Review Article

The Indian scenario of head and neck oncology – Challenging the dogmas

Vidisha Tuljapurkar, Harsh Dhar, Aseem Mishra, Swagnik Chakraborti, Pankaj Chaturvedi, Prathamesh S. Pai

Abstract

Head and neck cancers (HNCs) are the most common malignancies worldwide. Asian populations bear major burden of this disease, with certain unique characteristics. Although significant research in HNCs is ongoing globally, many clinical issues still remain unanswered. We performed a literature search to find noteworthy Indian studies that changed practice of HNC as well as to look for areas for further research in this field. Many randomized controlled trials as well as large patient series are reported in the field of radiotherapy, chemotherapy, and surgical management of HNC. Still, many areas such as palliative therapy, targeted agents, and newer chemotherapeutic agents remain unexplored. Planned collaborative research is need of the hour to provide more evidenced based.

Key words: Chemotherapy, head and neck cancers, radiation therapy, surgery

Introduction

Head and neck cancers (HNCs) affect the upper aerodigestive tract and are one of the most common cancers worldwide.[1] With 77,000 cases diagnosed per year, HNCs are the second most common cancers in the Indian population.[2] While smoked tobacco and alcohol are the major causative factors for HNC worldwide, smokeless tobacco, betel nut, and Epstein–Barr virus are etiological agents responsible for it in the Asian population.[3]

Global cancer research is on the rise with studies addressing important issues impacting management. In the recent years, advances in diagnostic methodologies, surgical techniques, and adjuvant treatment strategies have improved survival of HNC worldwide.[4] However, there are many clinical dilemmas. We reviewed the recent Indian literature to identify studies which have made significant impact in the management of HNC in the last decade.

Investigations in Head and Neck Oncology

A patient is investigated to prove the type of tumor, its extent, and plan treatment and for prognostication. However, with changes in treatment modalities, we need to move from traditional methods of investigations to a targeted approach. Challenging the dogmas is certain studies from India, which have changed our current practices.

Cervical lymphatic involvement

Cervical lymph node metastasis is a known poor prognostic factor, lowering survival by almost 50%. Predicting it in the early head and neck squamous cancers is a dilemma. The relation of tumor thickness on predicting lymph nodal metastasis is one approach. Kane *et al*.[5] in a prospective study on T1 and T2 cancers of the oral tongue evaluated the role of thickness in predicting the lymph node metastasis. They found the depth of invasion to be one of the most significant predictors of cervical node metastasis and concluded that tumors with depth >5 mm should undergo elective neck node dissection. This study helped promote practice of elective neck dissection (END) in tumors with thickness more than 5 mm. This study contributed in a meta-analysis on predictive value of tumor thickness in cervical lymph nodal metastasis by Huang *et al*.[6]

Access this article online

Quick Response Code:

Website: www.sajc.org

DOI: 10.4103/2278-330X.187573

Department of Head and Neck Surgical Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India

Correspondence to: Dr. Prathamesh S. Pai, E-mail: drpspai@gmail.com

How to cite this article: Tuljapurkar V, Dhar H, Mishra A, Chakraborti S, Chaturvedi P, Pai PS. The Indian scenario of head and neck oncology - Challenging the dogmas. South Asian J Cancer 2016;5:105-10.

Frozen section

Frozen section (FS) is extensively used globally, especially in oncology centers to ensure oncologic safety of surgery. In India, however, its use is limited to select centers due to constraints of infrastructure. Chaturvedi *et al*.[7] evaluated the efficacy of FS and its utility vis-a-vis gross examination (GE) in routine surgery. They found that FS has a high sensitivity and specificity, but its utility is low in routine surgical practice. On comparing GE of the margins by surgeon with FS, they found that GE is equivalent FS for ensuring a margin-free status in terms of sensitivity and accuracy. Taking it a step further, they conclusively showed that achieving a 7 mm gross margin obviates need for frozen confirmation and margin revision. Thus, GE of the specimen by the surgeon is adequate quality assurance in an oncologically safe surgery.

