




Successful Treatment of Recurrent Unresectable Oral Cancer with Sequential Targeted Therapy, Surgery, and Metronomic Chemotherapy

Diksha Dinker¹ Ananth Pai² Keshava Rajan¹ Naveena A.N. Kumar¹ 

¹Department of Surgical Oncology, Manipal Comprehensive Cancer Care Centre, Kasturba Medical College, Manipal Academy of Higher Education (MAHE), Manipal, Karnataka, India

²Department of Medical Oncology, Manipal Comprehensive Cancer Care Centre, Kasturba Medical College, Manipal Academy of Higher Education (MAHE), Manipal, Karnataka, India

Address for correspondence Naveena A.N. Kumar, MS, MCh, Department of Surgical Oncology, Manipal Comprehensive Cancer Care Centre, Kasturba Medical College, Manipal Academy of Higher Education (MAHE), Manipal, Karnataka 576401, India (e-mail: naveenkumar.an@manipal.edu).

South Asian J Cancer

Abstract



Naveena A.N. Kumar

A high incidence of locoregional recurrences in oral cavity cancers remains the biggest challenge leading to treatment failures post-surgery and radiotherapy. Our case report elaborates on one such recurrence pattern and the juxtaposition of various modalities applied to successfully not only eradicate the tumor but also to keep the recurrence at bay.

Keywords

- ▶ unresectable oral cancer
- ▶ OMCT
- ▶ targeted therapy
- ▶ head and neck squamous cell carcinoma
- ▶ recurrence

Case Presentation

A 70-year-old lady presented with an ulcer in her right cheek and swelling over the left side of her lower neck and upper chest wall. She was previously operated on two times for carcinoma buccal mucosa on the same side. The first incident was 20 years

back. She had also received adjuvant radiotherapy. The second incident was 1 year ago and underwent segmental hemimandibulectomy and reconstruction with a pectoralis major myocutaneous (PMMC) flap followed by adjuvant radiotherapy.

On current examination, there was a 1.5 × 2cm ulcer over the previously operated right buccal mucosa and a 4 × 3.5cm

DOI <https://doi.org/10.1055/s-0043-1773793> ISSN 2278-330X

How to cite this article: Dinker D, Pai A, Rajan K, et al. Successful Treatment of Recurrent Unresectable Oral Cancer with Sequential Targeted Therapy, Surgery, and Metronomic Chemotherapy. *South Asian J Cancer* 2023;00(00):00–00

© 2023. MedIntel Services Pvt Ltd. All rights reserved.

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

hard fixed swelling over the contralateral supraclavicular region extending over the clavicle and upper chest wall. Biopsy from the buccal mucosa lesion and fine-needle aspiration cytology from the left nodal mass was suggestive of moderately differentiated squamous cell carcinoma. The positron emission tomography-computed tomography (PET-CT) showed uptake in the right buccal mucosa and bulky hypermetabolic contralateral left cervical level III, IV, and supraclavicular conglomerate lymph node mass adherent to the medial end of the clavicle, sternum, and upper chest wall (–Figs. 1A, –1B, 2A and 2B). There was no other distant metastasis. In view of their unresectability and multiple recurrence status, she was planned for chemotherapy by a multidisciplinary tumor board. Having a good disease-free interval and no distant metastasis, she was planned for reassessment for surgery. She was started on targeted triple-agent therapy including cetuximab, paclitaxel, and carboplatin in the titrated dosage of 325 mg, 120mg, and 130mg weekly, respectively. The challenge during chemotherapy was the tolerability and completion of treatment because of old age.

