Locally Advanced Oral Cavity Cancers: What Is The Optimal Care?

Rajab Alzahrani, MD[1], Arwa Obaid, MD[1], Hadi Al-Hakami, MD[2,3,4], Ahmed Alshehri, MD[3,5], Hossam Al-Assaf, MD[6], Reem Adas, MD[7], Eman Alduhaibi, MD[8], Nabil Alsafadi, MD[8], Suliman Alghamdi, MD[3,4,8], and Majed Alghamdi, MD, FRCPC, DABR[8,9]

Abstract

Patients with oral cavity cancers often present late to seek medical care. Surgery is usually the preferred upfront treatment. However, surgical resection cannot be achieved in many cases with advanced disease without major impact on patient's quality of life. On the other hand, radiotherapy (RT) and chemotherapy (CT) have not been employed routinely to replace surgery as curative treatment or to facilitate surgery as neoadjuvant therapy. The optimal care of these patients is challenging when surgical treatment is not feasible. In this review, we aimed to summarize the best available evidence-based treatment approaches for patients with locally advanced oral cavity cancer. Surgery followed by RT with or without CT is the standard of care for locally advanced oral cavity squamous cell carcinoma. In the case of unresectable disease, induction CT prior to surgery or chemoradiotherapy (CRT) can be attempted with curative intent. For inoperable patients or when surgery is expected to result in poor functional outcome, patients may be candidates for possibly curative CRT or palliative RT with a focus on quality of life.

Introduction

Oral cavity cancer is one of the most common malignancies worldwide with geographic variation in incidence and mortality. Higher incidence rates are observed in developing countries compared to developed countries.[1] For instance, it is the second most common cancer in South Asia compared to the 15th and 17th most common cancer in North America and Europe, respectively.[1] Bangladesh, Pakistan, and India have the highest incidence rate of oral cavity cancer where it is the most common cancer in males and the second in females after breast cancer.[1] Moreover, oral cavity cancers in these countries represent the third, fifth, and ninth cause of cancer mortality, respectively.[1] In contrast, oral cavity cancers ranked the 21st for cancer mortality in North America and the 20th in Western Europe.[1]

As a result of the delay in presentation, most patients are diagnosed with advanced disease.[2] Regional metastasis is prevalent in up to 30% of cases at the time of diagnosis.[3] In

[1] Department of Surgery, Medical School, Al Baha University, Al Baha, Saudi Arabia
[2] Otolaryngology/Head and Neck section, Department of Surgery, King Abdulaziz Medical City, Ministry of National Guard, Jeddah, Saudi Arabia
[3] King Saud Bin Abdulaziz University, Jeddah, Saudi Arabia
[4] King Abdullah International Medical Research Center, Jeddah, Saudi Arabia
[5] Medical Oncology Section, King Abdulaziz Medical City, Ministry of National Guard, Jeddah, Saudi Arabia
[6] Radiation Oncology Department, Comprehensive Cancer Center, King Fahad Medical City, Riyadh, Saudi Arabia
[7] Medical Imaging Department, King Abdulaziz Medical City, Ministry of National Guard, Jeddah, Saudi Arabia
[8] Radiation Oncology Section, King Abdulaziz Medical City, Ministry of National Guard, Jeddah, Saudi Arabia
[9] Department of Medicine, Medical School, Al Baha University, Al Baha, Saudi Arabia

Corresponding Author:
Majed Alghamdi, Radiation Oncology, Internal Medicine, School of Medicine, Al Baha University, Prince Mohammed Bin Saud, Al Baha 65527, Saudi Arabia.
Email: malghamdi1984@gmail.com

Table 1. Stage Distribution of Patients With Oral Cavity Cancer at Initial Presentation in India, US, and Parts of Europe.

Country	Clinical Stages	Percentage
India	I	2.7
Singh et al,[5] 2015	II	5
	III	28.2
	IV	64.1
United States	I	16.2
Mehta et al,[6] 2010	II	47.6
	III	33.9
	IV	2.2
Republic of Ireland	I	19.6
Ali et al,[8] 2016	II	14.5
	III	14.1
	IV	35.1
	Unknown	16
Hungary	I	35.3
Nemes et al,[9] 2008	II	23.5
	III	26.1
	IV	15.1
France	I	16.1
Jéhannin-Ligier et al,[10] 2017	II	11.5
	III	11.1
	IV	54.4
	Unknown	7

addition, about 49% of patients present with neck lymph nodes without lesions in the oral cavity.[4] Generally, more patients present with locally advanced disease in developing countries compared to developed countries. For example, 64.1% of patients with oral cancer in India present with stage IV disease[5] compared to United States where most patients present with stage II.[6,7] Table 1 compares the distribution of patients with different stages at initial presentation in selected countries.

A remarkable improvement in overall survival (OS) of patients with locally advanced oral cancer was noticed in the past 2 decades owing probably to the improvement in diagnostic and treatment modalities.[11,12] However, when surgical resection is not feasible, the optimal therapy is largely unknown. In this review, we aim to summarize the different evidence-based treatment approaches and their outcomes for locally advanced oral cavity cancers.

Definitions

Oral cavity cancers are those that arise from any subsite within the anatomically defined oral cavity including oral tongue, buccal mucosa, retromolar trigone, hard palate, and floor of mouth. Lip cancers and nonsquamous cell carcinomas were excluded from this review. Locally advanced oral cavity cancers usually refer to T3/T4, N2/3 (American Joint Committee on Cancer [AJCC] seventh and eighth editions) tumors involving any anatomical subsite of the oral cavity. The term "resectability" will be used here to refer to the *technical* ability to resect the tumor with a clear margin. This depends on both the surgeon's skills and the extent of the tumor. On the other hand, if the tumor cannot be resected due to patients' poor

performance status or comorbidities, the term "inoperability" will be used in this review.

