

Survival Analysis of Buccal Mucosa Carcinoma Patients Treated with Definitive Chemo Radiotherapy: A Regional Cancer Centre Experience

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ABSTRACT

Background: In India, buccal mucosa carcinoma is one of the commonest oral cavity tumours which are aggressive in nature. **Objective:** The present study aim was to evaluate survival impact of buccal mucosa carcinoma in patients treated with definitive chemo radiotherapy. **Materials and Methods:** All the patients with primary buccal mucosa carcinoma treated with chemo radiotherapy were included between 2013 and 2016 in regional cancer centre of Tamil Nadu. Patient's demographic, clinical, type of chemotherapy and dose of radiotherapy and follow-up details were recorded. **Results:** A total of 79 patients included in the study, there were 45 (57%) male and 34 (43%) female, with a mean age of 54 years (range, 20-87 years). The chemotherapy regimen consist (Docetaxel, Cisplatin, and 5-Flurouracil) and concurrent irradiation of 66-70 Gy in 33-35 fractions over 7-8 weeks. All the patients were followed-up for 34 months (Median, 22 months). Of 79 patients, 1 (1%) identified with recurrence and 5 (6%) had disease-specific death. Actuarial, three years estimated overall and disease-free survival was 42% and 54%, respectively. Of 79 patients, 55(70%) showed complete response and followed 23(29%) partial and 1(1%) of patients

does not showed any response of treatment. After definitive chemo radiotherapy, patients had acute haematologic and non-haematologic, G3 and G4 toxicities. **Conclusion:** The present study demonstrated chemo radiotherapy definitive treatment response, toxicity and survival outcome of buccal mucosa carcinoma. Further, the study suggested early stage of treatment prevents distant metastasis, treatment failure and improves survival outcome.

Key words: Buccal mucosa carcinoma; chemo radiotherapy; survival; treatment response; toxicity

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INTRODUCTION

In India, Oral squamous cell carcinoma is one of the leading cause's morbidity and mortality.^[1] The age adjusted rates as per the Population Based Cancer Registry in males and females are 2.4 and 4.4, respectively.^[2] The incidence as reported by the Kidwai Memorial Institute of Oncology Hospital Based Cancer Registry was 6% of all malignancies, constituting 27% of all head and neck cancers.^[3] Cancer occurs in different subsites of oral cavity, buccal mucosa was one of the most common subsites which account 35% in south India.^[4]

Surgery with or without radiotherapy or chemo radiotherapy had a better survival and should be the mainstay of treatment.^[5] Approximately, 80-90% of patients with stage I and II head and neck cancer cured, whereas locally advanced stage III and IV were less promising and they need a combination of surgery, radiotherapy and chemotherapy.^[6] However, chemotherapy with concurrent radiotherapy should be reserved for patients with unresectable disease or patients who cannot tolerate a surgical procedure.^[7,8]

In the past 30 years, there has been a trend towards "organ preservation" regimes with treatment of chemotherapy to conventional radiotherapy instead surgery in head and neck squamous cell carcinoma, particularly in buccal mucosa.^[9-11] Therefore, the aim of this present study was to determine the treatment response and toxicity of primary buccal mucosa carcinoma treated with definitive chemo radiotherapy. The secondary aims of the study were to determine the survival outcome of disease.

MATERIALS AND METHODS

Patient's selection

The present retrospective study was performed in accordance with the Declaration of Helsinki ethical guidelines. Ethical approval from directorate of medical education (DME), Tamilnadu and informed

consent of patients was obtained prior to conduct study (Ref No. 24984/2013). We reviewed primary buccal mucosa carcinoma patients at Arignar Anna Memorial Cancer Hospital and Research Centre between 2013 and 2016.

Clinical and histopathological confirmed primary buccal mucosa carcinoma patients, who underwent chemo radiotherapy, were included. Recurrence, precancerous patients and who had previous treatment history of surgery and/or adjuvant chemo radiotherapy treatment modality were excluded from this study.

Data collection

A total of 79 patients were identified with previously untreated primary buccal mucosa carcinoma and subsequently received definitive chemo radiotherapy. Patient's demographics (Gender, age, body mass index, risk habits, ECOG-PS score), clinical characteristics (Cell differentiation and TNM stage), dose of radiation and type of chemotherapy treatments, acute and late toxicity and survival details were recorded from medical registers.

