Editorial Article

Neoadjuvant Chemotherapy in Technically Unresectable Oral Cavity Cancers - Are We Heading Towards Paradigm Shift?

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Oral squamous cell carcinoma (OSCC) constitutes a significant proportion (30%) of cancers in India1 and as per GLOBOCAN data 2020, are the second most common cancers in India and are about 10.3% of all cancers worldwide2. Advanced stage OSCC constitutes 70 to 90% of all the cases. The treatment approach is multimodality (surgery, radiation therapy, systemic therapy and various combinations) and is dependent on various factors like diseases stage, surgical skills, patient's age and performance status. In resectable diseases (T1-T4a), surgery is a favorable option, although radical radiotherapy may be used in some cases. But for technically unresectable (T4b) tumors radical radiotherapy with or without chemotherapy is the preferred approach, but questions have been raised for such approach recently by some authors who observed favorable outcomes with surgery.3-6 As per NCCN guidelines presently non-surgical treatment is advised for OSCC involving masticator space (Overall Survival 6.68 months).5 But Patil et al7 showed 43% response rate to neoadjuvant chemotherapy (NACT) and overall survival of 47% with surgery and 20% without surgical intervention, thus highlighting the importance of surgery in technically unresectable OSCC.

Although NACT seems to have a beneficial role in borderline/technically unresectable oral cavity cancers8 its role is yet to be realized fully. NACT is also useful in selected resectable OSCC9, offering us

organ preservation approach and giving improved locoregional control (LRC) and overall survival (OS). Thus, NACT in both borderline unresectable and resectable OSCC offers us an exciting area of research in future. There are some potential benefits of NACT in technically unresectable oral cavity cancers like enabling tumor shrinkage, significant pathological stage migration10 and reduced surgical margins, optimizing delivery of drugs through intact vasculature, reducing distant metastasis, assessing tumor responsiveness11 and help in achieving R0 resection, thereby improving DFS and OS12.

In order to define benefit of NACT in OSCC two RCT's were done, Licitra et al9 and Zhong et al13. The meta-analysis of these two RCT's by Marta et al14, with a pooled data of 451 patients reflected the findings of these two trials. A critical evaluation of this meta-analysis shows that majority of the patients were T1-T3. Patients with T4 OSCC were < 20% in both the trials. Thus, a significant fraction of patients actually belonged to the category of operable oral cancers and this might have resulted in the absence of any survival benefit with NACT. A more stringent selection criterion along with larger sample size might have given us a different result12.

Patil et al7 have tried to solve this problem by defining robust indications of NACT in technically unresectable cases:

1. Buccal mucosa primary, with diffuse margins and peritumoral edema going up to or above the level of zygomatic arch and without any satellite nodules.
2. Tongue primary {anterior 2/3rds} with the tumor extending up to or below the level of the hyoid bone.
3. Extension of tumor of anterior two third of oral tongue to the vallecula.
4. Extension of tumor into the high infratemporal fossa, as defined by the extension of tumor above an axial plane passing at the level of the sigmoid notch.
5. Extensive skin infiltration impacting the achievement of negative margins.

Another roadblock encountered is lack of global consensus over sub classification for T4b which has resulted in difficulty to define outcomes of surgery and proper patient selection for planning studies at large scale. Recently Trivedi et al10 have tried to bridge the gap by proposing a classification system for T4b OSCC, by dividing it into following three classes:

Class-I: involvement of any of the following structures below the sigmoid notch-masseter and medial pterygoid (lower masticatory space, infra-notch)

Class-II: involvement of lateral pterygoid, temporalis above the sigmoid notch (intermediate masticatory space, low supra-notch)

Class III: involvement of pterygomaxillary fissure, inferior orbital fissure and intracranial space (high-masticatory space, high supra-notch)

For T4b tumors surgery is technically challenging, leading to triaging many of these patients to non-surgical modalities but Pillai et al7 showed an encouraging incidence of only 3.2% positive margins even when they included supra-notch tumors (Class II and Class III), with OS and DFS of 59.9% and 61.0% respectively. Similar motivating results were shown by Liao et al3 and Mair et al5 and have emphasized the importance of achieving negative surgical margins when choosing surgery as primary treatment modality. Although, in both these studies, concept of assuming the entire masticatory component as one unit needs to be reconsidered. The oncological outcome of class III is poorer than class I and II which resembles the outcome of T4a disease.

Thiagarajan et al12 showed that NACT prolonged both OS and DFS in T4b OSCC. In this study there was improvement in DFS among patients with cT4b OSCC receiving NACT prior to surgery. It suggested a trend towards better DFS among patients with skin involvement and oral tongue primary receiving NACT prior to surgery. Patients with bone involvement [HR 0.64 (95% CI 0.39–1.07)] showed a trend favoring upfront surgery. For overall survival, patients with cT4b OSCC receiving NACT prior to surgery showed favorable results consistently [HR 5.2 (95% CI 1.39–19.36)]. Upfront surgery offered better OS for patients with cT4a OSCC [HR 0.49 (95%CI 0.33–0.77)].

