Indian Journal of Surgical Oncology (December 2023) 14(4):843–849
https://doi.org/10.1007/s13193-023-01790-0

ORIGINAL ARTICLE

Impact of Changes in Treatment Paradigms on Survival in Oral Squamous Carcinoma—a Population-Level Study

Natarajan Ramalingam[1] · Nithyanand Chidambaranathan[2] · Shivakumar Thiagarajan[3] · Arjun Singh[3] · Devendra Chaukar[4] · Pankaj Chaturvedi[3]

Received: 5 April 2023 / Accepted: 24 June 2023 / Published online: 1 July 2023

Abstract

There have been notable improvements in the treatment of oral cancers. The objective of this study was to see whether these improvements have translated into survival benefits at the population level from the SEER database. This is a retrospective study using the SEER 19 Custom database which included patients diagnosed with oral cancer between January 1, 1995, and December 31, 2015. The overall stage, age, sex, and treatment modalities were the covariates. For analysis, the patients were divided into four cohorts as per their year of diagnosis—cohort I included patients who were diagnosed between 1995 and 2000 ($n = 3873$), cohort II between 2001 and 2005 ($n = 5881$), cohort III between 2006 and 2010 ($n = 6233$), and cohort IV between 2011 and 2015 ($n = 12567$). Patients undergoing surgery with adjuvant therapy have increased significantly across cohorts and there is a significant fall in patients undergoing non-surgical treatment. Pairwise comparison by the Mantel-Cox test showed that cohort IV had significantly improved median overall survival (OS) and disease-specific survival (DSS) as compared to other cohorts and there was a significant impact of treatment modality on OS and DSS, especially in cohorts III and IV ($p<0.001$). Though geographical variations in the presentation and habits limit the generalization of these results, this study demonstrates that the changes and improvements in treatment paradigms incorporating level I evidence and surgical techniques have translated into improved survival outcomes at the population level. We recommend further studies on the local population to lend further credence to our observation.

Keywords Oral cancer · Treatment · Paradigms · Survival · SEER data

✉ Shivakumar Thiagarajan
drshiva78in@gmail.com

Natarajan Ramalingam
rnattu8906@gmail.com

Nithyanand Chidambaranathan
nithyanandc88@gmail.com

Arjun Singh
arjun193@gmail.com

Devendra Chaukar
dchaukar@gmail.com

Pankaj Chaturvedi
chaturvedi.pankaj@gmail.com

[1] Department of Head and Neck Oncology, Christian Medical College, Vellore, India

[2] Department of Head and Neck Oncology, Kovai Medical Centre & Hospital, Coimbatore, India

[3] Department of Head and Neck Oncology, Tata Memorial Centre and HBNI, Mumbai, India

[4] Department of Head and Neck Oncology, Max Nanavati Hospital, Mumbai, India

Introduction

Management of oral cancers has evolved over the last two decades with improvements in surgical techniques, radiation delivery techniques, and chemotherapy regimens. One of the notable improvements in the treatment of oral cancers has been the intensification of adjuvant treatment in patients with appropriate indications after the landmark trials by Bernier et al. and Cooper et al. However, whether these improvements have translated into an improvement in survival at the population level remains to be seen to date. The Surveillance, Epidemiology, and End Results (SEER) database provides information on cancer statistics of the various subsites treated in the USA over many years. This information would help understand the impact of the various improvements in the treatment modalities over the years and the impact of certain landmark studies/publications on the change in treatment patterns and on survival at a population level in general.

Materials and Methods

This is a retrospective study using data from the Surveillance, Epidemiology, and End Results (SEER) 19 Custom database. This cancer registry covers an estimated 27.8% of the US population. The study population included adult (≥ 18 years old) patients with primary squamous cell carcinoma (SCC) in the oral cavity site diagnosed between January 1, 1995, and December 31, 2015. Patients with multiple primaries and those with a previous history of cancers were included as this study aimed to look at the impact of practice-changing research on the survival of patients.