Pre-treatment evaluation

All patients were evaluated with blood investigations complete blood count; white blood cell count, liver function test includes total bilirubin,

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aspartate aminotransferase, and alanine aminotransferase and renal function test includes serum creatinine. The metastasis presence and location were confirmed with chest X-ray and computed tomography in head and neck regions.

Treatment details

Buccal mucosa carcinoma patients were planned for minimum of five cycles of weekly chemotherapy (docetaxel+cisplatin+5-fluorouracil). The study medication started Docetaxel with 5 mg/m² in first week of treatment and followed by Cisplatin or carboplatin-based chemotherapy (70 mg/m² in 3-hr infusion) and 5-Fluorouracil (700 mg/m² in 24-hrs infusion) was used as adjuvant for above 7 weeks. Treatment was repeated every 21 days. Concurrent radiation treatment (5 days/week) was administered at 66-70 Gy in 33-35 fractions over 7-8 weeks. The chemotherapy and radiotherapy were started within 7 days of each other [Figure 1].

Treatment response

Response to treatment was assessed as per a modified World Health Organization (WHO) response criterion.^[12] Tumour regression, if assessed >75% of original dimensions were graded as complete response, 50-75% regression of tumour was graded as partial response and below 50% regression was graded as a poor/ Non-responders.

Toxicity evaluation

All the patients were assessed for toxicity weekly treatment as per National Cancer Institute Common Terminology Criteria for Adverse Events v3 (CTCAE v3.0).^[13] They were assessed again 6 weeks after completion of treatment, toxicity and response.

Follow-up outcome

All patients were followed-up for six weeks after completion of treatment for response and toxicity assessment. Subsequently, patients were followed-up in the clinic every three months for the first two years and every six months thereafter. Missed follow-up were contacted through telephone to update the disease and patient status. The primary outcome measure was set as overall survival; this was calculated as the time from the first date of treatment to the date of death or last known date the patient was alive. Secondary outcome was set as disease-free survival; this was calculated from the first day of treatment to the date of disease recurrence.^[14]

Statistical analysis

SPSS version 16.0 was used for statistical analysis (SPSS Inc., Chicago, IL, USA). The results were expressed as numbers and percentages. Overall survival was assessed by Kaplan-Meier survival analysis. Multivariate Cox-regression hazard risk analysis was performed for evaluation of prognostic factors.

RESULTS

Patient's characteristics

From 2013 and 2016, a total of 79 primary buccal mucosa carcinoma patients were treated with definitive chemoradiotherapy with Docetaxel, 5-FU and CDDP and concurrent irradiation in our hospital. The patient characteristics were listed in Table 1. There were 45 (57%) male and 34 (43%) female in study population and most of patients from >80 years of age groups with a mean age of 54 years (range, 20-87 years). Of 79 patients, 35 (44.3%) were diagnosed with underweight and followed by others. At the time of diagnosis, 70 (88.6%) had poor physical performance score of 3 and 4.

In the study population, most of patients from advanced clinical TNM stage III and IV was 71 (89.8%) and rest of 9 (10.2%) from early stage of I and II. All the patients had squamous cell carcinoma with most frequent of 35 (44.3%) well differentiated and followed by 29 (36.7%) moderate and 15 (19%) of poorly differentiated buccal squamous cell carcinoma.

Treatment details

Figure 1 shows the treatment schedule. All the patients treated with curative intent and completed the planned chemo and radiotherapy. Chemotherapy comprised protracted infusion of 5-FU (700 mg/m²) combined with a 2 h infusion of CDDP (70 mg/m²) with adequate hydration and antiemetic coverage. Radiation treatment (10 MV) was administered for 6-7 weeks (5 days/week) at 2 Gy/day with a total radiation dose of 66-70 Gy concomitantly with chemotherapy. The chemotherapy and radiotherapy were started within 7 days of each other. Chemotherapy was terminated in the other patient because of disease progression after the first course of chemotherapy.

