Definitive radiotherapy for squamous cell carcinoma of the oral cavity: a single-institution experience

Kristin Lang¹,²,³, Melissa Baur¹, Thomas Held¹,²,³, Rami El Shafie¹,²,³, Julius Moratin⁴, Christian Freudlsperger⁴, Karim Zaoui⁵, Nina Bougatf¹,²,⁶, Jürgen Hoffmann⁴, Peter K. Plinkert⁵, Jürgen Debus¹,²,³,⁶,⁷, Sebastian Adeberg¹,²,³,⁶

¹ Department of Radiation Oncology, Heidelberg University Hospital, Heidelberg, Germany
² Heidelberg Institute of Radiation Oncology (HIRO), Heidelberg University Hospital, Heidelberg, Germany
³ National Center for Tumor diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany
⁴ Department of Oral and Maxillofacial Surgery, Heidelberg University Hospital, Heidelberg, Germany
⁵ Department of Otorhinolaryngology, Head and Neck Surgery, Heidelberg University Hospital, Heidelberg, Germany
⁶ Heidelberg Ion beam Therapy Center (HIT), Department of Radiation Oncology, Heidelberg University Hospital, Heidelberg, Germany
⁷ Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany

Radiol Oncol 2021; 55(4): 467-473.

Received 13 May 2021
Accepted 21 September 2021

Correspondence to: Kristin Lang, M.D., Department of Radiation Oncology, Heidelberg University Hospital, Im Neuenheimer Feld 400, D-69120 Heidelberg, Germany. E-mail: Kristin.lang@med.uni-heidelberg.de

Disclosure: No potential conflicts of interest were disclosed.

This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Background. Surgery is standard of care for oral cavity cancer (OCC). We provide a single-institution experience using definitive radiotherapy (RT) with or without concurrent systemic therapy for primary unresectable OCC.

Patients and methods. We retrospectively examined 49 patients with non-metastatic primary unresectable OCC treated with definitive RT between 2000 and 2019. The majority of patients (63.3%) were treated with definitive chemo-radiotherapy while 26.5% were given single-agent cetuximab weekly simultaneous to definitive RT. Five patients were treated with definitive RT alone because of limited disease and no nodal involvement.

Results. Median follow-up was 73 months (range, 6–236 months), median progression free survival (PFS) was 42 months (range, 2–157 months), median local disease-free survival (LDFS) was 44 months (range, 2–157 months) and median overall survival (OS) from the time of RT initiation was 52 months (range, 5–236 months). There were 65.3% loco-regional failures, 84.4% local and 15.6% distant metastasis. The majority of patients with local failure presented with American Joint Committee on Cancer (AJCC) Stage III–IV disease (59.2%). The 5-year Kaplan-Meier estimates for OS (III–IV vs. I–II) was 22.8% vs. 54.2% (p = 0.03, HR 2.090, 1.1–4.2). Patients who were treated with systemic therapy had a significant better 5-year overall survival compared to those with RT alone (43.9% vs. 23.1%, p = 0.05, 1.0–4.1). RT with doses less than 70 Gy (p = 0.046, HR 2.1 (1.0–4.5) was associated with worse overall survival. Mucositis was the most common ≥ grade 3 acute toxicity and occurred in 19 patients (39%). Incidences of chronic toxicities were loss of taste, trismus, osteoradionecrosis and xerostomia.

Conclusions. Definitive RT with or without concurrent systemic agents in patients with unresectable OCC resulted in an eloquent rate of locoregional control and good overall survival rates and is currently the best available treatment option in this patient collective.

Key words: oral cancer; systemic therapy; definitive radiotherapy; local failure
Introduction

Oral cancer includes cancers of all subsites of the oral cavity (oral tongue, floor of mouth, buccal mucosa, upper lip, lower lip, upper gum, lower gum, palate, and retromolar area) and is the eighth most common cancer worldwide. Worldwide incidence of oral cancer in 2018 was four cases per 100,000 people. Most related risk factors for oral cancer belong to tobacco and alcohol use.

Treatment of oral cavity cancer (OCC) includes single modality surgery, radiotherapy (RT) or various combinations of these modalities with or without systemic agents. The selection of treatment is based on disease stage, considerations of disease control, anticipated functional and cosmetic outcomes and expertise. Standard treatment option for OCC is surgery. Primary RT with or without systemic therapy is not used routinely. There are less prospective trials available which directly compared primary surgery vs. primary RT in oral squamous cell carcinoma (OSCC) specifically. In literature 5-year overall survival rate since first diagnosis in patients treated with RT alone was 15%.