Criteria for Unresectability

The standard treatment of patients with locally advanced oral cavity cancers is surgical resection which is often followed by adjuvant radiotherapy (RT) with or without chemotherapy (CT) based on the presence of certain pathological risk factors.[11] Surgical treatment of locally advanced tumors usually requires a significant reconstructive surgery to restore function.[13] The goal of the surgical resection is to achieve a clear resection margin which is defined by the National Comprehensive Cancer Network (NCCN) as the distance from invasive cancer front that is 5 mm or more from the resected margin.[11] However, margins of more than 1 mm were not to be associated with better local control in one study.[14]

Although, unresectability is somewhat a relative term, there are some features known to possibly predict poor functional outcome of patients with head and neck cancer (HNC) after surgery or technical difficulty in obtaining clear resection margins. These features are summarized by NCCN group as follows[11]:

1. Involvement of the pterygoid muscles, particularly when associated with severe trismus or pterygopalatine fossa involvement with cranial neuropathy;
2. Gross extension of the tumor to the skull base;
3. Direct extension to the superior nasopharynx deep extension into the Eustachian tube and lateral nasopharyngeal walls;
4. Invasion (encasement) of the common or internal carotid artery;
5. Direct extension of the neck disease to involve external skin;
6. Direct extension to mediastinal structures, prevertebral fascia, or cervical vertebrae; and
7. Presence of subdermal metastases.

Specific to oral cavity cancers, some unresectability features were adopted by Patil et al and included[15]:

1. Buccal mucosa primary, with diffuse margins and peritumoral edema, going up to or above the level of zygomatic arch and without any satellite nodules.
2. Tongue primary (anterior two-third) with the tumor extending up to or below the level of hyoid bone.
3. Extension of tumor of anterior two-thirds of the oral tongue to the vallecula.
4. Extension of tumor into the high infratemporal fossa, as defined by the extension of tumor above an axial plane passing at the level of the sigmoid notch.
5. Extensive skin infiltration impacting the achievement of negative margin.

Although TNM stage may provide a hint as to whether the tumor is resectable or not, it should not serve as the only tool to

assess resectability. Similar to NCCN and Patil et al features, AJCC TNM stage may be considered only as a surrogate for unresectability and should not replace an individual patient's evaluation. Unresectable disease correlates best with T4b. On the other hand, T4a tumors may often be considered as borderline resectable tumors, where using the NCCN and Patil et al features may be helpful. However, resectability assessment should be discussed on a case-by-case basis and within a multidisciplinary fashion.

In general, the studies in locally advanced oral cavity cancers are limited and suffer from low statistical power mostly as a result of mixing these patients with other HNCs.[16] In this review, we summarized the relevant studies in a categorical fashion based on resectability and treatment modalities. Palliative treatment including RT is often used for symptom control and is beyond the purpose of this review.

Resectable Disease

Surgery and Adjuvant RT Versus Chemoradiotherapy

Only 1 randomized controlled trial (RCT) initially published by Soo et al[17] and subsequently updated by Iyer et al[18] compared surgery with adjuvant RT to radical concurrent chemoradiotherapy (CCRT). That trial included 119 patients with locally advanced (stage III/IV) resectable HNCs and randomized them into 2 arms: surgery with adjuvant RT versus CCRT. Patients on surgery + RT arm underwent radical resection of the primary tumor with neck dissection as needed, followed by adjuvant RT of standard fractionation to a total of 60 Gy in 30 fractions. Patients on CCRT arm received 2 cycles of cisplatin and 5-fluorouracil (5-FU) known as cisplatin, fluorouracil (PF) concurrently given with 66 Gy in 33 fractions over 6.5 weeks. Only about 27% (32 patients) of all patients had oral cavity primaries. At a median follow-up of 13 years, patients with oral cavity cancers who underwent surgery had significantly improved 5-year disease-specific survival (DSS; 68% vs 12%, $P = .038$) and distant recurrence-free survival (92% vs 50% $P = .05$). There were no statistically significant differences in OS and DSS of the entire cohort between the 2 arms. Of note, this study was prematurely halted due to poor accrual. A total of 8 patients on surgery + RT arm and 39 on CCRT arm experienced toxicity mostly with grade ≤ 3. Grade 4 toxicities occurred only in 8 patients treated with CCRT (5 neutropenic sepsis and 3 neutropenia).

Data specific for oral cavity subsite is limited to retrospective studies. Gore et al retrospectively compared 2 cohorts of resectable oral cavity cancers treated with surgery + adjuvant RT versus CCRT with curative intent.[19] The 3-year OS rates were 86% versus 33% and 3-year DSS were 87% and 35%, both favoring surgery and adjuvant RT ($P < .001$). On multivariable analysis (MVA), patients treated with CCRT had a 16.6-fold higher rate of disease-specific death and a 10-fold higher rate of overall death compared to patients treated with surgery and adjuvant RT ($P < .001$). Osteoradionecrosis (ORN) rates were similar between the 2 groups (12% vs 13%, $P = .88$);

however, more patients required feeding tube longer than 30 days after treatment with CCRT compared to surgery and adjuvant RT patients (11% vs 30%, $P = .017$). The limitations of this study included the potential center based-bias in treatment selection as the study included patients from 2 centers with independent practices. For example, patients who were anticipated to need free flap in one of the centers ended up being treated with CCRT due to the limited ability to perform free flap procedures.

