Review

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Comparing the Effectiveness of Non-Surgical and Surgical Treatment Modalities in the Management of Oral Cancer: A Systematic Review and Meta-Analysis

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Abstract

Objectives: To answer the question of "how effective are non-surgical treatment modalities in the management of oral cancer, and can they serve as viable alternatives to surgical intervention?" **Method:** We conducted systematic searches for Randomized Controlled Trials and Controlled Clinical Trials in PubMed, Cochrane, Ovid Medline, and OpenGrey databases. The US National Institutes of Health Ongoing Trials Register and the World Health Organization International Clinical Trials Registry Platform were also searched for ongoing and past studies. Identified studies were retrieved and assessed for relevance. **Outcome measures:** The primary outcomes assessed in the trials included any combination of overall survival, disease-free survival, locoregional control, and recurrence. While secondary outcomes considered were complications of treatment, participants' satisfaction, costs to participants and health services, and quality of life. **Results:** Only 5 studies met all inclusion criteria and were selected for qualitative analysis. Two studies comparing radiotherapy with surgery, 1 compared chemoradiotherapy with surgery, and 2 compared brachytherapy with surgery. **Conclusion:** Based on results from this review, surgery is the mainstay of treatment of non-HPV-associated oral cancer and should always be considered unless surgical intervention is contraindicated. Primary radiotherapy or concurrent chemoradiotherapy may be instituted as non-surgical alternatives when surgery is contraindicated on the condition that clinicians follow the NCCN guidelines.

Keywords

oral cancer, nonsurgical and surgical management, systematic review

Introduction

Oral Cancers (OC) develop on the lip or oral cavity and originate majorly from squamous cells.[1] They include squamous cell carcinomas of the oral cavity originating from the labial mucosa, anterior two-thirds of the tongue, buccal mucosa, floor of the mouth, hard palate, upper and lower alveolus, and gingivae.[2]

Surgery is the mainstay of treatment for OC and it may be combined with other treatment modalities such as radiotherapy (external beam radiotherapy [EBRT] or intensity-modulated radiotherapy [IMRT]), brachytherapy, systemic therapy, or any combination of these. Appropriate treatment selection is made based on disease location and progression, consideration of disease control, patient general health status, functional and aesthetic outcomes, and availability of expertise and resources.[3] The success of surgery is measured primarily by the locoregional control (LRC) of the disease and disease-free survival. This explains why most surgeons excise cancerous tumors with a clinical margin of about 1 cm of normal tissue.[4] Despite a complete surgical excision clinically, the tumor may still be demonstrated at the margins histopathologically[5,6]; encouraging a more aggressive surgical intervention. This drawback of surgical intervention makes the need for alternatives with less morbidity and sacrifice of normal tissue paramount. In cases where combinations of

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other treatment modalities will give similar or better treatment outcomes, such combinations should be adopted as they will spare patients unnecessary surgeries.

A few studies[7-10] have reported the roles of radiotherapy and chemotherapy in the management of OC. However, to our knowledge, there has been no systematic review of the available evidence on the effectiveness of radiotherapy and chemotherapy as sole treatment modalities for OC without surgical intervention. It is therefore important to understand the effectiveness of any combination of non-surgical treatment modalities compared with surgical treatment with or without adjunct treatments. Such evidence will inform clinical decisions regarding the choice of these treatment modalities especially in cases where surgical intervention is contraindicated.

Therefore, this systematic review aimed to answer the question "How effective are radiotherapy and chemotherapy as single or combined treatment modalities in the management of OC, and can they serve as viable alternatives to surgical intervention (with or without adjunct treatments) in OC patients with an unresectable disease where esthetics or function is a major concern, patients with advanced medical conditions intolerant of surgery, and in patients who do not consent to surgery?"

Methodology

This systematic review was conducted and presented according to the methods of the Cochrane guideline for systematic reviews.[11]

Eligibility Criteria

Only randomized controlled trials (RCT) and controlled clinical trials (CCT) comparing any combinations of non-surgical treatment modalities with surgical intervention with or without other treatment modalities were included in this review. Participants were individuals of all ages with confirmed histopathologic diagnoses of OC as defined by the International Classification of Diseases for Oncology (ICD-O). Participants with squamous cell carcinoma (SCC) ICD-O codes C06 (oral cavity) were included in this review.[12] Also included were studies of HNC when at least 50% of participants were recorded as having OC, or in cases where data for OC could be extracted or were available separately.

The intervention was any combination of non-surgical treatment modalities (radiotherapy, brachytherapy, chemotherapy, and immunotherapy/targeted therapy) compared with surgery with or without other treatment modalities. Surgical treatment could have included traditional scalpel-based surgery, laser surgery, electrosurgery, cryosurgery, or robotic surgery. Also included were re-treatment cases where non-surgical interventions were initiated on a previously treated site either as a recurrent case or as a primary lesion in the same location.

