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LOCALLY ADVANCED UNRESECTABLE CANCER OF THE UPPER RIGHT ALVEOLUS: A CASE REPORT

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ABSTRACT

Background: Locally advanced oral cancers are very common as most of the patients report late to seek treatment. The overall 5-year survival is about 50%. Many treatment modalities have been employed such as surgery, radiotherapy, chemotherapy, chemoradiotherapy and others. However, there is still a need to search for the most appropriate therapeutic options that can further increase the patients' survival. **Objective:** The manuscript discussed various advances available in treatment of locally advanced oral cancer. **Methods:** Here we present the case of a 41-year-old male patient of locally advanced oral squamous cell carcinoma of the right upper alveolus. **Results:** Our patient underwent neoadjuvant chemotherapy followed by concurrent chemoradiotherapy followed by surgery. **Discussion:** We discuss various modalities of management available in treatment of locally advanced with emerging novel therapies to existing. **Conclusions:** Management of locally advanced oral cancer requires a multidisciplinary team approach.

KEYWORDS: Oral cancer, locally advanced.

INTRODUCTION

Head and neck cancers (HNCs) are heterogeneous tumors which include oral cavity, oropharynx, hypopharynx, larynx and several other subregions. Head and neck squamous cell carcinoma (HNSCC) is the most common type of HNC and accounts for approximately 3% of new cancer cases and 3% of deaths worldwide. Approximately 30%–40% of HNSCC patients have early-stage disease (phase I/II) at diagnosis and are usually cured by surgery or radiotherapy (RT) alone, while more than 60% of HNSCC patients are initially diagnosed as locally advanced (LA) and are treated by surgery combined with post-operative(chemo)radiotherapy.[1,2]

There have been major modifications in the 8th edition. These were changes in the T category for oral cavity cancer by incorporating depth of invasion of the primary tumor; inclusion of extranodal extension (ENE) in N staging except in p16+ oropharynx cancer and nasopharynx cancer.[3] Here we present a case of locally advanced squamous cell carcinoma (OSCC) of the upper right alveolus.

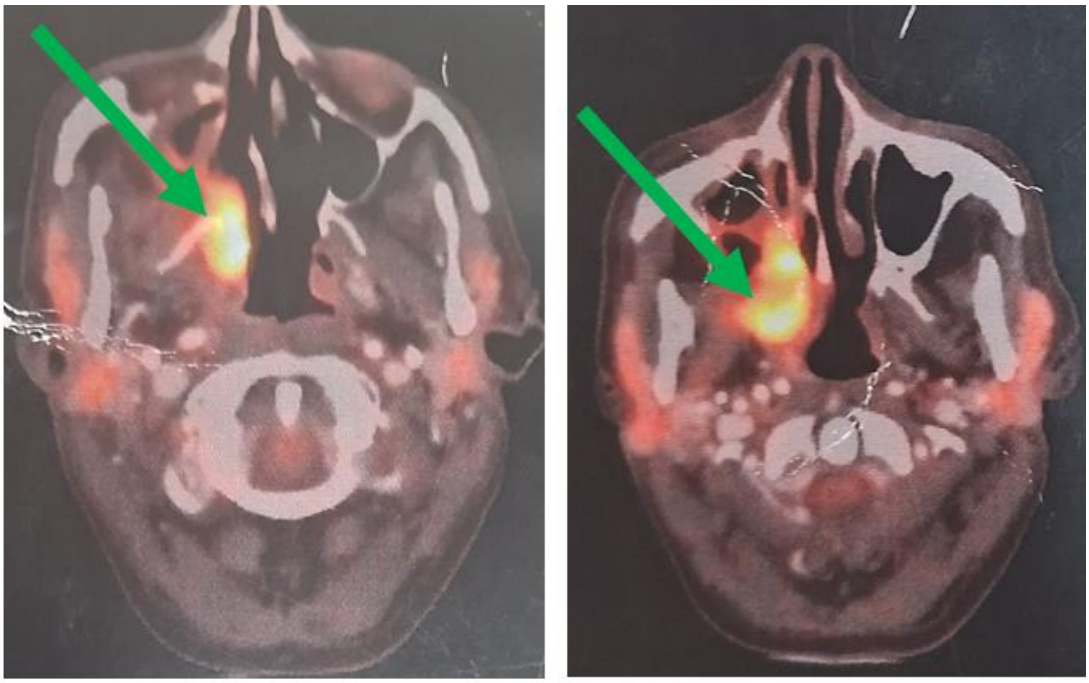
T4 was reclassified as T4a- Moderately advanced Local disease and T4b -as very advanced local disease. Thus, these tumors can be operable or deemed inoperable. T4 cancers contribute to greater than 80% of cases with margin positivity. Advanced oral can be subdivided as resectable, borderline rescetable or Unresectable. Complete surgical resection with negative margins is the most appropriate treatment. Adequate resection is defined as clear resection margins i.e. enough clearance from the gross tumor to obtain clear frozen section and permanent margins. Often 1.0–1.5 cm of visible and palpable normal mucosa is considered as adequate.

