

INVITED REVIEW MEDICAL REVIEW

Radiotherapy for the management of locally advanced squamous cell carcinoma of the head and neck

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BACKGROUND: Squamous cell carcinomas of the head and neck (SCCHN) affect approximately 35 000 people in the United States yearly. Although survival has improved with advances in therapy, patients with advanced stages of SCCHN continue to have a poor prognosis. An understanding of rationale for treatment selection, newer developments in therapy, and treatment toxicity is critical.

METHODS: Standard methods of treating locally advanced SCCHN are reviewed. Advances in medical and radiotherapeutic management are discussed and the toxicities of therapy are described.

RESULTS: Postoperative chemoradiation is used in patients with high-risk characteristics. Induction chemotherapy and altered fractionation radiation treatment have been evaluated as alternatives to definitive chemoradiotherapy. Targeted agents such as cetuximab may prove to increase survival with minimal increase in toxicity profile. Technological improvements such as the use of intensity-modulated radiation treatment have proven to decrease some debilitating side effects from radiation treatment.

CONCLUSIONS: Locally advanced SCCHN continues to present a therapeutic challenge. Survival, local control, and quality of life are all goals of treatment. The optimal method of treating locally advanced SCCHN is the subject of ongoing research. Long-term side effects can be minimized with the use of newer technologies and with careful treatment planning.

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Introduction

Approximately 34 000 patients develop head and neck cancers each year in the United States and 7550 of these patients will die of their disease (Jemal *et al*, 2007). In North America and Europe, tumors of the mucosal surfaces of the head and neck usually arise from the oral cavity, oropharynx or larynx, whereas in Mediterranean countries and in the Far East, nasopharyngeal cancer is more common (Titcomb, 2001). The incidence of head and neck cancers is twice as high in men as it is in women, but rates have been declining in men since 1975 and in women since 1980. Known risk factors for squamous cell carcinomas of the head and neck (SCCHN) are tobacco use (cigarette, cigar or pipe smoking, smokeless tobacco), HPV infection, and excessive alcohol use.

Early stage (Stage I and II) SCCHN accounts for 30–40% of cases with expected long-term disease free survival rates ranging from 60% to 90%. Locally advanced SCCHN (Stage III and IV without metastases) accounts for the remainder of cases. Approximately 50% of patients with SCCHN present with locoregionally advanced disease that is potentially resectable and have a projected 5-year overall survival (OS) in the range of 40–50%. Patients with unresectable locally advanced SCCHN have a distinctly poorer prognosis with a 5-year OS of approximately 10–40% (Greene *et al*, 2002; Jemal *et al*, 2007).

The therapy of SCCHN presents many challenges primarily because the head and neck region has many critical structures that can be damaged by tumor or treatment. These critical structures include the brain, brainstem, spinal cord, vertebral bodies, cranial nerves, carotid artery, pharynx, mandible, salivary glands, larynx and muscles of the pharynx critical to swallowing. Damage to these tissues by tumor or therapy can result in significant structural, cosmetic and functional deficits that negatively impact quality of life. Local recurrences and local progression of SCCHN are often incurable and eventually fatal. Because of the implications of local failure, the objective of many studies has been to improve locoregional control. Major secondary

goals for patients receiving therapy for SCCHN are preservation of organ function, minimizing toxicity of therapy, maximizing cosmesis, and minimizing the impacts of therapy on quality of life.

Many early stage head and neck cancers can be treated with single local modalities such as surgical resection or radiation therapy (RT). In contrast, local and distant failure rates are unacceptably high in patients with locally advanced disease treated with a single modality (Vokes *et al*, 1993; Adelstein *et al*, 1996; Soo *et al*, 2005). Recent efforts have incorporated multimodality treatment regimens in which surgery, radiation, and chemotherapy are combined in the hopes of improving disease control.

Although patients with locally advanced head and neck cancers have benefited from multimodality treatment regimens with improved local control and survival rates, the cost has been a significant increase in toxicity (Cooper *et al*, 1995; El-Sayed and Nelson, 1996; Pignon *et al*, 2000). In attempts to improve the therapeutic ratio, advances in surgical techniques, imaging (PET, MRI, CT), radiation (treatment planning, delivery technology), and chemotherapy have been implemented. An understanding of the rationale for embarking on multimodality therapy and an understanding of both the acute and late toxicities of these therapies is important for clinicians involved in the ongoing care and management of these patients. Finally, methods to assist in reducing and managing the expected toxicity of therapy are described.

Treatment modalities

Postoperative radiation treatment

Surgical therapy was long the primary treatment modality for patients with SCCHN. The high rates of local and regional failure in high-risk patients lead to the use of radiotherapy as an adjuvant. Postoperative RT has been considered the standard of care for a subset of patients for many decades. It is often recommended for major risk features identified pathologically in the resection specimen such as positive margins or extracapsular extension in lymph nodes and for minor risk features, including multiple positive lymph nodes or perineural/lymphatic/vascular invasion. Previously, preoperative RT was favored as it led to regression of tumor and improved OS relative to surgery alone. However, concerns about increases in operative morbidity with preoperative compared to postoperative RT led to the comparison of these two treatment strategies in randomized trials. RTOG 73-03 randomized patients with operable SCCHN preoperative RT (50 Gy) or postoperative RT (60 Gy). Higher doses of RT were used in the postoperative setting because of concerns that hypoxia in the surgical bed would decrease the efficacy of radiotherapy. This study found a 12% improvement in locoregional control (LRC) in the postoperative treatment group with marked increase in failures in the preoperative treatment group beyond 2 years (27% vs 8%). There was no significant difference in OS or toxicity profiles between the two groups (Tupchong *et al*, 1991). Based on this study, postoper-

ative therapy became the preferred regimen if both surgical therapy and radiotherapy were delivered.