Dana Farber Cancer Institute experience was published by Sher et al,[20] where more than half of the 42 included patients with oral cancer had locally advanced disease T3 and T4 (27 patients). The 2-year progression-free survival (PFS) and locoregional control (LRC) rates were superior in patients who had surgery and adjuvant RT compared to CCRT (82% vs 56%, $P = .03$, respectively, and 91% vs 64%, $P < .001$, respectively).[20] No significant grade 4 toxicities were noted. Only 1 patient developed symptomatic grade 3 ORN. In addition, among patients without evidence of recurrent disease, 35% experienced grades 2 to 3 late dysphagia with only 1 patient who was continuously percutaneous endoscopic gastrostomy dependent due to painful leukoplakic lesion. Treatment selection bias is overly obvious in this study as most of the patients who had CCRT were deemed not a candidate for surgery.

Furthermore, in a large National Cancer Database (NCDB) analysis including 6900 patients with stage III/ IVa oral cavity cancers in the United States, a 3-year OS benefit was observed in patients treated with surgery and adjuvant RT (51.8%) compared to definitive CCRT (39.3%) after a propensity score matching to adjust for baseline patients' characteristics.[21]

Along with NCDB, Manzoor et al[22] assessed the survival outcomes in 44 patients with advanced HNCs involving the carotid artery. About 80% were treated with curative intent surgery, while 21% were treated palliatively. Results showed that patients who were treated aggressively with carotid artery resection with or without reconstruction had improved OS compared to the palliative group (median OS, 13.5 months vs 3.6 months, respectively, $P = .001$).

On the other hand, Tangthongkum et al[23] retrospectively showed that CCRT is comparable to surgery with adjuvant RT/chemoradiotherapy (CRT). The study included 189 patients with resectable oral cavity cancer (stage III/IVa) of whom 61 received CCRT and 128 underwent surgical excision followed by adjuvant RT/CRT. Chemotherapy consisted of 2 to 3 cycles of high dose of cisplatin or carboplatin given concurrently with 66 to 70 Gy delivered in a conventional fractionation fashion. The decision of treatment choice was made in a multidisciplinary discussion which considered patient's preference, comorbidities, performance status, and risk from anesthesia. There were no differences in 5-year OS (33% vs 24%, $P = .191$) and DSS (27% vs 25%, $P = .857$) between patients treated with surgery and adjuvant RT/CRT compared to CCRT. Rates of ORN, dysphagia, and severe xerostomia were similar. Despite the comparable outcomes, patients in CCRT group had more advanced disease (T4a) compared to surgery and adjuvant therapy group (83.6% vs 57%, $P = .003$) and tend to have more

Table 2. Summary of Studies Comparing Surgery and Adjuvant RT Versus CCRT.

Study	No. of Oral Cavity Patients/ All Patients	Design	Treatments	Follow-Up	Outcomes
Iyer et al[18]	32/119	RCT	Arm 1: surgery + RT (60 Gy) Arm 2: CCRT (66 Gy + 2 cycles of cisplatin and 5-FU)	13 Y	OS [5 Y]: 45% (arm 1) and 35% (arm 2) [P = NS] DSS [5 Y]: 68% (arm 1) and 12% (arm 2) [P = NS]
Gore et al[19]	104/104	Retrospective	Arm 1: surgery + RT (60 Gy) Arm 2: CCRT (60 Gy + cisplatin)	2.9 Y	OS [3 Y]: 86% (arm 1) and 33% (arm 2) [P < .001] DSS [3 Y]: 87% (arm 1) and 35% (arm 2) [P < .001]
Sher et al[20]	42/42	Retrospective	Arm 1: surgery + RT Arm 2: Definitive RT (70 Gy)	2 Y	OS [2 Y]: 85% (arm 1) and 63% (arm 2) [P = NS] PFS [2 Y]: 82% (arm 1) and 56% (arm 2) [P = .03] LRC [2 Y]: 91% (arm 1) and 64% (arm 2) [P < .001] DC [2 Y]: 94% (arm 1) and 83 (arm 2) [P = NS]
Spiotto et al[21]	6900/6900	Retrospective	Arm 1: surgery + RT Arm 2: CCRT	3 Y	OS [3 Y]: 51.8% (arm 1) and 39.3% (arm 2) [P = NR]
Tangthongkum et al[23]	189/189	Retrospective	Arm 1: surgery + RT or CT Arm 2: CCRT	5 Y	OS [5 Y]: 33% (arm 1) and 24% (arm 2) [P = NS] DSS [5 Y]: 27% (arm 1) and 25% (arm 2) [P = NS]

Abbreviations: CT, chemotherapy; CCRT, concurrent chemoradiotherapy; DC, distant control; DSS, disease-specific survival; 5-FU, 5-fluorouracil; LRC, locoregional control; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RT, radiotherapy; NR, not reported; NS, not significant; Y, years.

comorbidities. The similar outcomes between surgery + RT and CCRT patients were maintained after adjusting for the effect of confounding variables.

Overall, for resectable oral cavity cancers, there is more evidence for surgery followed by RT compared to nonsurgical approach with CCRT. Table 2 summarizes the data presented in this section.

