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Review

Oral cancers: Current status

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ABSTRACT

Oral cancer is a global disease. Despite a well elucidated tumour progression model, these cancers present late. Attempts at early detection by way of adjunctive diagnostic technologies and screening have not lived up to expectations in spite initial promise. Surgery is the mainstay of treatment. Treatment intensification by way of adjuvant radiation/chemo radiation is warranted for those with high risk features. Recent studies have explored intensification in those with intermediate risk factors in an attempt to improve outcomes. There has been generation of recent robust evidence that has influenced the need and extent of neck dissection. Neoadjuvant chemotherapy (NACT) may have a potential role in organ preservation and borderline resectable oral cancers. Recurrent tumours should be offered surgery whenever feasible while the addition of biological agents to chemotherapy gives best results in the palliative settings.

Introduction

Oral cancer is a global problem with an incidence of 300,000 with approximately half the patients succumbing to the disease, primarily attributed to the advanced stage at presentation [1]. This is paradoxical given that these cancers have a well-defined tumour progression model and the fact that they are easily amenable to examination [2]. Efforts have been directed towards early detection by way of screening trials as well as adjunctive methods for diagnosis. There is no strong evidence however, to support the routine use of either of these two approaches [3]. In the only randomized screening trial with mortality as an end point, the addition of examination by a trained health worker to health education did not show benefit [4]. Similarly, a Cochrane meta-analysis showed a lack of robust evidence to support the use of adjunctive technologies like toluidine blue, brush cytology and florescent imaging [3]. Attempts at reversal of premalignant lesions by numerous chemo preventive approaches have also been tried. A meta-analysis of 14 Randomized Controlled Trials (RCT) did not show a conclusive benefit with this approach as well [5]. While efforts at early detection are ongoing including use of molecular technologies, the focus at this point in time is at appropriate management in an attempt to improve outcomes [6,7]. The recent past has witnessed the generation of new data and pivotal trials. This review attempts to place the evidence as it impacts today's standard best practice.

Management of the primary tumour

Primary surgery is the preferred modality of treatment for vast majority of operable oral cancers. Radiotherapy (brachytherapy ± External Beam Radiotherapy (EBRT)) is an alternate for early stage oral cancers with comparable control rates to surgery. However, given the fact that excision of early lesions is quick, simple, can be repeated in case of recurrence as well as does not result in significant cosmetic and functional disability makes surgery the modality of choice. Moreover, lesions need to be easily accessible, away from bone and superficial to be amenable to brachytherapy [8]. The need to supplement brachytherapy with EBRT for treatment of the neck may also be an overkill precluding its subsequent use. While there is no head to head comparison between surgery and radiotherapy for early lesions, it seems logical to prefer surgery for reasons enumerated above. This is borne out by the recently published National Cancer Data Base study of over 20,000 early oral cancers where surgery was the modality of choice in approximately 95% of patients [9]. This study also showed an overall survival (OS) benefit in favour of surgery. Brachytherapy, however, is preferred for large superficial lesions where excision would result in functional or cosmetic morbidity for e.g. lesions of the lip [10].

There have been two randomised trials to date attempting to address the primary modality of choice between surgery and radiotherapy in locally advanced operable oral cancers [11,12]. Robertson et al with a planned sample size of 350 patients had to abort the study as analysis of the first 30 patients showed survival with radiation to be inferior [11]. Iyer et al also needed to terminate their trial because of poor

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accrual. Subset analysis of oral cancer patients treated with surgery had a 58% survival compared to 12% with those in the non-surgical arm [12].

Chemoradiotherapy (CRT) with a goal at organ preservation, the accepted standard of care for the majority of head and neck cancers, has never found favour for oral cancers because of its intimate relationship to the mandible and perceived inferior outcomes [13,14]. Isolated reports have suggested its possibility but this is not widely practised given its applicability to select subset of patients and a high complication rate.

Surgery when performed should be with adequate margins, 5 mm being the minimum accepted standard. A meta-analysis looking at local recurrence following surgery without adjuvant radiotherapy found that there was a 21% risk reduction with margins > 5 mm ($p < 0.00001$) [15]. Close (1–5 mm) and positive (< 1 mm) margins warrant the need for adjuvant treatment emphasizing the importance of clear margins at first instance [16]. Recently Zanoni et al have reported similar outcomes with margins of 2.3–5 mm compared to those ≥5 mm, suggesting 2.2 mm to be adequate [17]. However, this finding needs to be ratified in further studies to be accepted as standard of care.