Although radiotherapy improves outcomes compared to surgery alone, the combination of the two modalities in patients with locally advanced SCCHN yields a disappointing 5-year OS of about 30% (El-Sayed and Nelson, 1996). In an attempt to improve these outcomes, the EORTC (European Organisation for Research and Treatment of Cancer) and RTOG (Radiation Therapy Oncology Group) performed clinical trials evaluating the addition of concurrent sensitizing chemotherapy to regimens of surgery and radiotherapy (Bernier *et al*, 2004; Cooper *et al* 2004). Both groups completed randomized trials of concurrent cisplatin based chemotherapy and RT delivered in the postoperative setting to patients with risk factors for local recurrence (positive surgical margins, extracapsular extension of lymph node, lymphovascular invasion, perineural invasion). Patients enrolled on these trials were randomized to postoperative RT alone or to postoperative RT with concurrent cisplatin. Both studies found improved locoregional control and disease free survival in the patients that received concurrent cisplatin compared to those that received postoperative radiotherapy alone. Based on these two studies, postoperative RT with concurrent cisplatin has become standard of care for patients with high risk pathologic features (NCCN guidelines).

Definitive concurrent chemotherapy and radiation therapy

Surgical therapy is not always employed for locally advanced SCCHN due to concerns of organ function or if a tumor is unresectable. In these patients, definitive radiotherapy was first used as a method for obtaining local control. The addition of chemotherapy to RT was explored in a number of randomized trials during the 1960s through the 1990s as a means to improve rates of OS and locoregional control compared to the rates obtained with radiotherapy alone. Because conflicting results were obtained in these studies, a large meta-analysis (MACH-NC) was performed that reviewed 63 randomized trials that evaluated the addition of chemotherapy to the management of these patients (Pignon *et al*, 2000). This meta-analysis was unable to show an OS benefit with neoadjuvant or adjuvant chemotherapy. An update of this meta-analysis added 24 more trials and found a survival benefit to concurrent chemotherapy both in the postoperative and definitive treatment settings (Pignon *et al* 2007). More recently, multiple randomized Phase III trials have shown an improvement in OS and LRC when chemotherapy is added to radiotherapy for the definitive management of locally advanced SCCHN. Table 1 briefly summarizes several of these trials.

While the addition of chemotherapy to RT can improve disease control, it often increases the rate of mucositis and prophylactic gastrostomy (PEG) tube requirements (Vokes *et al*, 2003; Cooper *et al* 2004; Ang *et al*, 2005). A recent study has shown that the addition of chemotherapy to RT continues to increase the rate of Grade 2–3 xerostomia (92% vs 37% (chemoradiation vs radiation alone), Grade 3 mucositis (75% vs 51%),

Table 1 Selected trials of concurrent chemoradiation

Study	Patient characteristics	Treatment	OS	LRC/PFS	Toxicity (G3-4)
GORTEC (Denis <i>et al</i> , 2004)	226 pts, site: OP Stage III, IV	RT alone vs RT + 5-FU and carboplatin × 3 cycles	5 year 16% (RT) 23% (CRT)*	5 year LRC 25% (RT) 48% (CRT)*	Mucositis 39% (RT) vs 71% (CRT)* Feeding tube 15% (RT) vs 36% (CRT)*
ECOG/SWOG (Adelstein <i>et al</i> , 2003)	295 pts Site: OC, OP, HP, larynx Stage III, IV	RT alone (RT) vs RT and cisplatin (CRT) vs Split course RT, 5FU, cisplatin(split CRT)	3 year 23% (RT) 37% (CRT)* 27% (split CRT)*	3 year DSS 33% (RT) 51% (CRT)* 41% (split CRT)*	52% (RT) 89% (CRT)* 77% (split CRT)*
Intergroup 0099 (Al-Sarraf <i>et al</i> , 1998)	147 pts NP Stage III, IV	RT alone vs RT and cisplatin post RT 5FU and cisplatin	3 year 47% (RT) 78% (CRT)*	3 year PFS 24% (RT) 69% (CRT)*	More hematologic and gastrointestinal toxicity in CRT arm
Duke University (Brizel <i>et al</i> , 1998)	116 pts OC, OP, NP, HP, larynx Stage III, IV and Stage II BOT	RT alone vs RT and cisplatin/5FU (with 1 week break at 40 Gy)	3 year 34% (RT) 55% (CRT)*	3 year LRC 44% 70%*	Sepsis was more common in CRT group. Mucositis not more common in CRT but took longer to resolve than in RT alone group
RTOG 91-11 (Forastiere <i>et al</i> , 2003)	547 pts Larynx Stage III, IV	RT alone vs Cisplatin/5FU → RT vs RT and cisplatin	5 year 56% (RT) 55% (C → RT) 54% (CRT)	2 year LRC 56% (RT) 61% (C → RT)* 78% (CRT)*	36% (RT) 24% (C → RT) 30% (CRT)
RTOG 95-01 (Cooper <i>et al</i> , 2004)	459 pts OC, OP, HP, larynx High-risk characteristics	RT alone vs RT and cisplatin (CRT)	No significant difference in hazard ratios for OS	2 year LRC 82% (CRT) vs 72% (RT)*	34% (RT) 77% (CRT)* primarily mucous membrane, hematologic, and GI toxicities
EORTC 22931 (Bernier <i>et al</i> , 2004)	334 pts OC, OP, HP, larynx Stage I, II with unfavorable characteristics, Stage III, IV	RT alone RT and cisplatin (CRT)	5 year 40% (RT) 53% (CRT)*	5 year LRC 69% (RT) 82% (CRT)*	21% (RT) 41% (CRT)*

RT, radiation therapy; 5FU, 5 fluorouracil; CRT, chemoradiation; OP, oropharynx; OC, oral cavity; HP, hypopharynx; NP, nasopharynx; BOT, base of tongue; OS, overall survival; LRC, locoregional control; PFS, progression free survival; GI, gastrointestinal. *p ≤ 0.05.

