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Current Role of Radiotherapy in the Management of Oral Cavity Squamous Cell Carcinoma

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Abstract

Study Design: Literature review.

Objective: To review the current role of radiotherapy (RT) in the management of oral cavity squamous cell carcinoma (SCC).

Methods: Review of selected literature.

Results: T1-T2N0 SCCs may be treated with either RT alone or surgery with a high likelihood of cure. The pendulum swung toward surgery with postoperative RT (PORT) added depending on the pathological findings in the mid 1980s. Patients with positive margins, extranodal extension (ENE), and/or 4 or more positive nodes receive concomitant chemotherapy (POCRT). Patients with T3-T4 and/or positive regional nodes are treated with surgery and PORT alone or POCRT. The likelihood of cure is moderate to low depending on extent of disease. The likelihood of major complications ranges from 10% to 30% depending on the method of reconstruction and the aggressiveness of postoperative PORT/POCRT. Patients with very advanced disease are treated with palliative RT, chemotherapy, or supportive care.

Conclusions: The role of RT in the management of oral cavity SCC is primarily in the postoperative setting with palliative RT being reserved for those with very advanced disease where the likelihood of cure is remote.

Keywords

head and neck, radiation therapy, otolaryngology, oral cavity, cancer outcomes

Introduction

The role of radiotherapy (RT) in the management of oral cavity squamous cell carcinoma (SCC) has evolved over the last 40 years with a shift from curative intent RT alone to surgery alone or combined with postoperative RT (PORT) in the 1980s.[1-5] The addition of concomitant chemotherapy to PORT (POCRT) was subsequently shown to improve the likelihood of cure for patients with positive margins, extranodal extension (ENE), and/or 4 or more positive nodes.[6-9] More recently, the widespread use of free flap reconstruction has impacted the treatment planning of PORT/POCRT to reduce the likelihood of complications.[10-12] Following is a review of the current role of RT in the management of oral cavity SCC.

Pretreatment Evaluation

Patients undergo a head and neck examination including nasopharyngoscopy followed by contrast enhanced computed tomography (CT) from skull base to clavicles and CT of the chest. Questionable findings on CT are further evaluated by magnetic resonance imaging (MR) and/or positron emission tomography (PET) CT. Patients are staged according to the 8th edition of the American Joint Commission on Cancer (AJCC) staging system.[13] Dentulous patients are evaluated by dentistry and, if RT is anticipated, teeth in areas likely to be included in the RT

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treatment volume are extracted if they are in poor repair.[14,15] Teeth in good repair unlikely to require extraction in the future are retained. Parenthetically, extracting teeth in good repair does not decrease the likelihood of subsequent osteoradionecrosis (ORN). Patients are presented at a Head and Neck Tumor Conference attended by head and neck surgeons, radiation oncologists, medical oncologists, neuroradiologists, and pathologists and a treatment plan is formulated and discussed with the patient and their family.

Treatment

T1-T2N0 SCCs are treated with a single modality, either surgery or RT. Surgery is usually the treatment of choice because of the fear of ORN following definitive RT. Parenthetically, those who subsequently require PORT probably have a risk of complications as high or higher than after curative intent RT alone. Patients who are not surgical candidates may be treated with RT alone. RT usually consists of combination of external beam irradiation to include the primary site and elective irradiation of the cervical lymph nodes.[16] Ipsilateral levels Ib through 4 are treated if the lesion is well lateralized, otherwise both sides of the neck are irradiated. With anterior tumors, level 1a is also included. Byers et al reported on nodal spread patterns in 277 patients with oral tongue SCC treated surgically at the M. D. Anderson Cancer Center (MDACC) and found skip metastases to levels III or IV without involvement of levels I and II in 16% of patients.[17] Oral cavity SCCs are more radioresistant than those arising in the oropharynx so it is key to give half or more of the total RT dose with brachytherapy if the primary site is suitable for an interstitial implant in order to reduce the overall treatment time.[1,2,18] A treatment schedule employed at the University of Florida (UF) is 30 Gy in 10 once daily fractions followed by 40 Gy over approximately 4 days with brachytherapy using iridium 192 and the plastic tube technique. Parenthetically, a significant drawback of definitive RT for oral cavity SCC is that most radiation oncologists have little or no experience with oral cavity brachytherapy and those who employ it do so infrequently so that it is a dying art. External beam irradiation is given with intensity modulated RT (IMRT) to create a conformal dose distribution. An intraoral stent may used to displace normal tissues, such the hard palate and upper lip, when irradiating tumors of the oral tongue and floor of mouth. Lesions close to or abutting bone, such the alveolar ridge and retromolar trigone, are not suitable for brachytherapy and are treated with external beam irradiation (EBRT). EBRT alone is less likely to be successful and altered fractionation using either hyperfractionation such 74.4 Gy in 62 twice daily fractions or the Danish schedule of 70 Gy in 35 fractions over 30 treatment days with a minimum 6 hour interfraction interval on days when patients are treated twice daily.[19] Depending on the dose per fraction, electively irradiated cervical lymphatics receive 45.6 Gy if treated with hyperfractionation and 56 Gy at 1.6 Gy per fraction if using simultaneous integrated boost (SIB). Depending on the location and extent of the tumor, proton irradiation may be considered to create a tighter dose distribution and reduce acute toxicity and the need for a temporary feeding tube which may impact long term swallowing.[20,21]

