Head and Neck Cancer

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Abstract

Head and neck radiotherapy is a continuously evolving field. The disease itself has changed with the increase in human papilloma virus (HPV) associated oropharyngeal cancer. With this new disease entity, oncologists are struggling to determine optimal therapy. As radiation oncologists, we are questioning our traditional use of chemotherapy as well as our radiation doses and volumes.

1 Introduction

Head and neck radiotherapy is a continuously evolving field. The disease itself has changed with the increase in human papilloma virus (HPV) associated oropharyngeal cancer. With this new disease entity, oncologists are struggling to determine optimal therapy. As radiation oncologists, we are questioning our traditional use of chemotherapy as well as our radiation doses and volumes.

While there has been little change in the incidence or biology of larynx cancer, there has been

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recent concern regarding the best overall care for locally destructive tumors. With the use of chemotherapy to bioselect for organ preservation and the improved larynx preservation seen with concurrent chemoradiation, there has been a sweeping adoption of chemoradiation for all locally advanced larynx patients. We will review the challenge of proper utilization of organ preserving chemoradiation compared with laryngectomy for overall patient outcomes, including survival.

One constant in head and neck radiotherapy is its morbidity. Still, practitioners search for agents to reduce both acute and long-term side effects including mucositis and xerostomia. We will review controversies regarding these agents as well as therapies for osteoradionecrosis. Many of these patients require feeding tube placement. We will review the controversy of prophylactic placement versus placement as needed.

Finally, as a technology-based specialty, radiation oncologists are continuing to explore the use of particle therapy in the management of head and neck cancer. We will review this topic with special attention to proton therapy, heavy ion, and neutron therapy.

2 Induction Chemotherapy

2.1 Induction Chemotherapy Is Dead

Five years ago, there was no greater controversy in head and neck radiotherapy than the question of the value of induction chemotherapy compared with chemoradiotherapy alone for locoregionally advanced head and neck cancer. The exciting results of TAX 324 showed improved 3-year survival (62% vs. 48%) when docetaxel was added to cisplatin and fluorouracil as induction chemotherapy in 501 patients with stage III/IV head and neck cancer (Posner et al. 2007).

However, since TAX 324, two large randomized phase III trials comparing induction chemotherapy followed by chemoradiation versus concurrent chemoradiation alone have failed to show a benefit in overall survival. PARADIGM was a multicenter, randomized phase III trial evaluating induction chemotherapy with three cycles of docetaxel, cisplatin, and fluorouracil (TPF) followed by concurrent chemoradiotherapy with either docetaxel or carboplatin compared with concurrent chemoradiotherapy alone (radiation with two cycles of cisplatin) (Haddad et al. 2013). This study only enrolled 145 patients with stage III/IV disease over 4 years. It failed to show a significant benefit to induction chemotherapy with 3-year survival of 73% compared with 78% in the chemoradiation alone arm (Fig. 1). Febrile neutropenia was more common in the induction chemotherapy group.

Shortly after the results of PARADIGM, another negative study comparing induction chemotherapy followed by chemoradiation versus chemoradiation alone was published in 2014. The DeCIDE (Docetaxel-based Chemotherapy plus or minus Induction Chemotherapy to Decrease Events in Head and Neck Cancer) trial was a randomized phase III trial of 285 patients with N2 or N3 nodal disease (Cohen et al. 2014). Here, patients received either chemoradiation alone (docetaxel, fluorouracil, hydroxyurea every other week plus 150 cGy BID to 74–75 Gy) or two 21-day cycles of induction chemotherapy (docetaxel 75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1, and fluorouracil 750 mg/m^2 on days 1–5) followed by the same chemoradiation. At a median follow-up of 30 months there was no statically significant difference in overall survival, relapse-free survival, or disease-free survival.