The overall stage at presentation (I, II, III, IV) was defined according to the summary stage of the SEER database. The summary stage was available for all patients in the SEER database whereas the TNM stage (7th edition) was not available in 41.7% (18,029 patients) of the entire study population. Other covariates available for statistical analysis included age, sex, stage, a subsite of the tumor (tongue, floor of mouth, other mouth), and treatment modalities (surgery alone, radiation alone, chemotherapy + radiation, surgery + radiation, triple therapy [surgery + radiation + chemotherapy], other combinations, no treatment/unknown). The subsite of the oral cavity site was classified using the following primary site ICD-O-3 codes. Squamous cell carcinoma was determined by the histological type codes 8070, 8071, 8072, 8073, 8074, 8075, 8076, and 8078, according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3).

The type of treatment received was gathered from the surgery codes, type of radiation, and chemotherapy codes. SEER registries collect information on radiation therapy (RT) and chemotherapy given as part of the first course of treatment. Combining these variables along with the sequence of radiation/chemotherapy received, the treatment fields were recoded as "None," "Surgery," "Surgery with adjuvant RT/Chemoradiotherapy (CTRT)," and "RT/CTRT only." Cases with missing or unknown values were excluded from the analyses. The survival months' flag variable was used to exclude the cases with missing or incomplete data on survival time, including unknown survival time, death reported by autopsy or death certificate only (no determination of diagnosis date), or no follow-up time recorded. Patients with survival ≤ 60 months were taken for analysis to have a common denominator for each time frame cohort. The reason for this was essentially only to make a presentation of up to 5 years of follow-up of the patients. The final cohort meeting the inclusion criteria consisted of 28,554 patients (Fig. 1).

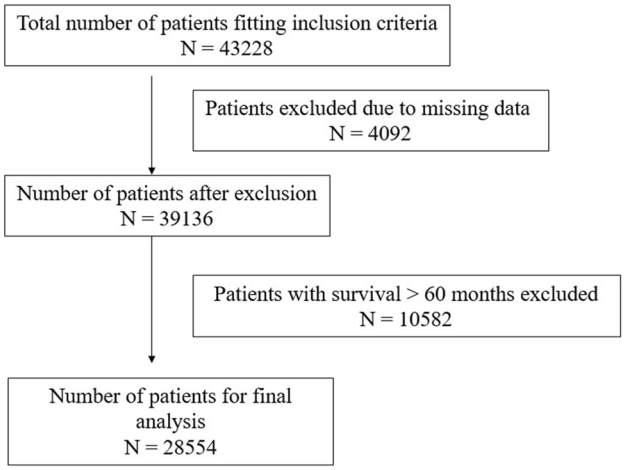


Fig. 1 Flow chart representing the total number of patients screened, those excluded (with reason) and the final number or eligible patients included in the study

Results

A total of 28,554 patients were included in the final analysis. For analysis, the patients were divided into four cohorts as per their year of diagnosis—cohort I included patients who were diagnosed between 1995 and 2000 (n = 3873), cohort II included patients who were diagnosed between 2001 and 2005 (n = 5881), cohort III included patients who were diagnosed between 2006 and 2010 (n = 6233), and cohort IV included patients who were diagnosed between 2011 and 2015 (n = 12567).

In the overall cohort, 10,742 (37.6%) patients had an age ≤ 60 years while 17,812 (62.3%) patients had an age > 60 years and 60.1% were males and 39.9% were females (Table 1). There were no significant differences seen in these distributions in the cohorts (p not significant (NS)). The three-stage groupings (as per the Summary Stage of the SEER database) were localized (51.2%), regional (39.9%), and distant (8.9%) (Table 1). There was a significant shift in the trends of the stage at presentation across the four cohorts with the majority of patients in cohort IV being in the localized stage (56.8%) (p<0.001). However, the distant metastasis rate was similar. The tongue formed the major subsite among all subsites of the oral cavity (48.3%) (Table 4 supplement). Also, across all four cohorts, the tongue was the most common subsite.

