after surgery alone and a combination of surgery and postoperative radiation therapy [21]. However, these studies included only a few patients, and it was difficult to adjust baselines. Focusing on oral cavity cancers generally, Luryi et al. and Sowder et al. analyzed the data from the SEER database with a large number of cases and revealed that treatment with adjuvants led to significantly worse OS and DSS than surgery alone for early-stage oral cancers [23,24]. However, they did not determine whether postoperative radiation therapy was beneficial for each subsite. Our results are consistent with those of previous studies that suggested that early-stage patients should not receive aRT after surgery. This would increase the cost of treatment and reduce the quality of life of these patients, and the radiation exposure to the oral cavity and oropharynx may lead to unfavorable complications.

In contrast, some other reports have suggested that aRT is beneficial for early-stage head and neck SCC. Tsai et al. confirmed that aRT could improve neck control and survival status in patients with early oral cancers with a single nodal status in the Taiwan Cancer Registry database [25]. Furthermore, Schiff et al. suggested that aRT could improve regional failure in patients with pN1 tongue cancers, although the results were not significant (P=0.32) [26]. Torrecillas et al. confirmed significant survival benefit of aRT for patients with T1N1 and T2N2 oral cavity SCC [27]. Qian et al. suggested that aRT resulted in better survival in patients with pN0 [28]. Shrime et al. suggested that aRT was associated with the most significant improvements in cancers of the tongue after verifying its effects on T1N1 or T2N1 oral SCCs [29]. Several factors were responsible for these divergent conclusions: first, the sources of their data were variable, and the characteristics of patients and aRT modalities could be different; second, some studies have focused on the oral cavity or head and neck rather than a specific subsite, which may influence the survival status of patients; third, some early-stage patients may suffer from occult node metastases. We speculate that advanced benefits of aRT may be identified in larger cohorts with occult metastases.

Compared with these studies, we conducted a more accurate study based on a large number of patients in the SEER database and included SCCs of the entire tongue body (anterior 2/3 and base of tongue). We also included various patient characteristics and treatment options. Considering that patients with different tumor stages could have different characteristics, we made some adjustments to the basic characteristics of the patients to reduce bias. We performed a subgroup analysis and conducted PSM based on baseline variables. For both the original and PSM groups, we explored the effects of postoperative radiation therapy on OS and DSS. After adjustment, we did not detect any significant changes in the results compared to the original data. We used PSM to match all variables at a 1:1 ratio between aRT and non-aRT receivers; 1502 cases were included. We discovered that aRT could worsen the survival of patients with Stage I SCC, even after adjustment and matching. In addition, we found that aRT could not always extend the duration of survival for late-stage tumors. aRT can only improve the survival of patients with Stage IV SCC of the tongue and is not significantly associated with survival benefits in the original and propensity-score matching populations. Our PSM and adjusted results provide dual authentication that patients with different stages of SCC cannot always benefit from aRT after surgery. The provision of appropriate therapeutic regimens is of great importance. This should be based on several factors, including patient characteristics, disease progression, and quality of life following surgery.

Because of its retrospective nature, this study inevitably had several limitations. Due to the lack of therapeutic parameters of radiation (including definitive versus palliative intent, dose/fractionation) in the SEER database, we could not evaluate the effects of these factors on survival and prognosis. The list of variables included in our analysis was not exhaustive, and some potentially important factors (e.g., smoking status, alcohol drinking, and vascular invasion) were not available in the SEER database. Additionally, we do not have access to the information on various patient characteristics in the SEER database, including quality of life, complications, tumor resection margins, recurrence, and treatment of recurrence, all of which may have affected our aRT analysis. Advances have been made in radiotherapy technology; however, as a result of differences in

selection criteria, techniques, and equipment, toxicity and quality of life within a given period of time can be compromised more than survival outcomes [34].

In conclusion, we suggested that there were significant survival benefits associated with aRT for Stage IV SCC of the tongue and that patients with Stage I SCC of the tongue cannot benefit from aRT. Thus, survival and other benefits of aRT for early-stage SCC need some further justification, especially for Stage I patients. Otherwise, these patients may not be subjected to unnecessary radiation and morbidity. Our results provide an orientation for research interest in the biological mechanism, and future researchers can provide reasonable explanations and feasible methods of improvements for aRT.

