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Review

Evolving multidisciplinary treatment of squamous cell carcinoma of the head and neck in India☆

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ABSTRACT

In this article, we highlight the evolution of a multimodal approach in the overall management of squamous cell carcinoma of the head and neck (SCCHN) in India; present advances in technology (newer surgical techniques), novel medical and radiotherapy (RT) approaches; review their roles for an integrated approach for treating SCCHN and discuss the current role of immunotherapy in SCCHN. For locally advanced (LA) SCCHN, the multidisciplinary approach includes surgery followed by RT, with or without chemotherapy (CT) or concurrent chemoradiotherapy. Improved surgical techniques of reconstruction and voice-preservation are being implemented. Advanced forms of high-precision conformal techniques like intensity-modulated radiotherapy are used to deliver highly conformal doses to tumors, sparing the surrounding normal tissue. Compared with RT alone, novel CT regimens and targeted therapeutic agents have the potential to improve locoregional control and survival and reduce treatment-induced toxicities. Several clinical trials have demonstrated efficacy, safety, and quality of life benefits of adding cetuximab to RT regimens in LASCCHN. Studies have also suggested a cetuximab-related laryngeal preservation benefit. At progression, platinum-based CT combined with cetuximab (a monoclonal anti-epidermal growth factor receptor antibody) is the only validated option available as the first-line therapy. Thus, an integrated multidisciplinary approach plays a key role in maximizing patient outcomes, reduction in treatment related morbidities that consequently impact quality of life of survivors.

Introduction

Head and neck cancers (HNCs) involve various malignancies of the upper aerodigestive tract and are one of the most frequently diagnosed cancers worldwide [1]. These include cancers of the lip, oral cavity, oropharynx, larynx, hypopharynx, salivary glands, nasopharynx, nose, paranasal sinus, and middle ear. In 2008, over 260,000 cancers of the oral cavity were diagnosed globally. A wide variation exists in the incidence of oral cancer within the Asian region; South Central Asia had among the highest rates of oral cavity cancers (9.4/100,000 in males and 5.5/100,000 in females) while Eastern Asia had the lowest rates (2.1/100,000 in males and 0.9/100,000 in females). The Asian region also has the highest rates of nasopharyngeal cancers worldwide [2]. In India, squamous cell carcinoma of the head and neck (SCCHN) is the third most common cancer in both sexes. The male to female ratio is 4:1 [3].

The burden of cancer is higher in developing countries than in developed countries; it may be more complex, masking the true

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incidence because of inadequate reporting and substantially lower number of cancer registries [4-6]. Smoked tobacco and alcohol are the major causative factors for HNCs worldwide. In the Asian population, smokeless tobacco, betel nut, and Epstein-Barr virus are recognized etiological agents [7]. Association of Human papillomavirus (HPV) infection and prognosis of SCCHN has been increasingly recognized in the West, but the situation remains unclear in India [8].

The tumors can be classified into four distinct subtypes based on gene expression patterns assayed on complementary deoxyribonucleic acid (DNA) microarrays. They include a subtype with a possible epidermal growth factor receptor (EGFR) pathway signature, a mesenchymal-enriched subtype, a normal epithelium-like subtype, and a subtype with high levels of antioxidant enzymes [9].

The prognosis of SCCHN is largely based on the size and location of tumors and the presence of lymph node metastases. Several other prognostic factors like extracapsular invasion, peri-neural invasion, and presence of lympho-vascular invasion and other molecular markers like CXC chemokine receptor 2, CXC chemokine receptor 4, and CC chemokine receptor 7 have been identified [10-11]. SCCHN primarily presents as a locoregionally advanced (stage III or IV) cancer, especially in developing world [12].

Recent improvements in surgical techniques, radiation techniques, and chemotherapy (CT) agents have improved the overall outcomes of SCCHN; however, a significant percentage of this cancer recurs [13].

HNC treatment has evolved over the years. The outcomes of treatment modalities such as surgery and radiotherapy (RT) have shifted the focus of curative efforts from radical ablation to function preservation and restoration [14]. In this review we have tried to trace the evolution of HNC management in India from single modality treatment to multimodality approach and adoption of newer techniques and drugs in the fields of surgical, radiation and medical oncology (Fig 1).

Surgical treatment

Surgery has been the mainstay of treatment in head and neck cancers in primary lesion and metastatic neck nodes. Improved techniques of en bloc resection and reconstruction with voice-preserving laryngectomy and hemi-laryngectomy are now being implemented. In 1951, the surgical procedure of choice for clinically positive necks was radical neck dissection with sacrifice of the internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve [15].

Over the period of time, the focus shifted on modified radical neck dissection and selective neck dissection, permitting effective fascial compartment dissection of the cervical lymph nodes with preservation of the nonlymphatic structures leading to improvement in function and cosmetic preservation.

Vandenbrouck et al. (1980) demonstrated that metastases from subsites within the head and neck follow predictable patterns to specific lymph node levels within the neck. On the basis of these patterns of metastasis, elective dissection of select lymph node levels most at risk was offered as an alternative to elective modified radical neck dissection. In addition, extracapsular spread (ECS) was identified as the most important negative prognostic factor [16].