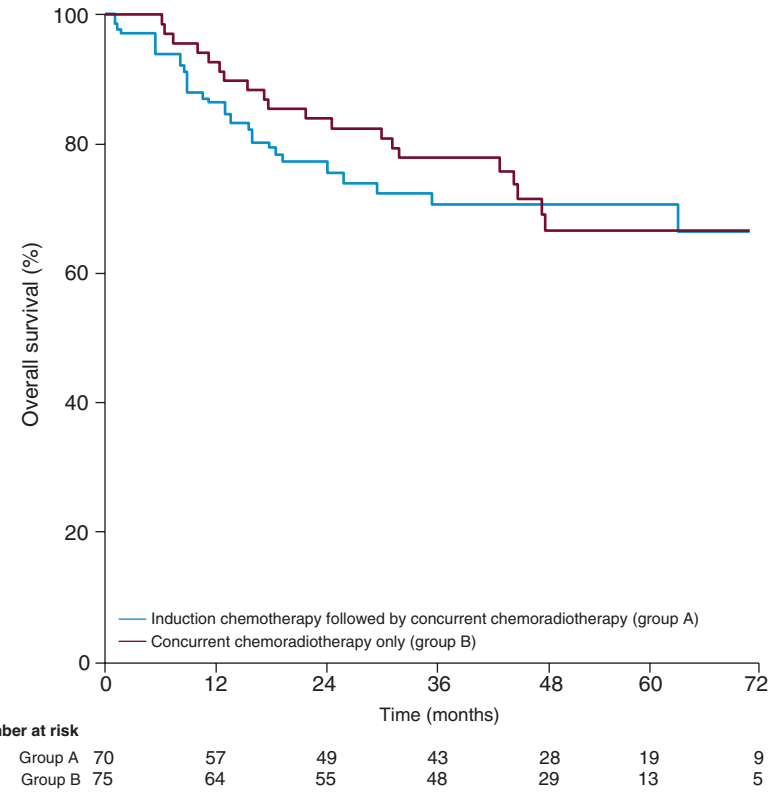

Fig. 1 PARADIGM Kaplan–Meier overall survival. Figure courtesy: Haddad et al. Lancet Oncol 2013;14: p 260 (Haddad et al. 2013)

2.2 Induction Chemotherapy: A Historic Perspective

While induction chemotherapy may not provide improved survival in locally advanced head and neck cancer, there has been significant interest in pursuing its use in bioselection. Wolf et al. didn't set out to improve survival in the VA Larynx trial first published in 1991; the goal was organ preservation (Wolf et al. 1991). Here, patients received two cycles of induction cisplatin and fluorouracil as a means to select patients who could appropriately receive definitive radiation to provide the best chance to preserve the larynx. Patients with either a complete (31%) or partial (54%) response to induction chemotherapy went on to receive a third cycle of chemotherapy followed by definitive dose radiation. The control arm in this study was treated with upfront surgery with total laryngectomy followed by post-operative radiation. Survival was not compromised by this organ preservation approach with 68% survival at 2 years in both study arms. Using induction chemotherapy to select the appropriate patients allowed for larynx preservation in 64%. The EORTC 24891 study also used induction chemotherapy to achieve laryngeal preservation in patients with hypopharynx and larynx cancers (Lefebvre et al. 2012). In this study, 202 patients were randomized to either laryngectomy with partial pharyngectomy and neck dissection followed by radiation or to chemotherapy with up to three cycles of induction cisplatin and fluorouracil followed by definitive radiation in those patients achieving a complete clinical response. At a median follow-up of 10.5 years, although survival was poor, it was not compromised by the induction chemotherapy for organ preservation strategy: 13.8% in the surgery arm and 13.1% in the induction chemotherapy arm. Using the induction chemotherapy approach allowed more than half of the surviving patients to retain their larynx (59.5% at 5 years).

2.3 Induction Chemotherapy in the HPV Era

In the last 20 years, there has been a change in the epidemiology of head and neck cancer (Gillison et al. 2000). HPV-associated oropharyngeal cancer has increased in frequency and is now the most common head and neck cancer diagnosed in 2016. Much has been written and much is continuing to be learned about HPV-associated oropharyngeal cancers, but one thing is clear: these tumors have better outcomes when treated with chemoradiation than HPV-negative tumors. Ang et al. performed a retrospective analysis using patients treated on RTOG 0129 showing improved survival in HPV-associated oropharyngeal cancers (Ang et al. 2010). A total of 743 patients were enrolled on RTOG 0129. Of these patients, the majority had oropharyngeal cancers (60.1%). HPV status was known in 74.6%. HPV-positive cancers were more common in the never or low pack-year smokers. Patients with HPV-associated tumors had improved overall survival over their HPV-negative counterparts: 3 year overall survival was 82.4% vs. 57.1%. Progression-free survival was also improved (Fig. 2).

