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Review

Nonsurgical management of resectable oral cavity cancer in the wake of COVID-19: A rapid review and meta-analysis

David Forner^{a,b,1}, Christopher W. Noel^{b,c,1}, Vincent Wu^{c,1}, Ambica Parmar^{b,d}, Kelvin K.W. Chan^{b,d}, John R. de Almeida^{b,c}, Zain Husain^e, Antoine Eskander^{b,c,*}^a Division of Otolaryngology – Head and Neck Surgery, Dalhousie University, Halifax, Canada^b Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada^c Department of Otolaryngology – Head and Neck Surgery, University of Toronto, Toronto, Canada^d Department of Medical Oncology, University of Toronto, Toronto, Canada^e Department of Radiation Oncology, University of Toronto, Toronto, Canada

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ABSTRACT

Objective: Surgery is the preferred treatment modality for oral squamous cell carcinoma (OSCC). However, due to limited resources, re-assessment of treatment paradigms in the wake of the Coronavirus Disease 2019 (COVID-19) pandemic is urgently required. In this rapid review, we described contemporary oncological outcomes for OSCC using non-surgical modalities.

Methods: A systematic literature search was conducted for articles published between January 1, 2010 and April 1, 2020 on MEDLINE and Cochrane CENTRAL. Studies were included if they contained patients with OSCC treated with either neoadjuvant, induction, or definitive radiotherapy, chemotherapy, immunotherapy, or combination thereof, and an outcome of overall survival.

Results: In total, 36 articles were included. Definitive radiotherapy or chemoradiotherapy were the focus of 18 articles and neoadjuvant chemotherapy or chemoradiotherapy were the focus of the other 18 articles. In early stage OSCC, definitive radiotherapy, with or without concurrent chemotherapy, was associated with a significantly increased hazard of death compared to definitive surgery (HR: 2.39, 95% CI: 1.56–3.67, I²: 63%). The hazard of death was non-significantly increased with definitive chemoradiotherapy in studies excluding early disease (HR: 1.98, 95% CI: 0.85–4.64, I²: 84%). Two recent randomized control trials have been conducted, demonstrating no survival advantage to neoadjuvant chemotherapy.

Conclusion: This review suggests that primary radiotherapy and chemoradiotherapy are inferior to surgical management for OSCC. Strategies for surgical delay warranting consideration are sparse, but may include several neoadjuvant regimens, recognizing these regimens may not offer a survival benefit over definitive surgery alone.

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has placed significant strain on healthcare systems across the world. To increase the capacity of these systems, surgical cases, including oncological surgery, have been either delayed or cancelled across various jurisdictions [1,2]. As COVID-19 pressures mount, head and neck surgeons must adapt to meet healthcare system needs during this unprecedented time. With resource constraints intensifying and surgical waitlists becoming longer, it may become increasingly difficult to meet established targets for treatment initiation. Head and neck oncologists may need to

evaluate non-standard management options and weigh the best available evidence.

In oral cavity squamous cell carcinoma (OSCC), surgery has remained first line therapy for decades, with the National Comprehensive Cancer Network (NCCN) recommending primary surgical management in both early and late stage disease [3]. Delays in cancer surgery may risk losing a window of opportunity for resection, potentially worsening both oncologic and functional outcomes [4–6]. As human resources, including nursing and critical care personnel, become less available during the pandemic, perioperative outcomes may worsen [7]. In the immediate postoperative period, nosocomial spread of COVID-19 is also

* Corresponding author at: Sunnybrook Health Sciences Centre, 2075 Bayview Ave., Room M1 102, Toronto, Ontario M4N 3M5, Canada.

E-mail address: antoine.eskander@mail.utoronto.ca (A. Eskander).

¹ Equal contribution.

a significant concern for OSCC patients, who are often elderly and medically complex, both of which correlate with increased COVID-19 related morbidity and mortality [8–12].

Multiple societies, including the Canadian Association of Head & Neck Surgical Oncology (CAHNSO), have released statements and guidelines for the management of patients with head and neck cancer during COVID-19 [13–16]. By necessity, these high-level guidelines do not provide specifics on disease management and patient-specific care, given the inherent complexity of such decision making and the variability in resource availability that may exist between institutions. As pandemic related health system changes accumulate, the need for non-surgical treatment of OSCC may become necessary. To better inform such decision making during both this initial surge and possible second wave surges, we have provided a review of contemporary oncological outcomes associated with non-surgical treatment modalities (primary radiation, chemoradiation, and immunotherapy) used for either definitive management or as potential bridging therapies in the management of surgically resectable OSCC.

Methods

Search strategy

This study was informed by the Cochrane COVID-19 Rapid Review templates [17]. A literature search was conducted for articles published between January 1, 2010 and April 1, 2020 on MEDLINE and Cochrane CENTRAL. The search strategy contained head and neck cancer terms and terms related to OSCC, non-surgical treatment modalities, and oncological outcomes. Snowballing and reference review techniques were used, including evaluation of previously published reviews [18–22]. The full search strategy is outlined in **Supplemental Figure S1**.

Eligibility criteria

Inclusion and exclusion criteria were defined *a priori* and applied to identified publications. Studies were included if they contained a population of patients (≥ 18 years of age) with potentially resectable OSCC, with a treatment intervention of either neoadjuvant, induction, or definitive radiotherapy, chemotherapy, immunotherapy, or combination thereof, and an outcome of overall survival. Studies involving non-OSCC head and neck cancer were considered eligible if OSCC-specific treatment and outcome details could be delineated. Induction therapy was considered to be treatment given before definitive non-surgical treatment, and neoadjuvant therapy was considered to be treatment given before definitive surgical treatment [23]. Publications were excluded if they contained populations of patients with salivary gland cancer or included an exclusive cohort of patients with lip cancer, basaloid squamous cell carcinoma (SCC) or verrucous SCC. Additionally, studies that described a cohort of patients with surgically unresectable disease, or those undergoing palliative therapy were also excluded. Treatments involving intra-arterial chemotherapy, brachytherapy, or photodynamic therapy were also excluded as these treatments would not be practical to administer in a pandemic setting, and would not eliminate the need for perioperative resources. Additionally, studies were excluded if they were non-English, abstract only, protocols, case-reports, case series of less than 10 patients, or studies with no primary data.

Review process and data extraction

Titles and abstracts were independently screened by three reviewers (CN, DF, VW) in duplicate to assess for initial relevance. Full articles were screened by two reviewers (CN, DF) to determine eligibility. All disagreements during the review process were resolved by consensus. Screening was facilitated using the Covidence systematic review

software (Veritas Health Innovation, Australia).