The patient completed nine divided cycles of chemotherapy without any significant toxicity. She had a complete clinical response in the right buccal mucosa and contralateral lymph node mass at the end of chemotherapy. The response assessment, PET-CT, and CT scans suggested interval resolution in size in the primary site and the number and size of contralat-

eral lymph node mass (–Figs. 3A, –3B, 4A and 4B). Given the excellent response, she was planned for excision of the right buccal mucosa lesion and contralateral lymph node mass. Considering her age, there were two challenges during surgery, including reconstruction at the primary site and the extent of resection at the contralateral neck and chest wall mass. Because of old age and the long duration of surgery, we did not plan any free flap reconstruction, which was the ideal option considering previous surgery and previous reconstruction with PMMC flap. We performed a completion hemimandibulectomy and a pedicled latissimus dorsi flap was used for reconstruction. The contralateral neck mass clearance was challenging because of extensive fibrosis due to chemotherapy. The left internal jugular vein was ligated. The lymph node mass was cleared from the base of the neck, medial end of the clavicle, and upper chest wall to achieve R0 resection. The patient developed a postoperative chyle leak, which was managed with surgical exploration in the neck and ligation of the chyle duct posterior to the left common carotid artery. The patient was recovered without any other complications.

The histopathology was reported to be ypT1N0M0. The patient was started on oral metronomic chemotherapy (OMCT) that comprised celecoxib 200mg twice a day and methotrexate 15 mg/m² once weekly, which continued for 18 months. At the end of 24 months of follow-up, the patient has remained disease free.

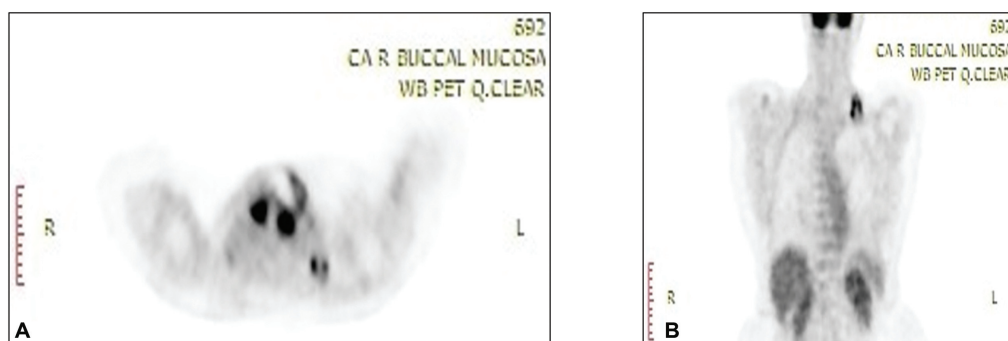


Fig. 1 (A, B) Axial and coronal positron emission tomography-computed tomography sections, respectively, showing disease uptake.

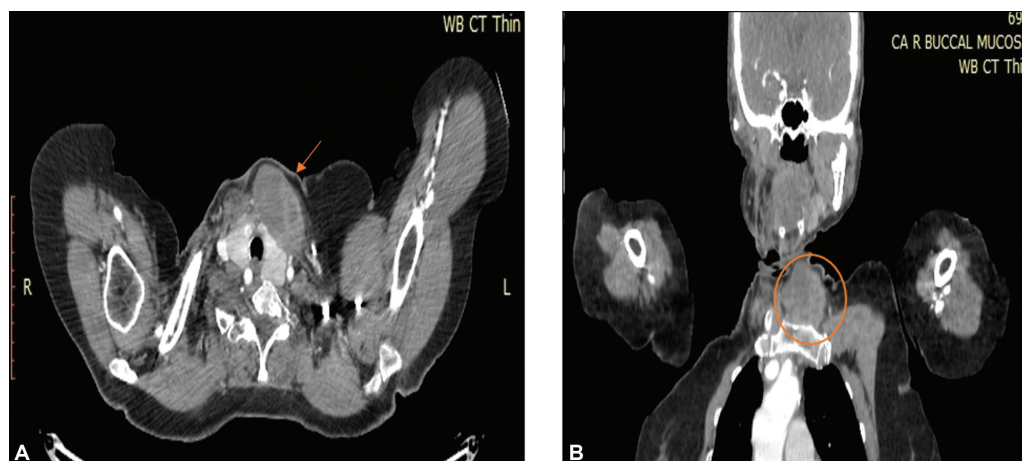


Fig. 2 (A, B) Axial and coronal computed tomography sections, respectively, showing lymph node mass (the arrow and the circle are depicting the disease).