Surgery and Adjuvant RT Versus Induction CT Followed by Surgery and Adjuvant RT

The goals of induction CT (ICT) for resectable oral cavity cancer are either to improve disease-related outcomes such as PFS and OS or to improve the chances of organ preservation. Two RCTs have examined these roles of ICT followed by surgery and RT compared to surgery and RT in locally advanced resectable oral cavity cancer.[24-26] Both studies used 3 cycles of PF as ICT[24,25] or 2 cycles of docetaxol, cisplatin, and 5-FU (TPF).[26] Postoperative RT doses ranged from 50 to 60 Gy. The results of both RCTs were consistent with no improvement in any disease-related outcomes. With regard to organ preservation, the study by Licitra et al[24] showed a less mandibular resection in patients who had ICT.

A recent meta-analysis of individual patient data of the 2 studies above confirmed the lack of clinical benefit from ICT compared to upfront surgery in all patients.[27] However, for cN2 patients, an OS benefit was found in favor of ICT (P = .04).

On the other hand, Sadighi et al. published a small pilot study on 24 patients with T3 or T4a resectable oral cavity cancer who were randomized to either surgery and adjuvant RT or ICT followed by surgery and adjuvant RT.[28] Induction chemotherapy was associated with better PFS (P = .014) with no OS benefit. There was no difference in organ preservation

rate which was the primary end point. However, the improved PFS in this study should be interpreted cautiously given the small number of patients. Drug toxicity was acceptable and did not interfere with subsequent surgical treatment.

The proven advantage of ICT in these studies was the prognostication effect of pathological response (PR) to ICT as it was correlated with better outcomes.[25-27] However, ICT cannot be considered as a routine indication for all patients with resectable disease. Table 3 summarizes the data presented in this section.

Preoperative Chemoradiotherapy

In a phase II single-arm RCT by Harada et al,[29] the effect of preoperative CT using S-1 and concurrent RT was evaluated in 39 patients with stage III/IVa oral cavity cancer. All patients received a total radiation dose of 40 Gy along with S-1 CT (oral fluoropyrimidine preparation consisting of tegafur, 5-chloro-2, 4-dihydroxypyridine [gimeracil], a dihydropyrimidine dehydrogenase inhibitor, and potassium oxonate) at 65 mg/m^2/d for 5 consecutive days, over 4 consecutive weeks with concurrent RT. Reconstruction was performed using microvascular transfer in 30 patients, split-thickness skin graft in 3 patients, and primary closure in 4 patients. At a median follow-up of 3 years, LRC, DSS, and OS rates at 3 years were 91.5%, 83.8%, and 83.8%, respectively. Observed hematological toxicities were grade 1 to 2 (43.6% had leukocytopenia and 28.2% had anemia). All patients developed mucositis (grade 1-3) including grade 3 mucositis in 84.6% of them but this was transient and tolerable.

A retrospective study conducted by Driemel et al[30] and included 228 patients with resectable oral cancer stage II to IV treated with preoperative CRT followed by radical surgery.

Table 3. Summary of Studies Reporting Surgery and Adjuvant RT Versus Induction CT Followed by Surgery and Adjuvant RT, and CRT Followed by Surgery.

Study	No. of Oral Cavity Patients/ All Patients	Design	Treatments	Follow-Up	Outcomes
Bossi et al[25]	198/198	RCT *phase III*	Arm 1: ICT (3 cycles of PF) + surgery ± RT Arm 2: surgery ± RT	11.5 Y	OS [10 Y]: 46.5 (arm 1) and 37.7% (arm 2) [P = NS] DFS [10 Y]: 48.5% (arm 1) and 36% (arm 2) [P = NS]
Zhong et al[26]	222/222	RCT *phase III*	Arm 1: ICT (2 cycles of TPF) + surgery + RT (60 Gy) Arm 2: surgery + RT	30 M	OS [2 Y]: 68.8% (arm 1) and 68.2% (arm 2) [P = NS] DFS [2 Y]: 62.2% (arm 1) and 63.6% (arm 2) [P = NS]
Sadighi et al[28]	24/24	Pilot study	Arm 1: ICT + surgery (2 cycles of TPF + surgery) Arm 2: surgery alone	16 M	OS [3 Y]: 45% (arm 1) and 27% (arm 2) [P = NS]
Harada et al[29]	39/39	RCT *phase II*	CRT (S-1 + RT 40 Gy) + surgery	38 M	OS [3 Y]: 83.8% DSS [3 Y]: 83.8% LRC [3 Y]: 91.5%
Driemel et al[30]	228/228	Retrospective	CRT (cisplatin + RT 40 Gy) + surgery	5.2 Y	OS [2 Y]: 95.8% OS [5 Y]: 86.9% DFS [2 Y]: 86.2% DFS [5 Y]: 76.3% DFS [10 Y]: 66.7% LRR [5Y]: 18%
Klug et al[31]	222/222	Retrospective	CRT (mitomycin C and 5-FU + RT 50 Gy) + surgery	5 Y	OS: 62.4%
Braun et al[32]	30/41	Retrospective	CRT (mitomycin C and 5-FU) + surgery: + RT 50Gy	30 M	Good responders: 56% Bad responders: 44% LRR: 34%
Eder-Czemirek et al[33]	144/144	Retrospective	CRT (mitomycin C and 5-FU) + surgery: + RT 50Gy	5 Y	OS [5 Y]: 58%

Abbreviations: CT, chemotherapy; CRT, chemoradiotherapy; DFS, disease-free survival; DSS, disease-specific survival; ICT, induction chemotherapy; 5-FU, 5-fluorouracil; LRR, locoregional recurrence; M, months; NS, not significant; RCT, randomized control trial; RT, radiotherapy; OS, overall survival; PF, cisplatin, fluorouracil; PFS, progression-free survival; TPF, docetaxel, cisplatin, fluorouracil; Y, years.