Grade 3 dysphagia (82% vs 48%) and Grade 3 pain (29% vs 10%) (Nuyts *et al*, 2008).

Altered fractionation

For patients with locally advanced SCCHN that receive definitive radiation, chemotherapy can improve both LRC and OS. However, chemotherapy can significantly increase the toxicity profile and thus may not be appropriate for patients with specific contraindications, such as preexisting renal dysfunction. Efforts to improve outcomes without chemotherapy in patients treated with radiotherapy have included the use of altered radiation fractionation schemes.

Radiation is commonly delivered in a single daily fraction over the course of weeks (i.e. standard or conventional fractionation). Some subsets of tumors, such as SCCHN, have been found to grow rapidly. To combat this rapid growth, some have explored the use of alternative fractionation schemes such as hyperfractionation and accelerated fractionation to deliver more radiation dose in a shorter time. Hyperfractionation regimens deliver many smaller fractions of radiation and exploit the difference in fractionation sensitivity between tumors and normal tissues. Accelerated fractionation regimens attempt to reduce tumor proliferation, which is

a major cause of RT failure, by compressing the treatment schedule without major reductions in fraction size. Studies of altered fractionation schemes in patients with SCCHN have found improvements in local control at the cost of higher toxicity compared to conventional fractionation schemes (Table 2).

It remains unclear if concurrent chemotherapy or altered fractionation approaches are the preferred method of treatment in patients that receive definitive RT for locally advanced SCCHN. Although toxicity is sizable with both approaches, local failures remain a concern. For this reason, additional studies have been completed that have evaluated the combination of hyperfractionation and chemotherapy, RTOG 0129. Additional studies will need to be completed to compare these approaches and define the optimal regimen based on disease control rates and toxicity. It is possible that treatment will need to be individualized based on both disease stage, the functional status of the patient, and the goals of therapy.

Radiation therapy and targeted agents

The development of agents that target specific pathways selectively active or upregulated in tumors has provided a potential mechanism for treatment that may have less

Table 2 Selected trials of altered fractionation

Study	Patient characteristics	Treatment	OS	LRC	Toxicity
EORTC 22791 (Horiot <i>et al</i> , 1992)	356 pts OP excluding BOT size < 3 cm T2-3 N0-1	CONfx: 70 Gy in 7–8 weeks vs HF: 80.5 Gy in 70 fx in 7 weeks (1.15 Gy BID)	Difference NS	5 year 40% (CONfx)* 59% (HF)	Mucositis more severe in HF arm*
EORTC 22851 (Horiot <i>et al</i> , 1997)	512 pts intermediate to advanced H&N cancers (excluding HP)	AFX: 72 Gy, 1.6 Gy fx TID vs CONfx: 70 Gy, 1.8–2 Gy fx	Difference NS	5 year 59% (AFX)* vs 46% (CONfx)	14% (AFX)* 4% (CONfx)
RTOG 90-03 (Fu <i>et al</i> , 2000)	1073 pts Stage III-IV OC, OP, or supraglottic larynx Stage II-IV BOT, HP	CONfx: 70 Gy in 35 fx vs HF: 81.6 Gy in 1.2 Gy BID vs AFX-S: 67.2 Gy in 1.6 Gy BID with 2 week break after 38.4 Gy vs AFX-CB: 72 Gy total dose, 54 Gy in 1.8 Gy fx with 18 Gy boost in 1.5 Gy fx delivered as additional daily fraction for 12 days	2 year (all NS) 46% (CONfx) 54% (HF) 46% (AFX-S) 51% (AFX-CB)	2 year 46% (CONfx) 54% (HF)* 47% (AFX-S) 54% (AFX-CB)*	35% (CONfx) 54.5% (HF)* 50.4% (AFX-S)* 58.8% (AFX-CB)*

OP, oropharynx; BOT, base of tongue; HP, hypopharynx; OC, oral cavity; fx, fraction; SF, standard fractionation; HF, hyperfractionated; AFX, accelerated fractionation; AFX-S, split course accelerated fractionation; AFX-CB, accelerated fractionation with concomitant boost; CONfx, conventional fractionation; OS, overall survival; LRC, locoregional control; NS, not statistically significant. *p ≤ 0.5.