Treatment response

Tumor response was evaluated every two months after the initiation of

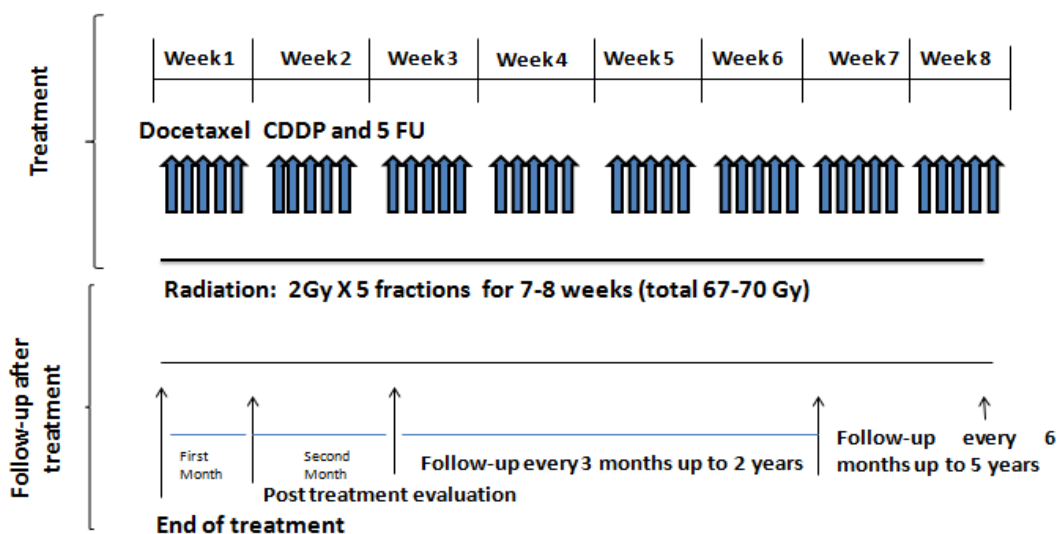


Figure 1: Treatment schema of chemoradiotherapy for buccal mucosa carcinoma patients

Table 1: Baseline characteristics of buccal mucosa carcinoma patients

Patient Characteristics		No. of patients (n=79)	Frequency (%)
Gender	Male	45	57
	Female	34	43
Age (yrs)	<40	5	6.3
	40-59	21	26.6
	60-79	21	26.6
	>80	32	40.5
Body Mass Index (BMI)	Underweight (<18.5 kg/m ²)	35	44.3
	Healthy weight (18.5-24.9 kg/m ²)	24	30.4
	Overweight (25-29.9 kg/m ²)	13	16.5
	Obese (30-35 kg/m ²)	7	8.9
ECOG score	Good performance (0-1)	9	11.4
	Poor performance (2-4)	70	88.6
Clinical TNM stage	Stage I	1	1.3
	Stage II	7	8.9
	Stage III	6	7.6
	Stage IV	65	82.3
Grade of tumour	Well differentiated	35	44.3
	Moderately differentiated	29	36.7
	poorly differentiated	15	19.0

treatment. The responses of the primary lesions were shown in Table 2. In the study population, 55 (70%) achieved a complete response with apparent regression of primary buccal mucosa carcinoma after chemoradiotherapy and 23 (29%) were identified with partial response. Of 79 patients, one patient (1%) does not show any response.

Adverse effects

Adverse events were demonstrated in Table 3. There were no grade 1/2 adverse events after treatment. Hematologic toxicity was reported with acute toxicities of grade 3 and 4; most common adverse effect of anaemia accounts 65 (82.3%) and followed leucopenia was 58 (73.4%), thrombocytopenia 43 (54.4%) and neutropenia 14 (17.7%). None of the patients died during the treatment. Non-hematologic toxicity was reported with most common prolonged mucositis 74 (93.6%), second most adverse event was nausea 72 (91.1%) and followed by stomatitis 70 (88.6%), dysplasia 70 (88.6%), neurotoxicity 68 (86.1%), constipation 64 (81%), weight loss 57 (72.1%), infection 43 (54.4%), vomiting 42 (53.1%) and gastrointestinal pain was 36 (45.5%) patients.

Survival outcome

All the patients were follow-up for 34 months (median, 22 months). Of 79 patients, 1 (1%) patient identified with recurrence and 5 (6%) had disease-specific death. Actuarial, three years estimated overall survival was 42% and disease-free survival was 54% [Figure 2].