Reconstruction after surgeries for oral malignancies is a challenge in India because of resource constraints and expertise. Pedicled flaps that address function and form need to be developed and propagated. The submental artery flap could be a simple and reliable option for oral cancer reconstruction in select cases, with acceptable cosmetic and functional results and reasonable oncological safety [17].

Pathak and Shah (2009) assessed the feasibility of marginal mandibulectomy for oral cancers in close proximity to the mandible without its involvement. They reported that cause-specific survival at 5 years was significantly better for buccal cancer than for floor of mouth cancer ($P = 0.041$) and stated that marginal mandibulectomy can be safely performed in select buccal mucosa tumors crossing the line of abutment but not involving the mandible [18].

Singh et al. (2013) retrospectively analyzed neck dissections for tongue lesion reaching or crossing the midline and concluded that ipsilateral nodal positivity was the best predictor of contralateral nodal metastasis. They recommended contralateral neck dissection in the presence of multiple ipsilateral-involved nodes [19]. Recently, D'Cruz et al. (2015) have reported better oncological outcome with elective neck dissection (END) as compared to therapeutic neck dissection (TND) and suggested that END should be considered the treatment of choice in the management of early oral cancers [20].

Radiotherapy

RT remains an important option for early SCCHN and has produced high cure rates that are comparable to those produced with surgical treatment, but with lower morbidity [21-22].

Concurrent chemoradiation

Concurrent chemoradiation with three-weekly concurrent cisplatin is the current standard of care for the nonsurgical management of locally advanced (LA) SCCHN. The standard dose of 100 mg/m^2 is associated with considerable hematologic and nephrotoxicity, which can reduce treatment compliance or result in suboptimal treatment delivery.

Anand et al. (2008) evaluated the impact of intensity-modulated

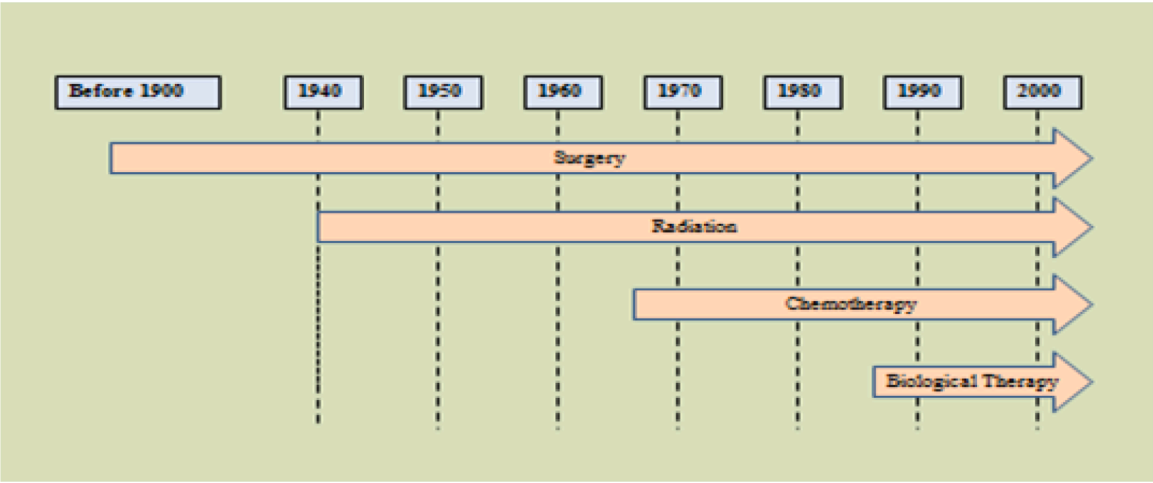

Fig. 1. Evolution and Advancement of Treatment of Squamous Cell Carcinoma of the Head and Neck.

radiotherapy (IMRT) on the incidence and severity of chronic dysphagia and xerostomia in patients with HNC. Sixty-two patients, of which 77.4% had advanced locoregional disease, were analyzed. Concurrent chemotherapy was given to 29 of the 45 patients treated with definitive IMRT. Seventeen patients received post-operative IMRT. At a median follow-up of 19months, 2-year actuarial locoregional control and survival was 77% and 74%, respectively. At 6months after IMRT, chronic dysphagia was Grade 0 in 77.1% of patients, Grade 1 in 10.5%, and Grade 2 in 12.3%. Xerostomia was Grade 0 in 61.4% of patients, Grade 1 in 31.5%, and Grade 2 in 7% of patients [23].

Gupta et al. (2009) studied 264 SCCHN patients who received definitive concurrent chemo-radiotherapy (CTRT) with weekly cisplatin 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. With a mean follow-up of 19 months, the 5-year local control, locoregional control, and disease-free survival (DFS) rates were 57%, 46%, and 43%, respectively. Acute grade 3 or worse mucositis and dermatitis were seen in 77 (29%) and 92 (35%) patients, respectively. 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. This regimen could be an optimal regimen in locoregionally advanced SCCHN, particularly in limited-resource settings [24].