Patients And Methods

Data collection

We retrieved the data of cases with SCC involving the anterior two-thirds of the tongue and base of the tongue from the SEER Stat 8.3.9. The data were part of the SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975–2016 varying). Relevant patient information in the SEER database includes demographic characteristics, histology, malignancy, therapeutic regimen, and survival duration, among others. Based on histology recode and the WHO definition of squamous cell tumors (8050–8089 squamous cell tumors), we ran the research modality in a cast-listing session. The selected neoplasms exhibited malignant behavior. The site and morphology (primary site-labeled) included C01.9-base of the tongue, not otherwise specified (NOS); C02.0-dorsal surface of tongue, NOS; C02.1-border of tongue; C02,2-ventral surface of tongue, NOS; and C02.3-anterior two-thirds of the tongue, NOS.

These data were retrieved and analyzed as follows: age (30–49; 50–59; 60–69; ≥70 years); sex (male, female); race (white, black, American Indian/Alaska Native, Asian, or Pacific Islander); year of diagnosis; grade (I, II, III, IV); SEER Combined Summary Stage 2000 (2004+) (regional lymph nodes involved only, regional by direct extension only, regional by both direct extension and lymph node involvement, localized only, distant site(s)/node(s) involved); anatomic site (C01.9-base of the tongue, NOS; C02.0-dorsal surface of the tongue, NOS; C02.1-border of tongue; C02,2-ventral surface of the tongue, NOS; C02.3-anterior two-thirds of the tongue, NOS); derived American Joint Committee on Cancer (AJCC) TNM stage, 6^{th} edition (2004-2015); surgery; aRT; and DSS and OS, both measured in months. SCCs were staged based on the AJCC 6^{th} edition, effective 2004 and onward. The analysis did not include patients without surgery. We only included patients who underwent surgery alone or post-surgery radiotherapy. A 5-year OS and DSS were the study's endpoints. Based on months from the date of initial pathological diagnosis to the date of death or the end of 60 months, OS or DSS was calculated.

Statistical analysis

The Kaplan–Meier method and log-rank test were applied to calculate and assess the survival curves of patients diagnosed with different stages stratified by aRT. We estimated the association between the stage and aRT and OS and DSS using HRs and the corresponding 95% CIs was calculated via Cox regression models. Patients with similar baseline characteristics were identified via PSM. Based on a series of baseline covariates including age, sex, race, primary site, grade, and chemotherapy, a propensity score is calculated as the conditional probability of being exposed to a given exposure (aRT yes versus no). The 1:1 matching protocol was employed without replacement (greedy-matching algorithm); the caliper width was estimated to be equal to 0.01 of the standard deviation of the propensity score. For all baseline covariates, standardized differences were estimated before and after matching to assess the pre-match and post-match balance. Standardized differences <10.0% for a given covariate indicate a relatively small imbalance. Using the Kaplan–Meier method and a log-rank test, we could generate and compare survival curves of patients stratified by aRT in the matched cohort. The association between aRT, OS, and DSS of patients with different stages of cancer was also studied using a Cox proportional hazards regression model.

All analyses were performed using the statistical software packages R (R Foundation for Statistical Computing, Vienna, Austria) and Empower Stats (X&Y Solutions, Inc., Boston, MA, USA). The significance level was determined by the two-tailed P-

value of 0.05.

Abbreviations

aRT, adjuvant radiotherapy

CI, confidence interval

DSD, disease-specific death

DSS, disease-specific survival

HR, hazard ratio

OD, overall death

OS, overall survival

PSM, propensity-score matching

SCC, squamous cell carcinoma

SEER, Surveillance, Epidemiology, and End Results

Declarations

Acknowledgments

Authors' contribution

Zhenyu Ding designed the study and collected the data. Run Yao analyzed the data. Zhenyu Ding and Run Yao wrote the manuscript. Ning Li and Jun Zuo reviewed and edited the manuscript. Zhenyu Ding and Run Yao share first authorship. All authors have read and approved the final manuscript.