Positron emission tomography-computed tomography scan in recurrence restaging and unknown primary

Positron emission tomography-computed tomography (PET-CT) scan came with a huge promise of tumor detection. However, there was no specific indication and its utility was untested. With a significant cost attached to this investigation, we needed to know its capabilities. Pantvaidya *et al*.[8] evaluated the role of PET-CT in patients with recurrence. They showed that PET-CT changed treatment plan in almost 40% of patients with recurrent lesions. Today, all treatable recurrent cancers undergo PET-CT, especially those with a shorter disease-free interval and it also helps to prognosticate the patients.

Evaluating unknown primaries, Dandekar *et al*.,[9] in 2011, analyzed the utility of the fluorodeoxyglucose-PET (FDG-PET) in the investigation algorithm. They found FDG-PET to have a sensitivity and specificity of 92.8% and 71.4% making it a useful tool in detecting infraclavicular primaries and distant metastasis in patients either with lower neck level nodal involvement or with multiple level neck nodes. This has made PET-CT a standard investigation in squamous cell cancers presenting as unknown primaries, especially those with multiple and/or lower neck nodes.

Computed tomography scan in oral cancers

Detection of mandibular invasion can impact on the management of squamous cell carcinoma (SCC) of the retromolar trigone area, a very common disease in the Indian population. Arya *et al*.[10] investigated the role of multidetector row computed tomography (MDCT) for detecting mandibular invasion in retromolar trigone cancers. They showed the usefulness of 16 or higher section MDCT. It has a sensitivity of 94% and a specificity of 90% in evaluating for mandibular invasion. Hence, with a simple CT scan with dedicated reporting, we can predict the incidence of bone involvement and plan treatment accordingly.

Ultrasound and ultrasound-guided fine needle aspiration cytology

Imaging of the clinically negative neck in detecting metastasis has been a point of debate. With randomized trials and meta-analysis,[11] establishing ultrasound (USG)-guided fine needle aspiration cytology (FNAC) is to be the most accurate imaging modality to detect cervical lymph node metastases. However, there were several inherent shortcomings in this ranging from operator dependence in USG, criteria for selection of the patients in studies, and inclusion of clinically node positive patients in the meta-analysis. Chaturvedi *et al*.[12] conducted a prospective study comparing the sentinel node biopsy to USG-guided FNAC in early oral cavity cancer. They have shown that USG-guided FNAC of the neck node is not a sensitive tool to investigate a clinically negative neck with a low sensitivity of 14.3%. With inherent issues of USG in the country with inter-operator variability, this study might change practice in India toward elective neck management obviating the need for evaluating the neck for occult metastasis.

Surgery

Surgery is the primary modality of therapy in oral cancers. However, certain issues have remained unresolved for long. Management of the neck in early oral cancers has remained a debate since time immemorial. The extent of neck dissection in a node-positive neck, management of the mandible in lesions of the buccal mucosa, and alternative pedicled flaps for reconstruction following conservative resection in early oral cavity cancers are some of the unresolved issues.

Elective neck dissection

Elective Neck Dissection (END) versus therapeutic neck dissection (TND) in node negative early oral cancers a randomized controlled trial (RCT) wascrecently published by D'Cruz AK *et al*.[13] and it addressed the unresolved issue of whether addressing the neck electively is superior to a wait and watch policy. The END arm had 245 patients whereas the TND arm had 255 patients. The overall survival (OS) in the END arm 80.0% was significantly better than the TND arm with 67.5%. The disease-free survival (DFS) in the END arm was also better than the TND arm (69.5% vs. 45.9%). Thus, END was conclusively proven to have that a better oncological outcome is the treatment of choice in management of the neck in early oral cancers.

Extent of neck dissection

Levels IIA and V

In their prospective study of 583 patients undergoing neck dissection, Pantvaidya *et al*.[14] elucidated the distribution of nodal metastasis for oral cancers. The overall incidence of metastasis to Levels IIB and V was extremely low, 3.8% and 3.3%, respectively. The factors associated with Level IIB metastasis were primaries in the tongue and retromolar trigone and Level IIA positivity (68.1%). Level V metastasis was associated with primaries in the buccal mucosa and lower alveolus and Levels IIA and III positivity. They thus recommend a selective neck dissection of Levels I–IV, sparing IIB even for node positive oral cancers if the Level IIA is negative. They also advised to include Levels IIB and V in the presence of Levels IIA and III positivity.