toxicity than cytotoxic chemotherapy and thus may have less toxicity when combined with radiation. SCCHN has been shown to overexpress epidermal growth factor receptor (EGFR) (Mendelsohn and Baselga, 2003; Hynes and Lane, 2005). In addition, radiation is known to induce EGFR-mediated radioreistance signaling pathways (Bonner *et al*, 1994; Liang *et al*, 2003), suggesting that inhibition of EGFR may provide an attractive means of selectively sensitizing tumors to radiation. Cetuximab is an immunoglobulin monoclonal antibody to the EGFR ligand binding domain (Fan *et al*, 1993) and has been used in trials in conjunction with RT. Cetuximab was tested in this setting in a multinational randomized trial in which patients with stage III/IV oropharyngeal, hypopharyngeal, and laryngeal primary tumors were randomized to cetuximab with RT vs RT alone, the standard treatment at that time (Bonner *et al*, 2006). This study found that RT combined with cetuximab improved 3 year LRC and OS rates compared to those obtained with radiation alone (from 45% to 55%). In addition to these encouraging results, there was no increase in mucosal toxicity with the addition of cetuximab to RT compared to RT alone, in stark contrast to the results observed with concurrent chemotherapy (Brizel *et al*, 1998). However, because this study tested RT alone as the control arm in a patient population in which concurrent RT and chemotherapy have become standard of care, the role of cetuximab as an alternative to chemotherapy has been questioned.

As discussed earlier, even with concurrent chemotherapy and RT, local recurrences continue to occur at unacceptable rates in patients with locally advanced SCCHN. Therefore, adding cetuximab to the current

standard of cisplatin based concurrent chemotherapy and RT was proposed. The RTOG is currently evaluating the addition of cetuximab to concurrent cisplatin based chemotherapy and RT. Other targeted agents are being evaluated in clinical trials in combination with RT for patients with locally advanced SCCHN including Bevacizumab (Avastin).

Technological advances

IMRT. Locally advanced SCCHN can be difficult to adequately treat secondary to its close proximity to many critical normal organs such as the brainstem, spinal cord, optic nerves, and optic chiasm (Chao *et al*, 2000; Nutting *et al*, 2001; Claus *et al*, 2002). Conventional radiation techniques used in the past have led to many unfortunate side effects that were permanent and severe, decreasing patients' quality of life (Scully and Epstein, 1996; Harrison *et al*, 1997; Eisbruch *et al*, 2004). The advent of conformal therapy such as intensity-modulated RT (IMRT) has allowed for precise application of increased dose to the tumor volume while sparing surrounding normal tissues from high radiation doses.

Intensity-modulated RT is a type of conformal RT that creates a high-dose volume that 'conforms' around the desired target volume while minimizing the dose to critical normal tissues (Figure 1) (Gunderson and Tepper, 2007). IMRT allows for sophisticated shaping of radiation dose with various techniques such as varying the radiation intensity within each beam. The use of dynamic multi-leaf collimators allows for dose intensity changes to be made or simultaneously administer integrated doses to different area during the same treatment. As opposed to 3D conformal RT,

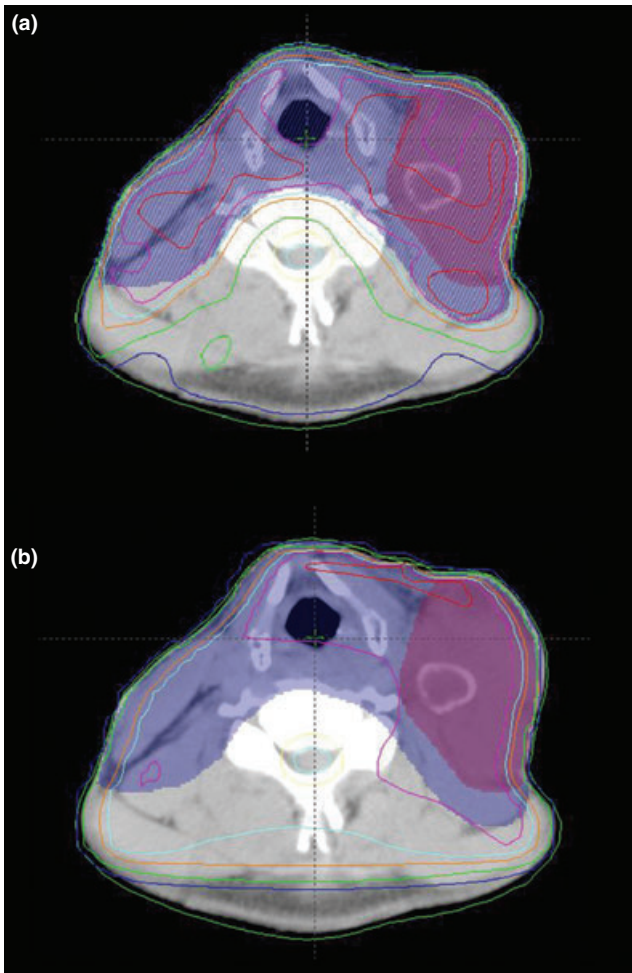


Figure 1 Comparison of intensity-modulated radiation treatment (IMRT) and 3D conformal radiotherapy plans for a patient with a large Level III tumor bearing lymph node. (a) Axial section depicting the isodoses delivered with the IMRT plan. (b) Axial section at the same anatomic level for the same patient with 3D conformal treatment planning. Note that the high radiation dose is not tightly conformed about the area of interest resulting in higher doses to structures such as the larynx. Shaded areas represent target volumes and lines represent radiation dose levels (isodose lines). Purple shaded area = gross tumor, blue shaded area = area at risk for spread of microscopic disease. Red line = 105% isodose line, magenta = 100%, light blue = 95%, dark blue = 50%

optimization of treatment beams is performed via computerized iteration (Leibel and Phillips, 2004) which is often described as inverse treatment planning.

