Multidisciplinary Management of Locally Advanced SCCHN: Optimizing Treatment Outcomes

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Disclosure: K. K. A. has acted in a consultant/advisory role for Bristol-Myers Squibb, ImClone, Sanofi-Aventis, and AstraZeneca, and has received research funding from Amgen and ImClone. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the authors, planners, independent peer reviewers, or staff managers.

Key Words. Cetuximab  Radiotherapy  EGFR  SCCHN  Head and neck cancer

ABSTRACT
The management of locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN) is highly complex. Data from recent clinical trials have altered the treatment landscape by refining the use of existing therapies, such as radiation therapy and chemotherapy, and providing new treatment options, such as cetuximab. Selecting the most appropriate treatment for an individual patient requires a multidisciplinary approach and careful assessment of the relative advantages and disadvantages of each treatment approach. Surgery is highly effective but can have debilitating long-term consequences. Chemoradiation and altered fractionation radiation therapy are more effective than conventional radiation therapy, but also more toxic; as a consequence of toxicity, suboptimal delivery of radiation may diminish, in practice, the efficacy observed in clinical trials of these strategies. Cetuximab plus radiation therapy is more effective than radiation alone and does not substantially increase radiation-related toxicity, or affect the delivery of planned radiotherapy. However, whether cetuximab plus radiation therapy is similar in efficacy to chemoradiation is unknown at this time. Ideally, multidisciplinary teams weigh all these factors when making individual treatment decisions. Data from current trials will help further optimize multimodality treatment for LA-SCCHN.

INTRODUCTION
The management of patients with head and neck cancer is complex, and treatment of squamous cell carcinoma of the head and neck (SCCHN) varies according to clinical characteristics and the expertise of the medical team. Comorbidity is frequent in SCCHN patients and can preclude aggressive therapy [1–4]. Moreover, SCCHN and its treatment may negatively affect basic physiological functions, senses, speech, and physical appearance [5]. As a result, the optimal management must often account for clinical and psychosocial factors beyond disease eradication.

 Approximately 60% of SCCHN patients present with locally advanced (LA) disease [5]. The majority of these patients will require multimodality treatment. Standard treatment in this setting includes surgery, radiation therapy (RT), chemotherapy (CT), and biological or targeted...
agents. Data from recent clinical trials have led to the refinement of current therapies and new treatment options.

Given the inherent complexity of SCCHN and wide range of treatment combinations available, a multidisciplinary approach is essential. This article reviews the recent data that have shaped the current approach to treatment for LA-SCCHN and addresses some of the practical challenges of implementing multimodality treatment.

**Current Treatment Modalities in SCCHN**

**Surgery**

Surgery continues to play an important role in managing resectable tumors of the larynx, hypopharynx, and oropharynx, despite the emergence of organ-preserving strategies as part of the standard of care, often regardless of resectability [5]. Larynx-preserving strategies may allow for natural speech conservation without compromising survival compared with total laryngectomy [6–8]. This opportunity for long-term survival with organ preservation has shifted the role of surgery toward managing the neck nodes (e.g., planned neck dissection) and disease recurrence. Technologic advances, however, now allow for nonradical surgical approaches with acceptable function recovery, such as laser-based procedures or transoral robotic surgery, and may offer an alternative to aggressive organ-sparing approaches (see below).

Even for operable patients, surgery is often accompanied by other treatment modalities. Multidisciplinary assessments are thus crucial to postoperative/adjuvant planning, which may include RT, a strategy shown to improve locoregional control (LRC) and recommended for patients with a moderate recurrence risk (i.e., multiple positive nodes or perineural, lymphatic, or vascular invasion) [5].

**RT**

Conventional RT typically consists of 2 Gy/day given in a single fraction 5 days/week for 7 weeks. Altered fractionation (AF) schedules have been developed in an effort to improve outcomes following RT without substantial worsening of the late toxicity profile. Accelerated fractionation reduces the total treatment time to hinder tumor cell repopulation between doses and improve LRC. Hyperfractionation involves daily administration of two reduced-dose fractions (1.1–1.2 Gy), which allows increasing the total dose by up to 15% without increasing the risk for late toxicity.