In the entire study population, 33.6% of patients underwent surgery only while 26.8% received either adjuvant RT or CTRT after surgery. 18.5% did not undergo surgery and received only RT/CTRT while 21.2% did not undergo any sort of treatment (Table 2). In the treatment pattern, the number of patients not undergoing any treatment remains similar across the four cohorts (Table 3). But the number of patients undergoing

Table 1 Demographic details

Characteristics	1995–2000		2001–2005		2006–2010		2011–2015	
	N = 3873		*N* = 5881		*N* = 6233		*N* = 12,567	
	No.	%	No.	%	No.	%	No.	%
Age								
< 60 years (*n*=10,742)	1229	11.4	2141	19.9	2330	21.7	5042	46.9
> 60 years (*n*=17,812)	2644	14.8	3740	21	3903	21.9	7525	42.2
Sex								
Male (*n*=17,161)	2343	13.7	3593	20.9	3765	21.9	7460	43.5
Female (*n*=11,393)	1530	13.4	2288	20.1	2468	21.7	5107	44.8
Stage								
Localized (*n*=14,628)	1774	45.8	2774	47.2	2937	47.1	7143	56.8
Regional (*n*=17,812)	2727	44.6	2568	43.7	2646	42.5	4438	35.3
Distant (*n*=2547)	372	9.6	539	9.2	3650	10.4	986	7.8

Table 2 Distribution of treatment patterns

Treatment pattern	1995–2000		2001–2005		2006–2010		2011–2015	
	N = 3873		*N* = 5881		*N* = 6233		*N* =12567	
	No.	%	No.	%	No.	%	No.	%
None	719	18.6	1290	21.9	1495	24	2545	20.3
Surgery	1128	29.1	1599	27.2	1810	29	5044	40.1
Surgery + adjuvant RT/CTRT	1131	29.2	1527	26	1563	25.1	3423	27.2
Definitive RT/CTRT	895	23.1	1465	24.9	1365	21.9	1555	12.4

surgery with adjuvant therapy has increased significantly across cohorts and there is a significant fall in the number of patients undergoing non-surgical treatment ($p<0.001$) (Table 2).

There is a marked improvement in median overall survival (OS) across the four cohorts over the years (Fig. 2). Pairwise comparison by log rank (Mantel-Cox) test showed that cohort IV had significantly improved median OS as compared to other cohorts ($p<0.001$). There were no significant differences in median OS between cohorts I and II (p 0.924) whereas cohort III had better median OS than cohorts I (p 0.041) and II (p 0.033).

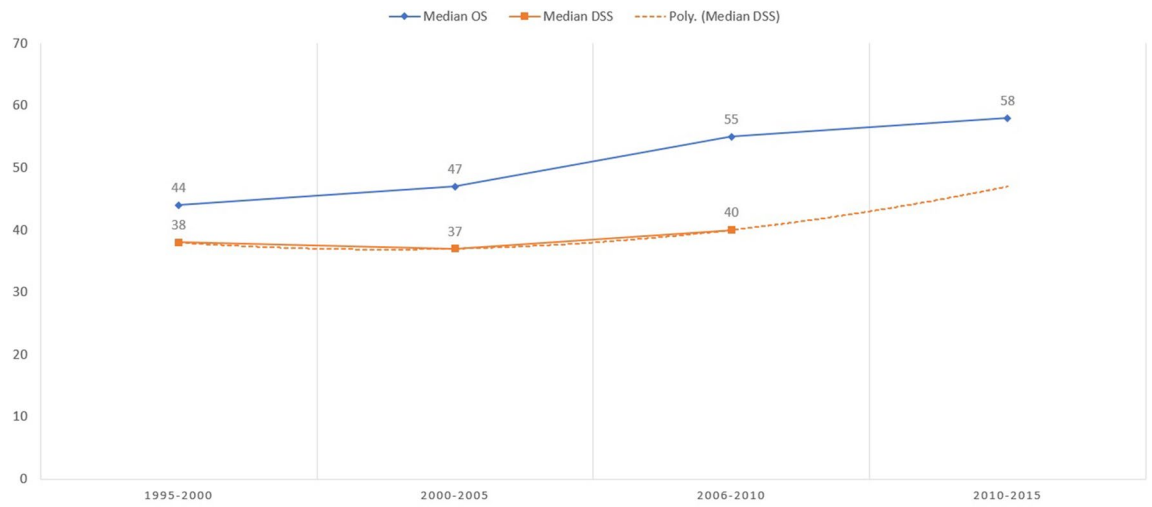
Table 3 Overall and disease specific Survival of the patients included in the study