Contralateral neck

Addressing the issue of contralateral nodal metastasis in oral tongue cancer, Singh *et al*.[15] retrospectively analyzed neck dissections done for tongue lesion reaching the midline or crossing it and concluded that ipsilateral nodal positivity was the best predictor of contralateral nodal metastasis, thus advocating opposite neck dissection in the presence of multiple ipsilateral involved nodes.

Marginal mandibulectomy

The safety of performing a marginal mandibulectomy for oral cancers in proximity to the mandible without its involvement was assessed by Pathak and Shah[16] retrospectively on 179 patients. Cause-specific survival at 2 and 5 years was 85.6% and 72.2%, respectively. Cause-specific survival at 5 years was significantly better for buccal cancer than floor of mouth cancer ($P = 0.041$). Thus, marginal mandibulectomy can be safely performed in select buccal mucosa tumors crossing the line of abutment but not involving the mandible.

Submental island flap

Reconstruction following surgeries for oral malignancies is a subject where Indian literature is still scarce. Microvascular reconstruction, though ideal, is a challenge in our country due to resource constraints and expertise. With the large number of HNCs, there is a need to develop and propagate pedicled flaps which address function and form. Sebastian *et al.*[17] from Regional Cancer Centre, Trivandrum, presented their experience on thirty patients of oral cancers reconstructed with the submental artery island flap and assessed the flap, donor-site morbidity, and oncologic outcomes. They reported only one total and one partial flap loss. While the hair growth was difficult to manage in one patient, the overall healing was excellent and the donor site had minimum morbidity. Thus, the submental artery flap is a simple and reliable option for oral cancer reconstruction in selected cases, with acceptable cosmetic and functional results and reasonable oncological safety.

Nonsurgical Therapeutics in Head-Neck Squamous Cell Carcinoma

Accelerated fractionation of radiotherapy-feasibility in resource-constrained conditions

One of the major biological factors affecting the outcome of radiotherapy (RT) is accelerated tumor repopulation during treatment[18] and there is enough literature[19,20] showing improvement in tumor control with reduction in overall treatment time. A shorter treatment course can be obtained either by increasing the dose per fraction or by increasing the number of fractions without altering the dose per fractionation. The former treatment modality results in disproportionate increase in late complications.[21-23] The DAHANCA trials 6 and 7 compared conventional RT (5 fractions a week) versus accelerated RT (6 fractions a week) and found a 15% overall benefit of accelerated course with acceptable number of complications.[19] However, it remained to be proved whether the benefit of accelerated form of treatment can be applied to the patients of the developing countries without significantly increasing the treatment-related morbidity (and thus the cost of treatment in resource-constrained conditions).

A multicenter clinical trial was conducted in a period of January 1999 to March 2004 on 908 patients from developing countries across the world (nine centers in Asia including Tata Memorial Hospital, Mumbai, Maharashtra, India) to assess whether accelerated fractionation could be applied in developing countries, where there are fewer therapeutic resources and where tumor burdens can be heavier.[24] Patients of oral cavity, larynx, and pharynx who were eligible for curative intent RT were divided into two groups – accelerated regimen of six fractions of RT per week ($n = 458$) and conventional RT regimen of five fractions per week ($n = 450$). The 5-year actuarial rate of locoregional control was 42% in the accelerated group versus 30% in the conventional group. Acute morbidity in the form of confluent mucositis was noted in 45 patients in the accelerated group and 22 patients in the conventional group. Severe skin reactions were noted in 87 patients in the accelerated group and fifty patients in the conventional group. There were no significant differences in late radiation-induced side effects. This study showed that accelerated RT results in better locoregional control in curable HNCs as compared to conventional fractioned RT with acceptable increased incidence of acute toxicities and no increased incidence of late toxicities. As accelerated fractionation does not require additional resources and does not significantly increase the morbidity burden, it can be used as a standard of care in resource-constrained developing countries.