In a meta-analysis of 15 clinical trials comparing AF with conventional RT in patients with SCCHN [9], AF was associated with longer overall survival (OS), longer cancer-related survival, and better LRC (Table 1). The OS improvement was attributed mainly to better local control. AF had no apparent effect on the development of distant metastases. Overall, the survival benefit was greater with hyperfractionated RT than with accelerated fractionation (p = .02), and in younger than in older patients (p = .007). However, some accelerated fractionation regimens were shown to yield LRC improvements similar to those seen with hyperfractionation [9, 10]. The tolerability of AF was difficult to assess in the meta-analysis because of the variability in toxicity assessment and reporting, particularly late radiation effects.

Intensity-modulated RT (IMRT), which conforms closely to the tumor volume, avoids or minimizes exposure to unaffected tissue [11–15]. The feasibility of this approach was demonstrated in a study in 15 patients with SCCHN. When compared with standard irradiation plans generated retrospectively for each patient, IMRT led to a higher minimum dose delivered to the targeted tumor (95.2% versus 91% of the prescribed dose; p = .02) and a lower maximal radiation dose to normal tissue (p < .001) [11].

Available data also suggest that IMRT is as effective as conventional RT or accelerated concomitant-boost RT, and can reduce some late toxicity [12, 14]. The locoregional progression-free and OS rates were similar in 112 patients with stage III/IV oropharyngeal cancer, 71 treated with accelerated concomitant boost RT and 41 treated with IMRT [14]. There was a substantial difference, however, in the

| Table 1. Absolute benefit at 5 years of AFRT compared with conventional RT: results of a meta-analysis of 15 clinical trials [9] |
|-----------------|-----------------|-----------------|---------------|---------------|
| Outcome         | Hyperfractionation, % | Accelerated fractionation without TDR, % | Accelerated fractionation with TDR, % | All 3 groups, % (p-value) |
| Survival        | 8.0             | 2.0             | 1.7           | 3.4 (<.0003)  |
| Cancer-related survival | 7.8             | 3.5             | 2.3           | 4.3 (.0002)   |
| Locoregional control | 9.4             | 7.3             | 2.3           | 6.4 (<.0001)  |

Abbreviations: AFRT, altered fractionation radiotherapy; RT, radiotherapy; TDR, total dose reduction.
rates of acute and late toxicities, with lower rates of skin toxicity, 10% versus 20%, mucositis, 66% versus 72%, and grade ≥2 xerostomia, 12% versus 67%, associated with the use of IMRT. The 2-year rate of dependence on gastric (percutaneous endoscopic gastrostomy [PEG]) feeding tubes was also significantly lower with IMRT (4% versus 21%; p < .02). At M.D. Anderson Cancer Center, we found that IMRT was effective in a retrospective review of 51 patients with small primary oropharyngeal carcinoma [13]. A substantial proportion of patients treated with IMRT still required a gastric tube (40%), although, consistent with previous observations, feeding tube use was brief: only 10% still required the tube 6 months after treatment, all patients were tube-free after 1 year, and only three patients had chronic difficulty swallowing. Based on our results, we now use IMRT to treat most patients with small and even advanced oropharyngeal tumors. IMRT has been increasingly adopted for SCCHN treatment, but involves a learning curve for the practitioner, and standardization (in terms of target definition and dose specification) still needs to be resolved [5, 14].

CT

In parallel to the development of AF schedules, numerous trials have evaluated adding CT to locoregional treatment for patients with LA-SCCHN. In a meta-analysis of 87 trials of CT plus locoregional treatment, CT was found to improve survival, with an absolute benefit of 5% at 5 years (Table 2) [16, 17]. The improvement was particularly noteworthy when CT was given concomitantly with RT: 8% at 5 years. Platinum-based CT was more effective than non–platinum-based regimens (p < .01). More recent trials of platinum-based CT generally support these findings [8, 18–22]. As with AFRT, chemoradiotherapy (CRT) was associated with more toxicity than RT alone, and had no apparent effect on the rate of distant metastasis. The potential advantage of CRT, however, may be outweighed by the impact of treatment-derived complications in certain patients that may contribute to non–cancer-related deaths [23]. This may be particularly evident as these patients are followed up in the long term [23], or in the subpopulation of elderly patients, who seem to consistently derive less benefit from concurrent CRT regimens [24].