The outcomes assessed included any combination of primary outcomes (overall survival, disease-free survival, locoregional control, and recurrence) and secondary outcomes (complications of treatment, participant satisfaction, cost of treatment, and quality of life).

Search Strategy and Selection of Studies

We conducted systematic searches for RCTs and CCTs in PubMed (NLM), Cochrane, Ovid Medline, and OpenGrey databases. The US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry (WHO clinical trials registry) were also searched for ongoing and past studies. Additional searches for relevant studies were done via the following methods: hand-search of the reference section of eligible studies and purposeful Google scholar searches. Only articles written in English or with English language translations were considered for the review. There were no other publication conditions. All databases were searched to September 2020.

Two of the authors (UPE and AAA) independently screened the titles and abstracts (when available) of all reports identified through the electronic searches. The search was designed to be sensitive to include only RCTs and CCTs. Non-control clinical trials, retrospective cohorts, and cross-sectional studies were filtered out in the selection process. For studies appearing to meet the inclusion criteria, or for which there was insufficient data in the title and abstract to make a clear decision, we obtained the full report. The full reports were also independently assessed by the first 2 authors (UPE and AAA) to establish whether the studies met the inclusion criteria or not. Disagreements were resolved by the third author (WLA). The search strategies, as well as the exclusion criteria for the selection of studies, are illustrated in Figure 1 according to PRISMA.[13]

Data Extraction and Management

The first 2 authors (UPE and AAA) independently extracted data from the included studies. The data extraction forms were piloted on several papers and modified as required before use. There were no disagreements in data extraction.

For each study, the following data were recorded (where available):

- Authors name, year of publication, recruitment of the first participant, country of origin, study design, and source of funding (if any).
- Socio-demographic characteristics of participants, criteria for inclusion and exclusion, the proportion of participants with OC or OPC in HNC trials, the staging of

