Indian Council of Medical Research consensus document for the management of buccal mucosa cancer

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EXECUTIVE SUMMARY

- The document is based on consensus among the experts and best available evidence pertaining to Indian population and is meant for practice in India.
- Evaluation of a patient with newly diagnosed buccal mucosa cancer should include essential tests: Biopsy of the primary lesion, complete blood counts, renal function tests and liver function tests, chest X-ray, dental evaluation, and ultrasonogram (USG) of the neck in patients with no clinically enlarged neck nodes. Computed tomography (CT) magnetic resonance imaging (MRI)/positron emission tomography (PET)-CT are not recommended for all patients.
- For early stage disease (I/II), single modality treatment with surgery (with or without postoperative radiotherapy (PORT) or radiotherapy (RT) (brachytherapy or external beam radiotherapy [EBRT] or in combination) is recommended.
- For locally advanced Stage (III–IV A), surgery followed by RT with or without chemotherapy, concurrent chemo-RT, altered fractionation RT schedules, induction chemotherapy, followed by surgery with or without RT are valid treatment options.
- Stage IV B/metastatic diseases are treated with intent of palliation with chemotherapy and/or RT along with best supportive care.
- Clinical examination including history and physical examination is done at each follow-up visit and no routine radiological investigation is recommended.

INCIDENCE

Carcinoma of the buccal mucosa (BMC) is the commonest cancer of the oral cavity in India. As per population based cancer registry data[1] of the National Cancer Registry Program, of the Indian Council of Medical Research, the males of Ahmedabad urban showed highest age adjusted rate (AAR) for mouth cancer (17.1) followed by Bhopal (12.5). For females however, Kamrup urban district (7.6) and East Khasi Hills of Meghalya (7.3) showed the highest AAR, followed by Bangalore (6.2). In the hospital-based cancer registry[2] report, cancer of the oral cavity is also ranked as the leading site in Mumbai in males and was within the first five leading sites in all registries in males. In the developed countries, BMC is relatively uncommon when compared to the Indian subcontinent.[3] As per the recent GLOBOCAN 2012, 77,000 new cases of oral cavity cancers are diagnosed every year in India and 52,000 die of this disease.[4] The high incidence of BMC in our country is attributable to the extensive use of tobacco in various forms and the locally advanced cancers account for about 70% of the cases at the time of presentation.

PURPOSE

Several international consensus guidelines are available for the management of oral cavity cancers, but none of

them addresses BMC in particular. Therefore, formulating reliable guidelines based on western data for Indian patients is questionable given the fact that buccal mucosa tumors are quite rare in the developed countries. There is obviously an urgent need to formulate consensus statement for the management of BMC based on Indian data[5-9] and experience which would not only incorporate the evidence available but would also be feasible to be practiced in the hospitals of India. Oral cancer in India is different compared to the western countries. Here, it involves the gingivo buccal sulcus (the site where the tobacco quid is commonly kept by the patient). The nature of spread, biological behavior and the treatment is also different. Based on the available evidence and expert consensus opinion, we present the proposed national consensus document for management of BMC.

DIAGNOSIS

Evaluation of a patient presenting with a lesion in the buccal mucosa should be aimed at pathological confirmation and staging of the disease. Essential test, which needs to be done in all patients include: Biopsy of the primary lesion, complete blood counts, renal function tests and liver function tests, chest X-ray, USG of the neck in patients with no clinically enlarged neck nodes, dental evaluation and CT scan except in patients with early lesions and clinically USG proven no lymphadenopathy in the neck. CT scan/MRI is advisable if mandible is involved clinically and ortho-pantomogram is negative, lesion is involving the retromolar trigone, there is suspected involvement of pterygoids or pterygoid plate, lesion is extending into the upper gingivo buccal sulcus and there is suspicious involvement of para-nasal sinuses or if there is need to assess the operability of cervical lymph nodes. Evaluation under anesthesia should be done in cases where clinical examination is not feasible. 2-[^{18}F] fluoro-2-deoxy-D-glucose PET (PET-CT) is not routinely recommended.