DISCUSSION

Although, many treatment modalities were tried to improve survival in unresectable head and neck squamous cell carcinoma; Docetaxel, Cisplatin and 5-Fluorouracil enhances the effect of radiation by synchronisation of cell cycle at the most sensitive phase (G2/M) and influences intracellular platinum metabolism and enhances radiosensitivity by inhibition of radiation induced DNA repair.^[15,16] Triplet chemotherapy routinely administered at a tertiary level centre with the supportive care and precautionary method for unresectable oral cancer patients.^[17] Patil *et al.* showed improved outcomes over platinum doublet with in oral squamous cell carcinoma.^[18] As previous reports, the present study shows incorporation of these three active agents along with concurrent radiotherapy and its efficacy of buccal mucosa carcinoma.

Generally, the treatment plan for oral cavity cancers decided based on the functional and cosmetic outcome and also the preference of clinician.^[19] However, based on the physicians and patient consent in the present study a total of 79 buccal mucosa carcinoma patients were undergone definitive chemo radiotherapy between the period of 2013 and 2016.

The demographic characteristics of male frequency with the mean age of 54 years and poor physical ECOG performance of patients reflect

Table 2: Treatment response rate of buccal mucosa carcinoma patients

Treatment Response	No. of subjects (n=79)	Frequency (%)
Complete response	55	70
Partial response	23	29
No response	01	01

Table 3: Adverse events of study population after definitive chemo radiotherapy treatment

Characteristics	No. of subjects (n=79)	Frequency (%)
Hematologic		
Neutropenia	14	17.7
Anaemia	65	82.3
Thrombocytopenia	43	54.4
Leukopenia	58	73.4
Non-hematologic		
Mucositis	74	93.6
Nausea	72	91.1
Diarrhoea	56	70.8
Vomiting	42	53.1
Anorexia	57	72.1
Stomatitis	70	88.6
Neurotoxicity	68	86.1
Infection	43	54.4
Weight loss	57	72.1
Constipation	64	81
Esophagitis, dysphagia, or Odynophagia	70	88.6
Gastrointestinal pain	36	45.5

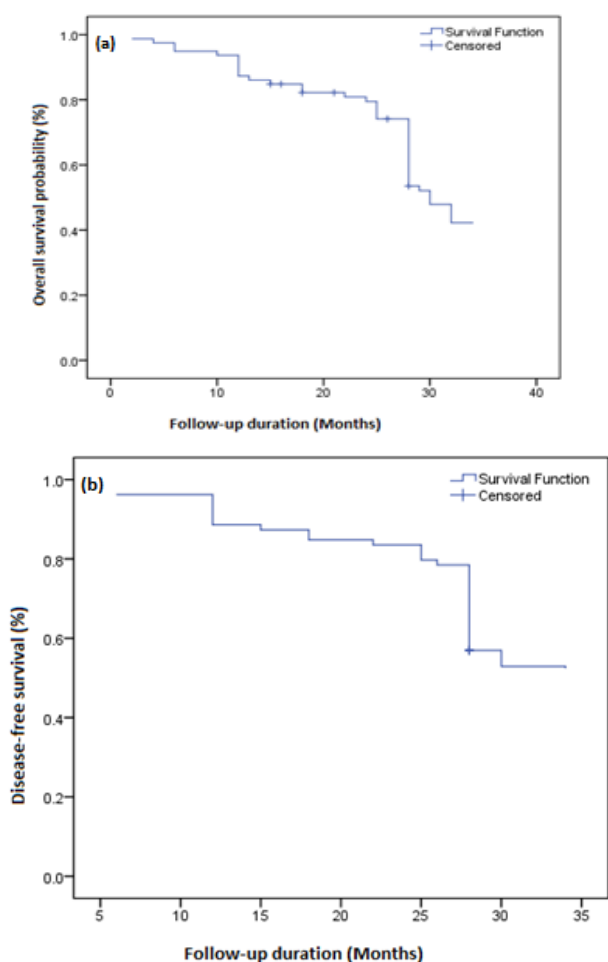


Figure 2: Kaplan-Meier survival curves of buccal mucosa carcinoma. a) Overall survival b) Disease-free survival

those of other published in oral squamous cell carcinoma.^[18] In the present study, most of patients presented with advanced stage of disease and had well differentiated squamous cell carcinoma as similar with previous reports.^[8]