Funding

This study was supported by the Natural Science Foundation of Hunan Province (project no. 2018JJ2546) and the Scientific Research Project of Hunan Provincial Health Commission (project no. 202218013370).

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Role of the funding source

Statistical analysis and language editing.

Competing interests

The authors declare no competing interests.

References

1. Christopherson K, Morris CG, Kirwan JM, et al. Radiotherapy alone or combined with chemotherapy for base of tongue squamous cell carcinoma. Laryngoscope. 2017;127(7):1589–1594. doi:10.1002/lary.26460
2. Saba NF, Ward K. Gender and Ethnic Disparities in Incidence and Survival of Squamous Cell Carcinoma of the Oral Tongue, Base of Tongue, and Tonsils : A Surveillance, Epidemiology and End Results Program-Based Analysis. Published online 2011:12–20. doi:10.1159/000330807
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424. doi:10.3322/caac.21492
4. Wang L, Fossati P, Paganetti H, et al. The Biological Basis for Enhanced Effects of Proton Radiation Therapy Relative to Photon Radiation Therapy for Head and Neck Squamous Cell Carcinoma. Int J Part Ther. 2021;8(1):3–13. doi:10.14338/ijpt-20-00070.1
5. Mukdad L, Heineman TE, Alonso J, Badran KW, Kuan EC, St. John MA. Oral tongue squamous cell carcinoma survival as stratified by age and sex: A surveillance, epidemiology, and end results analysis. Laryngoscope. 2019;129(9):2076–2081. doi:10.1002/lary.27720
6. Zhu Y, Zhou C, He Q. Radiation therapy's efficacy on tongue cancer: A population-based survival analysis. Onco Targets Ther. 2018;11:7271–7276. doi:10.2147/OTT.S169231
7. Patel SC, Carpenter WR, Tyree S, et al. Increasing incidence of oral tongue squamous cell carcinoma in young white women, age 18 to 44 years. J Clin Oncol. 2011;29(11):1488–1494. doi:10.1200/JCO.2010.31.7883
8. JE T, WF A, C C, et al. Rising incidence of oral tongue cancer among white men and women in the United States, 1973–2012. Oral Oncol. 2017;67:146–152. doi:10.1016/J.ORALONCOLOGY.2017.02.019
9. Leoncini E, Ricciardi W, Cadoni G, et al. Changing epidemiology of oral squamous cell carcinoma of the tongue: A global study Jia. Head Neck. 2014;36(10):1391. doi:10.1002/HED
10. A B. Cancer of the oral cavity and pharynx in young females: increasing incidence, role of human papilloma virus, and lack of survival improvement. Semin Oncol. 2009;36(5):451–459. doi:10.1053/J.SEMINONCOL.2009.07.005
11. Li Y, Zhao Z, Liu X, et al. Nomograms to estimate long-term overall survival and tongue cancer-specific survival of patients with tongue squamous cell carcinoma. Cancer Med. 2017;6(5):1002–1013. doi:10.1002/cam4.1021
12. Alabi RO, Mäkitie AA, Pirinen M, Elmusrati M, Leivo I, Almangush A. Comparison of nomogram with machine learning techniques for prediction of overall survival in patients with tongue cancer. Int J Med Inform. 2021;145. doi:10.1016/j.ijmedinf.2020.104313
13. SR M, NW J, AM P, DF W. The epidemiology of mouth cancer: a review of global incidence. Oral Dis. 2000;6(2):65–74. doi:10.1111/J.1601-0825.2000.TB00104.X
14. M R, C K, M R, et al. Oral squamous cell carcinoma of the tongue: Prospective and objective speech evaluation of patients undergoing surgical therapy. Head Neck. 2016;38(7):993–1001. doi:10.1002/HED.23994
15. A M, R M. Head and neck cancer: global burden and regional trends in India. Asian Pac J Cancer Prev. 2014;15(2):537–550. doi:10.7314/APJCP.2014.15.2.537
16. CC C, YJ Y, YJ L, et al. Corrigendum to "MicroRNA-17/20a functions to inhibit cell migration and can be used a prognostic marker in oral squamous cell carcinoma" [Oral Oncol. 49(9) (2013) 923–931]. *Oral Oncol*. 2017;72:202–203. doi:10.1016/J.ORALONCOLOGY.2017.06.021
17. Selek U, Garden AS, Morrison WH, El-Naggar AK, Rosenthal DI, Ang KK. Radiation therapy for early-stage carcinoma of the oropharynx. Int J Radiat Oncol Biol Phys. 2004;59(3):743–751. doi:10.1016/j.ijrobp.2003.12.002
18. JS C, TF P, AA F, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med. 2004;350(19):1937–1944. doi:10.1056/NEJMOA032646