CRT postsurgery has also been the object of two recent phase III studies: the Radiation Therapy Oncology Group (RTOG)-9501 trial and the European Organization for Research and Treatment of Cancer (EORTC)-22931 trial [25, 26]. Both studies randomized patients with high-risk surgical-pathologic features after surgery to RT or RT plus cisplatin (100 mg/m² every 3 weeks for three cycles). In the RTOG-9501 trial [25], CRT resulted in a significantly lower risk for locoregional recurrence compared with RT alone (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.41–0.91; p = .01), but did not lead to a longer OS. In the EORTC-22931 trial [26], both progression-free survival (HR, 0.75; 95% CI, 0.56–0.99; p = .04) and OS (HR, 0.70; 95% CI, 0.52–0.95; p = .02) were significantly longer with CRT. Notably, neither trial found a significant effect on distant metastases.

Postoperative CRT was also more toxic than RT alone (grade ≥3 adverse events in the CRT arm: RTOG, 77% versus 34%, p < .001; EORTC, 41% versus 21%, p = .001), an observation that triggered a pooled analysis to identify those patients most likely to benefit from intensive postoperative CRT [27]. Based on the only two risk factors found to be significantly associated with benefit from CRT across both trials, CRT following surgery is now recommended for patients at high risk for recurrence, as defined by the presence of extracapsular extension and/or positive surgical margins [5, 27].

Given the demonstrated benefit of adding CT to RT, concomitant CRT is the standard of care for unresectable LA-SCCHN patients who are medically fit to receive CT, and for organ preservation in patients with resectable disease. Postoperative CRT is also an option for patients at high risk for recurrence.

As management trends move forward, the addition of CT to RT regimens beyond conventional fractionation will probably become more relevant. As discussed above, AFRT may lead to superior efficacy over conventional schedules, and CT may enhance the efficacy of AFRT as it does with conventional regimens [22, 28–33]. However, the exacerbation of toxicities associated with such regimens could become a concerning issue, and, to date, it may be considered an area in need of optimization [22, 31].

As improvements in LRC have altered patterns of treatment failure and placed greater emphasis on control of dis-

**Table 2. Meta-analysis: survival outcomes when adding CT to RT [17]**

<table>
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<th>Survival</th>
<th>Absolute benefit at 5 years, %</th>
<th>p-value</th>
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<tr>
<td>All CT: adjuvant, neoadjuvant, concomitant (n = 87 trials)</td>
<td>0.88 5</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Concomitant CRT (n = 50 trials)</td>
<td>0.81 8</td>
<td>&lt;.0001</td>
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Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; HR, hazard ratio; RT, radiotherapy.
tant metastases, interest has been renewed in induction CT, which may reduce the rates of systemic relapse [6, 16, 34–36]. Although early clinical trials did not demonstrate overall therapeutic advantages to adding an induction component prior to definitive therapy, and this strategy seemed to fare worse than concurrent CRT [8, 16], the cisplatin–infusional fluorouracil regimen as pre-RT induction showed a survival benefit when compared with RT alone [16, 34, 36, 37]. Recent studies, following up on those initial findings, have demonstrated that adding a taxane to the classic platinum-based induction CT may lead to better efficacy. Objective response rates (complete response plus partial response) varying in the range of 93%–100% and 3-year OS rates of 62%–78% were observed across these studies, suggesting that adding docetaxel may provide superior clinical benefit over standard platinum-based induction CT [38–44]. These preliminary results were confirmed in several large phase III trials, which found that adding a taxane to standard platinum-based induction CT prior to RT resulted in significantly longer OS in patients with LA disease, including resectable patients, unresectable patients, and those considered candidates for organ preservation [45–47]. Hitt and colleagues [46] treated 121 patients (resectable and unresectable) with induction paclitaxel, cisplatin, and fluorouracil, and achieved a significantly longer median OS time compared with 127 patients given cisplatin and fluorouracil alone (36 versus 26 months, respectively; \( p = .04 \)). Similar results were also observed in the EORTC-24971 phase III study with unresectable tumors. At 51 months of follow-up, a significantly longer median OS time was observed for the docetaxel–cisplatin–5-fluorouracil treatment arm (\( n = 177 \)) than for the cisplatin–5-fluorouracil patients (\( n = 181 \); 18.6 versus 14.2 months, respectively; \( p = .0052 \)) [45]. Finally, in the TAX324 study conducted in the U.S. with resectable and unresectable patients (\( n = 501 \)) [47], the addition of docetaxel to cisplatin plus 5-fluorouracil also resulted in a longer OS time (median, 71 months versus 30 months; \( p = .006 \); median follow-up, 42 months) [47]. Throughout these studies, the addition of a taxane was found to be generally tolerable, and no negative impact on quality of life was observed in the EORTC-24971 study, which included it as a secondary endpoint [48]. In addition, because induction CT prior to RT has been developed in pursuit of longer survival times, this approach has been shown to be effective for laryngeal preservation [6, 49, 50].