To improve local control and overall survival rates intensified treatment with concurrent chemotherapy to RT is necessary instead of RT alone. Stenson et al. reported in a retrospective series overall survival rates with 66.9% in locally advanced oral cancer patients (stage III–IV) undergoing concurrent chemoradiotherapy (CCRT).

In a meta-analysis from Pignon et al. of individual patient data from clinical trials comparing RT vs. CCRT (MACH-NC) in locally advanced head and neck cancers, OCC comprised 21% of cases. Results showed an improvement of survival in OCC with CCRT compared to RT alone.

To examine the clinical significance and outcome in patients who do not underwent surgery we retrospectively reviewed our experience in treating OCC with primary RT with or without concurrent systemic therapies.

Patients and methods

This study was performed following institutional guidelines and the Declaration of Helsinki of 1975 in its most recent version. Ethical approval for the study was given from the local ethics committee at University Hospital Heidelberg (S421-2015).

Clinical, operative, and hospital course records were reviewed. We analyzed data from Nationales Centrum für Tumorerkrankungen (NCT) Cancer Registry in Heidelberg and imported data into our HIRO Research Database. All patients underwent systemic workup including cross-sectional imaging with referring providers prior to commencing RT. Afterwards, the patients underwent CT simulation with a standard immobilization 5-point mask. Target volume definition was based on CT and MRI scans with contrast agents, included the primary tumor region as well as nodal involvement according to the International Commission on Radiation Units and Measurements (ICRU) definition.

Patients underwent regular follow-up, including CT examinations every three months in the first two years after definitive treatment, in year three and four every 6 months and year five and six once a year as well as regularly clinical examinations at the Department of Oral and Maxillofacial Surgery. All follow-up CT-scans were reviewed by an experienced radiologist by the institutions own diagnostics. We excluded all patients with a metastatic disease (M1) at initial diagnosis.

Treatment toxicity

Acute toxicity was evaluated during and at the end of RT. Late toxicity was evaluated minimum 90 days after completion of RT and was described according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria (version 4.03, U.S. Department of Health and Human Services, Washington, DC, USA).

Statistical analysis and outcome evaluation

Overall survival (OS), progression free survival (PFS) and local disease-free survival (LDVF) were calculated using Kaplan-Meier analysis. OS was calculated from the time of RT initiation until death or the date of last follow-up. PFS was calculated as the time from the date RT initiation to tumor progression or death/ date of last follow-up, whichever occurred first. LRFS was defined as the time from the date RT initiation until local tumor progression at the primary tumor site. Patients still alive at the time of analysis, without tumor progression, or patients lost to follow-up were censored. Kaplan-Meier estimates were calculated using IBM SPSS software version 24. Subgroups were compared using the log-rank test. p-values of 0.05 or less were considered statistically significant. For comparison between groups, the Chi-squared test was performed in categorical and continuous variables. Kaplan-Meier estimates of potential prognostic factors were compared us-
ing the log-rank test for univariate analysis and the cox-regression model for multivariate analysis.

Results

Patient characteristics

There were 49 patients treated either with definitive RT alone or in combination with chemotherapy/immunotherapy at the Department of Radiation Oncology, University Hospital of Heidelberg. Only patients with cancer of the oral tongue (23 patients), floor of mouth (21 patients) and buccal mucosa (4 patients) were included (ICD-O-3 topography codes C02-C06).

Information regarding a risk factor history was available for all patients, there were 19 patients current and former smokers, 10 patients with alcohol consumption and 61 patients had a smoking and drinking history. Detailed patient characteristics are shown in Table 1.

Treatment characteristics

RT was carried out using photon irradiation with either 3D-planned (17 patients, 34.7%), IMRT (32 patients, 65.3%) (TomoTherapy®, Accuray, Sunnyvale, CA, USA) or volume-modulated RT (VMAT) (Elekta, Sweden), with treatment delivered one fraction per day with 5 fractions per week. The main RT treatment features are listed in Table 2.