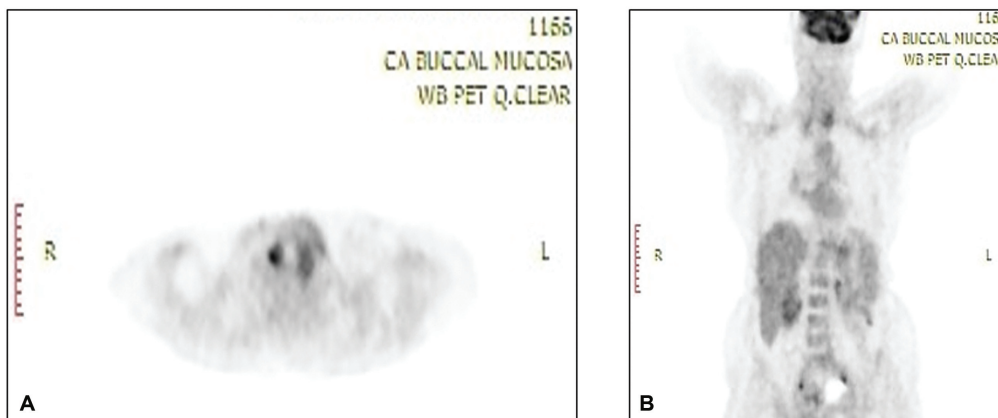


Fig. 3 (A, B) Axial and coronal positron emission tomography-computed tomography sections, respectively, showing lesser disease uptake compared with the previous scans.

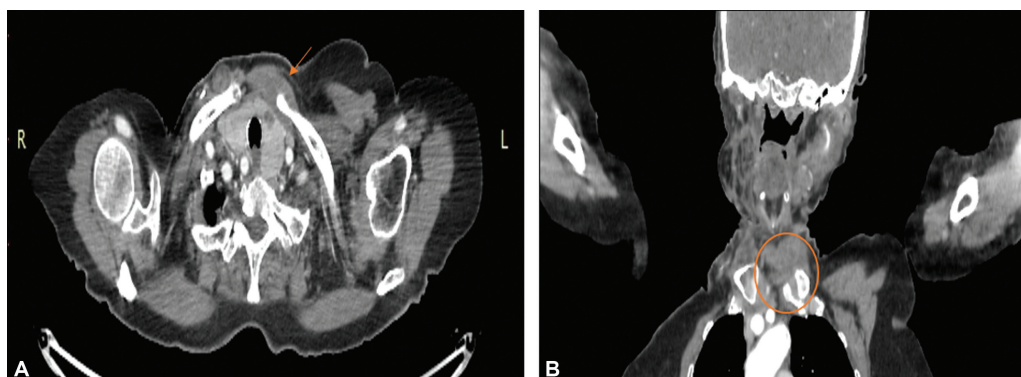


Fig. 4 (A, B) Axial and coronal computed tomography sections, respectively, showing partial response compared with the previous scans (the arrow and the circle are depicting the disease).

Discussion

A high incidence of locoregional recurrences in oral cavity cancers (OCC) following definitive surgery and adjuvant radiotherapy remains the biggest challenge leading to treatment failures¹ Recurrent OCC displays an aggressive and invasive form of their preceding counterparts. In one-third of OCC, it usually presents as clinically occult ipsilateral or contralateral cervical node metastasis due to freely communicating lymphatics across the midline allowing for spread from the primary subsite to any level of the neck.² These are responsible for 90% of treatment failures.³⁻⁵ The recurrence rate can vary from 18 to 76% for patients post standardized treatment, and it is associated with poor survival rates. Literature on OCC also specifies the median time to recurrence as 7.5 months after treatment, and it can also stretch as 86% of the recurrences occur within 24 months^{2,4,6}

Chemotherapy remains the only option for patients who are deemed unfit for salvage surgery or reradiation; however, its efficacy is limited by the development of drug resistance.¹ A combination of standard chemotherapeutic drugs with modulating agents to combat drug resistance has opened a gateway to achieve various therapeutic benefits. With the growing arena of cancer research, the introduction of targeted agents

against selective sites and molecules responsible for cancer progression has optimized superior therapeutic activity even in refractory cancers.¹