Dimri et al. (2013) reported similar findings in 188, stage III/IV, treatment-naive SCCHN patients (excluding nasopharynx and paranasal sinus cancer patients) treated with weekly CDDP 35 mg/m^2 and RT to the dose of 60–66 Gy (at 2 Gy/fraction, five fractions per week) [25].

Adjuvant radiation therapy

Adjuvant RT is indicated for T3, T4 tumors, positive lymph nodes, and other risk factors, such as ECS, positive margins, perineural invasion (PNI), lymphovascular invasion (LVI) etc. An increased total dose to at least 63 Gy improves locoregional control when ECS is present [21]. A 10% absolute increase in 5-year cancer-specific survival and overall survival (OS) has been demonstrated for patients with lymph node-positive SCCHN who were treated with RT [26].

Cooper et al. (2004) evaluated if concurrent postoperative administration of cisplatin and RT would improve the rate of local and regional control. After a median follow-up of 45.9 months, the rate of local and regional control was significantly higher in the combined therapy group than in the RT group (hazard ratio for local or regional recurrence, 0.61; 95% confidence interval [CI], 0.41 to 0.91; $P = 0.01$). The estimated 2-year rate of local and regional control was 82% in the combined therapy group, compared with 72% in the RT group. DFS was significantly longer in the combined therapy group than in the RT group (hazard ratio for disease or death, 0.78; 95% confidence interval, 0.61 to 0.99; $P = 0.04$). However, combined treatment is associated with a substantial increase in adverse effects ($P<0.001$). Four patients who received combined therapy died because of the treatment [27].Noronha et al. (2017) also assessed the noninferiority of cisplatin 30 mg/m^2 given once a week compared with cisplatin 100 mg/m^2 given once every 3 weeks. Once-every-3-weeks cisplatin at 100 mg/m^2 showed superior locoregional control (LRC), with more toxicity, than did once-a-week cisplatin at 30 mg/m^2, and must remain the preferred chemoradiotherapy regimen for LAHNSCC in the adjuvant setting [13].

I. Altered fractionation radiotherapy

Hyperfractionation RT is dividing the treatment into smaller than conventional doses per fraction, usually given twice a day, 6 h apart without changing the overall treatment duration to increase the therapeutic differential between late-responding normal tissues and tumors. Accelerated fractionation is defined as shortening the overall treatment duration of a regimen using conventional dose fractions with a goal to minimize tumor growth during treatment [28-29].

A multicenter clinical trial was conducted from January 1999 to March 2004 on 908 patients from developing countries across the world (9 centers in Asia) to assess whether accelerated fractionation could be applied in developing countries, where there are fewer therapeutic resources and where tumor burdens can be heavier. The 5-year actuarial rate of locoregional control was 42% in the accelerated group versus 30% in the conventional group (hazard ratio [HR] 0.63, 95% CI 0.49–0.83; $p = 0.004$). Differences in radiation-induced side effects were not significant [31]. A phase 3 randomized controlled study comparing accelerated fractionated RT versus conventional RT in SCCHN found no difference in 2-year locoregional control and OS in the postoperative setting [30]. As accelerated fractionation does not require additional resources and does not considerably increase the morbidity burden, it can be used as an alternative to concurrent chemo-radiation in resource-constrained developing countries. However, twice a day visit to hospital is a major drawback and not may be possible in many centers.

II. Intensity-modulated radiotherapy and image-guided radiotherapy

IMRT is an advanced form of high-precision conformal technique that uses nonuniform radiation beam intensities to deliver highly conformal doses to tumors with improved sparing of the surrounding normal tissue. Computer-based optimization is employed to achieve the desired dose distribution.

Anand et al. (2006) published the results of IMRT in their patients of LAHNCs. The authors showed that sparing of even one-sided salivary gland (usually contralateral) can conserve saliva in most patients [32].

Nutting et al. (2009) compared two RT delivery methods—computed tomography (CT)-planned parallel opposed lateral fields or parotid-sparing IMRT—in the treatment of 94 patients with pharyngeal tumors (T1–4, N0–3, M0). Twelve-month Late Effects of Normal Tissue/Somatic Objective Management Analytic scale (LENT-SOMA) ≥G2 xerostomia scores were observed in 74% (25/34) of RT and 40% (15/38) of IMRT patients ($P = 0.005$). Corresponding values at 18 months were 71% (15/21) and 29% (9/31) ($P = 0.004$). On the Radiation Therapy Oncology Group (RTOG) scale, 12-month ≥G2 xerostomia was reported in 64% (21/33) of RT versus 41% (15/37) of IMRT patients ($P = 0.06$). Corresponding values at 18 months were 81% (17/21) and 20% (6/30) ($P<0.001$) [33].

Gupta et al. (2012) compared the 2 high-precision modes of RT techniques—3D-CTRT and IMRT—in 62 patients. Acute xerostomia was significantly less ($P = 0.009$) in patients receiving IMRT than in patients receiving 3D-CTRT. Differences in any other acute toxicity were not significant. Late xerostomia and subcutaneous fibrosis were also significantly less in patients receiving IMRT. Recovery of salivary functions was significantly better in patients receiving IMRT that in patients receiving 3D-CTRT. However, locoregional control in 3-year survival was identical in the two groups [34].