Patients received preoperative treatment consisting of cisplatin or carboplatin during the first week of treatment and fractionated RT with a total dose of 40 Gy, followed by radical surgery to remove the primary oral cavity cancer. Neck dissection was performed 10 to 14 days after the initial surgery. Complete histological local tumor regression after surgery was observed in 21.9%. After a median follow-up of 5.2 years, 2-year DSS rate was 86.2%, 5-year DSS was 76.3%, and 10-year DSS was 66.7%. The 2-year and 5-year OS were superior in patients with complete histological tumor regression after CRT (P = .029).

In 1989, a study included 41 patients with stage III/IV squamous cell cancers of the head and neck, 30 of them had oral cavity cancer was conducted by Braun et al.[32] All patients were treated preoperatively with a single dose of 15 mg/m^2 mitomycin C and 5 doses of 750 mg/m^2 5-FU during the first 5 days of treatment and concomitant RT with a total irradiation dose of 50 Gy. Histologic grade of regression after preoperative CRT were examined and classified into 4 grades, grades 1 and 2 (good responders to preoperative CRT) and grades 3 and 4 (bad responders to preoperative CRT). At a median follow-up of 2 years, 56% responded well to preoperative CRT (grade1 and 2) and 44% were considered bad responders (grade 3 and 4). About 34% had a locoregional recurrence. There was a statistically significant correlation between tumor regression grade and probability of survival (P = .001).[32]

Another study by Eder-Czemirek et al[33] reported the authors' experience with preoperative CRT followed by radical surgery. They included 144 patients with locally advanced stage III/IV oral cavity cancer treated with preoperative CRT and followed by radical surgery 6 to 8 weeks later. After a median follow-up of 5 years, the 5-year OS was 58%. On univariate analysis (UVA), regression grade 4 was most significantly associated with reduced survival (P < .001), followed by elevated neutrophils (P = .01) and elevated C-reactive protein (P = .03).

In summary, the role of preoperative CRT has not been examined thoroughly in patients with resectable oral cavity cancers and was not compared to surgery followed by RT/CRT. Only one study reported on toxicities of preoperative CRT.[29] Table 3 summarizes the data presented in this section.

Unresectable Disease

Induction Chemotherapy Followed by Chemoradiation Versus Definitive CRT

The 2 large RCTs that examined the role of ICT are PARA-DIGM[34] and DeCIDE.[35] Both studies randomized loco-regionally advanced patients with HNC into ICT followed by CRT versus CCRT. Eligibility criteria in PARADIGM study were unresectable disease or when organ preservation was felt achievable. PARADIGM study which has only 26 oral cavity patients out of 145 patients. Patients were randomized to receive ICT with 3 cycles of TPF followed by CRT with either docetaxel or carboplatin or CCRT with 2 cycles of bolus cisplatin. Radiotherapy was delivered once daily over 7 weeks to a total dose of 70 Gy in 2-Gy fractions. There was no difference in survival or recurrence rates between the 2 arms ($P = .77$). The use of concurrent carboplatin was superior to docetaxel in ICT group with respect to 3-year PFS and OS. Percutaneous endoscopic gastrostomy tube was placed in 64% in CCRT group versus 55% in ICT followed by CRT group. Grade 3 to 4 febrile neutropenia was significantly higher in ICT followed by CRT group (23%) compared to the CCRT group (1%).

DeCIDE study included patients with N2 or N3 disease of whom 39 patients with oral cavity cancers out of 285 enrolled patients. Patients were randomized into 2 arms; ICT with two 21-day cycles of TPF followed by CRT or CCRT with docetaxel, 5-FU, and hydroxyurea. Radiotherapy was delivered in a standard fractionation to a total dose of 75 Gy. Survival outcomes of this trial showed statistically nonsignificant findings with 3-year OS and 3-year disease-free survival of 74% and 70%, respectively, in ICT followed by CRT group versus 71% and 63%, respectively, in CCRT group. Serious side effects were more common in ICT followed by CRT group (47% vs 28%, $P = .002$). Like PARADIGM, this study failed to show clinical response (CR) to ICT. The results of these 2 studies should be interpreted with caution as both were terminated early due to poor accrual.

Another phase III RCT by Hitt et al[36] compared 2 ICT regimens of 3 cycles of TPF versus 3 cycles of PF in 382 patients (26 with oral cavity primary) with locally advanced HNCs (stage III or IV). After ICT, patients underwent clinical examination and computed tomography scan of primary tumor and neck. All patients with more than 80% response with no nodal disease progression received CRT of cisplatin concomitantly with conventional RT of 70 Gy. Patients with less than 80% response after ICT and stable neck disease received CRT after surgery for neck dissection. Patients with no response were taken off study and treated individually at discretion of treating physician. There was a nonsignificant trend toward better OS with TPF compared to PF.