Assessment of quality

Risk of study bias was assessed using Version 2 of the Cochrane risk-of-bias tool (RoB 2) for randomized trials and the Newcastle-Ottawa Scale (NOS) for observational studies by a single reviewer (CN). For the RoB 2 tool, studies were categorized as: low risk of bias, some concerns, or high risk of bias across 5 domains and assigned an overall risk of bias judgement [24,25]. The NOS encompasses 3 subscales, each of which is scored separately and has a different maximum score (selection: 4 stars, comparability: 2 stars, outcome: 3 stars) [25]. Higher scores represent higher-quality studies, with decreased amounts of potential bias. Studies are considered good quality if they score 3–4 on selection, 1–2 on comparability, and 2–3 on outcome; fair quality if 2–3 on selection, 1–2 on comparability, and 2–3 on outcome; and poor quality if 0–1 on selection or 0 on comparability or 1 on outcome.

Statistical analysis

Inter-rater agreement during title and abstract screening was assessed by percent agreement, and inter-rater agreement during full-text review was analyzed by Cohen's kappa statistic [26]. In studies where overall survival was not directly reported in the body of the text, digitization of the Kaplan-Meier curves using the DigitizeIt software (version 2.3, Germany), allowed for generation of summary survival statistics.

Pre-determined pooled analyses were performed. Meta-analysis was performed to examine pooled differences in the hazard of death between definitive radiotherapy, concurrent chemoradiotherapy (CCRT), and primary surgery. Studies which reported adjusted hazard ratios (HRs) underwent analysis. Standard errors were computed from the 95% confidence interval (CI) or p-value and log transformed HRs were used in the analysis [27]. Meta-analysis was performed using a random effects model and the generic inverse variance method; HRs and 95% CIs were reported. Heterogeneity was quantified using the I^2 test statistic. [12] Meta-analysis was performed on observational studies with two separate analyses; studies that included only early stage disease were analysed separately from studies that included only advanced disease or that included all stages. Meta-analysis was also used to provide pooled proportions of osteoradionecrosis (ORN) following definitive CCRT through a DerSimonian-Laird binary random effects model. Meta-analysis was completed using Review Manager (version 5.3, Denmark).

Results

Study selection

The search strategy yielded 2,261 non-duplicate articles (Figure 1). An additional eight studies were identified through snowballing and reference review techniques. After title and abstract screening, 80 studies underwent full text review. Agreement between three independent reviewers during title and abstract screening was 95.9% (2,176 / 2,269). During full text review, 38 articles were excluded (Figure 1). Inter-rater agreement of two independent reviewers during the full text screen was high (Cohen's kappa = 0.713, percent agreement = 86.8%). Six studies were excluded during the data extraction phase (total excluded, n = 44) due to the inability to differentiate outcomes of unresectable disease (n = 4) or inability to differentiate disease-specific from overall survival (n = 2). Experts in the field ensured there were no missing studies (AP, KC, ZH, AE). Therefore, 36 studies were included in the review [28–61].

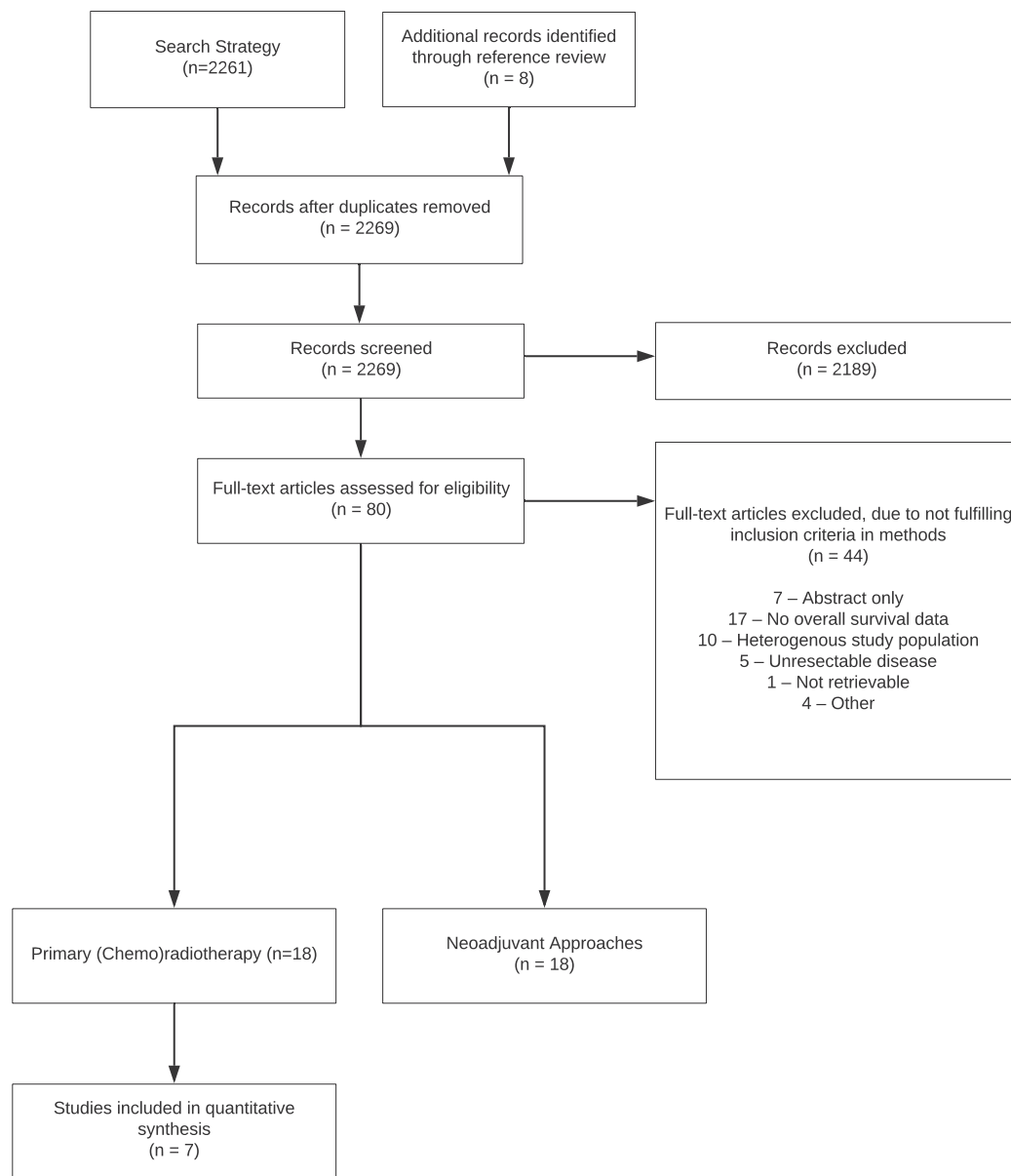


Fig. 1. PRISMA flow diagram.