Survival (in months)	1995–2000	2001–2005	2006–2010	2011–2015
Median OS by stage				
Localized	15	16	20	58
Regional	15	13	13	22
Distant	14	11	9	12
Median DSS by stage				
Localized	39	39	39	Not achieved
Regional	38	38	42	Not achieved
Distant	42	30	37	Not achieved

When stratified by stage of the disease at presentation, we found that there was a significant improvement in the median OS in localized and locoregionally advanced OSCC, especially in cohorts III and IV ($p<0.001$ Mantel-Cox test) (Table 3).

Similarly, there is a marked improvement in disease-specific survival (DSS) across the four cohorts (Fig. 2) with the median being not yet achieved in cohort IV. Pairwise comparison by log rank (Mantel-Cox) test showed that cohort IV had significantly improved median DSS as compared to other cohorts ($p<0.001$). There were no significant differences in median DSS between cohorts I and II (p 0.445) whereas cohort III had better median DSS than cohort II (p 0.048). When stratified by stage of the disease at presentation, we found that there was a significant improvement in the median DSS in cohort IV as the median was not yet achieved (p 0.017) (Fig. 3).

Looking at the impact of treatment patterns on OS and DSS, we found that there is a significant impact of treatment modality on OS and DSS, especially in cohorts III and IV in localized and locoregional disease but not in distant metastases ($p<0.001$) (Table 5 and Table 6 in supplement). Also, we found that both non-surgical modalities are largely ineffective in the treatment of OSCC. Logistic regression analysis showed that treatment modalities like surgery (OR 0.48, 95% CI 0.44–0.51), surgery with adjuvant RT (OR 0.84, 95% CI



OS (months)	44±0.96	47±0.60	55±0.37	58±0.96
DSS (months)	38±1.63	37±1.23	40±1.06	Not achieved