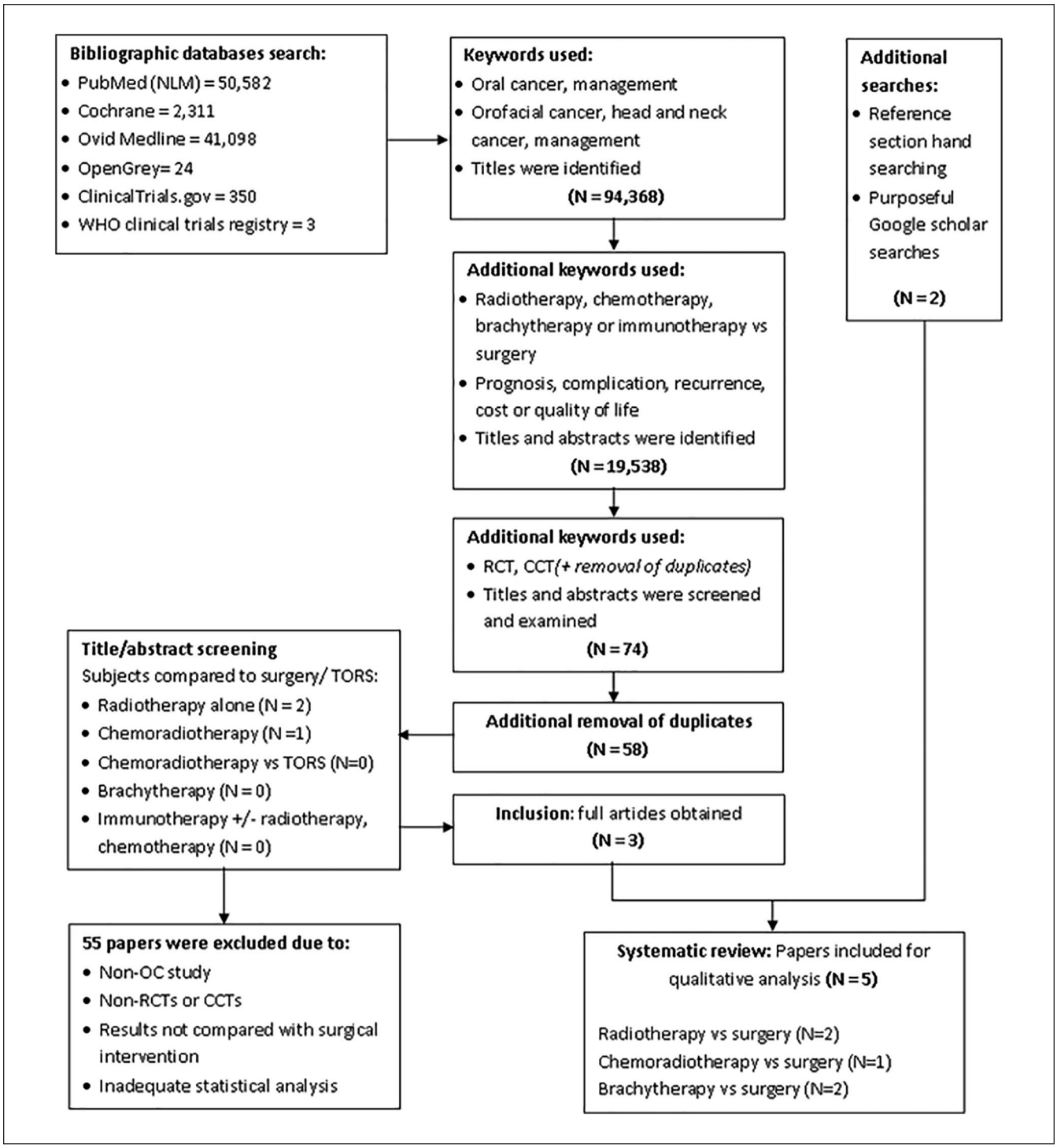

Figure 1. Flow chart of the study search strategy and selection process.

SCC,[2] location of SCC, duration of the review, prognosis, recurrence, complications, quality of life.

- Details of treatment duration, dosage, cost, and follow-up.
- Details of the outcomes evaluated, including, assessment measures and time intervals.

Assessment of Risk of Bias in Included Studies

Two review authors (UPE and AAA) independently assessed the risk of bias in included studies using a design-specific risk of bias modified from the adapted risk of bias criteria for individual studies in systematic reviews of healthcare

intervention by Viswanathan et al[14] and other studies[11,13,15] risks of bias assessments. We proposed 7 criteria for the assessment: (a) sequence generation (selection bias); (b) allocation method (selection bias); (c) performance bias; (d) attrition bias; (e) detection bias; (f) reporting bias; and (g) other bias.

Statistical Analysis

We planned to conduct quantitative analysis for combinable data reporting the same outcome with similar measures using the generic inverse variance method and random-effects model. All statistical analyses were done with Revman version 5.4 (Review Manager Version 5.4, The Cochrane Collaboration, 2020).[16]

Results

Description of Studies

Results of the search. Fifty-eight research papers were identified after the inclusion of all the keywords and removal of all duplicate studies (Figure 1). Full-text copies of these articles were retrieved for detailed review. Additional searches were also done. Finally, only 5 studies[17-21] met all inclusion criteria, and they were selected for qualitative analysis.

Participants. Participants were recruited over periods ranging from 2 to 6 years, with the earliest recruitment in May 1973 reported by Kramer et al.[18] A total of 608 participants with HNC were allocated to treatments with 211 (34.7%) participants diagnosed with OC included in the outcome evaluations. All included trials reported tumor stage using the TNM classification.[2]

Interventions. Five studies[17-21] compared non-surgical with surgical interventions in the management of OC. Of the 5 studies included in the review; 2 compared radiotherapy with surgery,[17,18] 1 compared chemoradiotherapy with surgery,[19] and 2 compared brachytherapy with surgery.[20,21] None of the included trials compared immunotherapy/target therapy with surgery. Table 1 shows the characteristics of selected studies.

Risk of Bias in Included Studies

The risk of bias in included studies was assessed through the design specific risk of bias modified from the adapted risk of bias criteria for individual studies in systematic reviews of health care intervention by Viswanathan et al.[14] Of the 5 studies,[17-21] 3 were RCTs[17-19] and 2[20,21] did not explicitly state their study design and were assessed as being at unclear overall risk of bias.

Sequence generation (selection bias). Of the 3 RCTs, 1[17] reported adequate randomization sequence generation methods and was assessed as being at low risk of bias for this domain. In the remaining 2,[18,19] the methods of sequence generation were unclear and they were assessed as being at unclear risk of bias.

Allocation method (selection bias). Of the 3 RCTs, only 1[17] reported adequate allocation concealment and was assessed as being at low risk of bias for this domain. In the remaining 2,[18,19] the methods for allocation concealment were unclear.

Performance bias. Blinding of participants and clinicians is difficult in surgical trials and was not assessed. In the 3 trials[17-19] assessed for bias, researchers ruled out any impact from concurrent interventions and unintended exposures and maintained fidelity to their intervention protocol. They were assessed as being at low risk of bias for this domain.

Attrition bias. We assessed the 3 RCTs[17-19] as being at low risk of bias concerning incomplete outcome data because all the participants were adequately accounted for in the outcome evaluation.

Detection bias. Blinding of outcome assessment is both possible and desirable. However, because mortality, DFS, and LRC were the primary outcomes most frequently and reliably reported; a decision was made to assess all trials[17-19] as being at low risk of bias for the blinding of the outcome assessment domain.

Reporting bias. We assessed the 3 RCTs[17-19] as free of selective reporting bias as they reported on expected, prespecified clinically important outcomes.

Other bias. We assessed 2 trials[18,19] at low risk of other bias because the intervention groups appeared to be similar at baseline and there were no other sources of bias. We assessed the trial by Robertson et al[17] at high risk of other bias because, although planned recruitment was 350 participants, this trial was stopped after only 35 participants were recruited because clinicians felt it was unethical to continue. Additionally, more than half of the participants in this trial did not receive radiotherapy as planned due to problems with faulty equipment. This would likely have had a greater effect on the outcomes of the RT-only arm of the trial.