A larger phase III RCT by Hitt et al[37] compared ICT of 2 regimens followed by CRT to CCRT in 439 patients with unresectable locally advanced HNC. It included 93 patients with oral cavity cancer. Induction chemotherapy group received 3 cycles TPF or PF followed by CRT. The CCRT group received a high dose of cisplatin (100 mg/m^2) with 70 Gy delivered in a standard fractionation. The median PFS were 14.6, 14.3, and 13.8 months in ICT with TPF + CRT, ICT with PF + CRT, and CCRT arms, respectively ($P = .56$). The median OS was 27.0, 27.2, and 26.6 months, respectively. This RCT failed to show any benefit of ICT over CCRT in patients with unresectable HNCs. Thirteen deaths due to study treatment toxicity were reported, 7 in TPF-CCRT arm, 4 in PF-CCRT arm, and 2 in CCRT arm, mainly by febrile neutropenia before granulocyte colony-stimulating factor was implemented. Nonhematological toxicities were mostly manageable stomatitis during RT in both arms.[37]

Conversely, the Italian 4 arms RCT by Ghi et al[38] showed an improvement in PFS and OS with ICT followed by CRT (arm 3, 4) compared to CCRT (arm 1, 2; $P = .031$ and .013, respectively). The study randomized 421 patients with unresectable locally advanced HNC (19.5% oral cavity cancers) to receive CRT, 2 cycles of PF with RT of 70 Gy (arm 1), cetuximab with RT (arm 2), 3 cycles of TPF followed by the same CRT (arm 3), or 3 cycles of TPF followed by cetuximab with RT (arm 4). The 3-year OS rates were 46.5% in arms 1 and 2 versus 57.5% in arm 3 and 4 ($P = .031$) and 3-year PFS were 38.5% in arms 1 and 2 versus 47% in arms 3 and 4 ($P = .013$). Grade 3 to 4 neutropenia was higher in ICT arm (4% vs 1%, $P = .038$). However, the 4-arm complex study design and the frequent interruptions of RT put some limitations on the study.[39]

The role of ICT before CCRT remains an area of controversy. Only 1 RCT out of 4 showed a benefit from that approach. With respect to double or triple CT agents, triple ICT was shown to be superior to double agent as shown in 3 RCTs.[36,40,41] The benefit of TPF over PF was observed across all clinical end points; OS, LRC, and distant control (DC) in a meta-analysis by Blanchard et al.[42] Table 4 summarizes the data presented in this section.

Induction Chemotherapy Followed by Surgical Resection With or Without Adjuvant RT

The main goal of this approach is to convert borderline or unresectable disease to technically resectable with clear margin using ICT. Clinical trials examining this approach are lacking. However, there are multiple recent studies which provide us with level III evidence. Most of the studies here are from India.

Rudresha et al[43] has recently reported their single-institution experience with T4b oral cavity disease treated with ICT. That study included 119 patients who received 2 to 3 cycles of ICT with TPF or paclitaxel and carboplatin followed by the assessment of resectability. About 19% of patients were deemed resectable after ICT and most of them underwent resection. Clear margin was achieved in all of them. Following surgery, patients received adjuvant RT concurrent with CT. For those who had persistently unresectable disease following ICT, they received various individualized treatments. The median OS was profoundly superior in patients who underwent resection (19.7 months vs 7.1 months, $P = .000$). Noticeably in this study, no patients achieved complete clinical response (cCR)

Table 4. Summary of Studies Reporting Induction CT Followed by CRT Versus Definitive CRT.

Study	No. of Oral Cavity Patients/ All Patients	Design	Treatments	Follow-Up	Outcomes
Haddad et al[34]	26/145	RCT phase III	Arm 1: ICT (3 cycles TPF) + CCRT (cisplatin + RT 70 Gy) Arm 2: CCRT (cisplatin + RT 70 Gy)	49 M	OS [3 Y]: 73% (arm 1) and 78% (arm 2) [P = NS] PFS [3 Y]: 67% (arm 1) and 69% (arm 2) [P = NS] PEG tube: 55% (arm 1) and 64% (arm 2)
Cohen et al[35]	39/285	RCT phase III	Arm 1: ICT (2 cycles of TPF) + CCRT (docetaxel, 5-FU, and hydroxyurea + RT 75 Gy) Arm 2: CCRT arm: docetaxel, 5-FU, and hydroxyurea + RT 75Gy	30 M	OS [3 Y]: 74% (arm 1) and 71% (arm 2) [P = NS] DFS [3 Y]: 70% (arm 1) and 63% (arm 2) [P = NS]
Hitt et al[36]	26/382	RCT phase III	Arm 1: ICT (PF) + CRT (cisplatin, RT 70 Gy) Arm 2: ICT (TPF) + CRT (cisplatin, RT 70 Gy)	23.2 M	OS [2 Y]: 53.6 (arm 1) and 66.5 (arm 2) [P = NS]
Hitt et al[37]	93/439	RCT phase III	Arm 1: ICT (PF) + CRT (cisplatin, RT 70 Gy) Arm 2: ICT (TPF) + CRT (cisplatin, RT 70 Gy) Arm 3: CCRT (high dose of cisplatin + RT 70 Gy)	Arm 1: 31.4 M Arm 2: 26.4 M Arm 3: 24.9 M	Median OS: 27.0 M (arm 1), 27.2 M (arm 2) and 26.6 M (arm 3) [P = NS] Median PFS: 14.6 M (arm 1), 14.3 M (arm 2) and 13.8 M (arm 3) [P = NS]
Ghi et al[38]	NR/ 415	RCT phase II-III	Arm 1: CRT (PF/ RT) Arm 2: CRT: (CET/RT) Arm 3: ICT (TPF) + CRT (PF/RT) Arm 4: ICT (TPF) + CRT (CET/RT)	44.8 M	OS [3 Y]: 46.5% (arm 1,2) and 57.5% (arm 3,4) [P = .031] PFS [3 Y]: 38.5% (arm 1,2) and 47% (arm 3,4) [P = .013]
Lorch et al[40]	71/ 501	RCT phase III	Arm 1: ICT (PF) + CRT (carboplatin + RT 70 Gy) Arm 2: ICT (TPF) + CRT: (carboplatin + RT 70 Gy)	72.2 M	OS [5 Y]: 42% (arm 1) and 52% (arm 2) [P = .014] PFS [5 Y]: 34% (arm 1) and 45% (arm 2) [P = .0114]
Vermorken et al[41]	63/ 358	RCT	Arm 1: ICT (PF) + RT (70 Gy) Arm 2: ICT (TPF) + RT (70 Gy)	32.5 M	Median OS: 14.5 M (arm 1) 18.8 M (arm 2) [P = .02] Median PFS: 8.2 M (arm 1) and 11 M (arm 2) [P = .007]