Management of the neck in oral cancers

Management of neck in oral cancers has undergone a significant change in the last decade with generation of substantial new data on imaging, sentinel node biopsy (SNB), the need for treatment of clinically node negative neck and extent of neck dissection.

There have been numerous meta-analyses comparing various imaging modalities of the neck. Sun et al in a meta-analysis of 63 studies comparing Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) showed MRI to have higher specificity and CT a higher sensitivity for both the node negative and positive neck [18]. Wu et al showed that diffusion weighted MR was superior to conventional MR [19]. Ultrasound guided fine needle aspiration cytology (US-FNAC) had the highest diagnostic odds ratio compared to only Ultrasound (US), CT, MRI &MRI-USPIO [20]. In a meta-analysis specific to the node negative neck in oral cancers Liao et al showed a similar sensitivity for all conventional imaging modalities with CT having a higher specificity over the commonly used US [21]. Kyzas et al focussing on Positron Emission Tomography (PET) for neck imaging showed that PET had a good diagnostic accuracy in pre-treatment neck evaluation but was limited in its ability to detect metastasis in node negative neck with a sensitivity of just 50% [22]. The salient conclusion of these meta-analyses was that the diagnostic ability of the various imaging modalities is more or less similar and that imaging has its limitations in detecting occult metastasis. This couldn't be exemplified better than from results of the Sentinel European Node Trial (SENT), where despite extensive preoperative work up that included CT and/or MRI ± US-FNAC, diagnostic workup failed to detect metastasis in 23% of patients [23].

There has been a recent body of evidence exploring SNB in clinically node negative patients, resulting in its recommendation across various guidelines [24,25]. A recent meta-analysis of 66 studies including 3566 patients concluded that the procedure has a high diagnostic accuracy and could be an ideal alternative to Elective Neck Dissection (END) [26]. However, given the fact that the SNB procedure has a steep learning curve, is cumbersome, 2 staged (dye and radionuclide), requires serial step sectioning and immunohistochemistry it is unlikely to gain wide acceptance in routine practice. Moreover, it is primarily a diagnostic procedure and patients with SNB positive need to undergo a completion neck dissection.

The longstanding debate of END compared to the Wait and Watch (WW) approach for early oral cancers amenable to peroral excision has recent strong evidence in favour of the former. There had been numerous attempts by way of retrospective studies and 4 RCTs to address this issue, however given the small number of patients in each study conclusions were varied and the issue was in a state of clinical equipoise [27–32]. Fasunla et al in an attempt to address this conducted a meta-analysis of the 4 RCTs and showed a benefit of END in reduction of disease-specific deaths [33]. However, the meta-analysis had serious limitations and one study seemed to have influenced the conclusions leaving a need for more robust evidence [34]. In a recent RCT of over 500 patients our group for the first time provided level I evidence showing an absolute OS benefit of 12.5% and a 23.6% improvement in disease-free survival (DFS) in favour of END [35]. A subsequent meta-analysis of all 5 RCTs reported to date, of which 4 reported the OS comprising of 708 participants showed that there was a significantly higher OS in END group compared to WW (RR of 1.18; 95% CI 1.07, 1.29); $P = 0.0009$ and concluded that there was no need for further trials to address this issue [36]. These findings were corroborated in a larger meta-analysis of 3244 patients that included 20 retrospective studies and 3 RCTs reaffirming the benefit of END [37]. Given this compelling evidence in favour of END and limitations of imaging, END should be considered the standard of care in clinically node negative early oral cancers. END in the node negative neck is essentially a staging procedure and necessitates a supraomohyoid clearance (levels I-III) and the harvesting of a minimum of 18 nodes for proper assessment [38–40]. Some advocate an extended supraomohyoid (levels I-IV) clearance particularly for tongue cancers citing a high incidence of skip metastasis [41]. However, it must be borne in mind that the majority of studies on patterns of lymph node spread were retrospective in nature and fraught with the usual limitations of such studies.