There were 5 patients (10.2%) treated with RT alone because of limited disease or no nodal involvement. The majority of patients (31 patients, 63.3%) were treated with single-agent cisplatin 40 mg/m² chemotherapy weekly and 13 patients (26.5%) were given single-agent cetuximab 400 mg/m² one week prior to start of treatment followed by 250 mg/m² weekly as an alternative to chemotherapy.

Treatment results for the whole cohort

After a median follow-up of 73 months (range, 6–236 months), 11 patients (22.4%) were still alive, while 38 patients (77.6%) had died: 31 (81.6%) due to disease progression and 7 (18.4%) due to pulmonary infection, cardiac disease, secondary carcinoma or other comorbidities. There were 32 patients (65.3%) with locoregional failures in this cohort, 27 patients (84.4%) of which were local failures alone and 5 patients (15.6%) were distant. The majority of patients who failed locally presented with American Joint

| Characteristic | Number of patients (percentage) |
|---------------|--------------------------------|
| **Gender**    |                                |
| Male          | 30 (61.2%)                     |
| Female        | 19 (38.8%)                     |
| **Age, years**|                                |
| Median (range)| 61 years (17–85 years)        |
| **T-stage**   |                                |
| T1            | 8 (16.3%)                      |
| T2            | 12 (24.5%)                     |
| T3            | 7 (14.3%)                      |
| T4            | 22 (44.9%)                     |
| **N-stage**   |                                |
| N0            | 20 (40.8%)                     |
| N+            | 29 (59.2%)                     |
| **Grading**   |                                |
| 1             | 5 (10.2%)                      |
| 2             | 10 (20.4%)                     |
| 3             | 34 (69.4%)                     |
| **Risk factors** |                            |
| Smoking history | 29 (59.2%)                   |
| Alcohol consumption | 6 (12.2%)                  |
| none          | 14 (28.6%)                     |

| Technique                  | Number of patients (percentage) |
|----------------------------|--------------------------------|
| 3D-CRT                     | 17 (34.7%)                     |
| IMRT                       | 32 (65.3%)                     |

| RT-Dose                    |                                |
|----------------------------|                                |
| Median total dose base plan | 57.5 Gy (range: 50.0–65.9 Gy)   |
| [without boost]            |                                |
| Median single dose base plan | 1.9 Gy (range: 1.7–2.1 Gy)      |
| [without boost]            |                                |
| Boost                      |                                |
| Yes                        | 45 (91.8%)                     |
| SIB                        | 38 (84.4%)                     |
| Sequential                 | 7 (15.6%)                      |
| no                         | 4 (8.2%)                       |
| Median total dose boost plan | 12.0 Gy (range: 8.0–20.0 Gy)    |
| [base + boost plan]        |                                |
| Median single dose boost plan | 2.2 Gy (range: 2.0–2.2 Gy)     |
| Cumulative total dose      | 70.0 Gy (range: 60.0–72.0 Gy)   |
| [base + boost plan]        |                                |

| RT-Volume                  |                                |
|----------------------------|                                |
| CTV dimension base plan    | 829.6 ccm (range: 61.7–1554.4 ccm) |
| CTV dimension boost plan   | 178.5 ccm (range: 31.4–535.8 ccm) |

CTV = clinical target volume; Gy = gray; IMRT = intensity modulated radiotherapy; RT = radiotherapy, SIB = simultaneous integrated boost; 3D-CRT = three dimensional-conformal radiotherapy.
Committee on Cancer (AJCC) Stage III–IV disease (n = 29, 59.2%), while there were 20 patients (40.8%) that occurred in patients with early (Stage I–II) disease. The 5- and 10-year Kaplan-Meier estimates for OS, PFS, and LDFS were 37.9%, 35.9%, and 44.9%, and 23.0%, 28.6%, and 36.0% respectively. The median time to development of distant metastases was 66 months (range, 3.0–236 months).

The 5-year Kaplan Meier estimates for OS using systemic treatment versus RT alone was 43.9% vs. 23.1% (p = 0.05, Figure 1, HR 2.1, 1.1–4.2), there was no significant difference for PFS and LDFS.

### Results of univariate analysis

The 5-year Kaplan-Meier estimates for OS (III–IV vs. I–II) was 22.8% vs. 54.2 % (p = 0.03, HR 2.090, 1.1–4.2).