Abbreviations: CT, chemotherapy; CCRT, concurrent chemoradiotherapy; CET, cetuximab; CRT, chemoradiotherapy; DFS, disease-free survival; ICT, induction chemotherapy; 5-FU, 5-fluorouracil; M, months; NR, not reported; NS, not significant; RCT, randomized control trial; RT, radiotherapy; OS, overall survival; PF, cisplatin, fluorouracil; PEG, percutaneous endoscopic gastrostomy; PFS, progression-free survival; TPF, docetaxel, cisplatin, fluorouracil; Y, years.

using RECIST criteria. Partial clinical response (pCR) was found in 17.3%, while most of the others (58.6%) had stable disease. Almost all cases who were converted to resectable post ICT had complete PR. Toxicity from ICT was found to be manageable. The disease respectability assessment before and after ICT was determined in a multidisciplinary fashion; however, there were no objective assessment criteria.

Joshi et al[44] reported a similar study in patients with T4b oral cavity cancer. One hundred ten patients received ICT of 2 to 3 cycles (same regimen as Rudersh et al[43]). The rate of pCR was 28% and there were no cases of cCR. Resectability was achieved in 30.9% of the patients. The median time interval between completion of ICT and surgery was 1.58 months. Unlike Rushera et al,[43] post ICT resectability was mainly determined by clearance of masticator space and infratemporal fossa. Median OS was better for patients who underwent resection (18 vs 6.5 months, P = .0001). Hematological side effects grade 3 to 4 was more common with 3-drug regimen compared to the 2-drug regimen (36.36% and 4.5%, respectively, P = .0001). The investigators statistically proved the positive

correlation between resectability and pCR (P = .0001). Among some significant factors affecting resectability on UVA, only the involvement of masticator space below jugular notch remained significant on logistic regression analysis.

In a large study by Patil et al[15] that included 721 patients with unresectable oral cavity cancers T4a (73.2%) and T4b (26.8%), 43% had adequate downstaging after 2 cycles of ICT (2-3 agents: taxane and platinum with or without 5-FU) and underwent resection with mostly R0 resection (100%). Overall CR rate using RECIST criteria was 25.1%. The 2-year LRC rates were 20.6% for all cohort, 32% in patient underwent resection, and 15% in patients received nonsurgical treatment with CRT or palliative approaches (P = .0001). Median OS was 10.8 months for entire cohort, 19.6 months with surgery, and 8.16 months without surgery (P = .0001). Of note, the criteria of unresectable disease in this study were objectively defined as discussed in the criteria for unresectability section (Patil et al criteria) and patients with frank skull base invasion, prevertebral fascia involvement and carotid encasement were excluded from this study. Other observations from this study

Table 5. Summary of Studies Reporting Induction CT Followed by Surgical Resection With or Without Adjuvant RT.

Study	No. of Oral Cavity Patients/ All Patients	Design	Treatments	Follow-Up	Outcomes
Rudresha et al[43]	116/116	Retrospective	ICT (TPF) $\pm$ surgery	NR	Median OS: 19.7 M (underwent surgical resection) and 7.1 M (nonsurgical treatment) [$P = .000$] Median PFS: 6.1 M
Joshi et al[44]	110/110	Retrospective	ICT (TPF) $\pm$ surgery	NR	Median OS: 18 M (underwent surgical resection) and 6.5 M (nonsurgical treatment) [$P = .0001$] Median PFS: 5.07 M
Patil et al[15]	721/721	Retrospective	ICT (2-3 agents) $\pm$ surgery	28 M	OS [2 Y]: 47% (underwent surgical resection) and 20% (nonsurgical treatment) [$P = .0001$] LRC [2 Y]: 32% (underwent surgical resection) and 15% (nonsurgical treatment) [$P = .0001$]

Abbreviations: CT, chemotherapy; ICT, induction chemotherapy; LRC, locoregional control; M, months; NR, not reported; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; TPF, docetaxel, cisplatin, fluorouracil; Y, years.

were that 69.3% had buccal mucosa primary and 73.2% had T4a disease. The only factor that was associated with higher rate of resectability on binomial logistic regression analysis was the use of 3-drug regimen ($P = .011$). Interestingly, 30.2% of patients who had stable disease after ICT underwent resection which highlights the high subjectively of assessing upfront resectability even with the use of "semi-objective" criteria. A major drawback of this study was the lack of information about treatment toxicities.

