Chemotherapy for Oral and Maxillofacial Tumors: An Update

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KEYWORDS

• Chemotherapy • Locally advanced • Maxillofacial tumors • Oral cavity tumors
• Squamous cell carcinoma

KEY POINTS

- Surgery has always been the primary intervention in oral and maxillofacial tumors and under ideal circumstances is curative.
- Squamous cell carcinoma is by far the most common histologic subtype of head and neck tumors, including oral and maxillofacial tumors. Therefore, the results of chemotherapy trials for head and neck cancer are likely to be applicable to oral and maxillofacial cancers too, despite the lack of studies on these tumors specifically.
- There is no evidence to support the use of induction or adjuvant chemotherapy in the initial therapy of early-stage oral and maxillofacial tumors.
- Locally advanced tumors, nonresectable tumors, as well as recurrence in early-stage disease need a multimodality therapeutic approach involving chemotherapy.
- Palliative chemotherapy plays an important role in the treatment of patients with metastatic oral and maxillofacial tumors.
- Chemotherapy and targeted agents play an important role in the treatment of patients with rare oral and maxillofacial tumors, such as sarcomas, lymphomas, and giant cell tumors.

There will be more than approximately 25,000 new cases of oral cavity tumors involving the mouth and tongue in 2013 according to the American Cancer Society.[1] Early-stage oral and maxillofacial tumors—those that are less than or equal to 4 cm in greatest diameter and that do not invade surrounding structures or involve lymph nodes—account for 30% to 40% of these tumors and are usually treated with either surgery or radiation alone; this patient group has a 5-year overall survival (OS) rate exceeding 80%. Roughly 50% of patients present with locally advanced disease, which requires a multimodal approach. The remaining 10% to 20% of patients present with recurrent or metastatic disease with a 5-year survival rate dropping to less than 30%, and therapy is considered only palliative.[2]

Squamous cell carcinoma (SCC) is by far the most common histologic subtype of head and neck tumors, including oral and maxillofacial tumors. Therefore, the results of chemotherapy trials for head and neck cancer are likely to be applicable to oral and maxillofacial cancers too, despite the lack of studies on these tumors specifically. The focus of this article is to review the role of chemotherapy in the treatment of these

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complex cancers including rare oral and maxillofacial tumors, such as sarcomas, lymphomas, and giant cell tumors. The current recommendations are reviewed and new modalities are explored. A shared understanding of what is available today and perhaps in the near future will allow surgeons and medical and radiation oncologists to provide the best care for their patients.

CHEMOTHERAPY FOR EARLY-STAGE DISEASE

There is no evidence to support the use of induction or adjuvant chemotherapy as part of the initial management of these patients. These tumors are treated with surgery or radiation alone, which is often curative.

CHEMOTHERAPY FOR LOCALLY ADVANCED RESECTABLE DISEASE

Role of Neoadjuvant Chemotherapy

For locally advanced resectable tumors, only one-half of these patients are cured using surgery or radiation alone.[3] There has thus been interest in neoadjuvant and adjuvant chemotherapy to reduce these recurrences. A 2003 study of 195 patients by Licitra and colleagues[4] was randomized to receive 3 cycles of cisplatin and fluorouracil (5-FU) followed by surgery or surgery alone for resectable, early-stage (T2-T4) SCCs of the oral cavity. The 5-year OS rate did not differ significantly between the 2 arms. However, those who received neoadjuvant chemotherapy were less likely to need mandibulectomy and/or radiation.

In a more recent study, Zhong and colleagues[5] conducted a randomized phase III trial to investigate whether 2 cycles of induction docetaxel, cisplatin, and 5-FU followed by surgery and postoperative radiation were superior to surgery alone followed by postoperative radiation in patients with resectable stage III/IVA oral SCCs. Although the 2 arms did not differ significantly in OS, the induction therapy arm did show a nonsignificant trend toward a lower incidence of distant metastasis than the other arm, which was not the primary end point of the trial. Patients who received induction chemotherapy and had a favorable pathologic or clinical response had a decreased risk for death and recurrence compared with the surgery followed by postoperative radiation arm. In addition, a lower risk for death and longer distant metastasis-free survival was observed in clinical N2 patients treated with induction chemotherapy compared with the surgery followed by postoperative radiation arm. Although these trials did not focus specifically on oral and maxillofacial tumors, their findings regarding induction chemotherapy are generally disappointing.

Role of Adjuvant Chemotherapy

The risk of recurrence after resection is significantly greater if the resected specimen reveals tumor cells extending beyond the lymph node capsule or capules (ie, extracapsular extension [ECE]) or positive resection margins.[6]

In these situations, adding adjuvant chemotherapy concurrently with radiation therapy after surgical resection has been shown to improve treatment outcomes. In a 2004 study by Bernier and colleagues,[7] patients with risk factors for recurrence who had undergone resection and had no distant metastasis randomly received either concurrent radiation (66 Gy over a period of 6.5 weeks) therapy and cisplatin (100 mg/m^2 on days 1, 22, and 43 after resection) or the same radiation therapy alone. The median progression-free survival (PFS) was superior for the combined approach, particularly in patients who had positive margins and/or ECE: 55 months, compared with 23 months for radiation alone. However, the addition of cisplatin did not benefit patients whose tumors had vascular emboli or perineural invasion, or those who had local spread to 2 or more lymph nodes.

CHEMOTHERAPY FOR LOCALLY ADVANCED UNRESECTABLE DISEASE

The goal of chemotherapy in patients with locally advanced oral and maxillofacial cancers is to shrink the tumor sufficiently to enable surgical resection or to treat those that do not qualify for surgery at all.

Induction Chemotherapy Before Radiation Versus Radiation

Studies have shown the benefits of platinum-based induction chemotherapy in SCC in locally advanced unresectable disease. Paccagnella and colleagues[8] showed that patients with either stage III or IV SCC tumors without distant metastatic disease who were not candidates for surgery had a 21% OS rate at 5 years when they underwent 4 cycles of neoadjuvant cisplatin and 5-FU followed by radiotherapy as opposed to an 8% OS rate in similar patients who received radiotherapy alone. The participants of the study who were deemed resectable after treatment and underwent surgical resection did not have any survival benefit with the addition of chemotherapy.