On univariate analysis, treatment with RT alone (p = 0.005), RT doses < 70Gy (p = 0.05) and nodal positive stage (p = 0.036) were associated with a greater risk of death (Table 3). For LDFS and PFS only positive nodal stage (p = 0.026 and 0.027) was associated with a significantly worse outcome.

### Results of multivariate analysis

Multivariate analysis was performed using the following variables: type of treatment, RT concept and nodal tumor stage. RT with doses less than 70Gy (p = 0.046, HR 2.1 (1.0–4.5) was associated with worse overall survival.

### Table 3. Overview about univariable cox regression analysis for overall survival (OS), progression free survival (PFS), local disease-free survival (LDFS), and metastasis free survival (MFS) in patients with oral squamous cell carcinoma (OSCC) undergoing definitive radiotherapy

| Parameter                           | OS HR (95% CI) | p-value | PFS HR (95% CI) | p-value | LDFS HR (95% CI) | p-value | MFS HR (95% CI) | p-value |
|-------------------------------------|----------------|---------|-----------------|---------|-----------------|---------|-----------------|---------|
| Age (≤ 60 years)                    | 1.2 (0.6–2.2)  | 0.637   | 0.9 (0.4–1.7)   | 0.647   | 0.6 (0.3–1.3)   | 0.224   | 3.4 (0.7–16.8)  | 0.120   |
| Sex male vs. female                 | 1.2 (0.6–2.4)  | 0.570   | 0.9 (0.5–2.0)   | 0.950   | 1.1 (0.5–2.4)   | 0.881   | 1.3 (0.3–5.1)   | 0.741   |
| T stage T1/2 vs. T3/4               | 2.1 (1.1–4.2)  | 0.036   | 1.3 (1.0–1.8)   | 0.077   | 1.4 (0.9–2.0)   | 0.072   | 2.1 (0.9–4.5)   | 0.071   |
| N stage N0 vs. N+                   | 2.1 (1.1–4.2)  | 0.036   | 2.4 (1.1–5.3)   | 0.026   | 2.7 (1.1–6.3)   | 0.027   | 2.8 (0.8–5.4)   | 0.071   |
| RT dose < 70.0 Gy vs. ≥ 70.0 Gy     | 1.9 (1.0–3.8)  | 0.05    | 1.5 (0.7–3.1)   | 0.267   | 1.4 (0.6–3.1)   | 0.393   | 1.7 (0.4–7.0)   | 0.428   |
| Concomitant therapies               | 2.1 (1.0–4.1)  | 0.05    | 1.2 (0.9–1.5)   | 0.227   | 1.5 (0.7–3.5)   | 0.294   | 0.4 (0.1–3.3)   | 0.409   |
| Concomitant therapies CHT vs. IT    | 1.2 (0.9–1.5)  | 0.216   | 1.5 (0.7–3.3)   | 0.296   | 1.2 (0.6–2.7)   | 0.586   | 0.7 (0.2–2.7)   | 0.580   |
| RT technique IMRT vs. 3D            | 0.6 (0.4–1.2)  | 0.183   | 0.7 (0.3–1.3)   | 0.258   | 0.7 (0.3–1.4)   | 0.282   | 1.2 (0.3–5.0)   | 0.765   |
| Risk factor history                 | 1.1 (0.8–1.4)  | 0.536   | 0.9 (0.7–1.3)   | 0.690   | 0.9 (0.6–1.1)   | 0.328   | 1.5 (0.7–3.0)   | 0.295   |

CHT = chemotherapy; CTV = clinical target volume; Gy = gray; IMRT = intensity modulated radiotherapy; IT = immunotherapy; LDFS = local disease-free survival; RT = radiotherapy, SIB = simultaneous integrated boost; 3D = three dimensional-conformal radiotherapy.
Toxicity

Mucositis was the most common grade > 3 acute toxicity present in 19 patients (39.0%) followed by dysphagia grade 3 in 12 patients (24.0%). Other significant acute toxicities grade 1/2 included dermatitis (56.3%) and xerostomia (39.7%). There were no treatment-related deaths. Late RT-related complications (grade 3) included xerostomia (64.4%), loss of taste (60.3%), trismus (26.0%) and osteoradionecrosis (9.6%). A total of 27 (56.0%) patients received a percutaneous endoscopic gastrostomy (PEG) tube: 5 (19.2%) prophylactically (reflecting the prior institutional practice of routine PEG placement prior to treatment), 22 acutely during treatment (80.8%). Toxicities are summarized in Table 4.