Superiority of concurrent chemoradiotherapy versus accelerated fractionation of radiotherapy

The updated meta-analysis of chemotherapy in HNC of 93 RCTs showed a benefit in OS and locoregional control of concomitant chemotherapy with RT over RT alone however at the cost of increased toxicities.[25] The DAHANCA trials 6 and 7 showed an overall treatment benefit of accelerated RT over conventional RT in patients with curable HNCs with acceptable increased toxicities.[19-24] However, there was sparse prospective literature comparing the treatment benefits and toxicity profile of concurrent chemoradiation with accelerated RT in the curative setting. To address this issue, a prospective, randomized clinical trial was conducted in Tata Memorial Hospital to compare standard conventional external beam RT (5 fractions per week) to concurrent chemoradiotherapy (CTRT) and accelerated RT (6 fractions per week) in the treatment of locally advanced head-neck SCC (HNSCC).[26] One hundred ninety-nine patients were enrolled and randomly allocated to 1 of the 3 arms between April 2000 and October 2007. The mean and median follow-up for surviving patients were 54 and 48 months, respectively. Patients in the CTRT arm had significantly improved locoregional control as compared to the two radiation arms. OS was also better in the CTRT arm; however, the difference was not statistically significant. Grade 3 acute mucositis was significantly more in the CTRT and accelerated RT groups as compared to conventional RT group. There was no significant difference in Grade 3 acute skin toxicity in the three groups. Late toxicities were similar in the three groups. This study clearly proved the benefit of concurrent CTRT over accelerated RT in locoregional control in advanced HNCs which happens to be the standard of care as of now.

High-precision radiotherapy – three-dimensional chemoradiotherapy or intensity-modulated radiation therapy?

Conventional RT comprises portals based on two-dimensional fluoroscopic imaging without major emphasis on shielding normal tissues resulting in considerable acute and late toxicities, most commonly xerostomia.[27] The increasing use of CT imaging for target volume delineation has resulted in precision of RT delivery to affected sites with sparing of normal tissues and is the basis behind three-dimensional CTRT (3D-CTRT).

The advent of intensity-modulated radiation therapy (IMRT) defined as an advanced form of high-precision conformal technique that uses nonuniform radiation beam intensities determined through computer-based optimization to achieve the desired dose distribution has revolutionized contemporary RT practice.[28]

An RCT was conducted in Tata Memorial Hospital from 2005 to 2008 comparing the two high-precision modes of RT techniques – 3D-CTRT and IMRT.[29] Sixty-two patients were enrolled in the study. Acute xerostomia was significantly less in patients receiving IMRT as compared to patients receiving 3D-CTRT. There was no significant difference in any other acute toxicity. Late xerostomia and subcutaneous fibrosis were also significantly less in patients receiving IMRT. There was also significantly better return of salivary functions in patients undergoing IMRT. There was, however, no difference in locoregional control in survival at 3 years between the 2 arms. This study highlighted the fact that though technically and economically more demanding, IMRT should be the treatment of choice whenever feasible.

Chemoradiation in the role of palliative treatment

The management of unresectable HNSCC is not clearly defined in literature. They are neither fit for radical surgery with adjuvant treatment or definitive RT or CTRT. Some of them undergo RT with escalating doses while others receive injectable or oral chemotherapy based on performance status. Still others with poor performance status not suitable for any treatment are candidates for best supportive care. A Phase II randomized study on 114 patients with unresectable HNSCC (nasopharynx and larynx excluded) was conducted by Kumar *et al*.[30] in AIIMS to address this issue. Patients were divided into 2 arms (57 in each arm) – arm A received short course RT alone (4 Gy/#/day for 5 days) and arm B received RT as arm A + concurrent cisplatin (CDDP) at 6 mg/m^2/day intravenous (IV) bolus for 5 days. Those with at least partial response were taken for further RT to complete biological equivalent dose of 70 Gy, in both the arms. In arm B, concurrent CDDP at a dose of 40 mg/m^2/week was administered. Patients going for further RT were significantly more in arm B. Progression-free survival (PFS) and OS were also significantly more in arm B. Although Grades 3 and 4 dysphagia were more in arm B, patients generally tolerated the arm B treatment well and there was a relative improvement in quality of life for most parameters in arm B. Although not enough to make definitive conclusions, this study can be a gateway for a future Phase III RCT which can standardize the treatment protocol of patients with advanced HNCs not suitable for curative intent treatment.