Although induction CT prior to RT alone may improve outcomes, and optimizing induction CT seems to be in progress with these combinations, current results are insufficient to validate this approach compared with the superior therapeutic benchmarks provided by concurrent CRT. There is no demonstration yet that, even with this optimized regimen, introducing an induction step improves efficacy over the currently established concurrent CRT on its own. Whether sequential incorporation of optimized induction regimens prior to established CRT regimens will improve outcomes is a focus of two actively recruiting trials in the U.S. [51, 52], as well as others outside the U.S. and no longer recruiting. Therefore, this intensive approach should be considered investigational. Other intensive “sequential” approaches involving induction CT, standard CRT, and salvage surgery are also under investigation in attempts to define an optimal integration of all three treatment modalities [46, 53, 54].

Cetuximab

Improvements gained with AFRT and CRT come at a price: both intensive approaches are associated with a higher rate of acute morbidity, particularly mucositis, which often leads to suboptimal delivery of therapeutic regimens. These issues underscore the need for new treatment options that are at least as effective as the current approaches but better tolerated.

Cetuximab (Erbitux®; ImClone Systems Inc., New York, and Bristol-Myers Squibb, Princeton, NJ) is an IgG1 monoclonal antibody that targets the epidermal growth factor receptor (EGFR) with high affinity. It binds to the epitope of the extracellular domain of the EGFR and promotes internalization of the receptor, thereby preventing activation by ligand binding; in addition, cetuximab may mediate antitumor immune effects such as antibody-dependent cell-mediated cytotoxicity [55–60]. EGFR has been implicated in the growth, survival, and invasive potential of tumor cells, as well as cell damage repair and angiogenesis [61–63]. Nearly all SCCHN expresses EGFR, and overexpression is associated with a poor prognosis [64–66], poor response to RT [67, 68], and higher risk for locoregional recurrence following definitive therapy [67]. Cetuximab and RT have synergistic effects in preclinical models [69–71]. Blockade of the nuclear influx of EGFR and of the subsequent formation of DNA-PK, Ku70/80 complexes involved in repairing DNA double-strand breaks induced by irradiation was recently shown to be a mechanism by which cetuximab sensitizes tumor cells to RT [72]. Results from a phase I study indicate that cetuximab can be given safely in combination with RT [73].

A multinational phase III study compared RT plus cetuximab with RT alone in patients with LA-SCCHN [74]. In total, 424 patients were randomized to high-dose RT (one of three possible schedules) or high-dose RT plus concomitant cetuximab (400 mg/m² initial dose, followed by 250 mg/m² weekly for the duration of the RT). With a me-
dian follow-up of 54.0 months, LRC (median, 24.4 versus 14.9 months; HR, 0.68; \( p \leq 0.005 \)) and OS (median, 49.0 versus 29.3 months; HR, 0.74; \( p \leq 0.03 \)) (Fig. 1, Table 3) were significantly better in patients who received cetuximab.

Notably, adding cetuximab to RT did not increase the incidence of RT-related adverse events such as mucositis, xerostomia, dysphagia, pain, and weight loss (Fig. 2). Severe late radiation effects were reported in \( \sim 20\% \) of patients in both treatment groups. Patients who received cetuximab had a higher incidence of grade 3 or 4 acneiform rash (17\% versus 1\%; \( p < 0.001 \)) and infusion reactions (3\% versus 0\%; \( p = 0.01 \)).