Discussion

The primary purpose of the present study was to evaluate the outcome and prognostic factors for patients with unresectable OCC who underwent definitive RT. Several studies reported local control rates and 5-year OS for definitive RT in OCC ranging between 27% to 70%9,11,13 and 37–67%14, which goes in line with our results.

In our study 59.2% of patients had advanced-stage disease III–IV with significant OS in stage I–II. Over the last decades the role of concomitant systemic therapy has become clearer. Pignon et al. reported in MACH-NC about better outcome and locoregional control rates when using concurrent chemotherapy and RT with a better absolute benefit of 4.5% at 5 years.9,16 In our study there were 10.2% patients treated with RT alone due to either comorbidities, worse performance status or because of denied surgery. Patients who were treated with systemic treatment had a significantly better 5-year OS compared to those without (43.9% vs. 35.6%).

### Table 4. Early and late toxicity after radiotherapy

| Early treatment toxicity (< 90 days) | Late treatment toxicity (> 90 days) |
|-------------------------------------|-------------------------------------|
| CTCAE grade | No of patients n (%) | CTCAE grade | No of patients n (%) |
| Mucositis | | | |
| 1 | 6 (13.0) | 1 | 19 (39.7) |
| 2 | 17 (35.6) | 1 | 17 (35.6) |
| 3 | 2 (3.4) | 2 | 5 (11.0) |
| Dermatitis | | | |
| 1 | 12 (24.7) | 1 | 19 (39.7) |
| 2 | 15 (31.5) | 2 | 5 (11.0) |
| 3 | 5 (11.0) | 3 | 4 (8.9) |
| Xerostomia | | | |
| 1 | 15 (30.8) | 1 | 15 (30.8) |
| 2 | 4 (8.9) | 2 | 5 (11.0) |
| 3 | 1 (2.1) | 3 | 4 (8.9) |
| Dysphagia | | | |
| 1 | 9 (19.2) | 1 | 15 (30.8) |
| 2 | 17 (34.9) | 2 | 5 (11.0) |
| 3 | 12 (24.0) | 3 | 4 (8.9) |
| Loss of taste (late toxicity) | 29 (60.0) |
| Trismus (late toxicity) | 13 (26.0) |
| Osteoradionecrosis (late toxicity) | 4 (8.9) |

CTCAE = Common Terminology Criteria for Adverse Events

### Table 5. Summary of the most important studies for definitive radiotherapy in patients with oral cavity cancer as an overview radiotherapy

| Study Period | Radiotherapy | No. of patients | CHT/IT | LDFS | PFS | OS |
|--------------|--------------|-----------------|--------|------|-----|----|
| Lin et al.16 | 1995–2007 | 42% IMRT | 115 | 46% CHT | 27% (3yr) | n/a | 15% (3yr) |
| Foster et al.17 | 1994–2014 | 54% IMRT | 140 | 100% CHT | 79% (5yr) | 59% (5yr) | 63% (5yr) |
| Studer et al.8 | 2002–2011 | 100% IMRT | 54 | 68% CHT/IT | n/a | 37% (4yr) | 37% (4yr) |
| Pederson et al.9 | 2001–2004 | 100% IMRT | 21 | 100% CHT | 76% (5yr) | 71% (5yr) | 76% (5yr) |
| Hosny et al.19 | 2005–2014 | 100% IMRT | 21 | 35% CHT | 42% (5yr) | 78% (5yr) | 50% (5yr) |
| Present Study | 2000–2019 | 74% IMRT | 119 | 86.5% CHT/IT | 61.9% (5yr) | 52.1% (5yr) | 47.2% (5yr) |

CHT = chemotherapy; IMRT = intensity modulated radiotherapy; IT = immunotherapy; LDFS = local disease-free survival; n/a = not applicable; OS = overall survival; PFS = progression free survival; yr = years
23.1%) (p = 0.05, HR 2.1, 1.1–4.2) but no significant difference for PFS and LDFS.

While other studies found T-stage, age, grading and gender to be prognostic factors for PFS and LC patient survival rates with moderate toxicity. Follow-up of 76 months good control and overall worse local control. For LDFS and PFS only positive nodal stage was associated with a significant worse outcome.