Modified radical neck dissection (MRND) is the recommended procedure for clinically node positive patients. This entails a comprehensive clearance of fibro fatty and lymphatic tissue from levels I-V preserving one or all of the non-lymphatic structures (Sternocleidomastoid muscle, spinal accessory nerve (SAN), internal jugular vein) if uninvolved. The MRND procedure despite preservation of the SAN is associated with shoulder morbidity in a significant number of patients directing efforts towards lesser procedures in an attempt to safeguard dissection in its vicinity [42]. In a meta-analysis that included studies comparing selective neck dissection (SND) versus comprehensive neck dissection (CND) in clinically node positive neck Liang et al could identify 5 studies with a total of 443 patients addressing this issue. There was no significant difference in regional recurrence, disease-specific death or overall death in the 2 groups suggesting SND in conjunction with adjuvant treatment had comparable outcomes to CND [43]. In probably the largest prospective study of 583 neck dissections in oral cancers, metastatic nodes were located at levels I-III in 91% of patients and in 96% of patients at levels I-IV. Skip metastasis occurred in 17.5% of neck dissections in patients with tongue cancer. Importantly there was no isolated skip metastasis to level IV in the absence of metastasis at level I-III. Incidence of nodal involvement of level IIb (supraspinal) and V was 3.8% and 3.3% respectively. Level IIa metastasis was independent predictor of involvement of level IIb and V. In addition, level IIb was at a higher risk of involvement in tongue and retromolar trigone (RMT) and level V for buccal mucosa and lower alveolus cancers. Therefore, clearance of levels I, II and III is adequate dissection for the node negative neck. Clearance of level IV is unnecessary in the absence of metastasis to these levels. Level IIa should guide the clearance of level IIb and V. Level IIa metastasis in Tongue/RMT and buccal mucosa/lower alveolus warrants level IIb and level V dissection respectively [44].

Radiotherapy is usually used in the adjuvant setting in treating neck disease in oral cancers given that it is rarely the primary treatment modality. When used in the definitive setting for early lesions 4500–5000 cGy is considered adequate to sterilize the occult neck [45].

The contralateral neck must be addressed in all oral cavity lesions that cross the midline. For lesions approaching the midline contralateral involvement is rarely seen in the absence of the ipsilateral nodal metastasis. In a retrospective analysis of 243 oral tongue cancer patients with lesions reaching or crossing the midline where bilateral neck dissection was performed, 97% of those with contralateral neck

metastasis had ipsilateral positive nodes. The presence of ipsilateral neck involvement was an important predictor of contralateral metastasis [46].

Neoadjuvant chemotherapy in oral cancers

The role of NACT has been explored in a trial setting with an aim at organ preservation as well as improving survival. Licitra et al randomised 195 operable oral cancer patients of stages T2-T4 to receive 3 cycles of 2 drug NACT (Cisplatin and 5-fluorouracil (5FU)) followed by surgery versus surgery alone ± adjuvant radiotherapy in both the arms. While the addition of chemotherapy failed to provide any survival benefit, it resulted in a lesser need for adjuvant radiation (33% vs 46%) as well as a higher incidence of mandibular preservation (52% vs 31%). Subset analysis further indicated that those with a pathological complete response (PCR) or minimal residual disease (microscopic residual foci) had a significantly better 5 yr DFS (85% vs 49%) [47]. A subsequent report with long term follow up of this trial confirmed a persistent absence of survival benefit except in patients with an excellent response to chemotherapy [48].

Zhong et al in a cohort of locally advanced oral cancers randomised patients in a similar fashion to the Licitra trial, except that the chemotherapy regimen was 3 drugs (docetaxel, cisplatin and 5FU). This trial also failed to demonstrate an OS or DFS benefit at a median follow up of 30 months. The NACT arm showed a trend towards reduced distant metastasis. Here again, subset analysis showed that patients with a favourable pathologic response (≤10% viable tumour cells) had a superior OS, locoregional and distant control. The benefit of NACT was also seen in a subset of patients who had cN2 disease [49].

Marta et al combined both these studies in a meta-analysis. The pooled data of 451 patients still failed to show any difference in OS, DFS and loco-regional recurrence between the 2 arms. Subset analysis of cN2 patients indicated significant benefit of NACT for OS but not for other end points like DFS or loco-regional relapse [50]. The lack of benefit of NACT on OS must be viewed in the context of both studies being underpowered. An adequately powered study with a realistic 8% improvement in survival, a power of 80% and an alpha of 0.5 would require close to 600 patients.

The role of NACT has also been explored in locally advanced cancers with borderline operability. In a study of 721 patients, 2 or 3 drug NACT was used with an aim to downstage disease and render them operable. Borderline cancers were defined by the authors as patients in whom achieving negative margins was uncertain in the judgement of the operating surgeon. This approach was successful in downsizing the tumour in 43% of patients who subsequently underwent surgery. These patients had a superior outcome as compared to non-responders [51].

From all these studies it is apparent that NACT does have a potential benefit amongst responders. This approach therefore is worth exploring in future trials to establish its exact role in the management of oral cancers.