Fig. 2 Median OS and DSS (in months) across cohorts

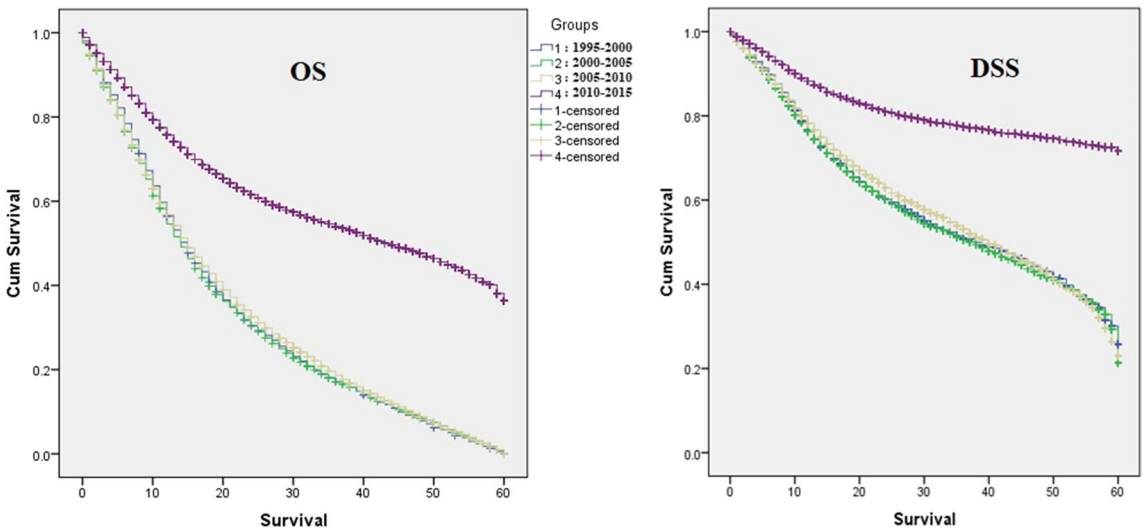


Fig. 3 OS and DSS survival curves

0.51–0.59), and surgery with adjuvant CTRT (OR 0.79, 95% CI 0.71–0.87) had a significant impact on OS while non-surgical modalities did not. For DSS, only surgery (OR 0.55, 95% CI 0.44–0.51) and surgery with adjuvant CTRT (OR 1.16, 95% CI 1.05–1.27) had a significant impact on logistic regression analysis.

Discussion

The majority of the patients who received treatment over the years between 1995 and 2015 were men, > 60 years of age, with localized disease. The number of patients

receiving surgery followed by adjuvant therapy had increased over the years and those receiving non-surgical treatment (RT/CCRT) had decreased over the years. Patients receiving surgery followed by adjuvant treatment had better OS compared to those receiving non-surgical treatment in patients with oral cancer. Overall, there was a marked improvement in the OS and DSS across the cohorts over the years. This gives further impetus to the existing evidence that oral cancer remains a surgical disease.

It has been found that there is an increasing trend in oral cancers being diagnosed as localized diseases. This increase is the reflection of better awareness among the patients of oral cancers with their tobacco habits. This could also indicate improvements in diagnostic modalities and screening programs. By awareness, we mean a better understanding of oral cancer at the population level in terms of risk factors like tobacco, alcohol, and HPV. Consequently, many patients are diagnosed at an early stage of their disease which is reflected in our analysis. The reasons for this may be multifactorial—better access to a healthcare facility, improved knowledge of the disease process, etc. Contrastingly, there was a steady decline in oral cancers with regional disease. The distant disease seems to be steady throughout the years but there was a drop from 2011 to 2015. Across all four cohorts, the tongue was the most common subsite as described in the literature [1, 2]. Though this was initially thought to be the result of HPV mediation, a meta-analysis by Ndiaye et al. [3] has shown the HPV DNA prevalence was 45.8% in the oropharynx but only 6.5% in the oral tongue [4].

The treatment pattern has changed; most importantly, there was a drop in the usage of definitive radiotherapy or chemoradiotherapy from 2011 to 2015. Surgery is continuing to flourish with newer technological advancements and improved reconstructive strategies which have made surgeons go beyond boundaries. There is a slow drift in focus from mere survival rates to better quality of life with microvascular reconstructive surgeries. The change over from radiotherapy/chemoradiotherapy to surgery with adjuvant treatment may be due to the impact of landmark trials/publications on patient care at the population level [5, 6]. There has been a steady increase in overall and disease-specific survival over the years, most importantly increased after 2006. Our results did not show the expected rise in adjuvant chemoradiation after the publication of the studies by Cooper et al. [7] and Bernier et al. [8]. However, there is an OS and DSS growth after 2006 (cohorts III and IV) and specifically in patients undergoing surgery followed by adjuvant radiotherapy/chemoradiotherapy. The plausible reasons for this may be because more patients may have been selected for chemoradiotherapy than before (though less than expected) compared to radiotherapy alone. However, in the analysis, both of these groups were clubbed together, hence probably showing better survival despite an absence of an expected rise in number of patients receiving adjuvant chemoradiotherapy.