The agents conventionally chosen in OCCs can be single such as cisplatin or an addition to the same with cisplatin backbone and paclitaxel (Taxanes) with or without 5 fluorouracil.⁷ Patients with recurrent OCC can be filtered into two categories—cisplatin-sensitive or cisplatin-refractory based on prior exposure to the drug in the last 6 months. According to the EXTREME trial, which demonstrated the effectiveness of cisplatin/5FU/cetuximab, cisplatin-sensitive groups can also benefit from cisplatin-based combinations. The KEYNOTE-048 validated a new regimen for cisplatin-refractory cases using pembrolizumab alone or in combination.⁸ The TAX 323 and TAX 324 studies demonstrated the efficacy of the triplet regimen, composed of 5-fluorouracil, cisplatin, and docetaxel, in the management of locally progressed head and neck cancers.^{9,10} Cetuximab is a savior in both cisplatin-sensitive and refractory cases. Even in a palliative situation, its addition to the standard combination of cisplatin and 5-fluorouracil has improved survival outcomes.^{7,9,11} In situations where cisplatin is ineffective, cetuximab has similarly demonstrated a response rate of 13% as a single drug.¹² However, in developing nations with limited resources, it

is not always feasible to apply this regimen. Hence, OMCT has come into the picture in India as it brings in a practical yet affordable option.

The OMCT refers to the continuous introduction of low doses of anticancer agents in the bloodstream. It works by various phenomena including but not limited to antiangiogenesis, modulating immune response, and promoting tumor cells inactivity.⁸ As per the conventional regimen, patients get a dose of 200 mg of celecoxib twice daily and 15 mg/m² of methotrexate once a week until the disease progresses or until severe side effects arise.⁸ Glück et al, in their pilot study, reported an effective combination of methotrexate and celecoxib in head and neck cancer with appreciable efficacy and nominal after-effects.¹³ In a randomized phase 3 trial of OMCT in head and neck cancer including 422 patients with newly diagnosed, recurrent, or relapsed head and neck squamous cell carcinoma conducted at Tata Memorial Center, Mumbai, the median overall survival was found to be 7.5 (range: 4.6–12.6) months in the OMCT group compared with 6.1 (3.2–9.6) months in the intravenous cisplatin group. It also concluded a 22% reduction in the risk of death and was associated with a 50% decrease in the risk of disease progression.¹⁴ In a retrospective study by Pandey et al, where adjuvant OMCT was used after completion of standard surgery and adjuvant chemoradiotherapy/radiotherapy in locally advanced oral squamous cell cancer, the use of metronomic chemotherapy showed improvement in disease-free survival (8 vs. 14 months) and overall survival (14 vs. 26 months).¹⁵ Pai et al also assessed the effectiveness of OMCT in advanced operable oral malignancies. A significant improvement in disease-free survival was observed in the group that received at least 3 months of OMCT in the adjuvant setting without any major toxicities.¹⁶

There were many challenges in the management of our patient. First, the recurrent nature of her disease despite former R0 resection with adjuvant radiotherapy each time. However, the patient had a good disease-free interval between the recurrences, recurrence only at locoregional sites without any distant metastases, and good response to the treatment pointing toward good disease biology. Second, the age and tolerability of chemotherapy were of concern. Instead of a conventional docetaxel, cisplatin, fluorouracil regimen, our patient received paclitaxel, and carboplatin with cetuximab, which was well tolerated by her.¹⁷ Third, major surgery on a 70-year-old lady who had previously undergone two major resections was a challenge. Current surgery was well tolerated by her including postoperative chyle leak, which required re-exploration.

Sandwiching the surgery between a combination of chemo-targeted therapy and OMCT has resulted in control of recurrence to date.^{14,15} This approach signifies the individualized multidisciplinary treatment for each case of recurrent head and neck cancer rather than deeming it unresectable or palliative upfront in this era of precision oncology.