Overall bias. We assessed 1 trial[17] at high risks of bias and the remaining 4[18-21] at unclear risk of bias, for all outcomes evaluated. A summary of the risk of bias assessment is presented in Figure 2.

Effects of Intervention on Oral Cancer

Five studies[17-21] were included in the qualitative analysis for nonsurgical versus surgical management of OC. OCs

Table 1. Characteristics of Selected Studies.

Author	Study design, country	Sample size, age range, TNM stage	Location	Treatment and interventions follow up	Duration, dosage	Outcome evaluated	Evidence/result
Radiotherapy versus surgery							
Robertson et al[17], first patient recruited December, 1991	Randomized controlled trial, multicentered (4), United Kingdom	Total participants = 35, oral cavity N = 29 (82.9%), oropharynx N = 6 (17.1%), 44 to 88 y, stage II to IV, majorly stage III and IV, (T2-T4; N0-N2; M0)	Floor of the mouth, alveolus, tongue (both anterior two-thirds and posterior third), retromolar trigone, or tonsil ± lateral pharyngeal wall and mandibular involvement	Radiotherapy alone. N = 18, radical surgery (1 cm margin) and post-op radiotherapy. N = 17, 23 mo	RT only: 66 Gy in 33 fr over 6.5 wk, S + RT: 60 Gy in 30 fr over 6 wk within 6 to 8 wk of surgery	Complications, residual disease (dx), overall survival	Subcutaneous fibrosis: RT only (13%) < S + RT (29%) $P = .042$, telangiectasia: RT only (20%) > S + RT (18%) $P > .05$, edema: RT only (40%) > S + RT (24%) $P > .05$, xerostomia: RT only (60%) > S + RT (59%) $P > .05$, trismus: RT only (0%) < S + RT (18%) $P > .05$, dysphagia: RT only (46%) > S + RT (29%) $P > .05$, residual dx: RT only (56%) > S + RT (0%) $P < .001$, patient death: RT only (88.8%) > S + RT (47%) $P = .009$
*Kramer et al[18], first patient recruited May, 1973	Randomized controlled trial, multicentered (19), Unites States of America	Total participants = 320, oral cavity N = 59 (18.4%), oropharynx N = 70 (21.9%), supraglottic larynx N = 118 (36.9%), hypopharynx N = 73 (22.8%), age range not specified, stage II to IV (majorly stage III and IV), T2 to T4, N0 to N2, M0	Oral cavity: oral tongue (anterior 2/3rd), floor of the mouth, buccal mucosa, lower gingivae	RT only (65-70 Gy). N = 19, pre-op RT (50 Gy) + S. N = 20, S + post-op RT (60 Gy). N = 20, 4 y	RT only: initial 50 Gy over 5 to 5.5 wk additional 15 to 20 Gy over 3/7, salvage surgery was performed for recurrent cases, RT + S: 50 Gy in 1.8 to 2 Gy per day × 5/7 over 5 to 5.5 wk. Surgery 4 to 6 wk after, S + RT: 60 Gy in 1.8 to 2 Gy per day × 5/7 over 6 to 6.5 wk within 4 wk of surgery	Survival, locoregional control	4-y survival: RT only (36%) > RT + S (34%) > S + RT (32%) $P = .81$, 4-y LRC: RT only (36%) < RT + S (40%) < S + RT (44%) $P = .21$

(continued)

Table 1. (continued)