Role of Chemotherapy in Head-Neck Squamous Cell Carcinoma – Recent Indian Data

Unlike hematolymphoid malignancy or germ cell tumors, HNSCCs are moderately chemosensitive precluding use of chemotherapy as the principle treatment modality. Role of chemotherapy is established mainly either in combination with RT for organ preservation[31] or in the adjuvant setting potentiating the role of radiation therapy to improve locoregional control.[32] Use of neoadjuvant chemotherapy (NACT) either for chemoselection (European Organization for Research and Treatment of Cancer – larynx preservation)[33] or for downsizing the tumor is still largely investigational. As opposed to curative setting, palliative chemotherapy is essential in treating recurrent or metastatic HNSCC. In the recent Indian literature, major focus is on reducing treatment-related toxicity by altering universally accepted chemotherapy regimens to improve outcomes in the Indian setting of resource constraints, poor general health, and lack of social support.

Neoadjuvant chemotherapy in unresectable oral head-neck squamous cell carcinoma

In a large retrospective series by Patil *et al*.,[34] they evaluated the role of NACT in unresectable oral HNSCC (oral squamous cell carcinoma [OSCC]) to assess efficacy of NACT in tumor volume reduction and increasing resectability. A total of 721 OSCC patients received 2 cycles of NACT and were reassessed after 2 cycles for resectability. A total of 310 patients (43%) had sufficient tumor reduction to merit surgical resection. The locoregional control rate at 24 months was 20.6% for the overall cohort with 32% of patients undergoing surgery in contrast to 15% of patients undergoing further nonsurgical treatment (P = 0.0001). The median OS was significantly better in those patients undergoing surgery (19.6 months) vis-a-vis patients treated with nonsurgical treatment (8.16 months [95%, CI 7.57–8.76] in [P = 0.0001]). This has impacted on treatment with patients who are generally fit and could afford NACT receiving NACT to downstage their tumor and improve outcomes.

Weekly cisplatin regime

Concurrent chemoradiation with 3 weekly CDDP is the current standard of care for nonsurgical management of locally advanced HNSCC. The standard dose of 100 mg/m^2 is associated with significant hematologic and nephrotoxicity which can reduce the treatment compliance or result in suboptimal treatment delivery.

In the article by Gupta *et al*.,[35] in 2009, they studied 264 HNSCC patients who received definitive CTRT at the dose of CDDP 30 mg/m^2 along with standard fractionation RT to a dose of 66–70 Gy in 33–35 fractions over 6.5–7 weeks. Two-thirds (65%) of patients received ≥85% of planned CDDP dose. With a mean follow-up of 19 months, the 5-year local control, loco-regional control, and DFS were 57%, 46%, and 43%, respectively. Acute Grade 3 or worse mucositis and dermatitis were seen in 77 (29%) and 92 (35%) patients, respectively, essentially in patients receiving doses ≥66 Gy and 6 or more cycles of chemotherapy. Other toxicities (hematologic, nausea, and vomiting) were mild and self-limiting. Many patients are now treated routinely with concurrent weekly CDDP with equal efficacy and acceptable acute toxicity with weekly chemoradiation having potential to be an optimal regimen in locoregionally advanced SCC of the head and neck, particularly in limited-resource settings.

Similar findings were reported by Dimri *et al*.,[36] who reported 188, Stage III/IV, treatment naive HNSCC patients (excluding nasopharynx and paranasal sinus) treated with weekly CDDP 35 mg/m^2 and RT to the dose of 60–66 Gy (at 2 Gy/fraction, 5 fractions per week).