Intensity-modulated RT for locally advanced SCCHN allows sparing of the parotid glands compared to older techniques that severely affected parotid functioning (Figure 2). Parotid dysfunction can lead to impaired dental health due to the lack of serous salivary flow. Parotid sparing leads to an improvement in xerostomia over time after treatment (Eisbruch *et al*, 2001; Braaksmas *et al*, 2003; Saarilahti *et al*, 2005). Additional areas to avoid with IMRT that may reduce long-term xerostomia include uninvolved oral cavity (reflecting minor salivary gland contribution) (Eisbruch *et al*, 2001).

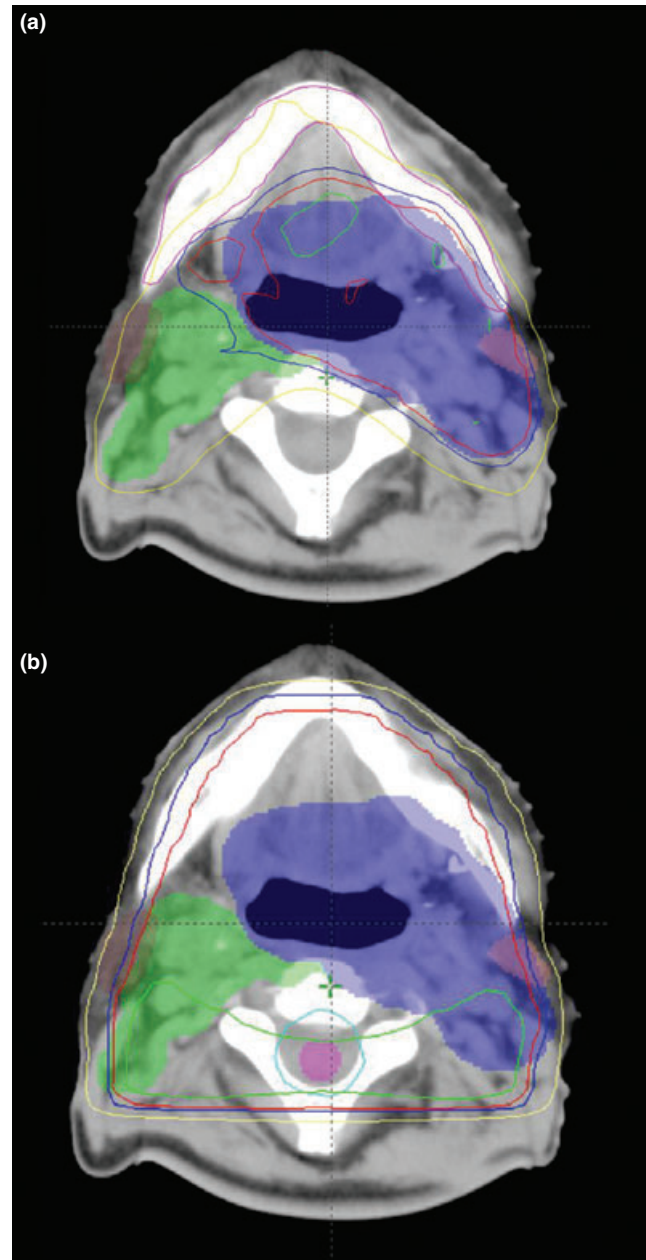


Figure 2 Comparison of intensity-modulated radiation treatment (IMRT) and 3D conformal radiotherapy plans for a patient with an oropharyngeal primary tumor. (a) Axial section depicting the isodoses delivered with the IMRT plan. (b) Axial section at the same anatomic level for the same patient with 3D conformal treatment planning. Note that the high radiation dose is not tightly conformed about the area of interest resulting in higher doses to structures such as the spinal cord, parotid, and uninvolved normal tissues. Shaded areas represent target volumes and lines represent radiation dose levels (isodose lines). Blue shaded area = gross tumor and involved lymph nodes, green shaded area = lymph nodes at risk. Green line = 105% isodose line, red line = 100%, blue = 95% and yellow = 75%

Another concern associated with definitive irradiation of the head and neck region is osteoradionecrosis (ORN) of the mandible, which can occur if high radiation doses are delivered to portions of the mandible, especially if that bone is damaged by infection

(tooth abscess) or tumor. The incidence of ORN in patients receiving RT alone for SCCN has been noted to be declining in recent decades: occurring prior to 1968 at a rate of 11.8%, at 5.4% from 1968 to 1992, and at 3% after 1997 (Wahl, 2006). A recent review of 176 SCCN patients treated using IMRT reveals a lack of ORN at a median follow up of 35 months (Ben-David *et al*, 2007). This appears to be meaningful data as the majority of cases of ORN are seen within 2 years of treatment (Reuther *et al*, 2003). The proposed hypothesis for the lack of ORN in recent series is a combination of reduced mandibular dose using newer planning and delivery methods with associated improved oral health and meticulous prophylactic dental care.

Recent studies have delineated that pharyngeal constrictors and the supraglottic larynx often malfunction after intensive chemotherapy and RT which can lead to dysphagia and aspiration (Eisbruch *et al*, 2004). They found that using IMRT targeted to spare the above mentioned structures lead to decreased dysphagia without compromising treatment to the tumor (Eisbruch *et al*, 2004). This motivated a clinical trial to spare these swallowing structures which shows promise that reducing dose to those areas correlates to less dysphagia and aspiration (Feng *et al*, 2007).

Image guided radiation treatment

Technologic advances have afforded radiation oncologists the ability to more accurately and precisely deliver radiation treatments. Image guided RT (IGRT) uses techniques such as on board imaging (daily localization) or to more accurately target tumor. This allows further refinements RT volumes to minimize the inclusion of uninvolved normal tissues.