III. Recurrent tumors

Surgery remains the modality of choice for recurrent HNC but is feasible only in selected cases. Palliative chemotherapy is considered a standard treatment in inoperable cases. However, re-radiation is also feasible and is increasingly being used in carefully selected patients specially if treatment for interval is more than 2 years since last radiation therapy. However, it was associated with higher incidence of > Grade 2 toxicity in 40–60% of patients. Recently re-radiation with IMRT has shown to significantly reduce morbidity as compared to older techniques of RT in these recurrent cancers. Kasperts et al. (2006) suggested that postoperative reirradiation is feasible for patients who undergo surgery for recurrent or second primary SCCHN [35]. Spencer et al. (2008) reported that reirradiation with CT may be offered in this setting with acceptable toxicities [36].

Stereotactic Body Radiotherapy (SBRT) is increasingly being used in palliative setting to treat various head and neck tumors because of its highly conformal dose distribution and stereotactic spatial accuracy of delivery [37-40]. Comet (2012) reported that a short SBRT treatment (3–5 days) is an effective salvage treatment with acceptable acute

toxicities in a population with previously irradiated HNCs . Addition of cetuximab to SBRT is feasible and has become reported favorable results [41].

Chemotherapy

With the introduction of cisplatin as an antineoplastic agent, further investigation of CT in HNC treatment flourished in the 1970s. The role of CT is established mainly either in combination with RT for organ preservation or in the postoperative adjuvant setting potentiating the role of RT to improve locoregional control. A meta-analysis (Pignon et al., 2009) showed that CT improved survival in patients curatively treated for nonmetastatic SCCHN, with a higher benefit with concomitant CT than with induction CT [12]. In Indian scenario also, concurrent radiation and chemotherapy has become standard of care as "solemodality" of treatment or in high risk post operative patients of LAHNC.

Induction or neoadjuvant chemotherapy

Gollin and Johnson (1971) compared patients who received 5-fluorouracil (5-FU) intra-arterially before RT with patients who received RT alone [42]. CT resulted in good tumor regression but not in an increase in survival. Despite the lack of survival benefit, several studies have demonstrated that response to initial CT predicted response to further treatment and responders had significantly greater survival than nonresponders [43-46].

In a landmark study, which investigated nonsurgical laryngeal preservation, induction CT followed by RT was compared with surgery (laryngectomy) followed by RT in locally advanced laryngeal cancer patients [47]. A similar study was designed by the European Organization for Research and Treatment of Cancer in hypopharyngeal cancer patients [48]. In both randomized trials, induction CT followed by RT in responders offered survival rates comparable to rates achieved with laryngectomy followed by RT with an added advantage of laryngeal preservation in approximate 70% of patients [47-48].

The addition of taxanes into induction chemotherapy has provided more alternatives. The induction triplet combination regimen of docetaxel, cisplatin, and 5-fluorouracil (TPF) is reported to be more effective in prolonging survival than the doublet platinum and 5-fluorouracil (PF) [49].

Indian study by Patil et al. (2014) evaluated the role of neoadjuvant CT in unresectable oral SCCHN to assess its efficacy in tumor volume reduction and increasing resectability. A total of 721 patients received two cycles of neoadjuvant CT and then were reassessed 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 patients treated with surgery (19.6 months) than in patients treated with nonsurgical treatment (8.16 months [95% CI, 7.57, 8.76] [$P = 0.0001$]) [50].

I. Chemotherapy in palliative setting

Approximately half of patients with LASCCHN develop locoregional or distant recurrences. CT is the standard of care for R/M SCCHN patients with a focus on palliation and prolonging survival. Bleomycin, taxanes, carboplatin, methotrexate, and 5-FU are active and produce response rates from 10% to 40% in recurrent SCCHN [51].

In a phase II randomized trial by Patil et al. (2015), oral metronomic chemotherapy (MCT) with celecoxib and methotrexate was compared with 3-weekly single-agent IV cisplatin (IP) in R/M SCCHN patients requiring palliative CT. Among 110 patients studied, patients in the MCT arm had significantly longer progression-free survival (PFS) (median 101 days) compared with patients in the single-agent cisplatin arm (median 66 days) ($P = 0.014$). The OS was increased significantly in the MCT arm (median 249 days) than in the IP arm (median 152 days) ($P = 0.02$). Grade 3/4 adverse effects were fewer with MCT than with IP and were not significant (18.9% versus 31.4%, respectively, $P = 0.14$) [52].

MCT is a low-cost, well-tolerated solution with an easy to access strategy that is an attractive therapeutic option in resource-limited settings.

Chemoradiation in palliative setting

Kumar et al. (2015) conducted a phase II randomized study on 114 patients with unresectable SCCHN (nasopharynx and larynx cancers were excluded). They divided patients into two 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 plus concurrent cisplatin (CDDP) at 6 mg/m^2/day intravenous (IV) bolus for 5 days. In both the arms, patients with at least partial response were taken for further RT to complete the biological equivalent dose of 70 Gy. Patients going for further RT were significantly more in arm B than in arm A. PFS and OS were also significantly more in arm B than in arm A. Although grade 3 and 4 dysphagia were more in arm B, the treatment was generally well tolerated. The quality of life was relatively improved for most parameters in arm B [53].