Author	Study design, country	Sample size, age range, TNM stage	Location	Treatment and interventions follow up	Duration, dosage	Outcome evaluated	Evidence/result
Chemoradiotherapy versus surgery							
*Iyer et al[19], first patient recruited August, 1996	Randomized controlled trial, single center, Singapore	Total participants = 119, oral cavity. N = 32 (27%), oropharynx N = 25 (21%), hypopharynx N = 14 (12%), larynx N = 38 (32%), maxillary sinus N = 10 (8%), 27 to 75 y, stage III to IV (majorly stage III), T3 to T4, N0 to N2, M0	Oral locations not specified	Combination chemotherapy, with cisplatin and 5-fluorouracil + concurrent RT N = 19, S + post-op RT N = 13, 6 mo to 14 y	CCRT: cisplatin 20 mg/m^2 and 5-fluorouracil 1000 mg/m^2 on days 1 and 28 of the RT course (66 Gy in 33 fractions over 6.5 wk), S + RT: 60 Gy in 30 fr over 6 wk within 4 to 5 wk of surgery	Overall survival (OS), disease specific survival (DSS), locoregional disease free survival (LRDFS), distant recurrence free survival (DRFS).	5-y overall survival: survival significantly better in S + RT than CCRT. $P < .05$, 5-y DSS: CCRT (12%) < S + RT (68%). $P = .038$, 5-y LRDFS: no significant difference between the two groups $P > .05$, 5-y DRFS: CCRT (50%) < S + RT (92%). $P = .05$
Brachytherapy versus surgery							
Strnad et al[20], first patient recruited 1999 (month not stated)	(Not explicitly stated), single center, Germany	Total participants = 104, oral cavity. N = 68 (65.4%), oropharynx N = 33 (31.7%), 21 to 81 y, stage II to IV (majorly stage II and III), T2 to T4, N0 to N2, M0	Oral cavity (tongue, floor of the mouth, buccal mucosa, lip), oropharynx (base of tongue, tonsil/palate)	Re-treatment with/without salvage surgery + brachytherapy ± RT ± CT: salvage surgery N = 53 (prior to BT), brachytherapy alone N = 81, brachytherapy + RT ± CT. N = 23, 60 mo	BT only: 56.7 Gy with dp of 0.45 to 0.7 Gy/h/24 h, BT (24 Gy with dp of 0.4 to 0.7 Gy/h/24 h) + RT (20-67 Gy) + CT (cisplatin 20 mg/m^2 or carboplatin as a short IV infusions daily and 5-flourouracil 800 mg/m^2 by continuous infusion for 120 h)	Disease free survival	DFS: BT + RT + CT (76%) > BT only (39%) > salvage surgery only (19%) $P = .014$
Rudzianskas et al,[21] first patient recruited December, 2008	(Not explicitly stated), single center, Lithuania	Total participants = 30, oral cavity plus unspecified OC. N = 15 (50%), oropharynx N = 5 (17%), hypopharynx N = 2 (7%), larynx and parotid 1 each (2%), nasal cavity/sinus N = 6 (20%), 41 to 79 y, stage II to IV (majorly stage II and III), T2 to T4, N0 to N2, M0	Oral locations not specified	Re-treatment for previous RT HNC: BT only. N = 17, S + BT. N = 13, 20 to 32 mo	BT only: 30 Gy with dp of 2.5 Gy/12 h/24 h, S + BT (30 Gy with dp of 2.5 Gy/12 h/24 h)	Locoregional control, overall survival	2-y LRC: BT only (47%) < S + BT (77%) $P = .013$, 2-y OS: BT only (35%) < S + BT (62%) $P = .035$

Note. S = surgery; RT = radiotherapy; CT = chemotherapy; BT = brachytherapy; H(L)DR = high (low) dose rate; fr = fractions; dp = dose per pulse; LRC = loco-regional control; CCRT = concurrent chemotherapy and radiotherapy; DFS = disease free survival; DRFS = distant recurrence free survival; OS = overall survival.
*Data extracted for specific location.

included in the trials were non-HPV induced. However, the trial by Robertson et al,[17] Strnad et al,[20] and Rudzianskas et al[21] reported majorly non-HPV induced OC, and also included unspecified pharyngeal carcinomas which could not be extracted from the combined data. Two studies[17,18] compared radiotherapy with surgery, 1 study[19] compared chemoradiotherapy with surgery, and 2[20,21] compared brachytherapy with surgery.

Radiotherapy versus Surgery

Two trials[17,18] compared radiotherapy with surgery in the management of OC. Robertson et al[17] compared radiotherapy alone with surgery plus post-op radiotherapy while Kramer et al[18] compared radiotherapy alone with pre-op radiotherapy plus surgery and surgery plus post-op radiotherapy.

In the trial by Robertson et al[17] participants in the radiotherapy only arm received a total of 66 Gy in 33 fractions over a period of 6 to 7 weeks. Participants in the surgery group had wide local excision of the primary tumor together with either a radical neck dissection or a more selective neck dissection at the discretion of the surgeon. The planned sample size was 175 participants with OC or OPC to each arm of the trial but after 35 participants had been recruited the trial was stopped due to the high mortality rate in the radiotherapy alone arm.

In the trial by Kramer et al[18] participants in the radiotherapy only arm received a total of 65 to 70 Gy, and surgery was reserved for salvage of patients with clinically persistent disease at day 90 from initiation of treatment whereas, participants in the surgery arm received surgery plus pre-op (50 Gy)/post-op (60 Gy) radiotherapy. All patients planned for the trial were included in the result of the study.

Overall survival (total mortality). The trial by Robertson et al[17] from an interim analysis of 35 participants after 23 months reported death in 16 out of 18 participants in the RT only group and death in 8 out of 17 participants in the S + RT group. The difference between these 2 arms was statistically significant ($P = .001$; relative death = 0.24; 95% CI = 0.10-0.59). The authors however stated that the result should be interpreted with caution as it may be exaggerated due to the small number of participants. Also, only 41% of participants in the radiotherapy only arm received their radiotherapy as scheduled due to faulty machinery and other protocol violations in the trial. Similar protocol violations were noted in the surgery plus radiotherapy arm. Kramer et al[18] reported similar 4-year survival for all 3 groups compared: 7/19 participants in the RT only group, 7/20 participants in the pre-op RT + S group, and 6/20 participants in the S + post-op RT group. The treatment differences seen in overall survival, were not significant ($P = .81$). The relatively high overall survival for the RT-only arm may be explained by the fact that salvage surgery was reserved for patients in the RT-only arm with recurrent cases at 90 days post-RT initiation. Fifty-eight