Although weekly CDDP regimen has comparable outcomes with better toxicity profile as compared to standard regimen,

there is currently no Level I evidence to support its use. An RCT comparing weekly versus 3 weekly CDDP is being undertaken at Tata Memorial Centre to address this controversy.

Metronomic chemotherapy

The administration of chemotherapy at low, minimally toxic doses on a frequent schedule, without prolonged drug-free breaks has recently emerged as a potential strategy to control advanced or refractory cancer. Metronomic chemotherapy (MCT) is a low-cost, well-tolerated solution with an easy to access strategy that is an attractive therapeutic option in resource-limited setting. MCT is being used not only for palliative patients but also for curative patients in the neoadjuvant setting.

Operable advanced oral cancer

In a retrospective matched pair analysis, Pai *et al*.[37] reported oral metronomic scheduling of anticancer therapy (MSAT) in advanced operable oral cancers, in conjunction with standard therapy. Advanced operable oral cancer patients having a waiting period for surgery >3 weeks were administered MSAT. Patients then underwent standard therapy (surgery ± adjuvant radiation/chemoradiation) as warranted by the disease, followed by MSAT maintenance therapy. Outcomes of the MSAT group were compared with stage-matched controls with similar waiting periods. Response was seen in 75% of 32 patients. Two-year DFSs in MSAT and control groups were 86.5% and 71.6%, respectively. Two-year DFS in MSAT group who received at least 3 months of MSAT was 94.6% (P = 0.03). This study highlighted oral MSAT as an economical, effective, and safe therapy in oral cancers. It has the potential for preventing progression of the disease and improving DFS. This led to a randomized control study currently underway at the TMH in operable oral Stage III/IV cancers randomized to standard surgery and postoperative radiation versus oral MCT alongside surgery and radiation therapy.

Palliative setting

In another Phase II randomized trial by Patil *et al*.,[38] oral MCT (celecoxib and methotrexate) was compared with 3 weekly single agent IV CDDP in patients with recurrent/metastatic HNSCC requiring palliative chemotherapy who could not afford cetuximab. Among 110 patients studied, patients in the MCT arm had significantly longer PFS (median 101 days) compared to the IP arm (median 66 days) (P = 0.014). The OS was also increased significantly in the MCT arm (median 249 days) as compared to the IP arm (median 152 days) (P = 0.02). There were fewer Grade 3/4 adverse effects with MCT, which was not significant (18.9% vs. 31.4%, P = 0.14). Although not the Level I evidence, these two studies emphasize the potential indications for the use of MCT, which need to be evaluated further.

Monoclonal Antibody

Majority of the HNSCC express epidermal growth factor receptor (EGFR) over the cell membrane. Molecular-targeted agents such as anti-EGFR antibodies are emerging as the recent treatment modalities in recent years. Cetuximab has shown efficacy in palliative setting along with conventional IV chemotherapy (extreme trial) and many other molecular-targeted antibodies against EGFR are currently under investigation. In a recent Phase IIb RCT from Kidwai Memorial Institute of Oncology, Bengaluru,[39] authors studied clinical utility of nimotuzumab, a monoclonal anti-EGFR antibody, used concurrently with RT and CTRT in inoperable SCC of the head and neck. In 92 patients studied, with follow-up of 5 years concurrent use of nimotuzumab with CTRT/RT was found to be safe with acceptable toxicity and provided long-term survival benefit.

