Chemotherapy in Locally Advanced Squamous Cell Carcinoma of Oral Cavity

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Introduction

Oral cavity cancers comprise approximately 25% of head and neck primaries.[1)]

According to evaluation of 556 oral cavity cancers in Norway, the subsite distribution was 40% tongue, 24% gingival, 23% floor of mouth, and 13% other. The stage distribution was 23.2% stage I, 21.2% stage II, 11.2% stage III, 39.7% stage IVA, 4% stage IVB, and 0.7%stage IVC.[2)] Standard treatment for advanced oral cavity cancer consists of a multidisciplinary approach, including surgery and radiation therapy. However, survival is unsatisfactory, because only less than 50% of these patients are cured.[3)]

The addition of chemotherapy has not proved effective and the combination of chemotherapy and radiotherapy has been reserved for patients with unresectable disease or patients who refuse surgery. The studies evaluating role of chemotherapy in oral cavity cancers are rare. Only few studies have been dedicated solely to patients with oral cavity cancers. To review available data can provide important guidance as to the use of chemotherapy in this setting.

Induction Chemotherapy before Surgery.

Induction chemotherapy before definitive local therapy has been persued with the goal of downsizing of tumors, decreasing distant metastasis, and increasing survival.

Licitra et al. reported randomized phase III trials evaluating role of induction chemotherapy before surgery in resectable oral cavity squamous cell carcinoma.[4)]

Patients were randomly assigned to three cycles of cisplatin and 5-FU followed by surgery or surgery alone. In both arms, postoperative radiotherapy was reserved to high-risk patients. 195 patients were enrolled during 10 years (1989−1999). The primary endpoint of study was the occurrence of local-regional or distant tumor relapse. A clinical complete response was 27% and a total of 82% objective response rate were noted treated with chemotherapy. Postoperative radiotherapy was administered in 33% of patients in the chemotherapy arm, versus 46% in the surgery arm. A mandible resection was performed in 52% in chemotherapy arm, 31% in surgery arm. In both arm, locoregional and distant relapse were not different.

Overall 5-year event-free survival revealed different trend (57% vs 46%) but 5-year overall survival was not different (for both arm, 55%). The authors concluded that induction chemotherapy did not improve long-term outcome. However, it may allow less aggressive surgery and spare radiotherapy to the oral cavity cancer patients.

Grau et al conducted prospective phase II trial evaluating the role of induction chemotherapy for patients with resectable or unresectable locally advanced oral cavity cancer.[5)] The primary endpoints were response to induction chemotherapy, local control, and survival. 135 out of 204 (66%) patients were responded (16%, CR and 50%, PR). After induction chemotherapy, 34 out of 46 patients considered inoperable initially (74%) obtained a disease-free status with surgery. 83% of surgical patients obtained a disease-free status versus 72% of radiation therapy patients. Disease-free survival rates at 5 years were 26% and 22%, respectively.

Ruggeri et al reported the results of 33 operable patients with locally advanced oral cavity cancer treated with cisplatin-based chemotherapy before surgery.[6)] The overall clinical and pathologic complete response were 48% and 30%, respectively.

The overall 5-year and 10-year survival were 54.5% and 39.5%, respectively. Patients who showed complete response to induction therapy had a significant increase in survival compared with patients who failed to achieve complete response ($p=0.05$).

Concurrent Chemoradiation

Some investigators have evaluated the role of concurrent chemoradiation for the organ preservation of oral cavity cancer.

Fuchihara et al. evaluated the role of concurrent chemoradiation using bleomycin or peplomycin in patients with resectable squamous cell carcinomas of the lower gingiva.[7] The patients with advanced stage tumor showed 35% complete response rate and patients who failed to achieve a complete remission went on to surgical salvage. Disease-specific 5-year survival rate was 71% for stage III, and 51% for stage IV. The complete response rate is substantially lower than would be expected and the reason is probably relation with the agents used.

Urba et al. conducted a clinical trial in patients with advanced resectable oral cavity cancers using induction chemotherapy as a marker of responsiveness.[8] Patients treated one cycle of cisplatin and 5-FU. Responders were to conduct to concurrent chemoradiation with salvage surgery and non-responders were to conduct to direct salvage surgery. Nine of evaluable 16 patients showed response to therapy and conducted to concurrent chemoradiation. Of the 9 patients, 6 had a complete remission. The 3-year survival rate was 47%, and the disease-specific survival rate was 68%.

Harrison et al reported the results of a phase II trial of 82 patients with unresectable disease.[9] 3-year survival rate for patients with oral cavity cancers was worse than other site (0 vs 47% ; $p=0.03$).

The RTOG trial that conducted concurrent chemoradiation with cisplatin for patients with unresectable disease showed lower complete response rate in oral cavity cancers rather than other sites (56% oral cavity, 74% oropharynx, 82% nasopharynx, 75% larynx, 37% hypopharynx).[10]

Oral cavity cancer patients have been included the phase III trials to evaluate the role of concurrent chemoradition in patients unresectable disease. Most of those phase III trial showed that concurrent chemoradiation improved overall survival. So concurrent chemoradiation should be considered standard of care for patients with unresectable oral cavity cancers.

Postoperative Chemoradiation

Two randomized clinical trials compared postoperative radiation with postoperative concurrent chemoradiation in high-risk patients. Oral cavity primary patients were included to both clinical trials. Primary site was one of stratification factor in RTOG trial; thus nearly equal number of patients with oral cavity primary were included in both arm (30% vs 20%). Neither study reported comparative results specifically for oral cavity cancer. So postoperative chemoradiation could be recommended to patients with high-risk recurrence based on two large randomized trials.

Conclusions

It is acceptable that the patients with unresectable disease and postoperative high-risk disease can be treated with concurrent chemoradiation. Oral cavity cancers are unique with regard to response and treatment-related sequele which makes extrapolation of data from other head and neck sites to oral cavity cancers problematic. To clarify the exact role of concurrent chemoradiation in patients with oral cavity cancers, conducting phase III trials including oral cavity primaries only will be mandatory.

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