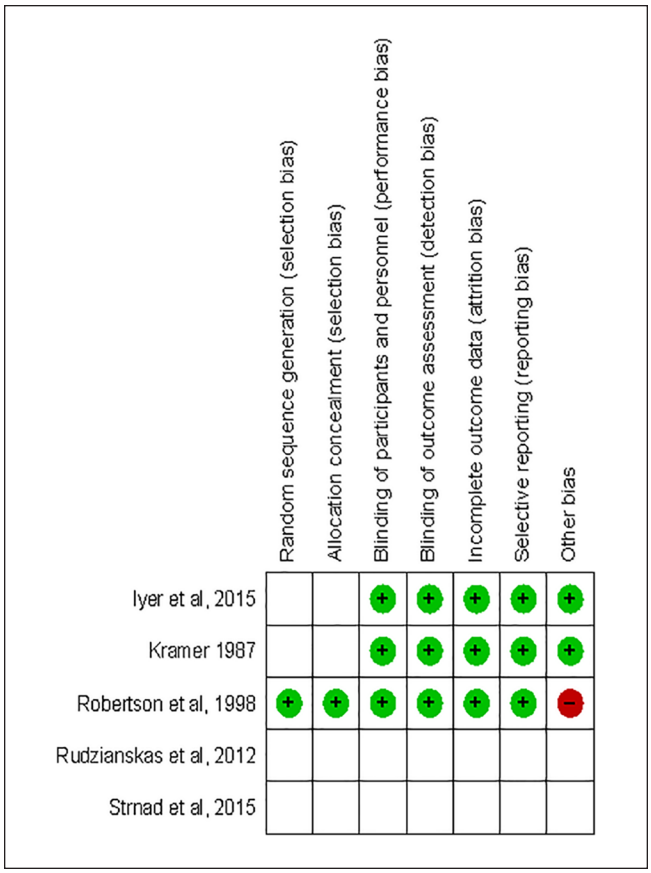

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

percent of participants in the RT-only group had recurrence and salvage surgery was performed for 60% of them.

DFS. Neither trials[17,18] reported this outcome. However, the trial by Robertson et al[17] reported the presence of residual disease. Twenty/thirty-five participants came down with residual disease after RT only while no participant in the S + RT group had residual disease ($P < .05$).

LRC: Robertson et al[17] did not report LRC. Kramer et al[18] reported 4-year LRC and showed slightly better results with planned surgery (45% overall; 40% preoperative RT + S, 44% postoperative RT + S, 36% definitive radiation therapy) but without statistical significance ($P = .21$).

Recurrence: Robertson et al[17] did not report recurrence. Kramer et al[18] did not report extractable data for recurrence for OCs. Total recurrence for all SCCs included in the study was higher in the RT-only group with 25/43 participants with recurrence, 20/43 participants in the pre-op RT + S group, and 19/43 participants in the S + post-op RT group. No *P*-value was given for this result.

Secondary outcomes. Robertson et al[17] reported that patients in RT-only group had significantly less subcutaneous fibrosis compared to those in RT + S group (13% compared with

29%; $P = .042$). There were no statistically significant differences in the severity of the extent of telangiectasia (20% with 1-4 cm^2 in RT only group, compared with 18% in RT + S group), edema (40% moderate/severe compared with 24%), xerostomia (60% moderate/severe compared with 59%), trismus (0% moderate/severe compared with 18%), or dysphagia (46% grade 2/3 compared with 29%). Kramer et al[18] reported similar results for total complications for all SCCs included in the study. Complications consisting of severe fibrosis, necrosis, edema, lymphedema, dysphagia, xerostomia, and stenosis occurred at 10% in the RT only arm, 14% in the pre-op RT + S arm, and 11% in the S + post-op RT arm. No *P*-value was given for these results. Both trials[17,18] did not report other secondary outcomes.

Chemoradiotherapy versus Surgery

Only the trial by Iyer et al[19] compared concurrent chemoradiotherapy (CCRT) with surgery in the management of OC. Participants in the CCRT arm received 2 cycles of CT comprising cisplatin at a dose of 20 mg/m^2 and 5-fluorouracil at a dose of 1000 mg/m^2 both given as continuous IV infusions for 96 hours on days 1 and 28 of the RT course. The total dose of RT given to the primary tumor and upper neck was 66 Gy in 33 fractions over 6.5 weeks whereas involved lymph nodes received at least 60 Gy. Patients with lymph node disease classified as at least N2 at the onset were scheduled to undergo elective neck dissection 4 to 6 weeks after CRT regardless of response. Patients on the S + post-op RT arm underwent radical resection of the primary tumor with comprehensive neck dissection (removing levels 1-5) for unilateral or bilateral disease as needed, followed by adjuvant RT given to primary tumor and upper neck at 2 Gy per fraction for 5 days per week to a total of 60 Gy in 30 fractions over 6 weeks. When lymph node disease was present, the lower neck was treated with a total dose of 50 Gy in 25 fractions over 5 weeks.