To summarize, a large number of clinical trials and studies are being conducted in various oncology centers in India. Significant data are emerging in the field of HNCs which provide quality evidence for managing important clinical issues. There is need to collaborate and plan future studies keeping the relevance of research to the local settings in India, which will help us optimize cancer care.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Grégoire V, Lefebvre JL, Licitra L, Felip E; EHNS-ESMO-ESTRO Guidelines Working Group. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v184-6.
2. GLOBOCAN 2012 (IARC) Section of Cancer Surveillance. Available from: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx. [Last accessed on 2016 Jun 23].
3. Mayne ST, Morse DE, Winn DM. Cancers of the oral cavity and pharynx. In: Schottenfeld D, Fraumeni FJ, editors. Cancer Epidemiology and Prevention. 3rd ed. New York, NY, USA: Oxford University Press; 2006. p. 674-96.
4. Amit M, Yen TC, Liao CT, Chaturvedi P, Agarwal JP, Kowalski LP, *et al.* Improvement in survival of patients with oral cavity squamous cell carcinoma: An international collaborative study. Cancer 2013;119:4242-8.
5. Kane SV, Gupta M, Kakade AC, D' Cruz A. Depth of invasion is the most significant histological predictor of subclinical cervical lymph node metastasis in early squamous carcinomas of the oral cavity. Eur J Surg Oncol 2006;32:795-803.
6. Huang SH, Hwang D, Lockwood G, Goldstein DP, O'Sullivan B. Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity: A meta-analysis of reported studies. Cancer 2009;115:1489-97.
7. Chaturvedi P, Datta S, Nair S, Nair D, Pawar P, Vaishampayan S, *et al.* Gross examination by the surgeon as an alternative to frozen section for assessment of adequacy of surgical margin in head and neck squamous cell carcinoma. Head Neck 2014;36:557-63.
8. Pantvaidya GH, Agarwal JP, Deshpande MS, Rangarajan V, Singh V, Kakade A, *et al.* PET-CT in recurrent head neck cancers: A study to evaluate impact on patient management. J Surg Oncol 2009;100:401-3.
9. Dandekar MR, Kannan S, Rangarajan V, Purandare NC, Chaukar DA, Deshmukh A, *et al.* Utility of PET in unknown primary with cervical metastasis: A retrospective study. Indian J Cancer 2011;48:181-6.
10. Arya S, Rane P, Deshmukh A. Oral cavity squamous cell carcinoma: Role of pretreatment imaging and its influence on management. Clin Radiol 2014;69:916-30.
11. de Bondt RB, Nelemans PJ, Hofman PA, Casselman JW, Kremer B, van Engelshoven JM, *et al.* Detection of lymph node metastases in head and neck cancer: A meta-analysis comparing US, USGFNAC, CT and MR imaging. Eur J Radiol 2007;64:266-72.
12. Chaturvedi P, Datta S, Arya S, Rangarajan V, Kane SV, Nair D, *et al.* Prospective study of ultrasound-guided fine-needle aspiration cytology and sentinel node biopsy in the staging of clinically negative T1 and T2 oral cancer. Head Neck 2015;37:1504-8.
13. D'Cruz AK, Vaish R, Kapre N, Dandekar M, Gupta S, Hawaldar R, *et al.* Elective versus therapeutic neck dissection in node-negative oral cancer. N Engl J Med 2015;373:521-9.
14. Pantvaidya GH, Pal P, Vaidya AD, Pai PS, D'Cruz AK. Prospective study of 583 neck dissections in oral cancers: Implications for clinical practice. Head Neck 2014;36:1503-7.
15. Singh B, Nair S, Nair D, Patil A, Chaturvedi P, D'Cruz AK. Ipsilateral neck nodal status as predictor of contralateral nodal metastasis in carcinoma