Study characteristics

Study characteristics are summarized in [Table 1](#). Definitive radiotherapy or CCRT was investigated in 18 studies, of which one was a randomized controlled trial and the remainder were observational studies. Comparatively, induction or neoadjuvant chemotherapy, radiotherapy, or CCRT was also the focus of 18 articles, of which 4 studies were randomized controlled trials reporting on 3 different trials. The majority of studies provided either a comparison against primary surgery, such as in studies where the primary exposure of interest was definitive CCRT, or a comparison against no neoadjuvant treatment, such as in studies where the primary exposure of interest was neoadjuvant treatment ($n = 24$, 66.7%). Half of the studies presented multivariable adjusted analysis of overall survival ($n = 18$, 50.0%).

Risk of bias assessment

Observational cohort studies ([Supplemental Table S1](#)) and randomized controlled trials ([Supplemental Table S2](#)) underwent risk of

bias assessment. Observational studies without a comparator arm were considered to be case series and thus no bias can exist. Overall, observational cohort studies were predominately low quality, primarily due to lack of adjusted analysis and insufficient detail on follow-up. Trials were generally of low risk of bias, except one [60], which was considered high risk due to insufficient information regarding the allocation concealment and randomization process, and some concern on how missing outcome data was handled.

Definitive radiotherapy/Concurrent chemoradiotherapy

Definitive radiotherapy or CCRT for OSCC was examined in 18 studies. Specific chemotherapy regimens varied substantially ([Table 2](#)). Among included studies there was only one randomized control trial, of which patients with OSCC (stage III-IV) were assigned to either upfront surgery or definitive CCRT [35]. The regimen used included cisplatin at a dose of 20 mg/m² and 5-fluorouracil at a dose of 1000 mg/m², as continuous intravenous infusions for 96 h on days 1 and 28 of the radiotherapy course. The primary tumor and upper neck received a

Table 1
Characteristics of Included Studies (n = 36).

First Author	Year	Journal	Country	Design	Data Source	Comparator	Matched	N	Adjusted Analysis	Stages
Cannon	2017	Head & Neck	USA	Retrospective Cohort	SEER	Yes	No	5856	Yes	III-IV
Crombie	2012	Oral Oncology	Australia	Retrospective Cohort	Chart Review	No	No	54	No	I-IV
Ellis	2017	Otolaryngology Head & Neck Surgery	USA	Retrospective Cohort	NCDB	Yes	Yes	1912 (matched); 20779(unmatched)	Yes	I-II
Fujiwara	2017	Oral Oncology	USA	Retrospective Cohort	NCDB	Yes	No	23,459	Yes	I-IV
Gogarty	2017	European Archives of Oto-Rhino-Laryngology	Ireland	Retrospective Cohort	National Cancer Registry Ireland (NCRI)	Yes	No	397	Yes	I-II
Gore	2014	Head & Neck	Australia	Retrospective Cohort	Unspecified Cancer Database	Yes	No	104	Yes	I-IV
Hauswald	2012	Acta Oncologica	Germany	Retrospective Cohort	Chart Review	Yes	No	66	No	I-IV
Iyer	2015	Cancer	Singapore	Randomized Controlled Trial	N/A	Yes	N/A	119	No	III-IV
Jenwithesuk	2010	Journal of the Medical Association of Thailand	Thailand	Retrospective Cohort	Chart Review	Yes	No	107	No	I-IV
Kjems	2015	International Journal Radiation Oncology, Biology, Physics	Denmark	Retrospective Cohort	Chart Review	No	No	942 (100 OSCC)	No	I-IV
McDowell	2014	Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology	Australia	Retrospective Cohort	Chart Review	Yes	No	31	Yes	T4
Pederson	2011	American Journal of Clinical Oncology	USA	Prospective Cohort	Chart Review	No	No	21	No	II-IV
Scher	2015	Oral Oncology	USA	Retrospective Cohort	Chart Review	No	No	73	No	I-IV
Sowder	2017	Head & Neck	USA	Retrospective Cohort	SEER	Yes	No	8274	Yes	I-II
Spiotto	2017	JAMA Otolaryngology	USA	Retrospective Cohort	NCDB	Yes	Yes	2286 (matched); 6900(unmatched)	Yes	III-IV
Stenson	2010	The Laryngoscope	USA	Retrospective Cohort	Chart Review	No	No	138	No	III-IV
Studer	2012	Radiation Oncology	Switzerland	Retrospective Cohort	Chart Review	Yes	No	160	No	I-IV
Wang	2010	Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology	Taiwan	Retrospective Cohort	Chart Review	Yes	No	88	No	I-IV
Bossi	2014	Annals of Oncology	Italy	Randomized Controlled Trial	N/A	Yes	N/A	198	Yes	T2-T4
Chinn	2014	JAMA Otolaryngology	USA	Prospective cohort	Chart Review	Yes	Yes	72	Yes	III-IV
Harada	2013	Cancer Chemotherapy and Pharmacology	Japan	Non-Randomized Trial	N/A	No	No	39	No	III-IV
Hauswald	2012	Acta Oncologica	Germany	Retrospective Cohort	Chart Review	Yes	No	66	No	I-IV
Hirakawa	2017	Japanese Journal of Clinical Oncology	Japan	Retrospective Cohort	Chart Review	Yes	No	164	Yes	I-IV
Inhestern	2017	Annals of Oncology	Germany	Non-Randomized Trial	N/A	No	No	59	Yes	I-IV
Irtjala	2012	European Archives of Oto-Rhino-Laryngology	Finland	Retrospective Cohort	Chart Review	No	No	10	No	I-IV
Kies	2012	Head & Neck	USA	Non-Randomized Trial	N/A	No	No	23	No	T2-3 NO-2
Kina	2016	Cancer Chemotherapy and Pharmacology	Japan	Retrospective Cohort	Chart Review	Yes	No	117	Yes	I-II
Kiritia	2012	International Journal of Oral & Maxillofacial Surgery	Japan	Prospective cohort	Chart Review	No	No	154	No	II-IV
Kreppel	2013	Journal of Cranio-Maxillo-Facial Surgery	Germany	Retrospective Cohort	Chart Review	No	No	139	Yes	II-IV
Kreppel	2012	Oral Oncology	Germany	Retrospective Cohort	Chart Review	Yes	No	151	Yes	IV
Lyu	2014	Journal of Oral and Maxillofacial Surgery	China	Retrospective Cohort	Chart Review	No	No	22	No	III-IV
Mucke	2011	Annals of Surgical Oncology	Germany	Retrospective Cohort	Chart Review	Yes	No	926	Yes	I-IV
Myers	2011	Otolaryngology Head & Neck Surgery	USA	Retrospective Cohort	Chart Review	Yes	No	70	Yes	III-IV
Sadighi	2014	Acta Medica Iranica	Iran	Randomized Controlled Trial	N/A	Yes	No	24	No	III-IVa
Zhong	2015	Oncotarget	China	Randomized Controlled Trial	N/A	Yes	No	256	Yes	I-IV
Zhong	2013	Journal of Clinical Oncology	China	Randomized Controlled Trial	N/A	Yes	No	256	Yes	I-IV

NCDB: National Cancer Database, SEER: Surveillance, Epidemiology, and End Results

Table 2
Survival Outcomes for Patients Undergoing Definitive Radiotherapy or Chemoradiotherapy for Oral Cavity Squamous Cell Carcinoma.