Docetaxel had a good response rate (35%) in recurrent head and neck squamous cell carcinoma as a single agent.^[20] A retrospective study of 70 patients with advanced head and neck cancers underwent chemo radiation (Cisplatin, 5-Fluorouracil and 60-72 Gy irradiation); complete response (100%) was reported with tumour clearance at 6 months correlated better with survival than at 4 weeks or 3 months.^[21] Another study from Ikeda *et al.* was reported good tumour regression with acceptable toxicity using doublet chemotherapy (CDDP and 5FU) combined with concurrent 40 Gy irradiation in advanced stage IV oesophageal squamous cell carcinoma and three years follow-up resulted in a response rate of 19%.^[22] In accordance to the previous

study, the present triplet concurrent chemo radiotherapy showed 70% of complete response in buccal cancer patients.

The previous studies reported several adverse effects of chemo radiotherapy treatment; Mucositis was reported 66% as most common acute Grade 3 toxicity and followed osteoradionecrosis, hypo salivation, dental caries and swallowing dysfunction were well documented and provide difficult management dilemmas.^[23,24] As previous reports, the present study also supports with acute hematologic and non-hematologic adverse effect after definitive chemo radiotherapy. There were many adverse events was reported during follow-up, mucositis was most common 74 (93.6%) and second most was 72 (91.1%) followed by dysphagia 70 (88.6%) and other non-hematologic effects and anaemia 65 (82.3%) observed as most common hematologic adverse effect of treatment.

The first study of definitive chemo radiotherapy with curative intent showed 29% of 5-years overall survival with 45 primary oral squamous cell carcinoma patients.^[7] Cohen *et al.* treated 39 patients with T4 oral squamous cell carcinoma with primary concomitant chemoradiotherapy between 1993 and 2001 and reported 5-years overall and disease-free survival was 56% and 51%, respectively.^[25] Another recent study from 111 advanced stage oral squamous cell carcinoma patients treated with primary concomitant chemoradiotherapy was reported a 5-year overall and disease-free survival was 65.9% and 66.9%, respectively.^[26] According to previous results, our study supports with 42% of overall and 54% of disease-free survival with three years follow-up of buccal mucosa carcinoma after definitive chemo radiotherapy treatment.

Conclusion and future directions

Our results suggest that curative intent of definitive chemo radiotherapy is a successful modality of treatment for unresectable buccal mucosa carcinoma patients. The tolerable adverse events was reported which may have a good impact on the patient's quality of life.

Further, this "organ preservation" definitive chemo radiotherapy treatment will be extended at larger level with more patients subsequently in the next phases with long five years follow-up period.

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Conflict of interest

The authors declare that they have no conflict of interests.