With improved outcomes seen in the increasingly common HPV-associated oropharyngeal cancer, investigators have recently sought to de-intensify therapy to reduce the morbidity of therapy without compromising the excellent outcomes already achieved. The concept of using induction chemotherapy as a way to bioselect patients for treatment de-intensification has been

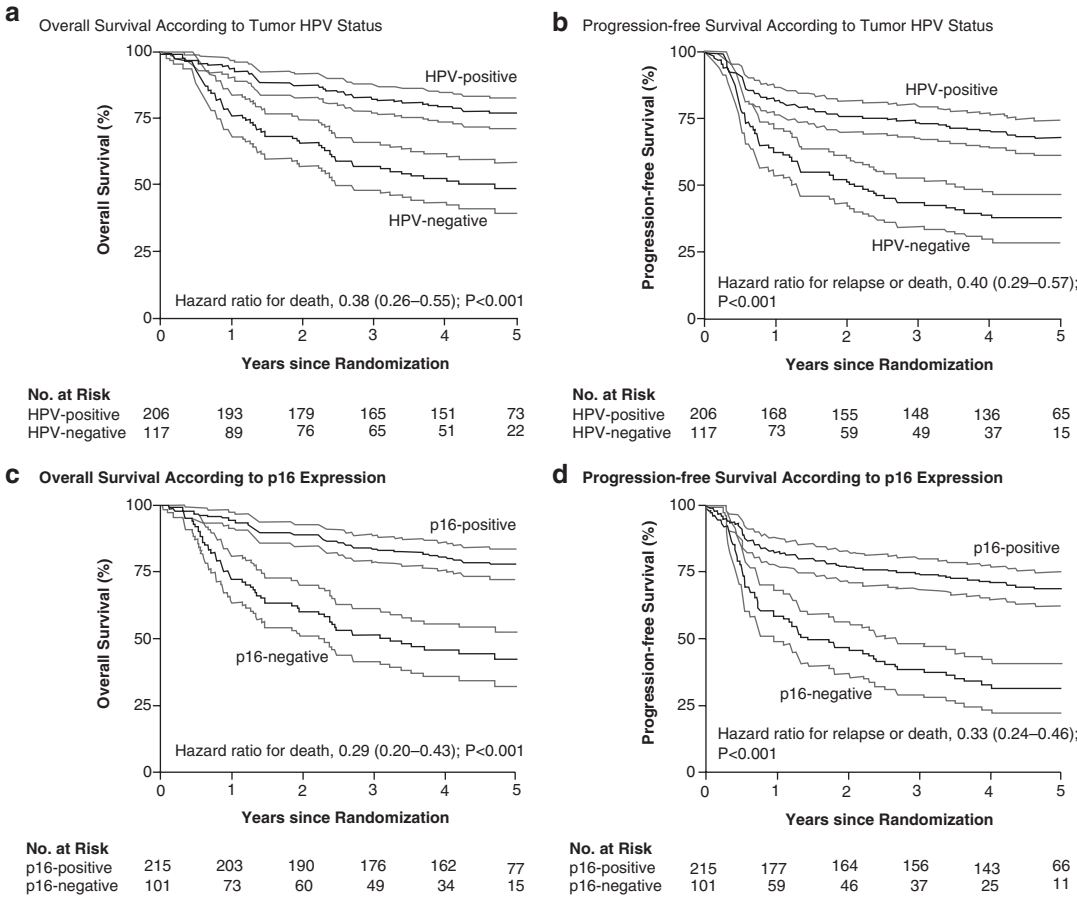

Fig. 2 Kaplan–Meier estimates of survival among the RTOG 0129 study patients with oropharyngeal cancer (**a**) Overall survival according to tumor HPV status. (**b**) Progression-free survival according to tumor HPV status. (**c**) Overall survival according to p16 expression. (**d**) Progression-free survival according to p16 expression. Figure courtesy of Ang et al. NEJM 2010;363: p 30 (Ang et al. 2010)

explored in the HPV-positive population. Results of ECOG 1308 were presented at the 2014 ASCO meeting (Cmelak et al. 2014). Here, patients with resectable HPV + oropharyngeal squamous carcinomas were treated with three cycles of induction cisplatin, paclitaxel, and cetuximab. Most of these patients (71%) had a clinical complete response to induction chemotherapy. These patients then went on to receive reduced dose (54 Gy) intensity-modulated radiation therapy (IMRT) with weekly cetuximab. Using 22% less radiation in this selected group still resulted in 2-year progression-free survival of 80% and overall survival of 93%. As seen in other HPV + series, patients with extensive smoking histories or T4 lesions did less well with this approach. Still, patients with T1–T3, N0–N2b tumors with less than 10 pack-year smoking histories did exceptionally well. In this select group, using induction chemotherapy to select patients to receive 54 Gy instead of 70 Gy, 2-year progression-free and overall survival was an impressive 96%.