In addition to the ability to accurately align patients for treatment, the use of newer imaging modalities may allow a more accurate definition of tumor volumes. Various imaging modalities have been studied to assist in target delineation such as ¹H-MRI, BOLD effect and invasive hypoxia marker techniques such as ³H labeled misonidazole (Hockel and Vaupel, 2001). FMISO

imaging has the largest existing body of experience for hypoxia imaging in head and neck cancers (Rajendran *et al*, 2006). ¹⁸F-FMISO fluoromisonidazole 3-fluoro-1-(2'-nitro-imidazolyl)-2-propanol is a hypoxia tracer that can be tagged with an appropriate label and its accumulation in hypoxic areas can be detected via positron emission tomography (PET) (Koh *et al*, 1992). FMISO PET scans are rapidly becoming the imaging modality of preference for investigation of target volume delineation for RT for head and neck cancers (Daisne *et al*, 2003). The incorporation of FMISO PET scans in RT planning remains investigational.

Chemotherapeutic advances

Induction chemotherapy. In the early 1980s, the use of induction chemotherapy for the treatment of patients with SCCN was described as a method with the intended goal of decreasing distant metastases and increasing organ preservation by initiating systemic therapy early and by minimizing the disease that RT would need to eradicate. A few studies showed impressive response rates to induction chemotherapy and many groups adopted induction chemotherapy as standard of care (Harari, 1997). A Phase III European study evaluated induction chemotherapy with cisplatin and 5FU followed by locoregional treatment or locoregional treatment alone. Among operable patients, there was no difference in OS at 5 and 10 years between the two groups however among inoperable patients, the OS at 5 and 10 years was 21% and 16% for the group who had received induction chemotherapy and 8% and 6% for those who had received RT alone (Merlano *et al*, 1996; Zorat *et al*, 2004). Other trials have studied the use of induction chemotherapy in patients with oropharyngeal cancer and found a statistically significant improvement in survival with the addition of chemotherapy prior to definitive chemoradiation (Domenge *et al*, 2000). Table 3 gives an overview of a few important induction chemotherapy trials and their outcomes.

While these findings are encouraging, there are many aspects of induction chemotherapy to consider when

Table 3 Selected trials of induction chemotherapy

Study	Patient characteristics	Treatment	OS	DM	Comments
EORTC 24891 (Lefebvre <i>et al</i> , 1996)	194 pts Stage II-IV HP	Surgery + post-op RT (S+RT) vs cisplatin/5FU → RT (IND)	5 year OS 30% (S+RT) 35% (IND)	5 year DM 36% (S+RT) 25%(IND)*	Chemotherapy arm had 5 year larynx preservation of 36%
GETTEC trial (Domenge <i>et al</i> , 2000)	318 pts Stage T2-4N0-2b OP	Surgery ± post-op RT (S+RT) or RT alone vs cisplatin/5FU → surgery, RT (IND)	Median OS 3.3 years (S+RT or RT) 5.1 years (IND)*	NR	Less local recurrence in induction chemotherapy group
VA larynx (The Department of Veteran's Affairs Laryngeal Cancer Study Group, 1991)	332 pts Stage III/IV larynx	Surgery + post-op RT (S+RT) vs cisplatin/5FU → RT (IND)	2 year OS 68% (S+RT) 68% (IND)	NR	NA

OS, overall survival; DM, distant metastases; HP, hypopharynx; OP, oropharynx; 5FU, 5-fluorouracil; post-op, postoperative; IND, induction chemotherapy; S, surgery; RT, radiation treatment; NR, not reported. *p ≤ 0.05.

making treatment planning decisions (Eisbruch, 2007). Chemotherapy alone is not curative, and after induction chemotherapy many patients refuse to move onto definitive chemoradiation due to the toxicity that they have already experienced or anticipate they will experience or because the bulk of their disease has decreased with induction chemotherapy. This unfortunately increases the likelihood of having locoregional failure.

Induction chemotherapy may lead to radiographic shrinkage of tumor but there are likely many residual subclinical tumor cells remaining. It is not clear whether radiotherapy volumes should be significantly altered in the setting of a major response or if this will result in an unacceptable rate of local failures. Of additional concern is the concept of accelerated repopulation after induction chemotherapy. The term accelerated repopulation describes the phenomenon by which certain human tumors, including head and neck cancers, begin to proliferate more rapidly after exposure to cytotoxic agents (Hall and Giaccia, 2006). If definitive chemoradiation is delayed until after the administration of induction chemotherapy, the surviving clonogens are repopulating at a faster rate and poses a theoretical impediment to the patient's chance of cure (Eisbruch, 2007).

Treatment-related toxicity

Acute

While there have been many advances in the management of SCCHN, treatment associated toxicities can lead to decreased QOL and the need for medical intervention (Epstein *et al*, 2001). Acute toxicities of RT and chemoradiotherapy occur during or shortly after treatment and are important to consider as they can lead to sub-optimal adherence to protocol therapy and unplanned treatment breaks. Common acute toxicities observed in patients with SCCHN that receive radiation as a component of their care include mucositis, radiation dermatitis, xerostomia, dysphagia, regional alopecia (with IMRT it is classically seen along the occipital region), hoarseness, transient ear discomfort, dysgeusia, and weight loss (Huguenin *et al*, 1999; Vissink *et al*, 2003).