Oral metronomic scheduling of anticancer therapy in conjunction with standard therapy (Surgery ± adjuvant radiation/chemoradiation)

In a retrospective matched-pair analysis, Pai et al. (2013) reported oral metronomic scheduling of anticancer therapy (MSAT) in advanced operable oral cancers together 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 those of 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 [54].

Changing paradigms of management of squamous cell carcinoma of the head and neck

Advances in the management of SCCHN have multiple challenges. The efficacy of RT is limited by adverse events such as xerostomia, mucositis, and osteoradionecrosis. Toxicities (both short term and long term) resulting from platinum-based CT are concerning as they can have major implications on the quality of life of cancer survivors. Surgery which is usually extensive also has considerable acute and chronic morbidity especially difficulty in swallowing, trismus and disfigurement. Combined treatment regimens are no different. Improved understanding of molecular mechanisms underlying SCCHN disease progression and advances in molecular biology has led to the development of targeted therapeutic agents. EGFR overexpression is a strong and independent unfavorable prognostic factor in SCCHN and is correlated with decreased survival rates, RT resistance, locoregional treatment failure, and increased rates of distant metastases [55]. Cetuximab, a chimeric monoclonal antibody, binds with high affinity to the extracellular domain of the human EGFR, blocking ligand binding, resulting in receptor function inhibition. It also induces antibody-dependent cellular cytotoxicity (ADCC), which recruits cytotoxic T cells to attack and kill cancer cells.

ADCC is influenced by interactions between antibody Fc domains and other receptors like F_Y receptors expressed on immune accessory cells and the complement-activating protein C1q. This reaction can either activate mononuclear phagocytes, neutrophils, natural killer (NK) cells, and/or dendritic cells (DCs) or stimulate the secretion of interferon-α, opsonins, tumor necrosis factor-α, and chemokines that recruit immune effector cells. This results in inhibition of tumor cell

proliferation and angiogenesis, antigen presentation and lysis of tumor cells.

Many clinical studies have evaluated the efficacy and safety of cetuximab in various clinical and therapeutic scenarios. Fig. 2 depicts the evolution of treatment paradigm with cetuximab from 2006.

Bonner et al. (2006) reported the first pivotal study of a multinational randomized trial of RT alone compared with cetuximab plus RT for LASCCHN. For LASCCHN patients, cetuximab plus RT significantly improved OS at 5 years compared with RT alone, confirming cetuximab plus RT as an important treatment option in this group of patients. Cetuximab-treated patients with prominent cetuximab-induced rash (grade 2 or above) had better survival than patients with no or grade 1 rash [56].

The addition of cetuximab to cisplatin-based chemoradiotherapy (CRT) in LASCCHN patients was well tolerated and resulted in encouraging local control and survival rates [57-61]. Huang et al. (2016) compared chemoradiation with cetuximab-based bioradiotherapy in SCCHN patients. In a subgroup analysis, taking the effects of treatment and adverse events into consideration, cetuximab plus RT showed superior responses regarding OS and PFS in HPV-positive patients of primary oropharyngeal SCC [62].

An organ preservation Phase II study by the Spanish Head And Neck Cancer Cooperative Group showed that cetuximab with RT could improve functional larynx preservation in patients with stage III and IVA laryngeal cancers who responded to docetaxel, cisplatin, and 5-FU [63].

Bonner et al. (2016) reported laryngeal preservation rates were 87.9% at 2 and 3 years in the cetuximab plus RT group compared with 85.7% at 2 years and 76.8% at 3 years in the RT alone group with an HR of 0.57 (95% CI, 0.23–1.42; $P = 0.22$). The results demonstrated a possible cetuximab-related laryngeal preservation benefit in patients with hypopharyngeal or laryngeal cancer [64].

Ahn et al. (2015) recommends replacing cisplatin with cetuximab in case of platinum ineligibility and in patients at increased risk of platinum toxicity [65].

Dattatreya and Goswami (2011) treated 19 Indian patients with LA unresectable disease, unsuitable for platinum-based CRT, with concurrent regimen of RT for 7 weeks. The combination of cetuximab with RT was safe and a feasible treatment protocol in ECOG-0 for patients with unresectable LASCCHN [66]. Noronha et al. (2017), in a retrospective analysis of Indian patients (n = 100) treated with weekly paclitaxel and cetuximab as palliative CT, reported promising efficacy and good tolerability in the palliative setting in advanced SCCHN in platinum-sensitive and -insensitive patients [13].

Cetuximab when added to RT for patients with LASCCHN does not affect quality of life [64,67].

Cetuximab and induction chemotherapy

Argiris et al. (2010) incorporated cetuximab in induction CT and subsequent CRT. At 36 months, 3-year PFS and OS were 70% and 74%, respectively. The quality of life (QoL) scores showed a significant decrement at 3 months after weekly cetuximab, which normalized at 1 year [68].