The University of Chicago has creatively used an induction chemotherapy approach to select for a different way to de-intensify: response-adapted volume de-escalation (RAVD). Here, patients with locally advanced disease received two cycles of induction cisplatin/paclitaxel/cetuximab with or without everolimus. If patients had a "good response" with at least 50% tumor reduction to induction chemotherapy, they then received concurrent chemoradiation, but the radiation volumes only covered the initial gross disease plus margin. The concept here is that for the good responders, the tumor is chemotherapy-sensitive. It was hypothesized that chemotherapy should sterilize microscopic disease in the regional nodes. The use of chemotherapy to sterilize microscopic carcinoma in regional nodes is extrapolated from lung cancer chemoradiation where omitting elective nodal radiation allows for the use of smaller radiation volumes while not compromising regional control (Rosenzweig et al. 2001). Even in those patients experiencing less than 50% response, these investigators reduced the radiation volume to include only the gross disease and the "next nodal station" for the first 45 Gy before reducing the volume to the gross tumor plus margin (Fig. 3) (Villaflor et al. 2016).

When specifically evaluating their 59 HPV+ oropharynx patients, 30 (51%) experienced a

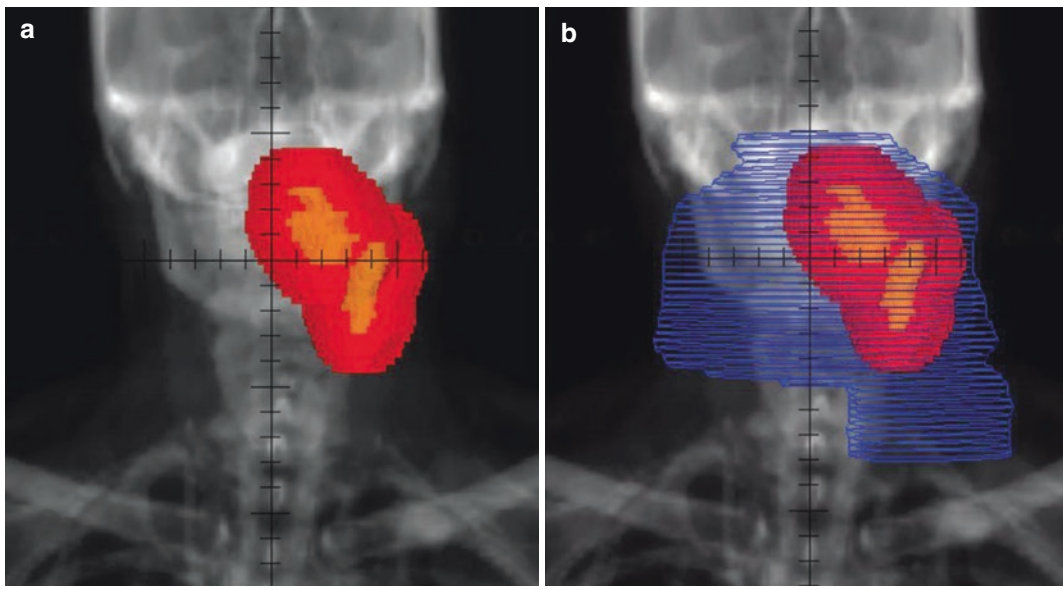

Fig. 3 Radiation treatment planning digitally reconstructed radiograph of a patient with oropharynx cancer and left level II adenopathy. (**a**) Represents a good response to induction chemo and was treated with RVAD, radiation delivered to a single volume to cover gross tumor volume plus 1.5 cm. (**b**) Non-responder to induction chemotherapy, treated with radiation field that includes the next nodal levels, this field is seen in *blue*. Figure courtesy: Villaflor et al. Annals of Oncology 2016;27: p 912 (Villaflor et al. 2016)

good response to induction chemotherapy. Two-year progression-free survival was 93% with overall survival 92%. None of these 30 HPV+ good responders had suffered a locoregional first failure at a median follow-up of 2 years. The authors reported decreased morbidity with this RAVD approach observing reduced gastrostomy tube dependence at 3 and 6 months in the good responders treated with smaller volume radiation.