Survival analysis translates the effects of change in treatment patterns across the years. Primary surgery has been the traditional approach in the management of oral cancers. For patients with unfavorable pathological features, addition of postoperative radiation therapy (PORT)/postoperative chemoradiotherapy (POCRT) has been shown to improve locoregional control and overall survival [7, 8]. Usual indications for PORT include the following: T3 or T4 tumor; compromised surgical resection margins, presence of lymphovascular invasion (LVI), and/or perineural invasion (PNI); and positive lymph nodes with or without extracapsular invasion (ECE) [9, 10]. Perineural invasion alone is not the sole indicator for adjuvant radiotherapy [11–13]. Even though depth of invasion (DOI) is considered a predictor of lymph node metastasis [14], there is not enough evidence to consider DOI as a sole indication for PORT [15]. Addition of chemotherapy to adjuvant radiation reduces the locoregional relapse by 13% at 5 years as reported in EORTC 22931 [8] and by 10% reduction at 2 years as reported in RTOG 9501 [7]. Trifeletti et al. [16] have shown multiple pathological positive lymph nodes also benefit from adjuvant chemoradiotherapy.

The rates of patients undergoing adjuvant radiotherapy/chemoradiotherapy have been stable over the years with a slight increase in 2011–2015. The OS and DSS increased from 2006 to 2010. This shows increased adoption of surgery as the primary treatment modality. Better surgical and reconstructive techniques have been the reason. Secondly, the results of Bernier and Cooper in 2004 showed an increased adoption in routine practice. Thirdly, a gradual decrease in radical radiotherapy or chemoradiotherapy in treating oral cancers has shown survival benefits. Head-on comparison of RT/CRT with surgery with adjuvant therapy has shown surgery to have survival benefits [5, 6].

We have noticed that the rates of overall death at 5 years were similar until 2006–2010 but significantly dropped from 2011 to 2015. Similar trends were also seen in the deaths due to oral cancer in 2011–2015. Even though oral cancer is easily accessible to direct examination, patients report only at advanced stages or decreased awareness among them was responsible for stable trends in mortality until 2010. A drastic change in treatment modalities as explained previously is responsible for the improvement in survival after 2011.

The median overall survival has improved drastically in localized disease from 20 months in 2006–2010 to 58 months in 2011–2016. The survival pattern in these groups has improved since 2011–2015 due to increased utilization of adjuvant therapy after the landmark trials. These observations show that the change in treatment paradigms due to the landmark trials has resulted in a significant improvement in

overall and disease-specific survival at the population level. The distant metastasis rates have been stable throughout the years, showing no treatment pattern was efficient in controlling them.

The present findings should be interpreted with the limitations inherent to a large population database such as missing data or inaccurate recording of variables, individual-level socioeconomic status, tobacco or alcohol use, incompleteness of the variables, biases associated with unmeasured reasons for receiving or not receiving RT/chemotherapy, and problems with interpretation of sequence data variables. Also, SEER does not report the date of recurrence of the disease, without which it would be difficult to evaluate the disease-free survival which reflects the effect of the treatment patterns. Nevertheless, this study demonstrates the impact of landmark trials on the incidence and changes in treatment patterns resulting in improved survival of oral cancers in a real-world scenario. Our analysis shows that the changes in the treatment patterns as a result of level I evidence have resulted in better outcomes at the population level (SEER database). To our knowledge, this study is one of the few studies to look into this aspect. We acknowledge the differences between populations that limit the generalization of our results. Hence, we suggest that similar studies need to be done to look into these variations in geographical areas. The main impediment to these studies is the lack of databases in other populations which needs to be addressed.

Conclusion

This study demonstrates that the changes and improvements in treatment paradigms incorporating level I evidence and surgical techniques have resulted in improved survival outcomes at the population level. A similar population-level study needs to be undertaken in other parts of the world, especially in regions where the incidence of oral cancer is among the highest in the world such as the Indian population, incorporating other variables such as habits, comorbidities, radiation fields, treatment breaks, and chemotherapy toxicity in the adjuvant setting to get a better understanding of the impact of treatment patterns.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13193-023-01790-0.

Acknowledgements Dr. Atanu Bhattacharjee, Statistician.

Declarations

Ethics Approval All the details necessary for analysis were collected from the SEER database. The data was accessed after an agreement with SEER regarding its usage [17]. There is no direct contact between the researcher and participants. All details regarding the patients are kept confidential. No details which can be used to identify the patient are published.