Primary outcomes. Iyer et al[19] reported that survival was significantly better in patients in the S + RT group compared with the CCRT group ($P < .05$); 5-year disease-specific survival was 68% versus 12% for the S + RT and CCRT arm, respectively ($P = .038$). The trial also reported 5-year distant recurrence-free survival (DRFS) which was lower in the CCRT group (46%) compared to the S + RT group (56%) ($P = .637$). No statistically significant difference was noted between the LRC of the CCRT group and the S + RT group (approximately 32% and 68% respectively approximated from the Kaplan Meier plot) ($P = .355$) although there was a trend favoring the S + RT arm. The trial by Iyer et al[19] did not report recurrence but reported distant recurrence-free survival (DRFS). Five-year DRFS for CCRT arm was 50% while 5-year DRFS for S + RT arm was 92% ($P = .134$). Iyer et al[19] did not report secondary outcomes.

Brachytherapy versus Surgery

Two studies compared brachytherapy with surgery in the management of recurrent OC. The study by Strnad et al[20] compared BT only, BT + RT ± CT, and salvage surgery while the study by Rudzianskas et al[21] compared BT only with surgery + BT.

In the study by Strnad et al[20] all patients were treated with interstitial pulsed dose rate (PDR) brachytherapy. Of the total group, 81 patients (78%) received salvage brachytherapy alone, using a median total dose of 56.7 Gy with dose per pulse (dp) values in the range of 0.45 to 0.7 Gy/hours/24 hours (median 0.55 Gy/hours). Salvage brachytherapy in combination with EBRT was performed in 23 patients (22%), using a median total dose of 24 Gy (dp median = 0.5 Gy) range (0.4-0.7 Gy). Simultaneously, concomitant chemotherapy was administered in 55.8% of patients. From days 1 to 5 of PDR brachytherapy, the majority of patients received 1 course of cisplatin (20 mg/m^2) or carboplatin (AUC1) as a short IV infusion each day, and 5-fluorouracil 800 mg/m^2 was given by continuous IV infusion for 120 hours. While in the study by Rudzianskas et al[21] patients in the BT-only group received BT 30 Gy with dp of 2.5 Gy/12 hours/24 hours while patients in the S + BT received BT 30 Gy with dp of 2.5 Gy/12 hours/24 hours.

Primary outcomes. The study by Strnad et al[20] reported no treatment-related deaths and an overall survival rate of 21% for all participants. This result was not however stratified into the 2 groups and no *P*-value was given. The study by Rudzianskas et al[21] reported the OS rate for the entire group as 63% at 1 year, and 47% at 2 years. The group treated with high dose rate (HDR) BT alone had worse 2-year OS compared with those treated with surgical resection and HDR-BRT (35% vs 62%, $P = .035$). For DFS, Strnad et al[20] reported DFS in the BT + RT ± CT group of 76%, >39% in the BT-only group, and 19% in the salvage surgery-only group. The study by Rudzianskas et al[21] did not report DFS. Also, Rudzianskas et al[21] reported that the patients treated with HDR-BRT only showed less improvement in 2-year LRC compared with patients in the surgical resection and HDR-BRT group (47% vs 77%, $P = .013$). The study by Strnad et al[20] did not report LRC. Both studies[20,21] did not report recurrence or secondary outcomes.

Quantitative analysis. No quantitative analysis was done for OC interventions due to a lack of combinable data and insufficient data.

Discussion

This review was undertaken to answer the question, "How effective are non-surgical treatment modalities in the management of OC, and can they serve as viable alternatives to surgical intervention?" On review of literature, we found

only 5 studies[17-21] with a total of 211 patients with OC meeting the inclusion criteria for qualitative analysis and were included in this review. We divided the 5 included studies into 3 major comparisons: Radiotherapy alone versus surgery plus radiotherapy, Chemoradiotherapy versus surgery, and Brachytherapy versus surgery.

Primary radiotherapy as a single modality treatment is not routinely used in the management of OC but may be employed in early-stage disease to avoid cosmetics and/or functional defects, in unresectable disease, in advanced disease in patients intolerant of surgery due to co-morbidities, in recurrent disease cases when multiple surgeries have been performed, and in patients preference.[3,22-25] However, studies[26,27] have reported a lower survival rate and LRC when primary radiotherapy is used compared to surgery.