Multidisciplinary evaluation, integration of disciplines involved in patient care, the surgical procedure, margins, and reconstructive plan should be developed prior treatment.

CASE PRESENTATION

A 41 years old male presented to us with a complaint of swelling on the upper right alveolus. Biopsy from the region revealed moderately differentiated OSCC. He underwent 3 cycles of neoadjuvant paclitaxel plus carboplatin outside as neoadjuvant chemotherapy (NACT). No baseline imaging was available. CECT face revealed ill-defined heterogeneously enhancing mass lesion in the right sphenopalatine fossa with bony erosion/destruction of posterolateral and medial wall of right maxillary sinus. It was abutting the inferior aspect of right temporalis muscle with loss of fat planes, superiorly extending into the right nasal cavity including inferior, middle and superior meatus and causing destruction of conchae. Mass lesion was extending into the ethmoid sinus with erosion of the right orbit and lamina papyracea. Posteriorly it was causing destruction of the right pterygoid process and infiltrated pterygoid muscles. It was also infiltrating right retromolar trigone.

Since the lesion was unresectable, the patient was administered concurrent cisplatin chemoradiotherapy with SIB–IMRT to a total dose of 66Gy in 30 fractions. Follow up clinical assessment was suggestive of residual disease. He underwent FDG PET/CT which revealed metabolically active ill-defined soft tissue density thickening like mass lesion arising from right upper alveolus involving right maxilla and maxillary sinus, adjacent palatal arch, right side of hard palate, right pterygoid plates, right pterygoid muscle and right side of nasopharynx measuring 4.0 x 2.1 x 4.5 cm(SUV max 10.1) along with multiple active neck nodes seen in right highest cervical, right submandibular and bilateral upper deep cervical region (Figure 1).



1a 1b

Figure 1: PETCT lesion with its extensions noted, 1a: destruction of the right pterygoid process and infiltrated pterygoid muscles, 1b: extending into the right nasal cavity including inferior, middle, and superior meatus and causing destruction of conchae.

Biopsy from right submandibular lymph node revealed metastatic OSCC with foreign body giant cell reaction. The lesion became borderline resectable and hence the patient underwent composite resection with comprehensive neck dissection and microvascular flap reconstruction. Postoperative histopathology report described two lymph nodes as positive with minor ENE. Also, medullary bone of the maxilla was involved by tumor. pTNM staging was ypT4aN2a.

DISCUSSION

Locally advanced oral cavity cancers are classified as moderately advanced local disease(T4a) and very advanced local disease(T4b).[3] The overall 5-year survival for the advanced stages is about 50%. Patients frequently develop relapse at the primary site, distant metastases and second primary tumours.[2] Resectability is decided primarily by the involvement of anatomical landmarks on clinical examination and on imaging. Some of the absolute contraindications to surgery are extension of the tumour to the base of the skull, prevertebral muscles and encasement or invasion of the carotid artery. However, involvement of other anatomical landmarks as mentioned by Patil et al. can limit the extent of surgery and make achievement of clear margins difficult. Such tumours may be labelled technically unresectable. Patel et al had grouped the locally advanced oral cavity cancers with the features depicted in Table 1 as technically unresectable.

Table 1: Technically unresectable tumours[4]

Technically unresectable tumors[4]
Buccal mucosa primary, with diffuse margins and peritumoral edema going up to or above the level of zygomatic arch and without any satellite nodules.
Tongue primary {anterior 2/3rds} with the tumour extending up to or below the level of the hyoid bone
Extension of tumour of anterior two third of oral tongue to the vallecula.

Extension of tumour into the high infratemporal fossa, as defined by the extension of tumour above an axial plane passing at the level of the sigmoid notch.
Extensive skin infiltration impacting the achievement of negative margins

These patients are suitable for NACT, and the choice of regimens was decided on the patients' performance status, creatinine clearance as calculated by the Cockroft–Gault formula, financial constraints and patient preference. There can also be patients with frank skull base invasion, prevertebral fascia involvement, carotid encasement, and these are considered inoperable.[4] Our patient was initially a case of unresectable OSCC, who had undergone NACT outside. He further underwent concurrent chemoradiotherapy (CCRT) at our institute, because of which the tumor regressed, and became borderline resectable, and hence resected by surgery.