First Author	Stage	n	T (%)			N (%)			Treatment Modality	Radiation	Chemotherapy	Overall Survival (years, %)										
			1-2	3-4	0	1	2-3	Technique				Dose (Gy)	Median	Range	Dose per fraction	1	2	3	4	5		
			41	58	22	26	39														RT*	CCRT
Cannon Crombie	I-II	5856	41	58	22	26	39	RT*	-	-	-	-	-	-	-	-	-	-	-	11-16		
	x	54	-	-	46	-	-	CCRT	3DC	69.7	44-73.6	2	Various: 1. Cisplatin 100 mg/m ² IV q21 days; 2. Cisplatin 100 mg/m ² IV, 5-FU 1000 mg/m ² IV q21 days; 3. Cisplatin 75 mg/m ² IV, TPZ 290 mg/m ² IV q21 days; 4. Carbo 300 mg/m ² IV, 5-FU 1000 mg/m ² IV q28 days; 5. CTX 400 mg/m ² IV then 250 mg/m ² IV q7 days	-	-	-	-	-	-	-	-	29
Ellis	x	20,779	100	0	100	0	0	RT	Various: 1. EBRT 2. 3DC 3. IMRT 4. Other	-	-	-	-	-	-	-	-	-	-	58.7 ^a		
Fujitwara Gogarty Iyer	x	23,459	68	32	74	12	15	RT/GCRT	-	-	-	-	-	-	-	-	-	-	-	46.0		
	x	397	100	0	100	0	0	RT/GCRT	-	-	-	-	-	-	-	-	-	-	-	55.4 ^c		
Gore Hauswald	x	119	19	82	30	18	51	CCRT	-	66	66	2	Cisplatin 20 mg/m ² IV × 4 days, 5-FU 1000 mg/m ² IV x4 days, day 1 and 28 of RT course	-	-	-	-	-	-	35		
	x	104	35	36	-	-	-	CCRT	3DC	-	-	2	Platinum-based, other	-	-	-	-	-	-	52.1 ^c		
Jenwithesuk Kjems	x	66	70	26	26	27	39	RT/GCRT	Various: 1. 3DC 2. IMRT	66	-	-	-	-	-	-	-	-	-	30.9 ^c		
	x	117	-	-	-	-	-	CT/RT	2. IMRT	-	-	-	-	-	-	-	-	-	-	30.5 ^c		
McDowell	x	942	57	42	22	13	65	RT/GCRT	Various: 1. 2D 2. 3DC 3. IMRT	-	66-68	2	Cisplatin 40 mg/m ² IV q7days	-	-	-	-	-	-	48 ^c		
	x	31	0	100	32	13	55	CCRT, GCRT	-	70	70	2	Various: 1. Cisplatin 100 mg/m ² IV on weeks 1,4, 7; 2. Carbo, 5-FU three times weekly; 3. Cisplatin, TPZ 4. Chemoboost, Carbo, 5-FU	-	-	-	-	-	-	0		
Pederson	x	21	24	76	29	19	52	CCRT, CT + CCRT	IMRT	-	72-75	1.5-2	Various: 1. FHX (600-800 mg/m ² × 5 days, 500-1000 mg PO BID × 14 days) q14days, with one of: 2. Paclitaxel 100 mg/m ² IV q14days; 3. Bevacizumab 2.5-10 mg/kg/m ² q14days; 4. +/- Induction Carbo AUC 2, paclitaxel 135 mg/m ² q7days × 6 cycles	-	-	-	-	-	-	-	-	76

(continued on next page)

Table 2 (continued)

First Author	Stage	n ^{***}	T (%)		N (%)		Treatment Modality	Radiation	Dose (Gy)		Chemotherapy	Overall Survival (years, %)							
			1-2	3-4	0	1			2-3	Technique		Median	Range	Dose per fraction	1	2	3	4	5
Scher	x x	73	21	80	33	16	51	RT/CCRT	Various: 1. 2D 2. 3DC 3. IMRT	70	8.24-73.1	Various: 1. Cisplatin 100 mg/m ² IV q21days × 2-3 cycles; 2. Cisplatin 100 mg/m ² IV q21days x2-3 cycles, Other; 3. Carbo 70 mg/m ² IV × 4 days 4. Carbo 70 mg/m ² IV, 5-FU 600 mg/m ² IV × 4 days; 5. Carbo 70 mg/m ² IV, paclitaxel 50 mg/m ² IV × 4 days; 6. CTX 400 mg/m ² then 250 mg/m ² IV q7days 7. CTX 400 mg/m ² then 250 mg/m ² IV, paclitaxel 50 mg/m ² IV qweeklyx7							15 ^c
Sowder	x	8274	100	0	0	0	0	RT ^a	-	-	-	-	-	-	-	-	-	-	34.3 ^c
Spiotto	x	6900	29	70	-	-	44	CCRT	-	-	-	-	-	-	-	-	-	-	65.9
Stenson	x	111	22	78	-	-	-	CCRT	Various: 1. 2D 2. 3DC 3. IMRT	-	60-75	1.5-2	Various: 5-FU NOS and hydroxyurea NOS with paclitaxel, docetaxol, carbo, cisplatin, or other NOS						40
Studer	x x	160	-	-	-	-	-	RT/CCRT/CT + CCRT	IMRT	-	69.6-70	2	Various: 1. Cisplatin 40 mg/m ² IV q7days; 2. CTX 400 mg/m ² IV then 250 mg/m ² IV q7days 3. +/- Induction, taxotere, cisplatin, 5-FU						37
Wang	x x	88	41	59	78	5	16	CCRT	3DC	-	68-74	1.8-2	Cisplatin 100 mg/m ² IV q21days then (cisplatin 100 mg/m ² IV × 1 day and 5-FU 1000 mg/m ² IV × 4 days) × 2 cycles						15

^a overall survival for matched cohort
^b obtained from Licitra et al.
^c obtained from digitization of Kaplan-Meier curves
^d not reported
 2D = Conventional two-dimensional radiation; 3DC = Three-dimensional conformal radiation therapy; 5-FU = 5-fluorouracil; AUC = Area Under the Curve; Carbo = Carboplatin; CT = Chemotherapy;
 CTX = Cetuximab; CRT = chemoradiotherapy; EBRT = External Beam Radiation Therapy; FHX: 5-Fluorouracil, hydroxyurea, radiation; IMRT = Intensity-modulated radiation therapy; NOS = Not Otherwise Stated,
 RT = Radiotherapy; TPZ: Tirapazamine
^{*} obtained from SEER database which does not capture chemotherapy
^{**} stage 2-4
^{***} total study cohort, not just those receiving CRT/RT

radiation dose total of 66 Gy in 33 fractions over 6.5 weeks, whereas involved lymph nodes received at least 60 Gy. For the remaining observational studies, there was a wide variation in specific delivery and dosages of both chemotherapy and radiotherapy (Table 2).