Another recent study by Rudresha et al[45] looked exclusively at T4a unresectable disease in 80 patients. Treatment was similar to the other T4b study by the same group.[43] The observed pCR rate was 21.3% and resectability rate after ICT was 23.8%. Median OS was again better for patients who had surgical resection and adjuvant RT compared to a patient who had no resection (16.9 vs 8.8 months, respectively, $P = .000$). The most common toxicity was febrile neutropenia in 18.8%. Other grade 3 to 4 hematological toxicities were observed in 21.3%.

Similarly, Patil et al[46] reported on 123 patients with unresectable oral cavity cancers. The 3-drug ICT regimen was better in resectability rate compared to 2-drug regimen (68% vs 37.9%, $P = 0.029$). However, using 3-drug regimen was associated with higher febrile neutropenia (34.62% vs 3%). This observation was also confirmed by Noronha et al.[47]

Unlike resectable disease, ICT in patients with unresectable oral cavity cancers may be considered as it may increase the chance of resectablity and subsequently improving outcomes. On the other hand, if CCRT is planned, the role of ICT is more controversial as indicated in the above relevant section. Table 5 summarizes the data presented in this section.

Definitive CRT

In this section, studies that reported using CCRT for curative intent will be summarized. Of note, all of them are retrospective single- or muti-institutional experiences. It is common among these studies that there is no mention of whether disease was upfront resectable or not.

The 20-year experience of university of Chicago was originally published by Stenson et al[48] and recently updated by Foster et al.[49] It included 140 patients with advanced stage III/IV oral cavity cancers who received definitive CRT for organ preservation. Radiotherapy was delivered once or twice a day for a total dose of 70 to 75 Gy concurrent with 5-FU, hydroxyurea, and often with a third agent. About half of the patients had oral tongue primaries (47.9%). At a median follow up of 5.7 years, 5-year OS, PFS, LRC, and DC were 63.2%, 58.7%, 78.6%, and 87.2%, respectively. The other important outcomes assessed in this study were the rates of ORN and long-term feeding tube dependence which were 20% and 10%, respectively. Floor of the mouth primary site was associated with higher ORN rate on MVA ($P < .01$). Interestingly, the use of intensity-modulated radiotherapy (IMRT) showed no effect on ORN rate. The striking results of this study in terms of good outcomes with CCRT were attributed by the authors to better overall patients' selection compared to other studies along with the frequent use of hyperfractionation and or hydroxyurea/5-FU-based CT. Importantly, treatment-related mortality was 6.4% mostly due to sepsis (5/9 patients).

Conversely, poor 5-year OS rate of 15% was observed in another smaller study by Scher et al[50] which included 73 patients treated with RT to median dose of 70 Gy combined with CT in 62% of patients (2 or 3 cycles of single-agent cisplatin at 100 mg/m^2). The 5-year LRC and freedom from distant metastasis were 37% and 70%, respectively. Mucositis grade ≥ 3 was observed in almost half of the patients. Rates of grade 3 late dysphagia and trismus were 15% and 13%, respectively.

Unlike Foster et al study in which CCRT was used for organ preservation, the included patients in Scher et al study were inoperable due to comorbidities or had unresectable disease which may partly explain the observed differences in outcomes between the 2 studies. Furthermore, both studies used a variety of RT doses with different techniques and nonuniform regimen of CT. Table 6 summarizes the data presented in this section.

Table 6. Summary of Studies Reporting Definitive CRT.

Study	No. of Oral Cavity Patients/All Patients	Design	Treatments	Follow-Up	Outcomes
Foster et al[49]	140/140	Retrospective	CRT (cisplatin + RT 70 Gy)	5.7 Y	OS [5 Y]: 63.2% PFS [5 Y]: 58.7% LRC [5 Y]: 78.6% DC [5 Y]: 87.2%,
Scher et al[50]	73/73	Retrospective	CRT (cisplatin + RT 70 Gy)	73.1 M	OS [5 Y]: 15%. LRC [5 Y]: 37% DC [5 Y]: 70%

Abbreviations: CRT, chemoradiotherapy; DC, distant control; LRC, locoregional control; M, months; PEG, percutaneous endoscopic gastrostomy; PFS, progression-free survival; OS, overall survival; Y, years.

Despite that most of the studies discussed above reported the rates of significant treatment-related toxicities, it is evident that none of them specifically examined the quality of life (QoL) in patients with oral cavity cancer. These patients usually have several domains of QoL affected by the disease and/or the treatment.[51] The magnitude of the impact of the treatment on QoL generally depends on the type of treatment, number of treatment modalities used, and performance status of the patients. The extent of the surgical procedure and the type of reconstruction may have significant influence on the patients' QoL.[52,53] On the other hand, using IMRT was proven to significantly improve QoL in patients who underwent RT treatment compared to other techniques in a meta-analyses by Ge et al.[54]

Unfortunately, a large proportion of locally advanced oral cavity squamous cell carcinomas do not qualify for curative treatment for many reasons. Therefore, the goal of treating these patients should be palliative in nature. Radiotherapy is an effective palliative modality that many of these patients ultimately get with a focus on their QoL.[55]

Conclusion

Surgery remains the standard of care for all operable patients with resectable locally advanced oral cavity cancers followed by adjuvant RT with or without CT. In patients with unresectable disease, ICT may be offered. For inoperable patients or unresectable disease, curative CRT or palliative RT can be offered. In all cases, treatment should be individualized and discussed within a multidisciplinary approach taking into consideration the patient's QoL.

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ORCID iD

Arwa Obaid ![ORCID] https://orcid.org/0000-0001-8242-3637
Majed Alghamdi, MD, FRCP(C), DABR ![ORCID] https://orcid.org/0000-0003-0779-079X

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