Extensive investigations are not recommended in cases with (intent of treatment in these cases is primarily palliation) hard and fixed N3 nodes, extensive skin involvement with or without cutaneous nodules, severe trismus not due to oral submucous fibrosis or clinical involvement of infra temporal fossa.

Staging should be done with American Joint Committee on Cancer staging manual[10] (7th edition, 2009) and patients should be assigned a TNM and a group stage (which would remain unchanged throughout).

TREATMENT PLAN

Treatment decisions are based on the stage. The aim of treatment is "curative" for patients with Stage I–IV A and "palliative" for patients with Stage IV B (locoregionally advanced disease) and IV C (metastatic disease).

Early Stage (I/II)

For early Stage (I or II), single modality treatment is used: Either surgery or RT alone.

Wide local excision and supra-omohyoid neck dissection (SOND) should be the surgical procedure of choice. SOND may be avoided if the patient is highly compliant and meets all the criteria: T1 lesion, node negative status proven by USG, histologically well differentiated lesions and thickness of infiltration[11] is <4 mm. All patients with close/positive margin should be considered for re-excision. If the patient is not a candidate for the same, PORT should be considered. Multiple node positivity, margin positive disease and presence of extra-capsular spread[12,13] mandate the use concurrent chemo-radiation. The minimum required PORT dose is 60 Gy at 1.8-2 Gy/fraction. This may be delivered in a phased manner. The initial phase would deliver 44 Gy in 22 fractions over 4½ weeks to the primary and nodal areas using conventional treatment planning, three-dimensional conformal radiotherapy (3D-CRT) or intensity modulated radiotherapy (IMRT).[14] Every effort should be made to spare the contralateral parotids. In the second phase the spinal cord should be shielded and dose delivered to receive a minimum of 60 Gy. In presence of margin positive disease or extra-capsular spread 66 Gy is the recommended dose. This may be achieved using electrons or photon boost.

Interstitial brachytherapy alone is used in highly compliant individuals of early buccal mucosa cancers with all of the following tumor characteristics: Early lesions preferably <2 cm, accessible lesions, histologically well differentiated lesions, lesions situated well away from the bone, node negative status proven by USG. Brachytherapy may be delivered using low dose rate[15] (LDR) or high dose rate (HDR) systems. In general, dose prescription encompasses the primary with 1.0-1.5 cm margins. The regional nodes are not addressed at this time of treatment. Doses for LDR are 65-70 Gy over 6-7 days and for HDR is 48 Gy in 12 fractions (4 Gy twice a day over 6 days).

Patients who are not suitable for brachytherapy may be treated with EBRT. EBRT is delivered using conventional planning/3D-CRT/IMRT to doses of 66-70 Gy at 1.8-2 Gy/fraction over 7-8 weeks (or a biologically equivalent dose) with adequate margins all around the lesion and including Level I and II nodes. Neck needs to be observed through close follow-up. In conventional RT planning, initial lateral portals are treated to 44 Gy in 22 fractions/over 4.5 weeks, followed by 12-16 Gy after

spine shielding. Dose of EBRT is restricted to 45-50 Gy if interstitial boost (dose of 20–25 Gy [LDR] or equivalent [HDR]) is given.

When concurrent chemo-radiation is used, cisplatin is the preferred agent.[16] Weekly cisplatin 30-40 mg/m^2 should be used with minimum cumulative dose of 200 mg/m^2. Three weekly regimen of cisplatin with dose of 100 mg/m^2 (on day 1, 22, and 43 of RT) can be used. Monoclonal antibody therapy directed against epidermal growth factor receptor (cetuximab and nimotuzumab) added to radiation therapy improves outcome, however, there is limited evidence in the Indian literature[17] and cost benefit ratio may be considered before taking a decision. In patients who are not candidates for cisplatin, carboplatin and paclitaxel is the regime of choice for chemo-radiation. Feeding through nasogastric tube, gastrostomy or jejunostomy is strongly recommended during chemo-radiation.

Locally advanced (Stage III-IV A)

Patients should be offered combined modality treatment for these disease stages. Treatment options include: Surgery, followed by RT with or without chemotherapy, concurrent chemo-RT, altered fractionation RT schedules, induction chemotherapy, followed by surgery with or without RT.