This trial showed that adding cetuximab to RT provides a clinically meaningful improvement in disease control and survival without substantially more toxicity or a negative effect on RT delivery. A weakness of this trial by the current benchmark is that the control group received RT alone—the standard of care at the time of study design—rather than CRT, the current standard. Preliminary efficacy results of cetuximab plus CRT are encouraging [75–79] (this combination also seems to be feasible for esophageal cancer [80]), and an ongoing phase III trial (RTOG-0522) is evaluating whether cetuximab improves disease-free survival when added to CRT in LA-SCCHN [81]. Other recently completed or ongoing trials are evaluating cetuximab combined with induction CT [82] or adjuvant CRT [83], or as maintenance therapy following CRT [84].

These studies will help to define the potential role of cetuximab in treating LA-SCCHN, and in organ-preserving strategies in particular [45, 49].

**Clinical Practice: Prognostic Assessment and Factors That Drive Treatment Decisions**

The Challenges of Combined Modality Therapy

Given the complexity of managing patients with LA-SCCHN, a multidisciplinary team approach is essential [5, 85]. Input from various professionals with expertise in SCCHN (Table 4) is needed from the earliest phases of care to ensure appropriate diagnosis and assessment of baseline characteristics, risk factors, and prognosis [5]. The optimal surgical approach, RT plan, and CT use are dictated by disease site and extent and other pathological findings.

Specific types of supportive care may be determined by the treatment plan, the patient’s physical condition, comorbidities, and other psychosocial factors. Among the supportive measures available to ameliorate the radiation-related symptoms are comediations such as amifostine (for xerostomia) [86, 87] and palifermin (for mucositis) [88], although the utility of the latter in patients with head and neck cancer seems to be more limited than in patients with hematologic malignancies [89]. Randomized trials are ongoing to assess its relative efficacy. It is important to note that these agents are not without undesirable effects of their own, and their use may not be successful in all patients. Even with the availability of these measures, nearly two thirds of the patients treated with CRT or AFRT develop severe mucositis and may require PEG tubes [22, 53, 90]. Therefore, many patients with LA-SCCHN are not optimal for intensive treatment because of comorbidity or a poor performance status. Poor compliance is observed in about one third of the patients treated with intensive CRT, particularly when cisplatin is administered at 100 mg/m² every 3 weeks for three cycles [91, 92]. Lower cisplatin doses or substitution with carboplatin may be better tolerated, but whether similar survival outcomes can be achieved with these strategies is unclear [93]. Intensive treatment has also been shown to negatively affect quality of life. In patients with laryngeal cancer, CRT has been found to negatively affect quality of life to a similar degree as total laryngectomy [94, 95].

Individual roles in the multidisciplinary team continue to evolve as new data on multimodality therapy emerge. Head and neck surgeons play a pivotal role because they are often the first to perform a biopsy and confirm an SCCHN diagnosis, but organ-preserving strategies have diminished the primary role of surgery in some LA-SCCHN. However, as surgical options evolve, issues such as the optimal timing of surgical procedures within multidisciplinary treatments may become ex-
Radiation oncologists maintain a prominent role in planning the appropriate RT regimen and assessing feasibility for individual patients, both in single-modality therapy and postsurgical adjuvant treatment. The medical oncologist occupies a central role, together with the radiation oncologist, in the management of patients with unresectable disease. In patients with resectable disease, the medical oncologist role was previously small but has now been expanded as well, by the routine postoperative practice of administering CRT in patients with high-risk pathologic features and by the growing trends favoring organ-preserving combined modality therapy. In addition, emerging data on quality of life and depression after treatment have emphasized the need for psychosocial support for patients with SCCHN [96, 97].

In practice, implementing a multidisciplinary approach is complicated and requires considerable effort and resources. Many large treatment centers routinely review each new case of SCCHN in a multidisciplinary forum. RT planning benefits from multidisciplinary input [98], and as existing treatment options are refined and new options emerge, this will be even more critical in defining/implementing optimal treatment plans. Smaller community centers, however, may not have adequate resources and facilities to perform a multidisciplinary review of each case.

### Table 3. Clinical outcomes when adding cetuximab to RT: phase III results [74]

<table>
<thead>
<tr>
<th></th>
<th>RT alone, n = 213</th>
<th>RT plus cetuximab, n = 211</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Yr survival, %</td>
<td>45</td>
<td>55</td>
<td>0.74 (0.57–0.97)</td>
<td>.03</td>
</tr>
<tr>
<td>2-Yr progression-free survival, %</td>
<td>37</td>
<td>46</td>
<td>0.70 (0.54–0.90)</td>
<td>.006</td>
</tr>
<tr>
<td>2-Yr locoregional control, %</td>
<td>41</td>
<td>50</td>
<td>0.68 (0.52–0.89)</td>
<td>.005</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; RT, radiotherapy.