Indications for PORT may be stratified into adverse and very adverse prognostic factors. Adverse prognostic factors include close (<5 mm) margins, initially positive margins with negative final margins, perineural invasion, bone invasion, extension into the soft tissues of the neck, multiple positive nodes, and more than 5 mm of subglottic extension.[22] Nearly all T3 and all T4 SCCs will have 1 or more of these indications for PORT. Very adverse prognostic factors include positive margins, ENE, and 4 or more positive nodes. Patients with 1 or more very adverse prognostic factors are treated with POCRT.

Timing of PORT is critical. When a malignancy is treated and not completely eradicated, it may respond with accelerated repopulation making it more difficult to control. Thus, it is prudent to begin PORT as soon as the patient is adequately healed, preferably within 4 to 6 weeks of surgery.[23] It may be necessary to begin PORT before healing is complete in the occasional very high risk patient where the delay has been extensive. PORT is almost always administered with external beam RT. Patients with well lateralized primary lesions and pN0-pN2b neck disease may be treated with ipsilateral fields with a low risk of recurrence in the contralateral neck.[24] Patients with a cN0 neck who will require PORT can likely undergo resection of the primary alone and the neck irradiated in addition to the primary.[25,26] Fractionation schedules depending on margin status are: negative margins (R0), 60 Gy; positive margins (R1), 66 Gy; and gross residual disease (R2), 70 Gy. Patients treated with conventional fractionation receive 2 Gy per once daily fraction. Patients with very adverse prognostic factors may be considered for altered fractionation in addition to concomitant chemotherapy.[27] Concomitant chemotherapy usually consists of weekly cisplatin 30 to 40 mg/M2 or 2 cycles of cisplatin 100 mg/M2 every 3 weeks. There is evidence that the latter schedule is likely more effective and more toxic.[28] We prefer weekly cisplatin 30 mg/M2, particularly if altered fractionation is employed.[27,29] A problem increasingly encountered is a patient who has undergone free flap reconstruction, such as a fibular free flap (FFF), who has very adverse prognostic factors.[10] Doses more than 60 Gy may increase the risk of ORN and doses of 60 Gy or less may increase the risk of a local-regional recurrence which would likely be fatal. The choice is to avoid complex free flap reconstructions in patients likely to require POCRT doses > 60 Gy or to accept a higher risk of ORN and/or fatal local-regional recurrence.

Patients with very advanced disease and a remote chance of cure may be treated with a short course of

moderate dose palliative RT such as 30 Gy in 10 fractions over 2 weeks or 20 Gy in 2 fractions with a 1 week interfraction interval.[30] There is evidence that RT may increase tumor antigenicity and increase the likelihood of a favorable response to PDL-1 inhibitors.

Outcomes

Rodgers et al reported on 194 patients with floor of mouth SCC treated with surgery and/or RT at UF between 1964 and 1987.[31] The local control rates after RT alone were: T1, 32 of 37 (86%); T2, 25 of 36 (69%); T3, 11 of 20 (55%); and T4, 2 of 5 (40%). Complications after RT alone were: mild to moderate, 49 of 117 (42%) patients; and severe, 6 of 117 (5%) patients. Pernot et al reported on 207 patients treated with RT alone for floor of mouth SCC at the Centre Alexis Vautrin between 1976 and 1992.[32] The 5-year local control and cause specific survival (CSS) rates were: T1, 97% and 88%; T2, 72% and 47%; and T3, 51% and 36%, respectively.