Cetuximab in recurrent or metastatic stage

A decade ago, cetuximab added to platinum-based CT became the new standard of care in R/M SCCHN, which was incorporated in the EHNS–ESMO–ESTRO Guidelines. Cetuximab as a single agent remains the only targeted agent indicated in R/M SCCHN. The regimen documented in the EXTREME trial is supported by a Phase III randomized controlled trial and subsequent observational studies with median survival ranging from 10 to 14 months, overall response rates between 36% and 44%, and disease control rates of >80% [69-73].

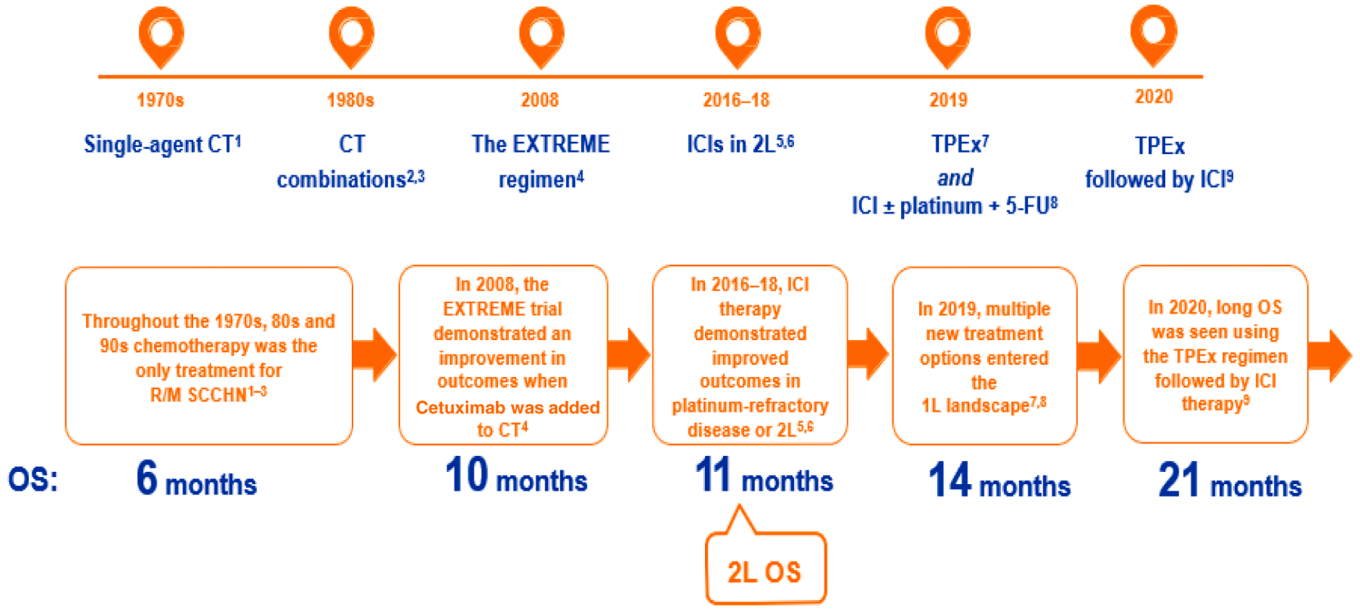

Fig. 2. Treatment paradigms of Cetuximab from 2006 to 2020

Note: The chronological order is according to the year of publication of respective Phase 2/3 trials.

Retrospective setting; * Combination did not improve outcome

B: Bevacizumab; CTX: Cetuximab; C: Cisplatin; Ca: Carboplatin; CDDP: Chemoradiotherapy with Concomitant Cisplatin; Da: Dasatinib; DC: Docetaxel; E; Erlotinib; FU: Fluorouracil or 5-FU; HU: Hydroxyurea; ICT: Induction Chemotherapy; IL-12: Interleukin-12; IMRT: Intensity-modulated Radiotherapy; TPF: Taxotere, Platin, Fluorouracil; P: Paclitaxel; Pe: Pemetrexed; S: Sorafenib

[1]Burtness et al., 2005 [69]; [2]Bourhis et al., 2006 [90]; [3]Vermorken et al., 2008 [70]; [4]Hitt et al., 2012 [91]; [5]Rangaraju et al., 2012 [74]; [6]Fury et al., 2012 [92]; [7]Argiris et al., 2013 [93]; [8]Guigay et al., 2015 [94]; [9]Jimeno et al., 2015 [95]; [10] Gilbert et al., 2015 [96]; [11]Matuschek et al., 2016 [97]; [12]Bhatia et al., 2016 [98]; [13]McMichael et al., 2016 [99]; [14]Bonner et al., 2006 [56];[15]Quon et al., 2009 [100]; [16]Kies et al., 2009 [101]; [17]Argiris et al., 2010 [68]; [18]Wanebo et al., 2010 [102]; [19]Merlano et al., 2010 [57]; [20]Kao et al., 2011 [58]; [21]Seiwert et al., 2011 [103]; [22]Adkins et al., 2013 [104]; [23]Keil et al., 2013 [105]; [24]Argiris et al., 2016 [106]; [25]Magrini et al., 2016 [107].

An Indian retrospective study of 35 R/M SCCHN patients who received cetuximab with weekly paclitaxel and platins (cisplatin/carboplatin) from August 2006 to October 2008 demonstrated that cetuximab with weekly paclitaxel and a platinum agent is a well-tolerated regime with similar efficacy [74].