The National Cancer Database (NCDB), which is a hospital-based registry and is a joint project of the Commission on Cancer evaluated 6900 patients with locally advanced OSCC. They compared the difference in survival between patients treated with surgery followed by postoperative radiotherapy (PORT) vs CCRT. Surgery+PORT was associated with improved survival of all patients.[5] As far as the treatment with radiotherapy alone is concerned, there is no strong evidence to support this approach to treat patients suffering from unresectable oral cancer. Use of external beam radiotherapy (EBRT) 50 Gy plus chemotherapy with cisplatin followed by high dose rate brachytherapy (HDR-BT) Gy has reported a complete response of 77.2%. Overall, this approach seems to be effective in treating patients with unresectable oral cancer, but more research about it is needed. CCRT followed by brachytherapy seems to be effective to treat patients with unresectable oral cancer, but more research about it is required.[6] In our patient, CCRT with SIB–IMRT to a total dose of 66Gy in 30 fractions was administered. SIB-IMRT is safe and can be used with concomitant chemotherapy/biotherapy in real-life daily clinical practice. SIB-IMRT alone is a valid alternative in patients unfit for systemic therapies.[7] Further intensifying CCRT, using hyperfractionated radiotherapy with concomitant chemotherapy could improve outcomes over CCRT for the treatment of locally advanced head and neck cancer. This treatment can be difficult to implement in daily practice, but could be suitable for the treatment of HPV-negative head and neck cancers.[8]

Benefits of NACT are to shrink the tumor, decrease the chances of distant metastases, increase the chances of organ preservation, and improve the outcomes such as overall survival and progression free survival. CCRT improves the chances of locoregional control, overall survival rates, and organ-preserving intent. Moreover, chemotherapy given as part of CCRT could act systemically and possibly prevent distant metastases and also improves function and cosmetic outcomes compared with surgical approaches. The chemotherapy part of the CCRT consists of platinum-based chemotherapy, most often single agent cisplatin, as used in our patient. For patients not eligible or intolerant to cisplatin, there are other alternatives (such as carboplatin with or without 5-fluorouracil, taxanes or cetuximab). However, none of them have shown superior results over the use of cisplatin in randomized trials. NACT based on taxanes followed with ideally CCRT is another strategy that has good results for selected patients with good performance status and minor comorbidities. Use of chemotherapy for the treatment of unresectable oral cancer has also been tested. Use of methotrexate as well as docetaxel-cisplatin-fluorouracil regimen have shown satisfactory results. However, effectiveness of chemotherapy alone for unresectable oral cancer still needs to be determined. A regimen comprising cetuximab-docetaxel-cisplatin, and 5- fluorouracil followed by bio-chemoradiotherapy with cisplatin and cetuximab is an effective and tolerable induction chemotherapy regimen for inoperable oral cancer. Neoadjuvant cetuximab plus paclitaxel, and cisplatin followed by cetuximab-based RT 70 Gy have also shown good

results.[6,8,9]. Cisplatin is Category 1 recommendation compared to Cetuximab (Category 2B). A phase III randomized trial (EXTREME) found that cetuximab plus cisplatin/5-FU had an improved response rate 36% compared to 20% with carboplatin/5-FU. Our patient underwent 3 cycles of neoadjuvant paclitaxel plus carboplatin. Thereafter he underwent concurrent cisplatin chemoradiotherapy, as a result of which the tumor became borderline resectable and surgery was performed under general anesthesia.

Effectiveness of treatments involving immunotherapy for unresectable oral cancer is uncertain as there is limited evidence. Pembrolizumab is monoclonal antibody targeting programmed cell death 1. It is currently approved by the US Food and Drug Administration for recurrent or metastatic head and neck squamous cell carcinoma (HNSCC). It has been found in patients with local regionally advanced OSCC treated with neoadjuvant pembrolizumab that serious adverse events are similar to those in patients who underwent standard-of-care treatment, which suggests that there is no increased perioperative morbidity in the use of preoperative treatment with immunotherapy. Gene therapy for the treatment has also been studied. Exome sequencing revealed mainly tumour suppressors are the significantly mutated genes are. Mutations in FAT1, CASP8, CDKN2A, and NOTCH1 are more frequently found in OSCC in comparison with non-OSCC head and neck cancers and other squamous cell carcinomas, and HRAS and PIK3CA are the only significantly mutated oncogenes. rAd-p53 gene therapy plus CT can improve the clinical outcomes for people suffering from unresectable oral cancer, but these results should be considered carefully because there is lacking evidence about the effectiveness of these treatment options.[6,10,11] Our patient did not undergo immunotherapy or gene therapy.

CONCLUSION

Management of locally advanced oral cancer requires a multidisciplinary team approach. There is a need to search for the most appropriate therapeutic options for locally advanced oral squamous cell carcinoma that can increase survival.

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DECLARATIONS

Conflict of Interest: The authors declare that they have no conflict of interest

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