Fein et al reported on 170 patients treated with RT and/or surgery for oral tongue SCC at UF between 1964 and 1990.[3] The local control rates after RT were: T1, 79% (18 patients); T2, 72% (48 patients); T3, 45% (29 patients); and T4, 0% (10 patients). Severe complications occurred in 9 (9%) of 105 patients. Pernot et al reported on the 5-year local control and overall survival rates of 448 patients treated with RT alone for oral tongue SCC at the Centre Alexis Vautrin: T1, 93% and 69%; T2, 65% and 41%; and T3, 49% and 25%, respectively.[33] The incidence of severe complications was 6%.

Nair et al reported on 234 patients treated with curative intent RT for buccal mucosa SCC in southern India in 1982 and observed the following 3-year disease free survival (DFS) rates: stage I, 85%; stage II, 63%; stage III, 41%; and stage IV, 15%.[34]

Hitchcock et al reported on 36 patients with retromolar trigone SCC treated at UF with curative intent RT between 1966 and 2013.[35] The 5-year local-regional control (LRC) rates were: stages I-III, 52%; and IV, 46%. When compared with 74 patients treated with surgery and PORT, patients treated curative intent RT had a significantly lower likelihood of cure ($p = 0.041$).

Hinerman et al reported on 226 patients with oral cavity SCCs treated at UF with continuous course PORT between 1964 and 2000; all patients had a potential 2-year minimum followup and no patients were lost to followup.[36] The 5-year LRC rates by pathologic stage were: I, 100%; II, 84%; III, 78%; and IV, 66%, respectively. The 5-year LRC rate for 68 patients with positive margins was 65% for 32 patients who received hyperfractionation to 74.4 Gy or more compared to 40% for 36 patients who received less than 74.4 Gy and/or were treated with other fractionation schedules ($p = 0.0477$). The 5-year distant metastasis free survival (DMFS) rates by pathologic stage were: I, 100%; II, 97%; III, 90%; and IV, 81%. The 5-year CSS rates by pathologic stage were: I, 100%; II, 91%; III, 72%; and IV, 58%. The 5-year overall survival (OS) rates by pathologic stage were: I, 63%; II, 70%; III, 48%; and IV, 40%. There were 33 (15%) severe complications including: ORN, 14; permanent gastrostomy, 7; wound dehiscence, 4; fistula, 3; soft tissue necrosis, 2; wound infection, 1; mandibular fracture, 1; and plate extrusion, 1.

Herman et al reported on 139 patients with oral cavity SCC treated at UF with PORT (116) or POCRT (23) between 1989 and 2010.[27] All patients were thought to be at very high risk for local regional recurrence based on positive margins (52%), close margins less than 5 mm (27%), and/ or ENE (45%). Median followup was 2.3 years (range, 0.1 to 16.7 years). Minimum followup for survivors was 2 years with the exception of 1 disease free patient who was lost to followup after 2 months. The 5-year outcomes were: LRC, 64%; DMFS, 85%; CSS, 51%; and OS, 36%. The combination of close/positive margins and ENE resulted in significantly worse outcomes compared with a single high risk indication: LRC, 37% vs 70% ($p < 0.001$); progression free survival (PFS), 26% vs 60% ($p < 0.001$); and OS, 13% vs 43% ($p < 0.001$). Treatment complications were graded according to the common terminology criteria for adverse events (CTCAE) version 4.03. Grade 3 or higher complications were observed in 25 patients (18%) including ORN in 15 (11%).

Dziegielewski et al reported on 74 patients who underwent osseous free flap reconstruction; 38 competed PORT.[10] Patients were followed for 6 months or more. The incidence of ORN was 0 for 28 patients who did not receive PORT. For those who received PORT, the rates of ORN were: 50-59.9 Gy, 0%; 60 Gy, 8%; 66 Gy, 40%; and 70 to 74.4 Gy, 56%. Mean time to ORN was 13.1 months. Multivariate analysis showed that the only variable significantly associated with ORN was PORT with doses exceeding 60 Gy.

Conclusion

Curative intent RT results in good outcomes in patients with stage I and II SCC of the oral cavity with a relatively low risk of complications. A significant drawback is that brachytherapy is necessary to optimize local control in patients with SCCs suitable for the procedure and few radiation oncologists have the expertise. PORT significantly improves LRC for patients at high risk for recurrence after surgery. The dominant mode of failure after PORT or POCRT is local-regional. It is likely that higher doses and altered fractionation improve the likelihood of LRC at the cost of increased complications, particularly for patients who have undergone osseous free flap reconstructions. Patients with very advanced disease and a remote chance of cure may benefit from a short course of moderate dose palliative RT.

Declaration of Conflicting Interests

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