19. J B, C D, M O, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004;350(19):1945–1952. doi:10.1056/NEJMOA032641
20. Monroe MM, Buchmann LO, Hunt JP, Hitchcock YJ, Lloyd S, Hashibe M. The Benefit of Adjuvant Radiation in Surgically-Treated T1-2 N1 Oropharyngeal Squamous Cell Carcinoma. Laryngoscope Investig Otolaryngol. 2017;2(2):57–62. doi:10.1002/lio2.64
21. Shim SJ, Cha J, Koom WS, et al. Clinical outcomes for T1-2N0-1oral tongue cancer patients underwent surgery with and without postoperative radiotherapy. Radiat Oncol. 2010;5(1):1–7. doi:10.1186/1748-717X-5-43
22. S G, N P, LM RS, R R, KV R, R C. Role of postoperative radiation therapy (PORT) in pT1-T2 N0 deep tongue cancers. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;120(6):e227-e231. doi:10.1016/J.OOOO.2015.08.002
23. AL L, MM C, S M, SA R, JA S, BL J. Treatment Factors Associated With Survival in Early-Stage Oral Cavity Cancer: Analysis of 6830 Cases From the National Cancer Data Base. JAMA Otolaryngol Head Neck Surg. 2015;141(7):593–598. doi:10.1001/JAMAOTO.2015.0719
24. Leoncini E, Ricciardi W, Cadoni G, et al. Treatment-related determinants of survival in early-stage (T1–2N0M0) oral cavity cancer: A population-based study. Head Neck. 2014;36(10):1391. doi:10.1002/HED
25. Tsai C-J, Kuo Y-H, Wu H-C, et al. Adjuvant Radiotherapy Significantly Increases Neck Control and Survival in Early Oral Cancer Patients with Solitary Nodal Involvement: A National Cancer Registry Database Analysis. Published online 2021. doi:10.3390/cancers13153742
26. BA S, DB R, A E-N, AS G, JN M. Selective vs modified radical neck dissection and postoperative radiotherapy vs observation in the treatment of squamous cell carcinoma of the oral tongue. Arch Otolaryngol Head Neck Surg. 2005;131(10):874–878. doi:10.1001/ARCHOTOL.131.10.874
27. Torrecillas V, Shepherd HM, Francis S, et al. Adjuvant radiation for T1-2N1 oral cavity cancer survival outcomes and utilization treatment trends: Analysis of the SEER database. Oral Oncol. 2018;85(May):1–7. doi:10.1016/j.oraloncology.2018.07.019
28. Qian X, Sinikovic B, Schreiber · Frank, et al. HEAD & NECK pN status predicts outcomes in surgically treated pT1-pT2 patients of various disease stages with squamous cell carcinoma of the head and neck: a 17-year retrospective single center cohort study. *Eur Arch Oto-Rhino-Laryngology*. 2018;275(3):2787–2795. doi:10.1007/s00405-018-5108-z
29. Shrime MG, Gullane PJ, Dawson L, Kim J, Gilbert RW, Irish JC. *The Impact of Adjuvant Radiotherapy on Survival in T1-2N1 Squamous Cell Carcinoma of the Oral Cavity*. Vol 136.; 2010. https://jamanetwork.com/
30. DG P, S S, DM B, et al. Head and neck cancers, Version 2.2014. Clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2014;12(10):1454–1487. doi:10.6004/JNCCN.2014.0142
31. K R, A B, D R, C C. Poor prognosis in patients with stage I and II oral tongue squamous cell carcinoma. Cancer. 2008;112(2):345–351. doi:10.1002/CNCR.23183
32. DS S, IA M. The radial forearm flap in intraoral reconstruction: the experience of 60 consecutive cases. Plast Reconstr Surg. 1986;78(1):1–8. doi:10.1097/00006534-198607000-00001
33. K R, A B, D R, C C. Poor prognosis in patients with stage I and II oral tongue squamous cell carcinoma. Cancer. 2008;112(2):345–351. doi:10.1002/CNCR.23183
34. Tasoulas J, Divaris K, Theocharis S, et al. Impact of tumor site and adjuvant radiotherapy on survival of patients with adenoid cystic carcinoma: A seer database analysis. Cancers (Basel). 2021;13(4):1–16. doi:10.3390/cancers13040589