3 Human Papilloma Virus-Positive Oropharynx Cancer: Dose De-Intensification

As discussed earlier, HPV-associated oropharyngeal cancers do better than their HPV-negative counterparts. These tumors respond better to chemotherapy and to radiation. The concept of increased inherent radiosensitivity in these HPV-related tumors is itself somewhat controversial. Vlashi et al. have reported HPV-positive cell lines having a lower frequency of cancer stem cells than HPV-negative cell lines (Vlashi et al. 2016). This lower number of cancer stem cells inversely correlated with radiosensitivity. Further, HPV-negative cell lines have enhanced ability to undergo radiation-induced dedifferentiation into radioresistant cancer stem cells.

O'Sullivan et al. at Princess Margaret Hospital in Toronto have proposed de-intensifying therapy for HPV-positive oropharynx cancer patients by using recursive partitioning analysis (RPA) to segregate HPV-positive patients into those with low and high risk for distant spread (O'Sullivan et al. 2013). In their analysis of 505 patients, HPV-positive T1–T3, N0–N2a and N2b patients with less than 10 pack-year smoking history had low risk of experiencing distant failure. These authors felt these low risk patients would be the best candidates for de-intensifying strategies.

Using concurrent cetuximab instead of cisplatin with IMRT has been explored as a de-intensification approach in RTOG 1016. This study has completed with 948 patients accrued. As of July 2016, we await the results of this large study.

Certainly much of the morbidity of head and neck chemoradiotherapy is from the radiation. In fact, most of the long-term effects can be attributed to radiation damage to the microvasculature and the resultant fibrosis. We have previously discussed ECOG 1308, where Cmelak et al. were able to use induction chemotherapy to select patients for lower dose radiotherapy using 54 Gy in good chemotherapy responders vs. 69.3 Gy in poor responders. Again, in this series of 77 patients, 81% were able to receive the lower radiation dose while experiencing an excellent 2-year progression-free survival rate of 80% and 2-year overall survival of 93%. In the select "best case" patients (T1–T3, N0–N2b with less than 10 pack-year smoking history), the 2-year progression-free and overall survivals were both 96%.

Given the lack of survival benefit seen in both the PARADIGM and DeCIDE studies using induction chemotherapy, many providers are more comfortable using treatment strategies with concurrent chemoradiation from the start. In 2015, Chera et al. reported a de-intensification of chemoradiation for select HPV-associated oropharyngeal squamous cell carcinomas (Chera et al. 2015). This small phase II trial included 43 patients with T0–T3, N0–N2c HPV+ cancers. Patients also had minimal smoking histories: less than 10 pack year or if greater than 10 pack year, no greater than 30 pack years and smoking abstinence for at least 5 years. IMRT dose was reduced to 60 Gy and was delivered concurrently with lower dose cisplatin at 30 mg/m^2 per week. The primary endpoint of this study was pathologic complete response based upon biopsies of the original primary site and neck dissection. In this series, the overall pathologic complete response rate was 86% – seen in 37 of 43 patients. Placement of a feeding tube was required in 39% of these patients for a median duration of 15 weeks. Current work from this group out of the University of North Carolina (study LCCC 1413) will utilize follow-up PET scan at 12 weeks post-therapy rather than relying on pathologic confirmation of complete response. Moreover, this follow-up study will further de-intensify therapy by omitting chemotherapy for early stage disease (T0–T2, N0–N1).

NRG oncology seeks to explore the possibility of de-intensification of chemoradiation for select HPV-associated patients in a multi-institutional intergroup trial. Study HN002 is a phase II trial for p16+ non-smoking patients with locoregionally advanced oropharynx carcinomas. Two treatment arms will be compared: chemoradiotherapy and radiotherapy alone. Both arms have reduced intensity. Chemoradiation uses 60 Gy with lower dose chemotherapy with concurrent weekly cisplatin 30 mg/m^2. The radiotherapy alone arm radiation dose is also less at 60 Gy, but it is delivered using an accelerated fashion of six fractions each week over 5 weeks. This study plans to accrue 296 patients with T1–T2, N1–N2b, or T3 N0–N2b disease. Eligible patients must have 10 pack-year or less smoking histories. The primary objective of HN002 is to select the treatment arm with a 2-year progression-free survival rate of at least 85% without unacceptable swallowing toxicity assessed at 1 year post-therapy.