In a prospective Indian study in 50 patients of R/M SCCHN, the reported response rate of cetuximab plus CT was >45% with promising PFS rates [4]. In a prospective study conducted at a tertiary center in North India, cetuximab plus platinum plus 5-FU combination improved the overall response rate and PFS when given as first-line treatment in patients with R/M SCCHN. DCR was 92% and median PFS was 5.3 months (95% CI: 4.52, 6.14 months) [75]

Cetuximab with weekly combination CT (paclitaxel + *a* platinum compound) has shown promise and demonstrated comparable response and outcomes with acceptable toxicity in R/M SCCHN patients. Significant improvement in the QoL scores was seen with cetuximab, along with improvement in pain, swallowing, speech problems, and social eating [76-77].

Continuum of care in recurrent/metastatic squamous cell carcinoma of the head and neck

R/M SCCHN patients have a poor prognosis with a median OS of <1 year [78]. The "EXTREME" regimen is the first-line treatment of R/M SCCHN, combination therapy with cetuximab plus cisplatin/carboplatin plus 5-FU, followed by maintenance cetuximab until disease progression. A variation in this regimen allows for the substitution of 5-FU for a taxane (e.g., docetaxel or paclitaxel). Patients who progress on or are ineligible for the EXTREME regimen and other cetuximab-based first--line treatments are generally treated with methotrexate, docetaxel,