Figures

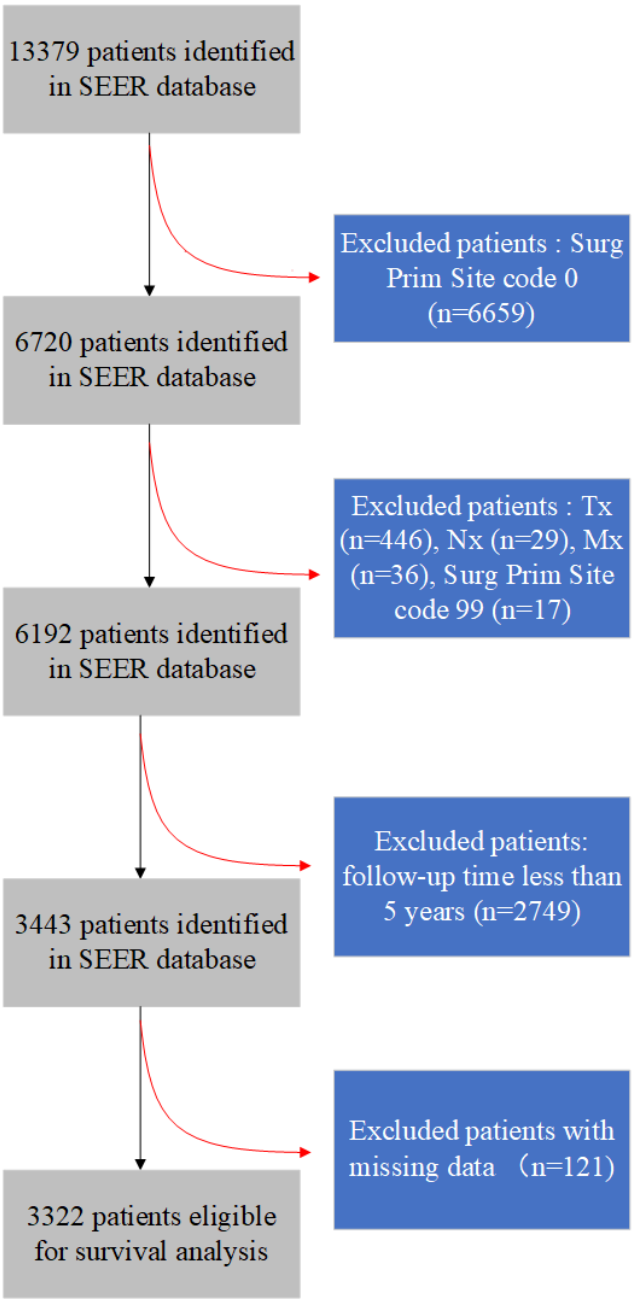

Figure 1

Flowchart of selection and exclusion of patients with squamous cell carcinoma from the Surveillance, Epidemiology, and End Results (SEER) database (2004–2015).