One of the clinical characteristics of HPV-associated oropharyngeal cancers is the presentation with cystic lymphadenopathy, which can be quite large while still having small primary tumors. In fact, the incidence of cervical squamous cell carcinomas of unknown primary has been increasing in the HPV era. Coinciding with this change in oropharyngeal tumor biology, surgical technology has evolved. Transoral robotic surgery (TORS) has become a viable surgical option to resect these small oropharyngeal primaries. This technique allows resection without requiring mandibulotomy to gain exposure. Since these primary tumors tend to be smaller, most surgical beds can heal without requiring grafts or microvascular flaps. Most importantly, results using TORS for select early stage tumors have been outstanding. With a median follow-up of 17 months, the University of Pennsylvania reports only 3.3% 2-year locoregional failure rate in 114 HPV+ oropharyngeal cancer patients treated primarily with TORS and neck dissection (Kaczmar et al. 2016). Continuing with the theme of de-intensifying therapy in HPV+ oropharyngeal cancers, ECOG 3311 is evaluating less intense adjuvant therapy after TORS and neck dissection for select patients (clinical T1–T2, N1–N2b tumors). The primary study question is whether post-operative radiation dose can safely be reduced from 60 Gy to 50 Gy in "intermediate risk" patients. Pathology must show negative (but less than 3 mm) surgical margins but includes high risk findings including perineural invasion, lymphovascular invasion, two to four metastatic nodes, and even nodes with minimal extracapsular spread (less than 1 mm). High risk patients with positive surgical margins, greater than 1 mm extracapsular nodal spread or five or greater involved lymph nodes still receive post-operative chemoradiation with 66 Gy over 33 fractions combined with weekly cisplatin 40 mg/m^2. Interestingly, low risk patients with T1–T2, N0–N1 disease undergo observation only with no adjuvant therapy for this favorable group. As of April 2015, 135 patients have enrolled in this important study of adjuvant care in the post-TORS setting.

4 Decreasing Radiation Treatment Volume

Of course, de-intensifying therapy doesn't just have to mean lowering the dose of radiation and chemotherapy. Reducing the volume of tissue irradiated can also lessen both acute and long-term morbidities of therapy.

One of the first examples of successfully reducing radiation treatment volumes actually pre-dates the IMRT era. The concept of sparing the contralateral neck when treating early tonsil cancers was introduced by Murthy and Hendrickson (1980). Jackson et al. first reported successful outcomes using ipsilateral radiation for early stage tonsil cancer in 1999 (Jackson et al. 1999). O'Sullivan et al. reported the Princess Margaret experience using ipsilateral radiotherapy techniques in 228 patients treated from 1970 to 1991 (O'Sullivan et al. 2001). Tumor location was important with lesions involving 1 cm or less of the "ipsilateral hemistructure" of the soft palate or tongue base (Fig. 4). Most (91%) of these patients were treated using wedge pair photon technique. In this large series, the total rate of contralateral nodal failure was only 3.5%.