Cumulative total doses of less than 70 Gy is standard in patients who underwent postoperative treatment and not suggested as definitive RT treatment concept which goes in line with literature. Early and late toxicity from definitive RT to the oral cavity of our collective is comparable to data from other published series. Most common acute RT-related complications (CTCAE grade > 3) in our study were oral mucositis (39.0%) and dysphagia (24.0%). Other significant acute toxicities grade 1/2 included dermatitis (56.2%) and xerostomia (39.7%). Late RT-related complications included xerostomia (64.4%), loss of taste (60.3%), trismus (26.0%), edema (47.3%). These late complications appear similar in other series. The rate of osteoradionecrosis in the present study was 9.6%, which falls in line with other studies – range of osteoradionecrosis in the present study was a parameter for osteoradionecrosis (ORN). This is survival rates with moderate toxicity.

The limitations of this study include its retrospective nature, which led to a shortage of necessary data on some single cases. However, we were able to retrieve follow-up data covering a lengthy time period for all patients at a large department with a lot of experience in the field of oral tumor diseases.

The power of this study is that we were able to show in a dedicated collective of patients with OCC undergoing definitive RT and an extended follow up of 73 months good control and overall survival rates with moderate toxicity.

References

1. Scully C, Bagan J. Oral squamous cell carcinoma overview. Oral Oncol 2009; 45: 301-8. doi: 10.1016/j.oraloncology.2009.01.004
2. Warnaalakulsiy S. Global epidemiology of oral and oropharyngeal cancer, Oral Oncol 2009; 45: 309-16. doi: 10.1016/j.oraloncology.2008.06.002
3. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Poiriers M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 2019; 144: 1941-53. doi: 10.1002/ijc.31937
4. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado M, Ferlay J, Franceschi S, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J Clin Oncol 2013; 31: 4550-9. doi: 10.1200/JCO.2013.50.3870
5. Sutton DN, Brown JS, Vaughan ED, Woolgar JA. The prognostic implications of the surgical margin in the oral squamous cell carcinoma. Int J Oral Maxillofac Surg 2003; 32: 30-4. doi: 10.1016/j.ijom.2002.03133
6. Scher ED, Romesser PB, Chen C, Ho F, Wu Y, Sherman EJ, et al. Definitive chemoradiation for primary oral cavity carcinoma: a single institution experience. Oral Oncol 2015; 51: 709-15. doi: 10.1016/j.oraloncology.2015.04.007
7. Foster CC, Melotek JM, Brisson RJ, Seiwert TV, Cohen EEW, Stenson KM, et al. Definitive chemoradiation for locally-advanced oral cavity cancer: a 20-year experience. Oral Oncol 2018; 80: 16-22. doi: 10.1016/j.oraloncology.2018.03.008
8. Lyer N, Tan DSW, Tan VMK, Wang W, Hwang J, Tan NC, et al. 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 2015; 121: 1599-607. doi: 10.1002/cncr.29251
9. Pignon JP, le Maitre A, Mailard E, Bourhis J, Group M-NC. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009; 92: 4-14. doi: 10.1016/j.radonc.2009.04.014
10. Stenson KM, Kunavakkam R, Cohen EE, Portugal LD, Blair E, Haraf DJ, et al. Chemoradiation for patients with advanced oral cancer. Laryngoscope 2010; 120: 93-9. doi: 10.1002/lary.20716
11. Studer G, Brown M, Reddell M, Graetz KW, Huber G, Linsemeyer C, et al. Follow up after IMRT in oral cavity cancer: update. Radiat Oncol 2012; 7: 84. doi: 10.1186/1748-717X-7-84
12. Kessel KA, Bohn C, Engelmann U, Oetzelt D, Bougatt N, Bendt R, et al. Five-year experience with setup and implementation of an integrated database system for clinical documentation and research. Comput Methods Programs Biomed 2014; 114: 206-17. https://doi.org/10.1016/j.cmpb.2014.02.002
13. Lang K, Akbaba S, Held T, Kargus S, Horn D, Bougatf N, et al. Definitive radiotherapy vs. postoperative radiotherapy for lower gingival carcinomas of the mandible: a single-center report about outcome and toxicity. Strahlenther Onkol 2019; 195: 819-29. doi: 10.1007/s00066-019-01484-z
14. Esbruch A. Intensity-modulated radiation therapy in the treatment of head and neck cancer. Nat Clin Pract Oncol 2005; 2: 34-9. doi: 10.1038/ncponc0058
15. Huang SH, O’Sullivan B. Oral cancer: current role of radiotherapy and chemotherapy. Med Oral Patol Oral Cir Bucal 2013; 18: e233-40. doi: 10.4314/medoral.18772
16. Pignon JP, Bourhis J, Domenges C, Descleze L. Chemotherapy added to lcoregional 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. doi: 10.1016/S0140-6736(00)02311-4
17. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. 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 RT0G (# 9501). Head Neck 2005; 27: 843-50. doi: 10.1002/hed.20279
18. Lin CY, Wang HM, Kang CJ, Lee CY, Huang SF, Fan KH, et al. Primary tumor site as a predictor of treatment outcome for definitive radiotherapy of advanced-stage oral cancer cancers. Int J Radiat Oncol Biol Phys 2010; 78: 1011-9. doi: 10.1016/j.ijrobp.2009.09.074
19. Hosni A, Chiu K, Huang SH, Xu W, Huang J, Baylely A, et al. Non-operative management for oral cavity carcinoma: definitive radiation therapy as a potential alternative treatment approach. Radiother Oncol 2020; 154: 70-5. doi: 10.1016/j.radonc.2020.08.013
20. Murphy V, Agarwal JP, Laskar SG, Gupta T, Budrukkar A, Pai P, et al. Analysis of prognostic factors in 1180 patients with oral cavity primary cancer treated with definitive or adjuvant radiotherapy. J Cancer Res Ther 2010; 6: 282-9. doi: 10.4103/0973-1482.73360
21. Zelefsky MJ, Harrison LB, Fass DE, Armstrong JG, Shah JP, Strong EW. Postoperative radiation therapy for squamous cell carcinomas of the oral cavity and oropharynx: impact of therapy on patients with positive surgical margins. Int J Radiat Oncol Biol Phys 1993; 25: 17-21. doi: 10.1016/0360-3016(93)90139-m