All studies reported survival by year or provided Kaplan-Meier estimated survival curves (Table 2). The 5-year survival ranged from 0% to 76%. A subset of studies directly compared definitive radiotherapy or CCRT against primary surgery. Of these studies, eight performed adjusted analysis of the hazard of death. However, one study did not report the HR and therefore, seven studies were meta-analysed. Three studies restricted recruitment to early stage disease and were analysed separately from studies that included advanced disease or did not restrict participation. In early stage disease, definitive radiotherapy, with or without concurrent chemotherapy, was associated with a significantly increased hazard of death (Figure 2A, HR: 2.39, 95% CI: 1.56–3.67, I²: 63%).

In the four studies which excluded early disease, there was no statistically significant increased hazard of death associated with definitive CCRT (Figure 2B, HR: 1.98, 95% CI: 0.85–4.64, I²: 84%). Only a single study showed a decreased hazard of death with definitive CCRT compared to primary surgery [38].

Four studies, none of which had comparator arms, provided outcomes related to ORN. The proportion of patients experiencing ORN ranged between 6.8 and 18.4%, with a pooled proportion of 10.1% (95% CI: 5.5–14.7%, I²: 14.05%). Only a single study specifically reported the rate of neutropenia with definitive CCRT, in which the rate of febrile neutropenia was 19% and grade was not reported [39].

Neoadjuvant chemotherapy/Concurrent chemoradiotherapy

Seventeen studies investigated neoadjuvant regimens. Nine of these studies explored neoadjuvant radiotherapy or CCRT and 8 evaluated chemotherapy alone (Table 3). Among chemotherapy only studies, four reported on three different randomized control trials. Bossi et al. report the long-term results of individuals randomized to three cycles of cisplatin 100 mg/m² and fluorouracil 1000 mg/m² (120-h infusion administered every 21 days) compared to upfront surgery in stage T2–T4, N0–N2 [46]. Zhong et al. reported short- and long-term results of a phase III trial of patients receiving TPF (docetaxel, cisplatin, 5-fluorouracil) induction in stage III/IVa OSCC [61,62]. Sadighi et al. also

reported trial results of a TPF induction protocol in advanced OSCC [60].

One study investigated induction chemotherapy [47]. Chinn and colleagues treated patients with induction cisplatin or carboplatin and fluorouracil. Tumor response was assessed at 3 weeks, and patients with a response of greater than 50% were treated with definitive CCRT. Patients with responses less than 50% were treated with definitive surgical resection. Of the 53% of patients who responded to the initial induction therapy, 30% had complete response after CCRT. Of the 70% who did not have complete response after CCRT, 14% were successfully salvaged with surgery. Overall, patients undergoing induction chemotherapy had a 2.5 times increased hazard of death compared to those undergoing definitive surgery, regardless of initial response status to induction chemotherapy.

For the 9 studies looking at neoadjuvant radiotherapy or CCRT the median radiation dose was 40 Gray. Typically, chemotherapy was administered concurrently, though induction protocols were also described.

Among all studies reporting neoadjuvant or induction regimens, the median length of the neoadjuvant/induction treatment period was 5.0 weeks (IQR 3.75 – 6.75 weeks, range 2 – 12 weeks). The length of time between conclusion of neoadjuvant or induction treatment to initiation of definitive treatment (either CCRT or surgery) was infrequently reported and varied between immediate and longer than 3 weeks. Few studies specifically reported the proportion of patients receiving neoadjuvant treatment who did not undergo surgery. Only one study reported deaths in this interval, of which the death was unrelated to the neoadjuvant treatment or cancer [62]. The majority of observational studies included only those patients who went on to have surgery.

Five studies reported rates of neutropenia, which ranged from 3.7% to 26.1% of varying grades [48–50,52,62]. Febrile neutropenia was specifically reported in three studies, ranging from 1.4% to 4.3% of varying grades [49,52,62].

Among all included studies, one study reported 1-year overall survival (47.0%), five studies reported 2-year overall survival (46.5–86.7%), two reported 3-year (42.0%, 83.8%), and 12 reported 5-year overall survival (23.0–90.0%). One study reported crude overall survival (48.0%) and one study reported 10-year survival (46.5%). Meta-analysis of induction CCRT was not performed as insufficient

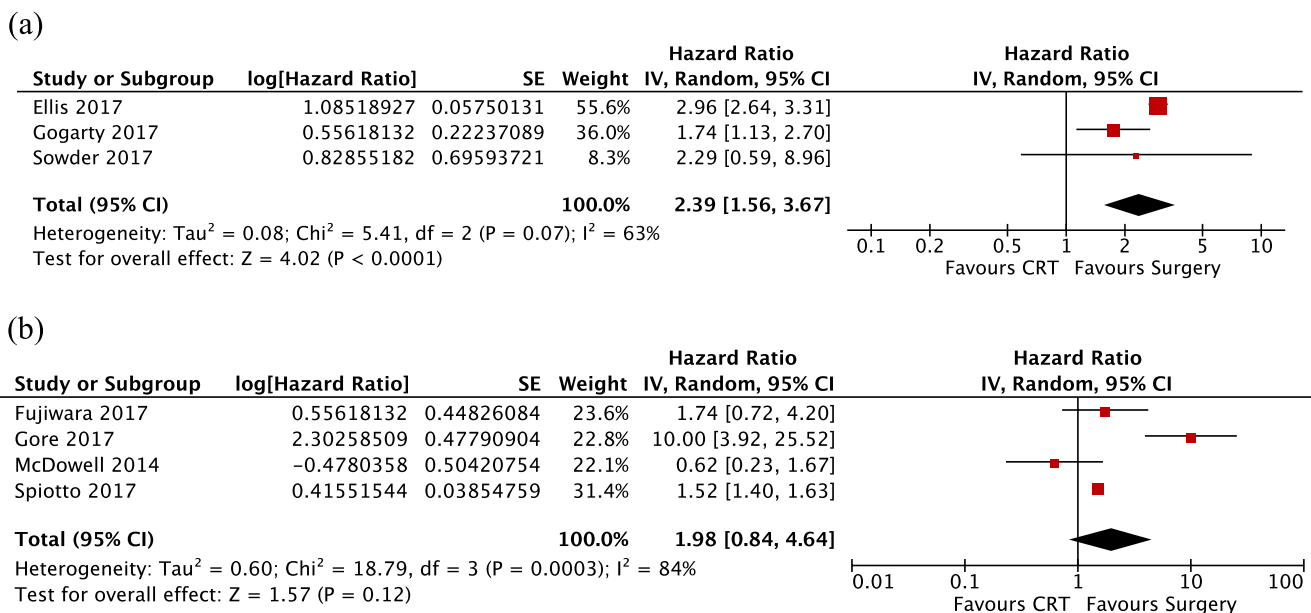


Fig. 2. Meta-analysis results for A) Early stage disease only and B) Late stage and all-stage disease. CI: confidence interval, SE: Standard error.