**Figure 2.** Grade 3–5 adverse events occurring in ≥5% of patients in a phase III trial comparing radiation therapy (RT) plus cetuximab with RT alone [74]. *p < .001; †p = .006.
The optimal choice depends on a variety of patient- and disease-related characteristics. In many cases, the decision is not only efficacy based; “quality of life” outcomes are used to make therapy choices that otherwise seem comparable in terms of cancer control outcomes. Among the factors to consider are toxicity burden, organ preservation, and the potential for sequelae or impact on long-term quality of life. In order to understand how these factors affect therapeutic outcomes in patients outside well-controlled clinical research settings, it is important to gain insights into actual practices for toxicity management or dose delivery modifications, as well as differences in practice between academic and community centers. An ongoing longitudinal oncology registry of head and neck carcinoma is attempting to gather and organize information about actual treatment and management choices that patients with head and neck cancer experience [99].

Some specific factors have already been identified that can help in selecting an appropriate therapy, such as age and comorbidity. A multivariate analysis of data from RTOG trials identified age, disease stage, and site as potential risk factors for developing late toxicity after CRT [100]. Two meta-analyses demonstrated that intensive treatment approaches such as AF or CRT are not as effective in older patients (aged >70 years) as in younger patients [24]. Older patients may not tolerate treatment as well as younger patients, as was found in an analysis of data from two phase III trials of palliative cisplatin-based CT, in which older patients experienced more nephrotoxicity, diarrhea, thrombocytopenia, and toxic deaths [101].

More research is needed to identify biological markers and imaging techniques to better determine prognosis and predict treatment response [102, 103]. For example, data were presented at the 2006 American Society of Clinical Oncology Annual Meeting on gene-expression profiling to predict distant metastasis and survival in patients with nasopharyngeal cancer [104]. If confirmed, this approach could be useful in selecting patients for induction CT, based on their risk of developing distant metastases.

Selecting an RT Fractionation Schedule
Determining the optimal RT plan for a patient with LA-SCCHN requires a specially trained team, including a radiation oncologist, physicist, dosimetrist, and radiation therapist/technologist. RT (primary or adjuvant) is determined by anatomic, tumor, and patient characteristics. Given the considerable variability in individual characteristics, optimal doses or fractionation schedules for all patients with LA-SCCHN, or even for subgroups, are difficult to generalize [5].

In general, AF schedules are associated with higher acute toxicity than the conventional regimen, and using AF with other treatment modalities is likely to further increase the toxicity burden. Whether AF is better than conventional regimens when combined with concurrent CT was addressed in two randomized trials by the RTOG and the Groupe d’Oncologie Radiothérapie Tête Et Cou, the results of which will likely become available by mid-2008. The National Comprehensive Cancer Network practice guidelines on head and neck cancer recommend AF specifically for patients with T1, N1 and T2, N0–1 oropharyngeal tumors, and for patients with unresectable/recurrent disease who are unable/unwilling to receive concomitant CRT [5]. At this time, IMRT is not the standard of care for SCCHN, but selected patients may benefit from IMRT when treated in centers having the expertise.

Is Radiation Alone a Valid Treatment Option?
Adding either CT or cetuximab to RT has been proven to improve treatment outcomes over RT alone. The efficacy of concomitant platinum-based CRT has been shown in multiple phase III trials conducted over the last 25 years [16, 17], while data on cetuximab plus RT are derived from one recent, large, international phase III trial that granted the regulatory approval of this agent in head and neck cancer by both the U.S. Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products [74].