Adverse prognosticators and the need for adjuvant therapy

Oral cancers present at an advanced stage, are biologically aggressive and adjuvant therapy is often indicated to improve outcomes (Table 1). The only randomised evidence comparing surgery with or without postoperative radiotherapy in locally advanced staged III, IV buccal cancers, confirmed the need of adjuvant therapy with a significant improvement on DFS (68% vs 38%, $p < 0.005$) [52]. There are a number of studies in literature that attempt to identify high risk groups that would benefit from adjuvant therapy. Adjuvant radiotherapy is indicated for primary stage (pT3/T4), N stage (N2/N3), multiple levels of node involvement and close margins across treatment guidelines [25]. In an attempt to further improve outcomes chemotherapy was added to radiotherapy and this approach was explored in 2 back to back landmark publications [53,54]. A comparative analysis of both these trials revealed that the maximum benefit was seen in patients with microscopic involved margins and extracapsular spread (ECS) of lymph nodes establishing these 2 indications for adjuvant CRT [16].

Table 1
Indications for adjuvant treatment.

Definitive factors for adjuvant radiotherapy	Definitive factors for adjuvant chemoradiotherapy	Others factors that may influence receipt of adjuvant radiotherapy[#]
• pT3[*]/T4 • N2/N3 • Close margins (< 5 mm)	• Extracapsular spread of lymph node • Positive margin (< 1 mm)	• Perineural invasion • Lymphovascular embolism • Grade • Single node positive • Worst pattern of invasion

[*] Includes depth of invasion > 10 mm.
[#] Indications of radiotherapy, in presence of these factors left to the discretion of clinician. Usually combination of factors influence decision (refer text).

Other pathological factors like perineural invasion (PNI), lymphovascular embolism (LVE), grade, and single node positive are also known to be associated with biologically aggressive tumours. However, there is no consensus as to the relative importance of these factors in deciding adjuvant treatment, more so when they occur individually. Even the most widely followed NCCN guidelines recommend consideration of adjuvant radiotherapy in this setting to the discretion of the treating physician. [25]. The MD Anderson group through a series of publications have attempted to address this issue [55–57]. Clusters of 2 or more factors placed patients at an increased risk of recurrence mandating the need for adjuvant therapy. Chen et al, in a retrospective analysis of 567 oral cancer patients used a similar approach. Risk factors were stratified into minor (pT4, positive nodes, close margin, tumour depth ≥1 cm, LVE, PNI, and poor differentiation as minor risk factors) and major (ECS and positive resection margin). The presence of 2 minor in absence of any major factors warranted adjuvant radiation, while 3 or more minor or any single major factor warranted CRT [58]. A similar approach of risk stratifying prognostic factors and deciding the need of adjuvant therapy has been used by others as well [59]. Gensler et al proposed a Histological Risk Assessment system based on PNI, worst pattern of invasion and Lymphocytic host response [60]. Another recently described approach is the use of nomograms that tend to overcome the limitations of the TNM staging and predict the need for adjuvant radiotherapy [61]. The combination of factors is plausibly the most rational approach in deciding the need for adjuvant radiotherapy. However, the relative risk associated with each of these adverse factors needs to be quantified to facilitate their incorporation into routine clinical practice. The decision should be made jointly by the clinician as well as patient weighing the pros and cons of adjuvant treatment versus observation.

Recently depth of invasion (DOI) (measured from basement membrane to the deepest point of infiltration) has gained renewed importance [62]. Traditionally DOI was used as a surrogate to identify patients at an increased risk of nodal metastasis and was never used as an independent factor for the prescription of adjuvant radiotherapy in treatment guidelines. An international consortium for outcome research in head and neck cancers, in a multicentric retrospective study of 3149 oral cancer patients from 11 institutions globally, showed that combining depth with pT size in a staging model outperformed the existing staging without depth, impacting disease-specific survival [63]. Incremental 5 mm increase in depth resulted in worsening prognosis. Lesions with a DOI > 1 cm placed patients in the T3 group. These findings have been accepted and incorporated in the recently published 8th edition AJCC/UICC TNM staging for oral cancer [64]. In light of this DOI greater than 10 mm now warrants adjuvant radiotherapy.

ECS is another new addition in the TNM staging system [64]. The

presence of ECS upstages disease to N2 if the node is ≤3 cm and N3 if > 3 cm. Prognostic implication of the extent of ECS needs to be further clarified. Woolgar et al found that ECS was a bad prognostic factor irrespective of whether micro or macroscopic [65]. Wreesman et al on the other hand found a cut off of 1.7 mm beyond the capsule to be associated with a worse prognosis [66]. Therefore, while ECS continues to be an indication for CRT, the recommendations are to capture the extent of ECS for future modification.