As per MACH-NC metanalysis induction chemotherapy has pronounced effect on reduction of distant metastasis compared to concomitant chemotherapy and established the superiority of three drug regime over two drug regimes15. Same results were corroborated by TAX 32316 and 32417 studies.

There are still some unanswered questions with respect to NACT followed surgery like optimal number of chemotherapy cycles, appropriate response assessment, proper selection of chemotherapy agents and incorporation of targeted therapy and biomarker-based chemotherapy in NACT treatment protocols. To answer all these questions, we need to perform well designed randomized prospective studies to quench the academic and clinical thirst of these vital questions related to OSCC management in technically unresectable cases.

REFERENCES:

1.Sankaranarayanan R. Oral cancer in India: An epidemiologic and clinical review. Oral Surg Oral Med Oral Pathol 1990;69:325-330

2. Gco.Iarc.Fr, 2021, https://gco.iarc.fr/today/data/factsheets/populations/356-india-fact-sheets.pdf.

3. Liao CT, Chang JT, Wang HM, Ng SH, Hsueh C, Lee LY, et al. Surgical outcomes of T4a and resected T4b oral cavity cancer. Cancer 2006;107:337–44.

4. Liao CT, Ng HS, Chang JT, Wang HM, Hsueh C, Lee LY, et al. T4b oral cavity cancer below the mandibular notch is resectable with a favourable outcome. Oral Oncol 2007;43:570–9.

5. Mair MD, Sawarkar N, Nikam S, Sarin R, Nair D, Gupta T, et al. Impact of radical treatments on survival in locally advanced T4a and T4b buccal mucosa cancers : Selected surgically treated T4b cancers have similar control rates as T4a. Oral Oncol 2018;82:17–22.

6. Trivedi NP, Kekatpure V, Kuriakose MA. Radical (compartment) resection for advanced buccal cancer involving masticator space (T4b): our experience in 30 patients. Clin Otolaryngol 2012;37:477–83

7. Patil VM, Prabhash K, Noronha V, Joshi A, Muddu V, Dhumal S, Arya S, Juvekar S, Chaturvedi P, Chaukar D, Pai P, Kane S, Patil A, Agarwal JP, Ghosh-Lashkar S, Dcruz A. Neoadjuvant chemotherapy followed by surgery in very locally advanced technically unresectable oral cavity cancers. Oral Oncol. 2014 Oct;50(10):1000-4.

8. Goel A, Singla A, Prabhash K. Neoadjuvant chemotherapy in oral cancer: Current status and future possibilities. CancerRes Stat Treat 2020;3:51-9

9. Licitra L, Grandi C, Guzzo M, Mariani L, Lo Vullo S, Valvo F, et al. Primary chemotherapy in resectable oral cavity squamous cell cancer:A randomized controlled trial. J Clin Oncol 2003; 21:327-33.

10. Pillai V, Yadav V, Kekatpure V, Trivedi N, Chandrashekar NH, Shetty V, et al. Prognostic determinants of locally advanced buccal mucosa cancer: Do we need to relook the current staging criteria? Oral Oncol 2019;95:43-51.

11. Pointreau Y, Atean I, Fayette J, Calais G, Lefebvre JL. Induction chemotherapy in head and neck cancer: a new paradigm. Anticancer Drugs. 2011 Aug;22(7):613-20.

12. Thiagarajan S, Dhar H, Bhattacharjee A, Fatehi KS, Shah SB, Chaukar D, Nair D, Deshmukh A, Prabhash K, Joshi A, Patil V, Noronha V, Laskar SG, Cruz AKD. Patterns of failure and outcomes in cT4 Oral squamous cell carcinoma (OSCC) undergoing upfront surgery in comparison to Neo-Adjuvant

Chemotherapy (NACT) followed by surgery: A Matched Pair analysis. Oral Oncol. 2020 Jan;100:104455

13. Sun Y, Li WF, Chen NY, Zhang N, Hu GQ, Xie FY, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. Lancet Oncol 2016;17(11):1509–20.

14. Marta GN, Riera R, Bossi P, Zhong L, Licitra L, Macedo CR, et al. Induction chemotherapy prior to surgery with or without postoperative radiotherapy for oral cavity cancer patients: Systemic review and meta-analysis. Eur J Cancer 2015;51(17):2596-603.

15. Pignon JP, le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol. 2009 Jul;92(1):4-14

16. Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, Stewart JS, Jelic S, Betka J, Preiss JH, van den Weyngaert D, Awada A, Cupissol D, Kienzer HR, Rey A, Desaunois I, Bernier J, Lefebvre JL; EORTC 24971/TAX 323 Study Group. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med. 2007 Oct 25;357(17):1695-704.

17. Lorch JH, Goloubeva O, Haddad RI, Cullen K, Sarlis N, Tishler R, Tan M, Fasciano J, Sammartino DE, Posner MR; TAX 324 Study Group. Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomised phase 3 trial. Lancet Oncol. 2011 Feb;12(2):153-9

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