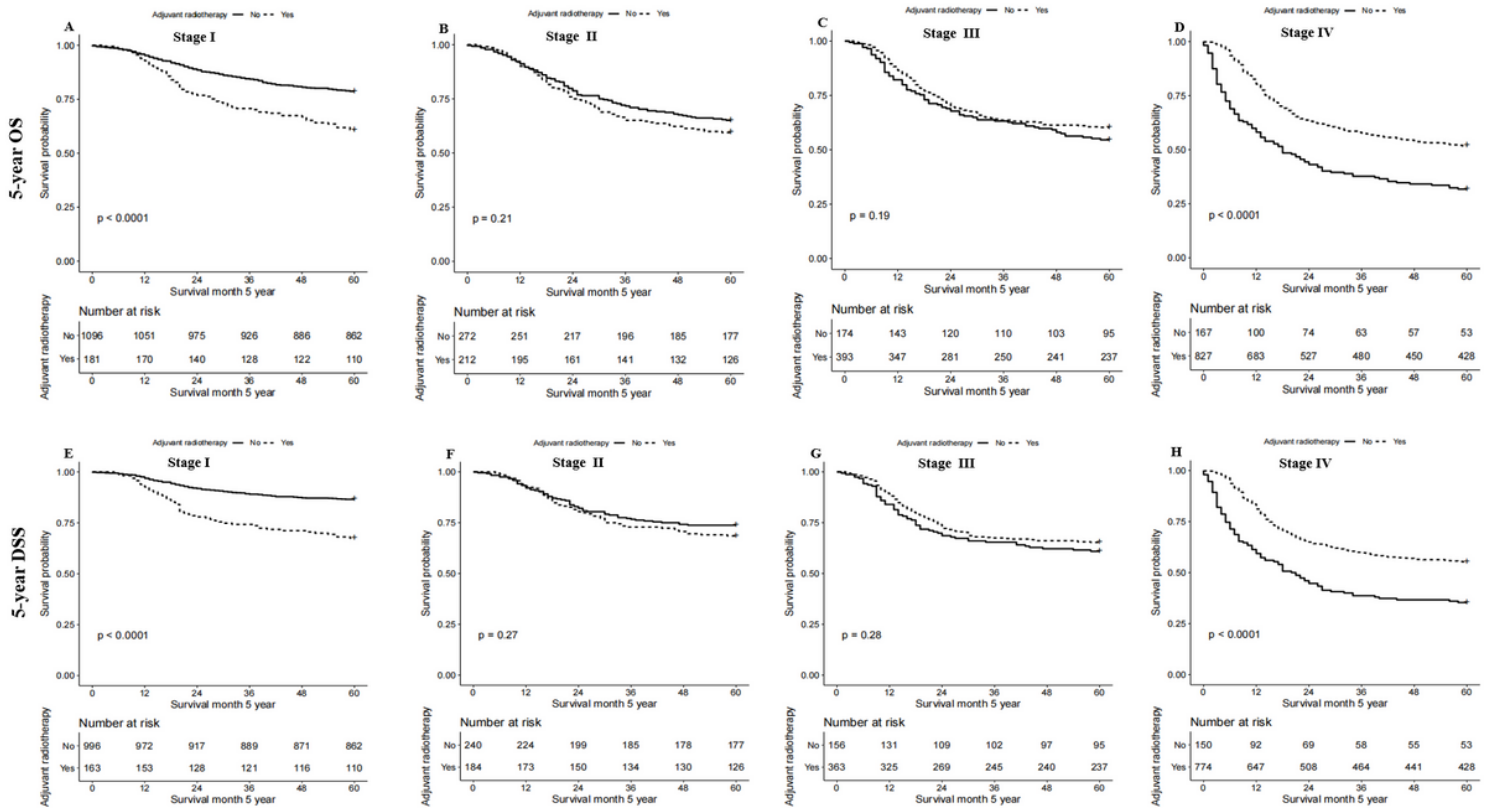

Figure 2

Kaplan–Meier survival curves of patients for 5-year overall survival (**a**: Stage I, **b**: Stage II, **c**: Stage III, **d**: Stage IV) and disease-specific survival (**e**: Stage I, **f**: Stage II, **g**: Stage III, **h**: Stage IV).