Mucositis is a common toxicity seen secondary to RT and can be the source of discomfort and pain resulting in dysphagia, odynophagia and weight loss (Trotti *et al*, 2003). This can lead to poor treatment compliance and thus poorer outcomes (Sonis, 2004; Rosenthal *et al*, 2006). The rate of mucositis in patients who receive chemotherapy alone is stated to be about 40–60% (Schubert *et al*, 1991; Woo *et al*, 1993; Sonis, 1997). Patients who receive chemoradiation may have an incidence of mucositis as high as 80–90% with somewhere between 30% and 60% of patients having severe (Grade 3 or 4) mucositis (Giles *et al*, 2003; Trotti *et al*, 2003, 2004).

Prophylactic and expectant care are critical in managing these toxicities. Multi-disciplinary evaluations of patients with SCCHN should include a nutritional evaluation prior to the initiation of therapy. This is

essential to optimize nutrition, provide education on particular foods or beverages that may cause an increase in symptoms (e.g. acidic beverages), and to help determine the need for PEG tube placement to prevent unacceptable weight loss during therapy. Patients may also require the use of systemic analgesics, commonly opioid analgesics to help with the pain associated with mucositis (Kim *et al*, 1986; Saadeh, 2005).

As mentioned above, the use of IMRT has altered the acute and chronic toxicity profile for many patients receiving this therapy. Although IMRT may spare certain tissues from radiation, it should be assumed that these patients will experience many of the same acute toxicities as spared structures often are those appreciated to have late toxicity, such as salivary glands. Organs such as skin, mucosa, and larynx that are associated with acute toxicities are often not spared with IMRT to an extent greater than that obtained with conventional planning (Sanguineti *et al*, 2004). It has been noted that salivary gland function can be maintained with IMRT without jeopardizing the local control rate in the treatment of locally advanced SCCHN (Saarilahti *et al*, 2005; Huang *et al*, 2008).

Late side effects

Late side effects due to radiation are thought to result from injury to stromal and supporting structures such as subcutaneous tissues and vasculature (Cooper *et al*, 1995) as well as due to ongoing inflammation and fibrosis (Bentzen, 2006). In head and neck cancers, the extent of long-term complications are largely affected by total dose and fractionation scheme (Maciejewski *et al*, 1990). These effects are long lasting, often permanent, and are an unfortunate cause of long-term morbidity. The combination of chemotherapy and radiation commonly results in xerostomia, loss of taste, telangiectasias (Figures 3 and 4) subcutaneous fibrosis (Figure 4), skin and mucosal atrophy, loss of subcutaneous fat, skin discoloration, chronic alopecia in the radiation treatment field (Mossman, 1983; Million and Cassisi, 1994). Less common long-term treatment adverse events include: loss of hearing, chronic swallowing dysfunction and severe subcutaneous fibrosis (Million and Cassisi, 1994). Rare late toxicities from RT include mandibular ORN, brain necrosis (unless patient has parotid or nasopharynx tumor), and cervical myelopathy (<1% incidence with restriction of spinal cord dose to ≤ 45 Gy) (Lee *et al*, 1988; Marcus and Million, 1990; Reuther *et al*, 2003).

Hypothyroidism is commonly seen among patients receiving head and neck radiotherapy; this association was noted as early as the 1920s (Grover *et al*, 1929). However, the development of hypothyroidism has not been significantly influenced by the use of chemotherapy alone (Posner *et al*, 1985; Little *et al*, 1990; Weissler and Berry, 1991; Bhandare *et al*, 2007). While some sources note that the incidence can be as high as 50% (Kuten *et al*, 1996) most sources note the incidence is about 20–30% (Jereczek-Fossa *et al*, 2004). The development of hypothyroidism is dependent on the dose of radiation delivered to the thyroid gland (Bhandare *et al*, 2007).



Figure 3 A 66 year old man with history of radiation treatment for cancer of the larynx with evidence of telangiectasias on his anterior neck surrounding the site of his prior tracheostomy



Figure 4 A 67 year old man with a history of radiation treatment for tonsillar cancer with evidence of neck fibrosis and telangiectasias

Xerostomia is a common complaint of SCCHN patients. During therapy, saliva becomes scant and viscous. This is not only uncomfortable for the patient but can lead to subsequent sequelae such as oral infections, difficulty speaking and dental caries. Prior to the advent of IMRT, the rate of xerostomia ranged from about 94–100% in patients with SCCHN treated with radiotherapy (Ramirez-Amador *et al*, 1997; Hughes *et al*, 2000; Kies *et al*, 2001).

As has been discussed previously in regards to IMRT, the incidence of mandibular ORN has been drastically declined this is thought to be a combination of decreased dose with the use of IMRT and improved prophylactic dental care. Recent attention to survivorship issues has

led to the realization that the toxicities of these therapies can have a significant impact on the long-term quality of life of survivors (Trotti *et al*, 2007).

Radiation protectors and mitigation of established toxicity

A radioprotector is defined as a chemical compound that protects against radiation damage in normal cells but does not provide similar protection to tumor cells (Leibel and Phillips, 2004; Hall and Giaccia, 2006). To be effective, radioprotectors must be present before or shortly after radiation. An alternative to radioprotectors are effective therapies to deal with toxicity once it develops.