Surgical aim should be to widely excise the tumor to obtain negative margins (0.5-1 cm) all around. Modified radical neck dissection (MND) should be the procedure of choice. Extended SOND is followed by MND if matted lymph nodes or extensive cervical lymph nodes involvement is found peroperatively and if nodes are positive on frozen section. Segmental mandibulectomy should be avoided just to facilitate access to primary cancers of oral cavity. However, it can be done in cases where there is: Gross invasion of mandible by tumor, proximity of oral commissure to the mandible in a previously irradiated patient, invasion of inferior alveolar nerve or canal by cancer or massive soft tissue disease is present adjacent to the mandible.

Principles of radiation and concurrent chemo-radiation remain the same as in early stage disease. Altered fractionation schedules are valid option for patients who are not candidates for surgery or are unsuitable for chemo-radiation.[18]

For borderline inoperable disease, chemotherapy may be considered to facilitate better resection. Based on recent evidences in the literature,[19] combination regimen with cisplatin, 5-flurouracil and taxane is considered the most effective neoadjuvant regimen. Alternative chemotherapy schedule is cisplatin plus 5-flurouracil.[20] Both chemotherapy regimens have Level I evidence[19,20] in terms of their efficacy in neoadjuvant setting in head and neck cancers. Resectability subsequent to induction chemotherapy is best assessed by clinical evaluation and imaging where indicated. CT or MRI scan (if available) may be used for assessment of disease in inaccessible areas such as pterygopalatine fossa or infratemporal fossa. It is also preferable that the pre- and post-chemotherapy assessments are performed by the same group of oncologists. Patients who have progressive disease after 3-4 cycles of induction chemotherapy should be considered for palliative treatment only.

Advanced Stage IV B/metastatic disease

Aim of treatment in these patients is palliation with maintenance of quality of life. If the primary with or without nodal disease is symptomatic, consideration should be given to palliative[21] EBRT. Doses of 30 Gy in 10 fractions over 2 weeks or weekly EBRT of 7-8 Gy/fraction/week for 2-3 weeks may be employed. Systemic disease or progressive local disease after RT could be treated with chemotherapy with any of the following regimens: Single agent methotrexate, single agent cisplatin, cisplatin plus 5-flurouracil, cisplatin plus paclitaxel, cisplatin plus docetaxel or cisplatin plus cetuximab.[22]

RECURRENT DISEASE

For recurrent disease, if recurrence is operable and patient is RT naïve, surgery followed by PORT with or without chemotherapy or radical RT (for recurrent T1/T2) may be employed. Concurrent chemo-radiation or radiation alone is a valid option in these patients, if surgery is not medically feasible or patient is not willing for surgery.

If surgery is not feasible and patient has poor performance status the treatment should be individualized. If RT naïve, palliative RT else palliative chemotherapy may be employed along with best supportive care.

FOLLOW-UP AND REHABILITATION

Patient should be encouraged to maintain abstinence from tobacco and alcohol and maintain oral hygiene. Dental prophylaxis, shoulder exercises, jaw stretching exercises, swallowing and speech rehabilitation should be instituted as appropriate. The aim of follow-up is to assess the recurrence in primary and nodal areas, to rule out any second primary and to assess any complication due to surgery/RT. Follow-up is done every 2-3 months for first 2 years, six monthly for next 3 years and annually thereafter. Clinical examination, including history and physical examination is done at each visit and no routine radiological investigation is recommended.

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Announcement

LATE DR KALLA VENKAT ANAND YOUNG RESEARCHER AWARD

ISMPO is now inviting abstracts for the first '*Late Dr Kalla Venkat Anand Young Researcher Award*'. The award honours a young medical oncologist from India (age ≤ 40 years as on 31.12.2014) whose research work is adjudged to be the best among those submitted for the Annual ISMPO Meeting to be held in Kolkata on 26 – 28 December, 2014. The Awardee will be conferred a Medal along with a grant. For detailed information please visit www.ismpo.org. **Last date of abstract submission is 30.10.2014 (Midnight).**