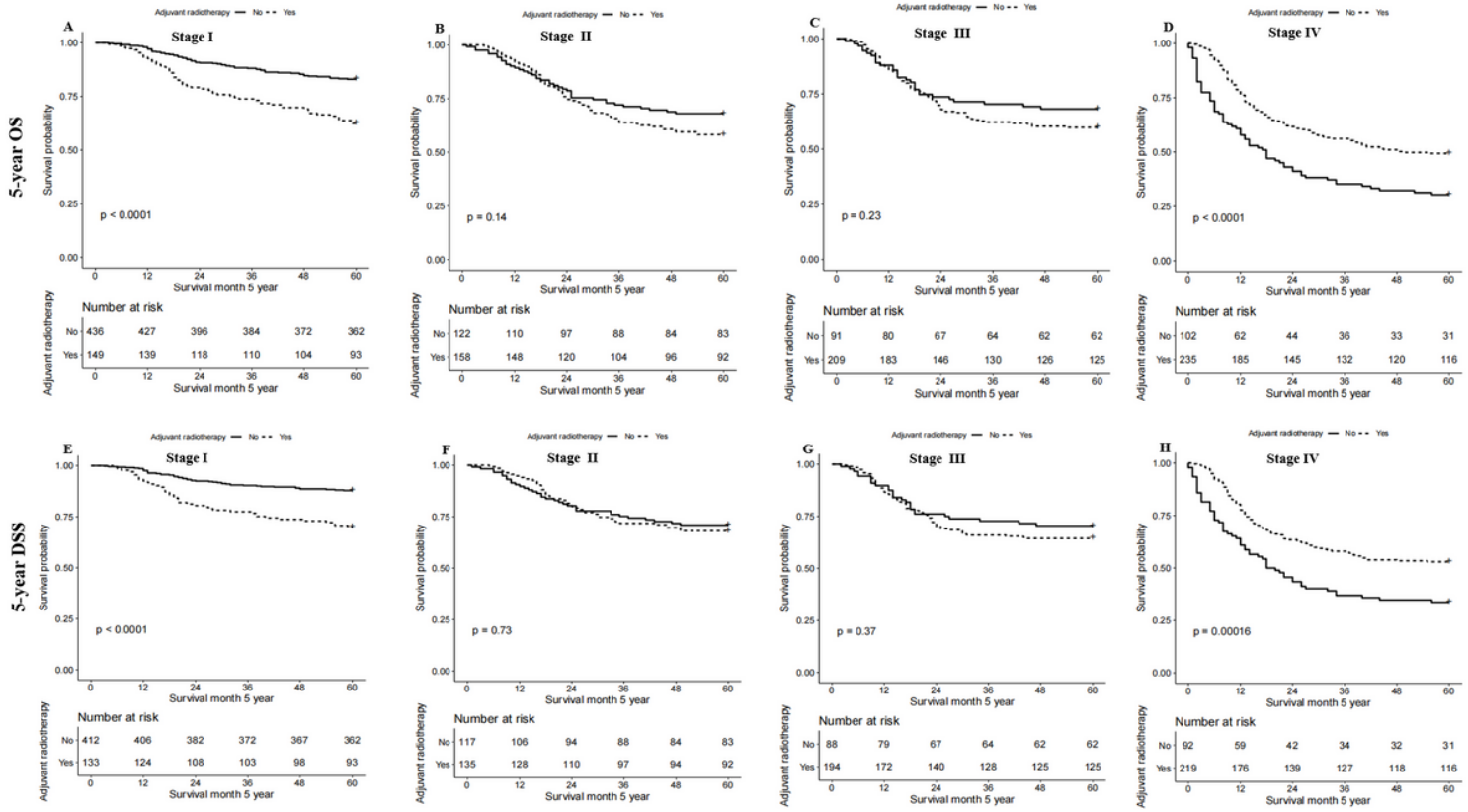

Figure 3

Kaplan–Meier survival curves of patients for 5-year overall survival (**a**: Stage I, **b**: Stage II, **c**: Stage III, **d**: Stage IV) and disease-specific survival (**e**: Stage I, **f**: Stage II, **g**: Stage III, **h**: Stage IV) in the matched cohort.