22. Salama JK, Seiwert TY, Vokes EE. Chemoradiotherapy for locally advanced head and neck cancer. J Clin Oncol 2007; 25: 4118-26. doi: 10.1200/JCO.2007.12.2697

23. Tobias JS, Monson K, Gupta N, Macbougal H, Glaholm J, Hutchison I, et al. Chemoradiotherapy for locally advanced head and neck cancer: 10-year follow-up of the UK Head and Neck (UKHAN1) trial. Lancet Oncol 2010; 11: 66-74. doi:10.1016/S1470-2045(09)70306-7

24. Pederson AW, Salama J, Witt ME, Stenson KM, Blair EA, Vokes EE, et al. Concurrent chemotherapy and intensity-modulated radiotherapy for organ preservation of locoregionally advanced oral cavity cancer. Am J Clin Oncol 2011; 34: 356-61. doi: 10.1097/COC.0b013e3181e8420b

25. Gebre-Medhin M, Brun E, Engstrom P, Haugen Cange H, Hammarstedt-Nordenvall L, Reizenstein J, Nyman 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. doi: 10.1200/JCO.20.02072

26. Shah JP, Gil Z. Current concepts in management of oral cancer – surgery. Oral Oncol 2009; 45: 394-401. doi: 10.1016/j.oraloncology.2008.05.017

27. Kerr P, Myers CL, Butler J, Alessa M, Lambert P, Cooke AL. Prospective functional outcomes in sequential population based cohorts of stage III/IV oropharyngeal carcinoma patients treated with 3D conformal vs. intensity modulated radiotherapy. J Otolaryngol Head Neck Surg 2015; 44: 17. doi: 10.1186/s40463-015-0068-4

28. Blanchard P, Baujat B, Holostenco V, Bourredjem A, Baey C, Bourhis J, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiother Oncol 2011; 100: 33-40. doi: 10.1016/j.radonc.2011.05.036

29. Reuther T, Schuster T, Mende U, Kübler A. Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients – a report of a thirty year retrospective review. Int J Oral Maxillofac Surg 2003; 32: 289-95. doi: 10.1054/ijom.2002.0332