This systematic review included 2 trials[17,18] comparing the effectiveness of radiotherapy with surgery. In both trials, almost 90% of cases were stage III and IV, the majority of whom had associated co-morbidities, thus necessitating the use of radiotherapy as primary treatment. The trial by Robertson et al[17] reported a significantly higher death rate (88.8%) in the RT-only arm ($P < .05$), and the trial by Kramer et al reported similar results with the surgery groups, which were not statistically significant ($P > .05$). Both trials[17,18] also reported a more favorable LRC in the surgery plus post-op RT arm compared to RT-only, similar to results of past studies.[26,27]

It is important to note that both trials did not follow the guidelines for radiotherapy administration proposed by the National Comprehensive Cancer Network (NCCN) which has evolved.[28] With the advent of newer radiotherapy techniques such as image-guided RT and IMRT, radiotherapy can now provide precise radiation delivery, reducing the dose to surrounding normal tissues, thereby reducing radiotherapy complications such as xerostomia, altered taste, and necrosis of soft tissue and bone without compromising target coverage.[29] Robertson et al[17] reported several protocol violations in radiotherapy administration which significantly affected treatment outcome, and this was evident in the high death rate reported in the RT-only arm. For the trial by Kramer et al[18] although they did not make reference to any specific protocols observed during RT administration, it can be surmised that they also did not follow the NCCN guidelines as the study was published years before the first NCCN guidelines were proposed in 1991.[28] NCCN guidelines on RT administration for OC[28] although may not yield better disease-free survival and LRC compared to surgical intervention,[26,27] it may result in an acceptable treatment outcome, better than what was reported by included trials.[17,18]

Concurrent chemoradiotherapy is used as primary treatment in cases similar to primary radiotherapy.[3] However, studies[30,31] have reported that CCRT provides an acceptable outcome in the management of OC compared to primary radiotherapy. Cohen et al[30] reported 5-year LRC to be significantly higher when CCRT was used in the management of 39 T4 OC patients compared to RT only. In the meta-analysis by Pignon et al[31] individual patient data from clinical trials comparing RT-only with CCRT in locally advanced OC showed a more favorable overall survival with CCRT compared to RT alone (HR = 0.8).

The comparison between chemoradiotherapy and surgery in this systematic review included results from 1 trial[19] that compared CCRT with S + RT. Although, the trial[19] reported a significantly more favorable treatment outcome in terms of overall survival, disease-specific survival, and distant recurrence-free survival ($P < .05$, $P = .038$, $P = .05$ respectively) favoring the S + RT arm; the CCRT arm reported acceptable results for all outcome measures. This was similar to the findings of Gore et al[32] who reported a reduced but favorable overall survival and LRC when CCRT was compared to surgery in the management of advanced OC. The results of past studies[30-32] and this systematic review seem to suggest surgery as the most effective treatment modality; but for patients unable to receive primary surgery, concurrent chemotherapy may be considered.

Brachytherapy may be employed in the management of OC as primary treatment for an early disease with a well-defined primary tumor, or as an adjuvant to surgery for cases with close or positive resection margins or in combination with RT to augment radiotherapy dose to high-risk areas.[3] This systematic review included 2 studies[20,21] comparing BT only with surgery plus BT. Overall survival and LRC were higher with surgery compared to BT only. Although the results of this review favor surgery similar to past studies,[33,34] a systematic review by Rodin et al[35] reported an improved LRC and overall survival when BT was used as an adjuvant to surgery in the management of recurrent OC compared to RT as an adjuvant to surgery and to BT as primary treatment. This supports the recommendation by Huang et al[3] that brachytherapy may only be instituted as an adjuvant to surgery and should rarely serve as primary treatment.

Limitations of this review were the paucity of recent randomized controlled trials with low bias comparing the non-surgical intervention of OC with the surgical intervention. And although studies have reported that 1 out of 4 OCs and 1 or more out of 3 oropharyngeal carcinomas are HPV-related,[36] the results of this meta-analysis included majorly HPV-negative OCs and may not be generalizable to HPV-associated OCs.

Conclusion

This review included 5 trials that evaluated non-surgical treatment modalities in patients with HPV-negative oral cancers and confirmed surgery as the mainstay of treatment. Based on the results of this review, radiotherapy as a single modality treatment in the management of oral cancers led to an unfavorable treatment outcome with increased total mortality, increased radiotherapy-associated complications, increased disease recurrence, and reduced locoregional control.

However, the included studies did not follow the NCCN guidelines for primary radiotherapy which may account for the poor treatment outcome. Primary radiotherapy may therefore be instituted as a non-surgical alternative when surgery is contraindicated on the condition that clinicians follow the NCCN guidelines. Similar results were seen when concurrent chemoradiotherapy was compared to surgical intervention. Concurrent chemoradiotherapy may also be instituted as a non-surgical alternative when surgery is contraindicated. We found insufficient evidence to conclude on the effectiveness of brachytherapy in the management of oral cancers.

It is obvious from this review that more randomized controlled trials are needed to address the most effective modalities for nonsurgical treatment of oral carcinomas, and it is recommended that researchers follow the CONSORT guidelines[37] while conducting and reporting clinical trials to reduce the high and uncertain level of bias.

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