of tongue crossing the midline. Head Neck 2013;35:649-52.
16. Pathak KA, Shah BC. Marginal mandibulectomy: 11 years of institutional experience. J Oral Maxillofac Surg 2009;67:962-7.
17. Sebastian P, Thomas S, Varghese BT, Iype EM, Balagopal PG, Mathew PC. The submental island flap for reconstruction of intraoral defects in oral cancer patients. Oral Oncol 2008;44:1014-8.
18. Kim JJ, Tannock IF. Repopulation of cancer cells during therapy: an important cause of treatment failure. Nat Rev Cancer 2005;5:516-25.
19. Overgaard J, Hansen HS, Specht L, Overgaard M, Grau C, Andersen E, *et al.* Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet 2003;362:933-40.
20. Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, Phillips TL, *et al.* A radiation therapy oncology group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: First report of RTOG 9003. Int J Radiat Oncol Biol Phys 2000;48:7-16.
21. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, *et al.* Hyperfractionated or accelerated radiotherapy in head and neck cancer: A meta-analysis. Lancet 2006;368:843-54.
22. Peters LJ, Ang KK, Thames HD Jr. Accelerated fractionation in the radiation treatment of head and neck cancer. A critical comparison of different strategies. Acta Oncol 1988;27:185-94.
23. Bernier J, Bentzen SM. Altered fractionation and combined radio-chemotherapy approaches: Pioneering new opportunities in head and neck oncology. Eur J Cancer 2003;39:560-71.
24. Overgaard J, Mohanti BK, Begum N, Ali R, Agarwal JP, Kuddu M, *et al.* Five versus six fractions of radiotherapy per week for squamous-cell carcinoma of the head and neck (IAEA-ACC study): A randomised, multicentre trial. Lancet Oncol 2010;11:553-60.
25. 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;92:4-14.
26. Ghosh-Laskar S, Kalyani N, Gupta T, Budrukkar A, Murthy V, Sengar M, *et al.* Conventional radiotherapy versus concurrent chemoradiotherapy versus accelerated radiotherapy in locoregionally advanced carcinoma of head and neck: Results of a prospective randomized trial. Head Neck 2016;38:202-7.
27. Jensen SB, Pedersen AM, Vissink A, Andersen E, Brown CG, Davies AN, *et al.* A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: Prevalence, severity and impact on quality of life. Support Care Cancer 2010;18:1039-60.
28. Tejpal G, Jaiprakash A, Susovan B, Ghosh-Laskar S, Murthy V, Budrukkar A. IMRT and IGRT in head and neck cancer: Have we delivered what we promised? Indian J Surg Oncol 2010;1:166-85.
29. Gupta T, Agarwal J, Jain S, Phurailatpam R, Kannan S, Ghosh-Laskar S, *et al.* Three-dimensional conformal radiotherapy (3D-CTRT) versus intensity modulated radiation therapy (IMRT) in squamous cell carcinoma of the head and neck: A randomized controlled trial. Radiother Oncol 2012;104:343-8.
30. Kumar A, Sharma A, Mohanti BK, Thakar A, Shukla NK, Thulkar SP, *et al.* A phase 2 randomized study to compare short course palliative radiotherapy with short course concurrent palliative chemotherapy plus radiotherapy in advanced and unresectable head and neck cancer. Radiother Oncol 2015;117:145-51.
31. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W, *et al.* Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091-8.
32. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, *et al.* Defining risk levels in locally advanced head and neck cancers: A comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck 2005;27:843-50.
33. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: Preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst 1996;88:890-9.
34. Patil VM, Prabhash K, Noronha V, Joshi A, Muddu V, Dhumal S, *et al.* Neoadjuvant chemotherapy followed by surgery in very locally advanced technically unresectable oral cavity cancers. Oral Oncol 2014;50:1000-4.
35. Gupta T, Agarwal JP, Ghosh-Laskar S, Parikh PM, D'Cruz AK, Dinshaw KA. Radical radiotherapy with concurrent weekly cisplatin in loco-regionally advanced squamous cell carcinoma of the head and neck: A single-institution experience. Head Neck Oncol 2009;1:17.
36. Dimri K, Pandey AK, Trehan R, Rai B, Kumar A. Conventional radiotherapy with concurrent weekly Cisplatin in locally advanced head and neck cancers of squamous cell origin – A single institution experience. Asian Pac J Cancer Prev 2013;14:6883-8.
37. 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;50:135-41.
38. Patil VM, Noronha V, Joshi A, Muddu VK, Dhumal S, Bhosale B, *et al.* A prospective randomized phase II study comparing metronomic chemotherapy with chemotherapy (single agent cisplatin), in patients with metastatic, relapsed or inoperable squamous cell carcinoma of head and neck. Oral Oncol 2015;51:279-86.
39. Reddy BK, Lokesh V, Vidyasagar MS, Shenoy K, Babu KG, Shenoy A, *et al.* Nimotuzumab provides survival benefit to patients with inoperable advanced squamous cell carcinoma of the head and neck: A randomized, open-label, phase IIb, 5-year study in Indian patients. Oral Oncol 2014;50:498-505.