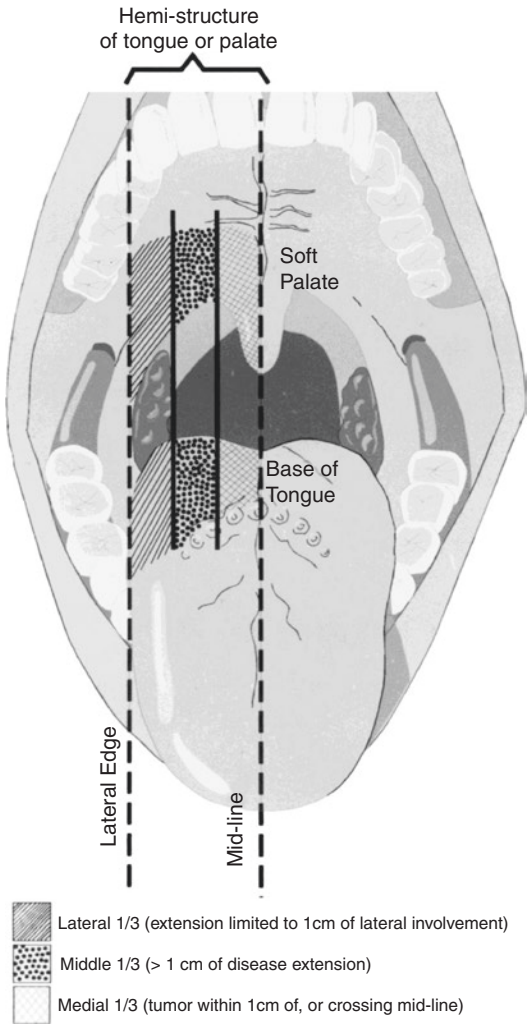

Fig. 4 Schematic of the lateral, middle, and medial hemi-structure involvement based on tumor location and extent of disease within the base of tongue and soft palate from the lateral edge of the tonsillar region to midline. Courtesy O'Sullivan Int J Radiat Biol Phys 2001;51: p 334 (O'Sullivan et al. 2001)

No patient with an N0 neck or a T1 primary tumor failed in the contralateral neck. MD Anderson has more recently published their experience with unilateral radiotherapy for tonsil cancer (Chronowski et al. 2012). In their experience of 102 patients, disease was limited to the tonsillar fossa or anterior tonsillar pillar with less than 1 cm involvement of the soft palate. Patients with any base of tongue involvement were excluded in this series. Most (67%) patients were treated using IMRT. Also, most (65%) had node positive disease with 42% having N2a or N2b necks. Even given the high incidence of positive ipsilateral adenopathy, only two patients suffered contralateral neck failure. Five-year freedom from contralateral nodal recurrence was 96%. In 2012, the American College of Radiology published "appropriateness criteria" for the use of ipsilateral radiation for tonsil cancer (Yeung et al. 2012). The following statements regarding appropriate patient selection for ipsilateral radiation were made: (1) The extent of soft palate or base of tongue invasion should be less than 1 cm. If the extension is 1 cm or greater, bilateral neck irradiation is recommended; (2) Bilateral neck irradiation is recommended for nodal stages N2b or higher; (3) There is "insufficient data at this time to alter treatment decisions based on HPV status". Patients should receive ipsilateral neck irradiation based upon the extent of the primary toward midline and the amount of ipsilateral nodal disease "regardless of the patient's HPV status."

Certainly, one key to decreasing the volumes irradiated in the IMRT era is to have a better understanding of the nodal regions at significant risk for microscopic spread of disease. Kjems et al. have recently questioned the need for routine irradiation of retropharyngeal and submandibular nodes in head and neck radiotherapy (Kjems et al. 2016). In this review from Denmark, 942 patients with oropharyngeal, hypopharyngeal, laryngeal, and oral cavity cancers were treated with primary radiation. The retropharyngeal region was only "routinely" irradiated in patients with tumors invading the posterior pharynx. The submandibular region (level IB) was only treated in cases that involved the oral cavity. Most (77%) of these patients were treated using IMRT. Seven hundred had treatment plans available for review. Of these only two (0.2%) recurred in the retropharynx and only seven (1%) failed in level IB. Since these recurrences were so uncommon, the authors conclude "restricting elective irradiation of the upper retropharyngeal region to cases with involvement of the posterior pharyngeal wall and level IB to cases involving the oral cavity is safe."

The challenge then comes in trying to adequately irradiate level IIA, the primary nodal drainage so frequently involved in oropharyngeal cancers while still meaningfully sparing IB and the submandibular gland. IMRT planning and delivery can only do so much in sparing adjacent critical normal tissues. The first step may be to better understand the radiation tolerance of the submandibular gland. Fortunately, the University of Michigan has performed this work (Murdoch-Kinch et al. 2008). This group evaluated 148 head and neck cancer patients before receiving IMRT and then followed them throughout treatment and for 2 years after radiation. Measurements of unstimulated and stimulated submandibular flow rates were performed. Both flow rates appeared to recover after radiation doses up to a threshold of 39 Gy.

As discussed earlier, perhaps we can apply the concept of chemotherapy to sterilize microscopic disease in regional nodes used in treating non-small cell lung cancer to head and neck cancer. The University of Chicago has certainly challenged our conventional beliefs of appropriate radiation target volumes with their Response-Adapted Volume De-Escalation (RAVD) based upon tumor response to induction chemotherapy. This may be even more relevant in the HPV era.