Table 3
Survival Outcomes for Patients Undergoing Either Neoadjuvant Chemotherapy or Neoadjuvant Chemoradiotherapy for Oral Cavity Squamous Cell Carcinoma.

First Author	Stage	n ^a	T (%)			N (%)			Neoadjuvant Modality	Radiation		Chemotherapy	Overall Survival (years, %)													
			1-2			3-4				0			1			2		3		4		5				
			Median	Range	Dose per fraction	Technique	Dose (Gy)	Technique		Dose (Gy)	Technique		Dose (Gy)	Technique	Dose (Gy)	Technique	Dose (Gy)	Technique	Dose (Gy)	Technique	Dose (Gy)	Technique	Dose (Gy)	Technique	Dose (Gy)	
Bossi	x ^{**}	198	41	59	57	27	16	CT	none	none	none	Cisplatin 100 mg/m ² IV, 5-FU 1000 mg/m ² IV q21days × 3 cycles											55 ^b			
Chinn	x ^{**}	72	24	76	26	22	51	CT	none	none	none	Various: Cisplatin NOS or Carboplatin, 5-FU NOS q21days × 1 cycle then CRT with: Cisplatin 100 mg/m ² IV q21days × 3 cycles; 1. Carbo AUC 6 IV q21days × 3 cycles S-1 50–100 mg PO 5 days/week × 4 weeks Platinum agent; immunotherapy (n = 1) Cisplatin 80 mg/m ² IV day 6, 5-FU 800 mg/m ² IV days 1–5, q21days × 1 cycle													47	32
Harada	x	39	26	74	33	28	38	CCRT	–	40	2	Docetaxel 30 mg/m ² IV, Cisplatin 40 mg/m ² IV, 5-FU 2000 mg/m ² IV days 1 and 8, q21days up to 3 cycles												60		
Hauswald	x	66	70	26	26	27	39	RT/CCRT	IMRT	40	2	Cisplatin 40 mg/m ² IV q7days × 4–6 cycles												78.9		
Hirakawa	x	164	20	80	34	21	45	CT	none	none	none	Paclitaxel 175 mg/m ² IV, Ifosfamide 1000 mg/m ² IV days 1–3, Carbo AUC 6 IV q21-28 days × 3 cycles												56.1 ^c		
Inhestern	x	54	43	57	9	4	87	CT	none	none	none	Met. Bleomycin 15 mg IV twice weekly, S-1 100 mg PO daily or UFT-E 450 mg PO TID × 3 weeks												63.8		
Irjala	x	10	20	80	60	10	30	RT/CCRT	–	63–65	–	Cisplatin 15 mg/m ² or Carbo 70–100 mg/m ² days 1–3 and peplomycin 5 mg/day or 5-FU 500–750 mg/day days 4–7, q28days × 2 cycles												90		
Kies	x ^{**}	23	57	43	43	–	–	CT	–	–	–	Cisplatin 15 mg/m ² or Carbo 70–100 mg/m ² days 1–3 and peplomycin 5 mg/day or 5-FU 500–750 mg/day days 4–7, q28days × 2 cycles												79		
Kina	x	117	100	0	0	0	0	CT	none	none	none	Docetaxel 70–80 mg/m ² IV Cisplatin 60 mg/m ² IV, 5-FU 750 mg/m ² IV × 5 days × 2–3 cycles												90		
Kiritia	x ^{**}	154	–	–	–	–	–	CCRT	–	–	–	Docetaxel 75 mg/m ² IV, Cisplatin 75 mg/m ² IV, 5-FU 750 mg/m ² IV on days1-5 q21days × 2 cycles												83		
Kreppel 2013	x ^{**}	139	41	59	20	17	63	CCRT	–	39.6	1.8	Carbo 60 mg/m ² /day IV × 5 days													45.5	
Kreppel 2012	x ^{**}	151	29	71	–	–	–	CCRT	–	39.6	1.8	Carbo 70 mg/m ² /day IV × 5 days													46.3	
Lyu	x	22	9	91	18	59	23	CT + RT	–	–	–	Docetaxel 75 mg/m ² IV, cisplatin 75 mg/m ² IV, 5-FU 750 mg/m ² IV days 1–5, q21days × 2 cycles												67.2		
Mucke	x	926	68	32	60	17	23	CCRT	EBRT	20	2	Cisplatin 12.5 mg/m ² IV × 5 days during first week of RT													68.6	
Myers	x	70	–	–	–	–	–	CT + RT/CCRT	–	68	1.2	Platinum agent/Taxane +/- 5-FU; CTX													31.1	
Sadighi	x	24	–	–	–	–	–	CT	none	none	none	Docetaxel 70–80 mg/m ² IV Cisplatin 60 mg/m ² IV, 5-FU 750 mg/m ² IV × 5 days × 2–3 cycles												23 ^c		
Zhong 2015	x	256	26	74	43	37	20	CT	none	none	none	Docetaxel 75 mg/m ² IV, Cisplatin 75 mg/m ² IV, 5-FU 750 mg/m ² IV on days1-5 q21days × 2 cycles													61.1 ^c	

‘.’ not reported. 2D = Conventional two-dimensional radiation; 3DC = Three-dimensional conformational radiation therapy; 5-FU = 5-fluorouracil, Carbo = Carboplatin, CT = Chemotherapy, CTX = Cetuximab, CRT = chemoradiotherapy; EBRT = External Beam Radiation Therapy, IMRT = Intensity-modulated radiation therapy, Met. = Metronomic, RT = Radiotherapy, S-1 = oral 5-FU, UFT-E = oral 5-FU overall survival for matched cohort

^a obtained from SEER database which does not capture chemotherapy

^b stage 2–4

^c total study cohort, not just those receiving CRT/RT

obtained from Litra et al.

obtained from digitization of Kaplan-Meier curves

information could be gathered from studies purporting to report adjusted analysis. Additionally, a recent *meta*-regression has already been published combining the results of the Zhong and Bossi trials [21].