REFERENCES

- Yeole BB, Sankaranarayanan R, Sunny MSL, Swaminathan R, Parkin DM. Survival from head and neck cancer in Mumbai, India. *Cancer* 2000;89:437-44.
- Population Based Cancer Registry Kidwai Memorial Institute of Oncology. Bangalore: Report; Head and Neck Cancers 2010.
- Hospital Based Cancer Registry Kidwai Memorial Institute of Oncology, Bangalore: Report; Head and Neck Cancers 2010.
- Singhania V, Jayade BV, Anehosur V, Gopalakrishnan K, Kumar N. Carcinoma of buccal mucosa: A site specific clinical audit. *Ind J Cancer* 2015;52:605-10.
- Huang SH, O'Sullivan B. Oral cancer: Current role of radiotherapy and chemotherapy. *Med Oral Patol Oral Cir Bucal* 2013;18:233-40.
- Mendenhall WM, Morris CG, Amdur RJ, Hinerman RW, Mancuso AA. Parameters that predict local control after definitive radiotherapy for squamous cell carcinoma of the head and neck. *Head Neck* 2003;25:535-42.
- Crombie AK, Farah C, Tripcony L, Dickie G, Batstone MD. Primary chemo radiotherapy for oral cavity squamous cell carcinoma. *Oral Oncol* 2012;48:1014-8.
- Dattatreya S, Goswami C. Cetuximab plus radiotherapy in patients with unresectable locally advanced squamous cell carcinoma of head and neck region: A open labelled single arm phase II study. *Ind J Cancer* 2011;48:154-7.
- Peters LJ. Changes in radio therapeutic management of head and neck cancer: A 30-year perspective. *Int J Radiat Oncol Biol Phys* 2007;69:S8-S11.
- Peters JP, Maitre A, Maillard E, Bourhis J. 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.
- Pignon JP, le Maitre A, Maillard E, Bourhis J. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. *Lanc* 2000;355:949-55.
- Paliwal R, Patidar AK, Walke R, Hirapara P, Jain S, Raj-Bardia M, *et al.* Palliative hypofractionated radiotherapy in locally advanced head and neck cancer with fixed neck nodes. *Iran J.Cancer prev* 2012;5:178-82.
- Das S, Thomas SK, Pal R, Isaih S, John S. Hypofractionated palliative radiotherapy in locally advanced inoperable head and neck cancer: CMC Vellore Experience. *Ind J Palliat Care* 2013;19:93-8.
- Zhang H, Dziegielewski PT, Biron VL, Szudek J, Al Qahatani KH, O'Connell DA, *et al.* Survival outcomes of patients with advanced oral cavity squamous cell carcinoma treated with multimodal therapy: a multi-institutional analysis. *J Otolary Head Neck Surg* 2013;42:1-8.
- Eswaran P, Azmi KS. Concurrent chemo radiation with weekly Cisplatin, Docetaxel and Gefitinib. A study to assess feasibility, toxicity and immediate response. *J Can Res Ther* 2013;9:392-6.
- Andreadis C, Vahtsevanos K, Sidiras T, Thomaidis I, Antoniadis K, Mouratidu D, *et al.* 5-Fluorouracil and cisplatin in the treatment of advanced oral cancer. *Oral Oncol* 2003;39:380-5.
- Babu S, Balasubramanian S, Bhatteejee A, Chakraborty S, Manuprasad A, Patil VM, *et al.* Tolerance and toxicity of neoadjuvant docetaxel, cisplatin and 5-fluorouracil regimen in technically unresectable oral cancer in resource limited rural based tertiary cancer center. *Ind J Cancer* 2014;51:69-72.
- Patil VM, Chakraborty S, Shenoy PK, Manuprasad A, Sajith Babu TP, Shivkumar T, *et al.* Tolerance and toxicity of neoadjuvant docetaxel, cisplatin and 5 fluorouracil regimen in technically unresectable oral cancer in resource limited rural based tertiary cancer center. *Ind J Cancer* 2014;51:69-72.
- Ow TJ, Myers JN. Current management of advanced resectable oral cavity squamous cell carcinoma. *Clin Exp Otorhinolaryngol* 2011;4:1-10.
- Glisson BS. The role of Docetaxel in the management of squamous cell carcinoma of head and neck. *Oncol* 2002;16:83-7.
- Kawashima M, Fujii H, Hayashi R, Tahara M, Nasu K, Arahira S, *et al.* Influence of delayed tumour clearance on reliability of complete response rate in chemoradiotherapy for head and neck cancer. *Jpn J Clin Oncol* 2007;37:559-67.
- Ikeda E, Kojima T, Kaneko K, Minashi K, Onozawa M, Nihei K, *et al.* Efficacy of concurrent chemoradiotherapy as a palliative treatment in stage IVB esophageal cancer patients with dysphagia. *Jpn J Clin Oncol* 2011;41:964-72.
- Shiley SG, Hargunani CA, Skoner JM, Holland JM, Wax MK. Swallowing function after chemo radiation for advanced stage oropharyngeal cancer. *Otolaryngol Head Neck Surg* 2006;134:455-9.
- Jacobson AS, Buchbinder D, Hu K, Urken ML. Paradigm shifts in the management of osteoradionecrosis of the mandible. *Oral Oncol* 2010;46:795-801.
- Cohen EE, Baru J, Huo D, Haraf DJ, Crowley M, Witt ME, *et al.* Efficacy and safety of treating T4 oral cavity tumors with primary chemoradiotherapy. *Head Neck* 2009;31:1013-21.
- Stenson KM, Kunnakkam R, Cohen EE, Portugal LD, Blair E, Haraf DJ, *et al.* Chemoradiation for patients with advanced oral cavity cancer. *Laryngoscope* 2010;120:93-9.