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**Table 4.** NCCN recommendations on multidisciplinary teams for SCCHN patients [5]

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Abbreviations: NCCN, National Comprehensive Cancer Network; SCCHN, squamous cell carcinoma of the head and neck.
Therefore, from an historical perspective, CRT is the prevalent treatment standard, but elucidating the relative merits of cetuximab plus RT versus CRT requires further evaluation. It is well known, however, that CT increases RT-related toxicity substantially, whereas cetuximab does not. Based on tolerability, cetuximab plus RT could represent the treatment of choice for patients with intermediate-stage disease, when relatively good outcomes do not justify the toxicity of CRT. Cetuximab plus RT may also provide an effective and well-tolerated alternative for high-risk patients who are ineligible for CT or unlikely to complete CRT as planned [105]. Because cetuximab improves treatment outcomes without exacerbating RT toxicity, it can be argued that the role of RT alone in the primary treatment of intermediate-stage and LA disease will shrink substantially. However, further data are needed to define which types of patients are appropriate for cetuximab plus RT, relative to CRT.

Toxicity Management and Long-Term Follow-Up

The primary side effects of cisplatin are nephrotoxicity and ototoxicity; emesis can now be well managed with antiemetic medication [93]. Cetuximab-related rash is not life-threatening and typically resolves after treatment; infusion reactions can be severe in a minority of patients [74, 106]. Long-term follow-up is needed for patients treated for LA-SCCHN to monitor for recurrent disease, prevent or manage treatment-related sequelae, and detect second primary tumors [5]. In general, follow-up should consist of a comprehensive head and neck examination with symptom management, social work, and other testing as indicated (Table 5). Adequate follow-up therefore requires a multidisciplinary team of individuals with expertise in SCCHN.

To date, there has not been standardized reporting of long-term toxicities and the impact on quality of life associated with aggressive CRT, although these concerns are greater for these patients. Important treatment sequelae include surgical morbidity requiring rehabilitation, RT-related toxicity, and systemic therapy side effects. RT-related toxicities such as mucositis and dysphagia are common and overwhelming, and sometimes potentially life-threatening or leading to long-term PEG dependence [107–110]. Long-term ototoxicity has been documented with RT portals extending up to the skull base. This side effect worsens when adding CT: the 10-year rate of sensorineural hearing impairment was 18% after RT alone and 30% after CRT [111]. RT to the head and neck can also damage dentition, and patients with SCCHN require special dental care and education before, during, and after RT [112]. Close cooperation among dental and medical professionals is needed to provide appropriate dental and oral care [112, 113].

Specific measures can be taken to prevent/minimize the impact of treatment sequelae. Adequate nutritional support throughout treatment can prevent weight loss [114, 115]. Smoking cessation counseling may improve outcomes, because continuing to smoke after treatment has been shown to be associated with a higher recurrence rate [116, 117]. Multiple strategies for preventing and managing swallowing disorders have been developed that may improve functional ability and quality of life following treatment [118].

CONCLUSION

Great strides have been made in recent years in managing patients with LA-SCCHN, and data from ongoing clinical trials will continue to refine existing therapies and provide new options. A multidisciplinary approach that considers tolerability and quality of life outcomes in addition to tumor control endpoints is therefore essential to making appropriate treatment decisions and providing optimal care and support.

Determining which treatment approach is best for each patient depends on multiple clinical factors and therapeutic goals, requiring a thorough assessment of each treatment’s expected efficacy/tolerability. The fact that most patients will undergo multimodality treatment further highlights the importance of multidisciplinary care. The next steps will include better integration of existing therapies and examining differences between clinical trial outcomes and daily clinical practice. Discovering biomarkers that can predict response to different therapy modalities will facilitate selecting the best therapy for individual patients.

Table 5. NCCN guidelines on follow-up of SCCHN patients [5]

<table>
<thead>
<tr>
<th>Pain and symptom management</th>
<th>Nutrition support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteral feeding</td>
<td>Oral supplements</td>
</tr>
<tr>
<td>Dental care for radiation effects</td>
<td>Xerostomia management</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>Tracheotomy care</td>
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<tr>
<td>Social work and case management</td>
<td>Palliative care</td>
</tr>
<tr>
<td>Screening for second primary tumor</td>
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Abbreviations: NCCN, National Comprehensive Cancer Network; SCCHN, squamous cell carcinoma of the head and neck.
The author takes full responsibility for the content of the paper but thanks Ryan Blanchard, B.S., Julia Saiz, Ph.D., and the Clinical Insights Inc. editorial team, supported by Bristol-Myers Squibb, for their assistance in researching references, creating the first draft in collaboration with the author, preparing figures and tables, and formatting the manuscript for submission.

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