Neoadjuvant immunotherapy

No published studies were identified that reported final results of neoadjuvant immunotherapy trials. Published abstracts reporting preliminary results, as well as ongoing trials, were identified by reference review and snowballing techniques. One manuscript was retrieved as a non-peer reviewed pre-print. Table 4 summarizes ongoing immunotherapy trials that include the oral cavity, the majority of which include other sites within the head and neck. Therefore, this literature is not yet mature for review and the results of these trials are as of yet unknown.

To date, four trials have reported preliminary trial results through published abstracts. One trial was restricted to oral cavity cancer, while the remaining three included all head and neck sites. Preliminary results of the latter trials do not stratify results by site. Checkmate 358 is a larger trial that includes non-head and neck cancer. Patients receive 2 cycles of preoperative nivolumab. Twenty-nine patients with head and neck cancer were reported, with 48% experiencing a reduction in tumor size, with 10% of patients having reductions of 40% or more. Amongst a cohort of 28 head and neck cancer patients enrolled in NCT02641093, a trial in which patients receive neoadjuvant pembrolizumab, followed by surgery and adjuvant pembrolizumab and radiation therapy, 47% of patients experienced a pathologic response greater than 10% of which 68% had a major response (greater than 70%) and one patient had a complete response. Lastly, in nine oral cavity cancer patients enrolled in NCT03021993, where patients receive 3–4 cycles of nivolumab, 44% of patients experienced a reduction in tumor size of more than 30%. Amongst preliminary reports, adverse effects appear infrequent.

In a non-peer reviewed pre-print report, results of NCT02296684 are available [63]. Thirty-six patients were enrolled to receive neoadjuvant pembrolizumab. Tumor response of more than 50% was shown in 22% of patients, and more than 10% in an additional 22% of patients. The one-year relapse rate was 16.7% amongst all-comers, and 0% in patients with low and intermediate risk pathology.

Discussion

The COVID-19 pandemic has placed significant strains on health-care systems world-wide. Within head and neck oncology, temporary alteration to treatment paradigms may be required given limitations of

resources due to the ongoing spread of COVID-19. Our review confirms the accepted notion that surgery remains the preferred treatment modality for OSCC. However, in the context of a pandemic, current standard of care may not be achievable within a preferred time frames, generally accepted as within one month [64]. Depending on regional variation in COVID-19 surge, some centres may be forced to use less than ideal treatments. It is therefore important both in terms of decision-making and patient counselling to have summarized data pertaining to these options.

This review reports on a contemporary repository of observational studies and randomized controlled trials that document survival outcomes for patients with surgically resectable OSCC undergoing non-surgical treatment. In some settings, primary CCRT offers near comparable survival outcomes, albeit with significant toxicity, most commonly and more specifically, ORN.

Definitive radiotherapy/Concurrent chemoradiotherapy

Primary surgical management of OSCC has been a mainstay of therapy for decades. Indeed, one of the included studies using recent National Cancer Data Base data determined that of more than 20,000 early oral cancers, surgery was the modality of choice in 95% of cases [30]. There have been two randomized trials attempting to compare surgery with primary radiotherapy. In 1998, Robertson et al. randomized individuals with a planned sample size of 350 patients, though the study was aborted after the first 30 patients showed inferior survival with definitive radiation [65]. Similarly, in 2015, Iyer et al. terminated their study early due to poor accrual [35]. However, this review does present evidence for primary radiation or CCRT through the assessment of observational studies of low to moderate risk of bias. The pooled hazard of death was assessed in those studies, which reported adjusted analysis, and revealed over a 100% increased instantaneous risk of death amongst early OSCC patients. In advanced disease, the increased hazard of death was non-significant, likely owing to individual studies within the pooled analysis being underpowered, and not a lack of true association.

Although not a primary outcome of this review, definitive CCRT was found to have a high rate of ORN, with pooled analysis suggesting over 10% of patients experience this complication. Previous studies have shown the risk of ORN to be both dose- and target volume-dependent, and as such, the oral cavity has been shown to have a more than four times risk of developing ORN compared to other sites [66,67]. Clinicians must balance the increased risk of mortality and morbidity associated with definitive CCRT, in light of improving radiotherapy

Table 4
Ongoing Neoadjuvant Immunotherapy Trials for Oral Cavity Squamous Cell Carcinoma.

Trial	Neoadjuvant/Induction Regimen	Sites	Recruitment Status	Time From 1st Dose to Primary Treatment
NCT02296684	Pembrolizumab	Any	Recruiting	2–3 weeks
NCT02641093	Pembrolizumab	Any	Recruiting	1 week
NCT02919683	Nivolumab, Nivolumab + Ipilimumab	OSCC	Active, Not Recruiting	2 weeks
NCT03021993	Nivolumab	OSCC	Recruiting	36–50 days
NCT02827838	Durvalumab	OSCC, OPCC	Recruiting	2 weeks + 3–17 days
NCT02488759	Nivolumab	Any	Active, Not Recruiting	–
NCT03174275	Carboplatin, Paclitaxel, Durvalumab	Any	Recruiting	8–14 weeks
NCT03700905	Nivolumab, Nivolumab + Ipilimumab	Any	Recruiting	2 weeks
NCT03737968	Durvalumab, Durvalumab + Tremelimumab	Any	Not Yet Recruiting	4 weeks
NCT02997332	Durvalumab, Docetaxel, Cisplatin, 5-FU	Any	Recruiting	7 weeks
NCT02882308	Olaparib Vs. Cisplatin And Olaparib Vs. Olaparib + Durvalumab	Any	Recruitment Complete	23–29 days
NCT03708224	Atezolizumab, Atezolizumab + Emactuzumab	Any	Recruiting	3–6 weeks
NCT03003637	Nivolumab, Nivolumab + Ipilimumab	Any	Recruiting	3 weeks
NCT03700905	Nivolumab	Any	Recruiting	2 weeks
NCT03721757	Nivolumab	Any	Not Yet Recruiting	2 weeks
NCT03247712	Nivolumab, Radiation	Any	Recruiting	2–6 weeks
NCT03342911	Nivolumab, Carboplatin, Paclitaxel	Any	Recruiting	6 weeks
NCT02777385	Pembrolizumab	Any	Recruiting	–

– not reported

techniques, against pandemic associated threats.

Additionally, while primary CCRT has the advantage of potentially facilitating primarily outpatient management, it poses unique challenges in the COVID-19 setting [68]. Chemotherapy is immunosuppressive and radiotherapy requires visits to a radiation centre. Early reports have noted that patients with a history of cancer were more likely to acquire COVID-19, and that individuals who are immunocompromised or have medical comorbidities are at higher risks for intensive care unit admission, morbidity, and mortality secondary to COVID-19 [12,69]. Moreover, patients undergoing non-surgical regimens may present with symptoms that mirror COVID-19, including cough and sore throat which may then interrupt treatment and impact survival outcomes [70].