Conflict of Interest The authors declare no competing interests.

References

1. Tota JE, Anderson WF, Coffey C, Califano J, Cozen W, Ferris RL et al (2017) Rising incidence of oral tongue cancer among white men and women in the United States, 1973-2012. Oral Oncol 67:146–152
2. Patel SC, Carpenter WR, Tyree S, Couch ME, Weissler M, Hackman T et al (2011) Increasing incidence of oral tongue squamous cell carcinoma in young white women, age 18 to 44 years. J Clin Oncol 29(11):1488–1494
3. Ndiaye C, Mena M, Alemany L, Arbyn M, Castellsagué X, Laporte L et al (2014) HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis. Lancet Oncol 15(12):1319–1331
4. Liang X-H, Lewis J, Foote R, Smith D, Kademani D (2008) Prevalence and significance of human papillomavirus in oral tongue cancer: the Mayo Clinic experience. J Oral Maxillofac Surg 66(9):1875–1880
5. Iyer NG, Tan DSW, Tan VKM, Wang W, Hwang J, Tan N-C et al (2015) Randomized trial comparing surgery and adjuvant radiotherapy versus concurrent chemoradiotherapy in patients with advanced, nonmetastatic squamous cell carcinoma of the head and neck: 10-year update and subset analysis. Cancer 121(10):1599–1607
6. Robertson AG, Soutar DS, Paul J, Webster M, Leonard AG, Moore KP et al (1998) Early closure of a randomized trial: surgery and postoperative radiotherapy versus radiotherapy in the management of intra-oral tumours. Clin Oncol (R Coll Radiol) 10(3):155–160
7. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB et al (2004) Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 350(19):1937–1944
8. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre J-L, Greiner RH et al (2004) Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 350(19):1945–1952
9. Peters LJ, Goepfert H, Ang KK, Byers RM, Maor MH, Guillamondegui O et al (1993) Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. Int J Radiat Oncol Biol Phys 26(1):3–11
10. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A et al (2005) Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck 27:843–850
11. Huang T-Y, Hsu L-P, Wen Y-H, Huang T-T, Chou Y-F, Lee C-F et al (2010) Predictors of locoregional recurrence in early stage oral cavity cancer with free surgical margins. Oral Oncol 46(1):49–55
12. Liao C-T, Chang JT-C, Wang H-M, Ng S-H, Hsueh C, Lee L-Y et al (2008) Does adjuvant radiation therapy improve outcomes in pT1-3N0 oral cavity cancer with tumour-free margins and perineural invasion? Int J Radiat Oncol Biol Phys 71(2):371–376

13. Bur AM, Lin A, Weinstein GS (2016) Adjuvant radiotherapy for early head and neck squamous cell carcinoma with perineural invasion: a systematic review. Head Neck 38(Suppl 1):E2350–E2357
14. Huang SH, Hwang D, Lockwood G, Goldstein DP, O'Sullivan B (2009) Predictive value of tumour thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity: a meta-analysis of reported studies [Internet]. Cancer Interdiscip Int J American Cancer Soc 115(7):1489–1497
15. Ebrahimi A, Gil Z, Amit M, Yen T-C, Liao C-T, Chaturvedi P et al (2019) Depth of invasion alone as an indication for postoperative radiotherapy in small oral squamous cell carcinomas: an International Collaborative Study. Head Neck 41(6):1935–1942
16. Trifiletti DM, Smith A, Mitra N, Grover S, Lukens JN, Cohen RB et al (2017) Beyond positive margins and extracapsular extension: evaluating the utilization and clinical impact of postoperative chemoradiotherapy in resected locally advanced head and neck cancer. J Clin Oncol 35(14):1550–1560
17. Surveillance, Epidemiology and End Results (SEER) Program-www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, 9 Registries, Nov 2020 Sub (1975-2018) - Linked To County Attributes - Time-Dependent (1990-2018) Income/Rurality, 1969-2019 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2021, based on the November 2020 submission