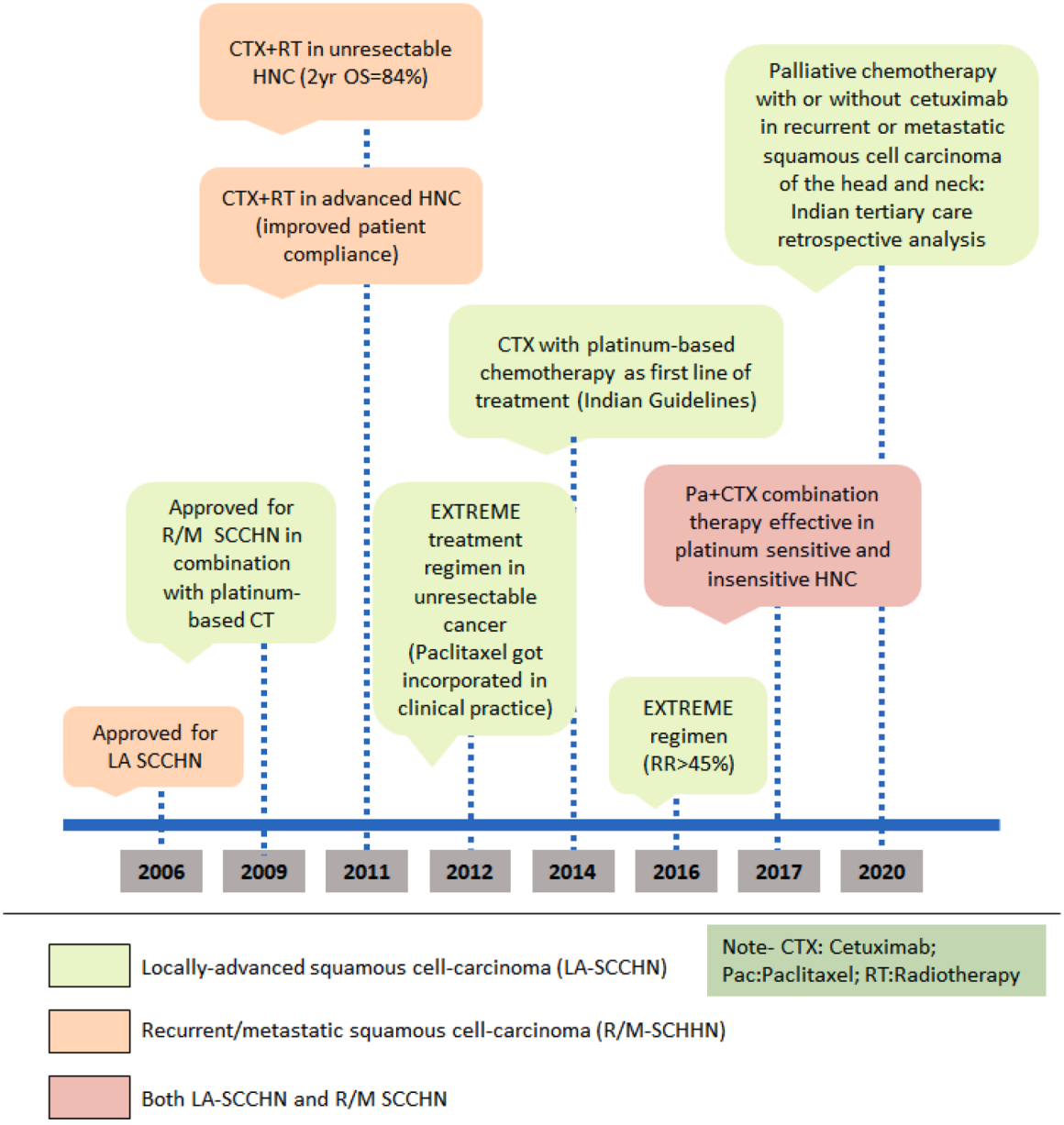

Fig. 3. Evolution of Treatment of Squamous Cell Carcinoma of Head and Neck with Cetuximab in India
Note: The chronological order is according to the year of publication of respective studies/retrospective analysis.
CTX: Cetuximab; RT: Radiotherapy; Pa: Paclitaxel; RR: Response rates
[1]Dattatreya et al., 2009 [65]; [2]Agarwal et al., 2011 [108]; [3]Rangaraju et al., 2012 [73]; [4]Patil et al., 2014 [49]; [5]Tiwari et al., 2016 [3]; [6]Noronha et al., 2017 [13]; Bahl et al., 2020 [109].

paclitaxel, and cetuximab as monotherapies. Immune checkpoint inhibitors (ICIs) are being proposed as another second-line treatment option that can be integrated into R/M SCCHN continuum of care paradigm [77]. Fig. 3

Current scenario - A Truly multidisciplinary approach

The management of HNC patients is complex, and a multidisciplinary approach, as advocated by the National Comprehensive Cancer Network and the European Society for Medical Oncology clinical practice guidelines, is required. Management should be tailored according to tumor characteristics, patient population, and multidisciplinary team (MDT) expertise and preferences. The goals of management in HNC patients are cancer treatment with minimal morbidity, preservation and restoration of organ function, and improvement of quality of life.

In recommendations for HNC management in Asian patients, an MDT approach with cross-specialty representation and opinion sharing at tumor boards has been strongly advocated at all stages [79].

Future horizons

The future of SCCHN therapy will probably be more personalized and may combine EGFR inhibitors with other agents for a synergistic benefit. It will be target based on the genetic make-up of patients, patient-specific prognostic markers, and location and stage of tumors [80-84]. Next-generation sequential regimens are emerging as an approach to increase activity while decreasing toxicity [85].

Many monoclonal antibodies targeting protein kinase B, mechanistic target of rapamycin, and phosphatidylinositol-4, 5-bisphosphate 3-kinase pathways are being investigated to sensitize tumor cells to RT. A combination of cisplatin, cetuximab, and valproic acid, a histone deacetylase inhibitor, is being evaluated in R/M SCCHN patients, by taking advantage of the possible positive interaction among histone deacetylase inhibitors, cisplatin, and/or an anti-EGFR antibody [86]. ICIs nivolumab and pembrolizumab have emerged as promising new treatment options for R/M SCCHN [77].

The overall efficacy of EGFR inhibitor-targeted therapy in SCCHN patients could also be enhanced by adding T cell-based immunotherapy. The combined treatment of cetuximab and ipilimumab, aimed at increasing immune response against tumors, is currently undergoing Phase Ib testing along with radiation in stage III-IV SCCHN (NCT01935921) [87]. After encouraging preliminary results, avelumab is being clinically evaluated in five clinical trials for safety and efficacy in SCCHN treatment. It is being studied in combination with standard of care CRT (cisplatin plus RT) and in combination with RT and cetuximab. Avelumab is also being evaluated in patients unfit for cisplatin and HPV-16-positive oropharyngeal SCCHN [88].

A large randomized trial ($N = 539$) showed that taxane based TPExtreme regimen followed by immunotherapy can give promising QoL and OS results in recurrent/metastaic HNSCC. The trial compared TPExteme regimen (four cycles every 3 weeks [Q3W] of docetaxel, cisplatin, and cetuximab with mandatory granulocyte colony-stimulating factor support followed by cetuximab maintenance every two weeks) with EXTREME regimen (six cycles Q3W of 5FU–cisplatin-cetuximab followed by weekly cetux maintenance). The TPExtreme arm had higher scores of Global Health Status, physical and role functioning ($p = 0.02$; $p = 0.009$ and $p = 0.013$, respectively) and lower appetite loss scores ($p = 0.041$) than the EXTREME arm. The median OS (95%CI) in the TPExtreme arm was higher than in EXTREME arm (21.9 vs. 19.4 months since randomization; 11.6 vs. 8.3 months since start of immunotherapy [89].

Conclusion

Multidisciplinary approach remains the mainstay for SCCHN treatment. An integrated multidisciplinary approach maximizes patient outcomes with conservation of the organ. A large number of clinical trials and studies are being conducted in various oncology centers worldwide as well as in India, providing a range of potential combinations of treatment regimens for SCCHN. In the recent Indian literature, major focus is on reducing treatment-related toxicities, resource constraints, poor general health, and lack of social support. The development of novel CT regimens with or without immunotherapy and targeted therapeutic agents has the potential to improve locoregional control and overall patient survival as well as aid in anatomical and functional organ preservation and reduce treatment-induced toxicities.

Conflict of Interest Statement

All the authors can confirm that they have no conflict of interest for this manuscript. Vaibhav Saxena is an employee of Merck Specialities Pvt. Ltd, India, an affiliate of Merck KGaA, Darmstadt, Germany.

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