Conclusion

Oral malignancies that are recurrent and incurable can be successfully treated with personalized therapy that includes

surgery, metronomic chemotherapy, and combinations of chemo-targeted therapy. The factors that favor good biology are good disease-free interval between the recurrences, recurrence only at locoregional sites without any distant metastases, and response to the treatment. Hence, “no one size fits all” and every treatment or therapeutic regimen should be individualized per the patient’s requirement.

Conflict of Interest

None declared.

References

- da Silva SD, Hier M, Mlynarek A, Kowalski LP, Alaoui-Jamali MA. Recurrent oral cancer: current and emerging therapeutic approaches. *Front Pharmacol* 2012;3:149
- Fan S, Tang QL, Lin YJ, et al. A review of clinical and histological parameters associated with contralateral neck metastases in oral squamous cell carcinoma. *Int J Oral Sci* 2011;3(04):180–191
- Leemans CR, Tiwari R, Nauta JJ, van der Waal I, Snow GB. Recurrence at the primary site in head and neck cancer and the significance of neck lymph node metastases as a prognostic factor. *Cancer* 1994;73(01):187–190
- Carvalho AL, Kowalski LP, Agra IM, Pontes E, Campos OD, Pellizzon AC. Treatment results on advanced neck metastasis (N3) from head and neck squamous carcinoma. *Otolaryngol Head Neck Surg* 2005;132(06):862–868
- Agra IM, Filho JG, Martins EP, Kowalski LP. Second salvage surgery for re-recurrent oral cavity and oropharynx carcinoma. *Head Neck* 2010;32(08):997–1002
- Kowalski LP, Carvalho AL, Martins Priante AV, Magrin J. Predictive factors for distant metastasis from oral and oropharyngeal squamous cell carcinoma. *Oral Oncol* 2005;41(05):534–541
- Forastiere AA, Shank D, Neuberg D, Taylor SG IV, DeConti RC, Adams G. Final report of a phase II evaluation of paclitaxel in patients with advanced squamous cell carcinoma of the head and neck: an Eastern Cooperative Oncology Group trial (PA390). *Cancer* 1998;82(11):2270–2274
- Burtneß B, Harrington KJ, Greil R, et al; KEYNOTE-048 Investigators. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet* 2019;394(10212):1915–1928
- Vermorken JB, Remenar E, van Herpen C, et al; EORTC 24971/TAX 323 Study Group. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med* 2007;357(17):1695–1704
- Posner MR, Hershock DM, Blajman CR, et al; TAX 324 Study Group. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med* 2007;357(17):1705–1715
- Pasquier E, Kavallaris M, André N. Metronomic chemotherapy: new rationale for new directions. *Nat Rev Clin Oncol* 2010;7(08):455–465
- Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *J Clin Oncol* 2007;25(16):2171–2177
- Glück S, Lau H, Mackinnon J, Syme R, Glück D. Metronomic therapy in recurrent and metastatic chemo-resistant SCCN: data from a pilot study. *Biomed Pharmacother* 2005;(59):S319
- Patil V, Noronha V, Dhupal SB, et al. Low-cost oral metronomic chemotherapy versus intravenous cisplatin in patients with recurrent, metastatic, inoperable head and neck carcinoma: an

- open-label, parallel-group, non-inferiority, randomised, phase 3 trial. *Lancet Glob Health* 2020;8(09):e1213–e1222
- 15 Pandey A, Desai A, Ostwal V, et al. Outcome of operable oral cavity cancer and impact of maintenance metronomic chemotherapy: a retrospective study from rural India. *South Asian J Cancer* 2016;5(02):52–55
- 16 Pai PS, Vaidya AD, Prabhash K, Banavali SD. Oral metronomic scheduling of anticancer therapy-based treatment compared to existing standard of care in locally advanced oral squamous cell cancers: a matched-pair analysis. *Indian J Cancer* 2013;50(02):135–141
- 17 Tahara M, Kiyota N, Yokota T, et al. Phase II trial of combination treatment with paclitaxel, carboplatin and cetuximab (PCE) as first-line treatment in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (CSPOR-HN02). *Ann Oncol* 2018;29(04):1004–1009