

What is the way forward for unresectable oral cavity cancers among Indian patients?

A R0 resection remains the cornerstone of management of squamous cell carcinomas of the oral cavity cancers (OCC),^[1] given that less than 1/3rd of patients with advanced OCC treated with nonsurgical modalities remain locoregionally controlled at 3 years.^[2] In this setting, the results of a large retrospective study employing neoadjuvant chemotherapy for unresectable advanced OCC, need careful scrutiny.^[3] The authors have reported an R0 resection rate of 40% after 2–3 cycles of neoadjuvant chemotherapy in OCC, which were deemed unresectable at presentation and an encouraging 2 years locoregional control rate of 32%.^[3]

The strategy of utilizing neoadjuvant chemotherapy for tumor downstaging and allowing a surgical resection is novel. The authors deemed patients as unresectable based on criteria, which if present, result in an unacceptably morbid R0 resection upfront.^[4] While most of these criteria have been evolved over a period based on the experience of the surgical team at the institute,^[5] some have support from the literature. For example, Liao *et al.* have shown that in disease extension above the sigmoid notch was associated with a significantly inferior 5 years disease-free survival of 14% compared with 64.7% in patients in whom the disease was localized below the sigmoid notch.^[6]

Despite the encouraging response rate, the toxicity of this form of treatment can be substantial. Despite the use of granulocyte-colony-stimulating factor prophylaxis, Grade III or more toxicities, are reported in nearly half of the treated patients in Indian series.^[4,7] Among the neoadjuvant schedules employed in the study, triplet chemotherapy while being most active, was associated with life-threatening toxicities in nearly 1/3rd of the patient population.^[4] Moreover as data from Mumbai show, patients who are both fit and can afford to undergo triplet neoadjuvant chemotherapy, account for only 10% of the patient population.^[3]

In the remaining 90% of the patient population, only 40% became resectable with the use of doublet chemotherapy. This finding is an indicator of the underlying heterogeneity in biological response as well as the need to test new strategies that such compromised patients will tolerate. Preoperative chemoradiotherapy is one such option, with Freier *et al.* reporting a response rate of 82.6% and a 5 years overall survival of 57% in OCC treated with preoperative radiotherapy to a dose of 40 Gy and concurrent chemotherapy with low dose cisplatin 12.5 mg/m² D1-D5.^[8] Use of lower doses of radiation due to concerns regarding wound healing, along with an impaired ability to deliver of adjuvant radiation have diminished the interest in preoperative radiotherapy in head-neck cancers.^[9] However, recent improvements

in conformal radiation techniques as well as use of free flap reconstruction techniques may allow safe use of preoperative radiation in this setting.^[10]

Hopefully, the results of this large study will encourage Indian researchers to investigate novel preoperative strategies. In future trials, in this setting, the criteria for unresectability need to be defined better, especially as some of the criteria like diffuse peritumoral edema are highly subjective and difficult to validate.^[3] A study of underlying biological pathways determining resistance to treatment is also imperative, with the aim to tailor the intensity, as well as nature of preoperative treatment to the disease biology. However, Patil *et al.* could treat over 700 patients within a short time span of 4 years,^[3] indicating that patient numbers are not an area of concern when such randomized trials are conducted.

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