The dose recommendation for adjuvant radiotherapy is 57.6 Gy with a boost to 63 Gy to high risk groups [55]. Increasing the radiation dose beyond these levels did not result in improved outcomes and adds to toxicity. In this study, primary disease site, T stage, nerve involvement; margins and nodal status were graded in a points-scale system to place patients into low and high risk groups.

Treatment package time (TPT) defined as the date of surgery to completion of radiotherapy is another important factor affecting outcomes. Attempts should be made to ensure a TPT of less than 85–100 days, which is associated with improved outcomes [57,67].

Recurrent and metastatic oral cancers

Recurrences occur in up to 2/3rd of patients with oral cancer. These are often detected late given the fact that patients have been extensively pre-treated and identifying recurrences in this setting is difficult. Moreover, these recurrences consist of resistant clone of cells that have escaped treatment, with a detrimental effect on outcomes. Whenever possible, salvage surgery must be considered as the first choice as it gives the best chance at control and survival [68–70]. In a study by Wong et al on salvage in recurrent head and neck cancers with a significant proportion of oral cancers, there were no 5 year survivors among patients who underwent non-surgical salvage [71]. In choosing patients, it is important to triage those who would benefit from salvage surgery given that surgery in this setting is technically challenging. Disease free interval > 6–12 months, stage of presentation of index cancers (T1/T2), stage of recurrent tumour, receipt of prior adjuvant treatment, comorbidities, age, complexity of excision and availability of reconstructive options dictate the choice of patients suitable for salvage [68–70]. The recurrent tumour must be treated with the same surgical principles as a primary cancer would. Assessing margins is often difficult given the fibrotic nature of the surrounding tissues and hence it is advisable that resection margins are wider than usual. Re-radiotherapy as an adjuvant treatment following salvage surgery though associated with higher toxicity has proven advantage for DFS and must be offered whenever possible [72]. Duration since first radiotherapy, prior dosage and fields of radiotherapy, current status of local tissues and the performance status of patient post-surgery are important determinants that influence the decision of re-irradiation [68].

In patients unsuitable for salvage surgery, re-irradiation should be considered. This approach has been demonstrated in a randomized setting to be feasible with acceptable acute and late toxicities. Benefit of response is more sustained with an estimated 2-year survival of 15.2% [73]. Unfortunately, this is often not possible in the large proportion of cases due to extensive prior treatment. A randomized trial exploring the possibility of re-irradiation with chemotherapy in this setting had to be abandoned because of difficult accrual with poor outcomes [74]. Similar criteria enumerated above that determinate suitability of adjuvant re-irradiation should be followed in this setting as well.

Palliative chemotherapy is the mainstay of treatment for recurrent/metastatic tumours unsuitable for salvage surgery/re-irradiation. Chemotherapy has evolved from single agent to doublet chemotherapy of platinum plus 5FU, benefit of which has been shown in the randomized setting [75,76]. The addition of taxanes in place of platinum though feasible did not confer survival advantage [77]. The current standard of care is the addition of epidermal growth factor receptor (EGFR) monoclonal antibody to doublet chemotherapy of platinum plus 5FU. In a randomized trial comparing platinum plus 5FU 3 weekly for maximum of 6 cycles and the same chemotherapy regimen plus cetuximab there was an OS benefit with the addition of cetuximab [78]. Recently there has been an interest for the use of Programmed Death Ligand (PDL)-1 immunotherapy as second line in recurrent head and neck cancers. Nivolumab and pembrolizumab have shown benefit in OS in this setting [79–82]. Despite the promise of immunotherapy there are limitations in terms of costs and role in platinum naïve patients. Its exact role in the recurrent and metastatic setting as the first line of treatment needs to be elucidated.

Conclusion

Oral cancer is primarily treated by surgery. Early stage disease is usually treated primarily by surgery and advanced stage necessitates multimodality therapy (surgery followed by adjuvant treatment). There is a limited role of radiotherapy as the initial primary treatment. END of the node negative neck results in improved survival. Avoidance of nodal clearance in an around the SAN is possible in a subset of patients. There is a potential role of NACT in oral cancers but further trials need to establish the definite role of this approach. Salvage surgery when feasible is the best option for recurrent oral cancers. Triplet chemotherapy that includes cetuximab is the standard of care in palliative setting with proven OS benefit. There is an emerging role of immunotherapy in recurrent/metastatic oral cancers.

Conflict of interest

None declared.

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