Neoadjuvant chemotherapy/Concurrent chemoradiotherapy

Neoadjuvant and induction chemotherapy have been studied in advanced head and neck cancers since the 1990s [71,72]. Over the past decade, two randomized control trials have examined the role of neoadjuvant chemotherapy in OSCC. Bossi, Licitra and colleagues reported on the early and long-term results of a randomized trial of 198 operable oral cancer patients (T2-T4) who were randomized to three cycles of cisplatin and 5-fluorouracil followed by surgery versus surgery alone [46,73]. The addition of chemotherapy failed to provide a survival benefit, though it resulted in reduced rates of adjuvant radiation (33% vs 46%) as well as a higher incidence of mandibular preservation (52% vs 31%). Zhong et al. conducted a similar trial, albeit with a different triple neoadjuvant chemotherapy regimen (docetaxel, cisplatin and 5-fluorouracil). This trial also failed to demonstrate an overall survival benefit, and was associated with grade 3 hematological toxicity in 6.6% of patients and grade 2 adverse events in over 70% of patients [61]. Marta et al. recently combined these studies in a meta-analysis. The pooled data of 451 patients failed to show any difference in overall survival [21]. A second meta-analysis of 27 randomized trials over a 40 year period also failed to identify any benefit [20].

While neoadjuvant chemotherapy may not have a demonstrated role in routine management of primary OSCC, there is a potential for it to provide symptom relief and even delay the need for surgery for a finite period of time. Indeed, there is even some evidence of benefit for neoadjuvant approach amongst responders [61]. In this systematic review, neoadjuvant regimens prior to surgery included both chemotherapy alone and CCRT. Specific treatment regimens were varied, resulting in an inability to adequately combine studies. Nevertheless, in the event where an institution has a clearly delineated target day to deliver surgical care, therapy delivered in the pre-surgical period could be considered as an option either for neoadjuvant intent, or simply as a bridging option until resource restrictions are loosened – the key difference being in specific dosing regimens delivered.

The avoidance of triple modality therapy through the use of induction chemotherapy has importance in both resource-constrained and resource-abundant settings. In patients who respond to initial induction chemotherapy, definitive CCRT would avoid and preserve the use of surgical treatment. However, only a single contemporary study was included in this review [47], which did not demonstrate survival benefit with the use of induction chemoselection. While over half of patients receiving induction chemoselection had an initial response, this strategy was associated with worse survival than definitive surgery with risk informed adjuvant treatment.

Neoadjuvant immunotherapy

Immunotherapy is governed by the principle that tumors can evade immune detection, and immunotherapies can activate immunologic effector mechanisms to kill cancer cells [74]. Integrating immunotherapeutics into upfront therapies has gained significant traction within the head and neck oncology community. While immunotherapy

has shown encouraging results in the salvage setting [75,76], neoadjuvant and induction immunotherapy remains under investigation. Of the 18 identified studies, only a single trial has produced mature results, which remain to undergo formal peer-review. For the management of patients in extremely resource constrained settings, upfront immunotherapy may afford additional time for definitive treatment, though this is not directly supported by current literature. Despite the potential benefits, limitations must be considered. Immune-mediated toxicity is a concern, and the question of hyperprogression has been raised [77]. In addition, immunomodulation could have implications with regards to post-operative wound healing, potentially necessitating, instead of protecting against, health system utilization [20]. Lastly, neoadjuvant immunotherapy in head and neck oncology is in its early randomized trial years and is far from standard of care, and therefore may not be accessible at many centers. Many centers have closed non-essential randomized trials in the context of COVID-19. It should also be noted that the vast majority of these trials are industry sponsored due to the very expensive cost of these agents and therefore even if these agents prove efficacious, rigorous cost-effectiveness analyses will be required before uptake. Further, some of these trials are window of opportunity studies, and thus the immunotherapy administered is considered experimental and not necessarily considered a component of the planned treatment [78].

Risk of surgical therapy in the wake of COVID-19

Although findings from our study suggest superiority of oncological outcomes for OSCC managed surgically, clinicians must balance the risk to both patients and healthcare providers, as well as limitations of available resources, that surgery would impose during COVID-19. Surgical management may involve increased duration and time spent inside hospitals, during the pre-operative, operative, and post-operative periods, potentially increasing the risk of nosocomial infections. Additionally, intubation, tracheostomy, surgical manipulation of the upper aerodigestive tract, and post-operative care with suctioning of the oral cavity, are all considered aerosol generating medical procedures and known transmission routes for SARS-COV-2 [2,79–81]. However, for many OSCCs, particularly early stage cancers, the short-term risks of surgery may be outweighed by the collective risk of daily presentation to a radiation centre over the course of 7 weeks and the increased susceptibility to infection that is associated with CCRT. Furthermore, there has been rapid progression in protocols to allow for safer surgical care of the OSCC patient during COVID-19 including, appropriate use of personal protective equipment, self-isolation prior to surgery, and COVID-19 testing pre-operatively [2].

Limitations

The strengths of this review must be taken in context. Firstly, this was a rapid review of the literature. We did not pursue all elements of a formal systematic review given the evolving nature of the COVID-19 pandemic and need for timely evidence. Despite this, a number of formal systematic review methods were utilized, including the use of multiple reviewers and meta-analytical techniques. Reviews are inherently limited by the evidence quality available in the literature, and as randomized controlled trials were both few in number and high in risk of bias limitations in conclusions drawn from our findings must be noted [82]. However, this study does offer the most comprehensive review of the contemporary literature on the non-surgical management of oral cavity cancer.

Conclusion

How the COVID-19 pandemic affects treatment decisions and resource availability is likely to change as the pandemic unfolds. While head and neck surgeons should strive to provide standard of care

therapies throughout the pandemic, reduced access to the operating room and availability of critical care services for post-operative management may necessitate the use of treatment strategies outside of standards of care, particularly in regions with an inability to manage a surge. This review suggests that primary radiation and chemotherapy are inferior to surgical management for oral cavity cancer. Strategies for oncologically safe surgical delay warranting consideration are sparse but may include select neoadjuvant regimens. Our hope is that this systematic review and meta-analysis will shed light on the risks and benefits of contemporary non-surgical options for OSCC within the nuanced COVID-19 pandemic setting. This is particularly important given the expected second wave or surge of COVID-19, which may again put head and neck cancer oncologists in a resource constrained environment. In times of profound uncertainty, the risks and benefits of all strategies must be weighed in the context of patients, healthcare providers, and the healthcare system.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.oraloncology.2020.104849>.

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