Amifostine

Amifostine is a thiophosphate that was first synthesized by the US Army to protect soldiers against ionizing radiation. It is a prodrug which is hydrolyzed *in vivo* by alkaline phosphatase to its active cytoprotective thiol metabolite which acts by scavenging free radicals and accumulating in epithelial tissues. The selective protection of normal tissues is believed to be due to higher alkaline phosphatase activity, higher pH, and vascular permeation of normal tissues. In a study involving 315 patients who received RT alone (60–70 Gy) for treatment of SCCHN, patients were randomly assigned to amifostine or no amifostine (Brizel *et al*, 2000). In this study amifostine reduced the incidence of significant acute xerostomia from 78% to 51%, and the incidence of significant chronic xerostomia at 12 months from 57% to 34%. There was no impact on mucositis or on tumor control at 2 years (Brizel and Wasserman, 2004). Currently, most centers with IMRT prefer to use this approach to reduce the risk of xerostomia due to the difficulty in administration of amifostine (frequent hypotension, the need for fluid boluses, and the requirement for timing close to the radiation delivery). IMRT can be used to spare the parotid gland contralateral to the tumor and potentially spare part of the ipsilateral parotid gland as well (Eisbruch *et al*, 2004; Saarilahti *et al*, 2005).

Palifermin

Palifermin is a recombinant keratinocyte growth factor (KGF) that has been evaluated in clinical trials as a method to reduce mucositis in patients receiving chemoradiation for SCCHN. KGF stimulates the growth of cells in certain tissues such as the skin and the surface layer of the mouth, stomach, and colon, helping to maintain the normal structure of these tissues and assists in the repair of damaged cells. Palifermin attaches to KGF receptors and stimulates cell growth. A multi-national study was recently reported that evaluated palifermin *vs* placebo in patients with advanced SCCHN who underwent concurrent chemotherapy and RT. This study showed that palifermin was more effective in reducing mucositis in patients who received hyperfractionated RT. Palifermin is known to be well tolerated but it does

not impact the morbidity among all patients receiving chemoradiation (Brizel, 2008).

Salagen

Salagen, pilocarpine, is a muscarinic alkaloid obtained from the leaves of tropical American shrubs from the genus *Pilocarpus*. It is a non-selective muscarinic receptor agonist in the parasympathetic nervous system, which acts therapeutically at the muscarinic acetylcholine receptor M3 (Spalding *et al*, 2002). Recently, the results for a prospective, double blinded, placebo controlled trial of 170 SCCHN patients who received RT with or without the use of pilocarpine were published. Patients who received concomitant pilocarpine did not have improved parotid flow or patient reported complaints of xerostomia. However, they did find that in a subgroup of patients who received a mean parotid dose > 40 Gy and received pilocarpine had improved function of their parotid gland (Burlage *et al*, 2008). As pilocarpine works on the acetylcholine receptor, it is not unexpected that adverse effects include excessive sweating, urinary frequency, lacrimation, and rhinitis.

Pentoxifylline and vitamin E

Pentoxifylline (PTX) is a phosphodiesterase inhibitor that causes vasodilation, improves erythrocyte flexibility, and enhances blood flow that has been found to reduce radiation induced fibrosis (Okunieff *et al*, 2004). It has also been shown to heal radiation-induced soft tissue necrosis significantly faster (Dion *et al*, 1990). Vitamin E has been used alone to treat radiation induced fibrosis as other agents such as superoxide dismutase that has antioxidant activity has been efficacious in treatment of fibrosis and was found to be minimally effective (Baillet, 1997). Thus a Phase II trial combining both PTX and vitamin E was performed and was found to regress radiation induced fibrosis surface (Delanian *et al*, 1999). This led to a randomized study of the use of PTX and vitamin E vs placebo and they found a significant regression of radiation induced fibrosis (Delanian *et al*, 2003). Currently there is a clinical trial looking at the effect of these two agents in the treatment of late radiation effects and findings in this trial may further support the recent promising results (Levin, 2005).

AdhAQP1

Xerostomia is a common toxicity in patients receiving RT for locally advanced SCCHN. As mentioned above, SCCHN irradiation can cause damage to parotid glands leading to xerostomia, dry mouth, and subsequent tooth decay, infections and difficulty swallowing. One investigational method for increasing salivary output in patients with xerostomia, gene transfer, is currently in clinical trials. The human aquaporin-1 gene (hAQP1) is a plasma membrane protein that facilitates water movement across cell layers. In preclinical studies AdhAQP1 recombinant serotype 5 adenoviral has been shown to restore salivary flow and it is currently being studied to see the safety of this dose in humans (Baum *et al*, 2004).

Conclusions

Treatment of SCCHN has evolved in the last few decades leading to improved tumor control. Although early stage SCCHN patients have a good prognosis, patients with advanced staged cancers continue to have an overall poor prognosis. For locally advanced SCCHN, a number of options exist including surgical resection followed by radiation or chemoradiation or definitive RT with or without chemotherapy. The use of chemotherapy may increase local control and survival but may be associated with more significant acute and late toxicities. Advances such as the use of induction chemotherapy and targeted therapy show promise to further improve outcomes.

While significant improvements in disease outcomes have occurred, toxicity remains a major consideration for all patients with SCCHN that receive RT. The use of newer modalities such as IMRT and IGRT has led to less chronic normal tissue damage in certain subsets of patients. Targeted therapies may offer similar benefits to chemotherapy without the associated toxicities. Continued research is needed to define new agents to use as radioprotectors and to define the appropriate use of those already identified. Perhaps most importantly, evaluation of survivors of cancer therapy will provide a more accurate estimation of rates of late toxicity and the impact of these toxicities on QOL.

Author contributions

C Ko and D Citrin contributed to the concept, manuscript writing, and editing.

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