5 Chemoradiation Vs. Laryngectomy Plus Adjuvant Therapy for Locally Advanced Laryngeal Cancer

With all the morbidities and fears that head and neck cancer and its treatment carry for our patients, total laryngectomy may be the most dreaded. We have already discussed the historic perspective of using induction chemotherapy to select appropriate patients for laryngeal organ preservation in the VA Larynx trial and in the European EORTC 24891 trial for hypopharyngeal and laryngeal tumors.

RTOG 9111 sought to improve outcomes in patients with locoregionally advanced larynx cancer. This trial consisted of three arms: radiation alone, induction chemotherapy followed by radiation as used in the VA Larynx trial, and radiation with concurrent chemotherapy (three cycles of cisplatin 100 mg/m^2 every 3 weeks during radiation) (Forastiere et al. 2013). Median follow-up of greater than 10 years with over 500 patients analyzed appears to favor the concurrent cisplatin and radiation arm of the study. While locoregional control and laryngeal preservation were significantly better in the concurrent chemoradiation arm over induction chemotherapy or radiation alone, this therapy failed to improve overall survival. Concurrent cisplatin and radiation resulted in an outstanding 88% laryngeal preservation rate at 2 years. Combined chemoradiation resulted in a 54% relative reduction in risk of laryngectomy compared with radiation alone and a 42% reduction compared to induction chemotherapy followed by radiation. Still, larynx preservation did not translate into improved overall survival. Ten-year survival is only 28% in the concomitant arm, not significantly different than 39% seen in the induction arm or 32% after radiation alone. Exploratory analysis has been performed regarding the cause of death: from larynx cancer or "death not caused by study cancer" (Fig. 5). At 10 years, the concurrent radiation and cisplatin arm has a significantly *worse* rate of survival in the analysis of those "deaths not related to larynx cancer": 52.8 vs. 69.8% in the other arms ($p = 0.03$). Although this study failed to report increased late toxicity or worse speech/swallowing function after concurrent chemoradiation, this increase in deaths unrelated to larynx cancer is troubling. Olsen, an otolaryngologist from the Mayo Clinic has postulated that concurrent chemoradiation results in increased atherosclerosis of the carotids leading to stroke and delayed but increased pharyngeal fibrosis and stenosis leading to aspiration and pneumonia (Olsen 2010).

Could it be possible that we are under-utilizing laryngectomy? After all, isn't the key to organ preservation *appropriate patient selection*? For large destructive tumors, does organ preservation really make sense when there is not enough remaining larynx to preserve speech and maintain adequate swallowing function? Grover et al. from the University of Pennsylvania specifically

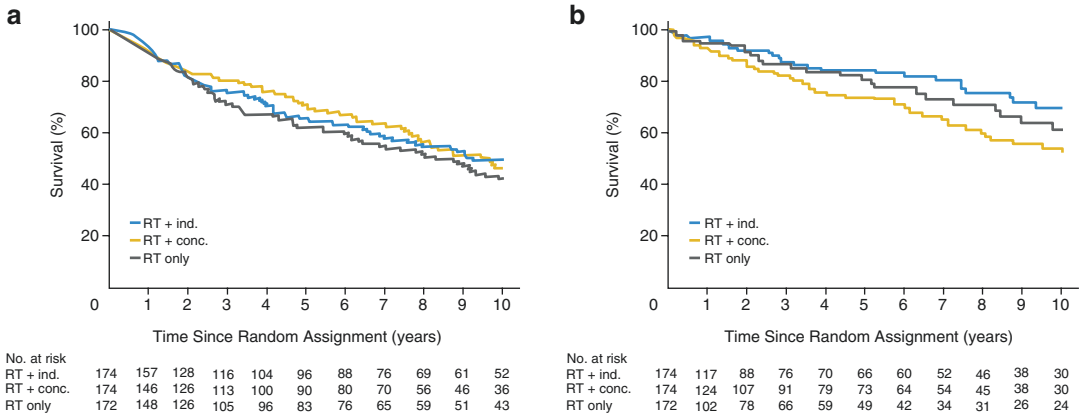

Fig. 5 RTOG 9111 Kaplan–Meier overall survival curves separated by (**a**) deaths from laryngeal cancer (**b**) deaths not caused by laryngeal cancer. Figure courtesy of Forastiere et al. J Clin Oncol 2012;31: p 850 (Forastiere et al. 2013)

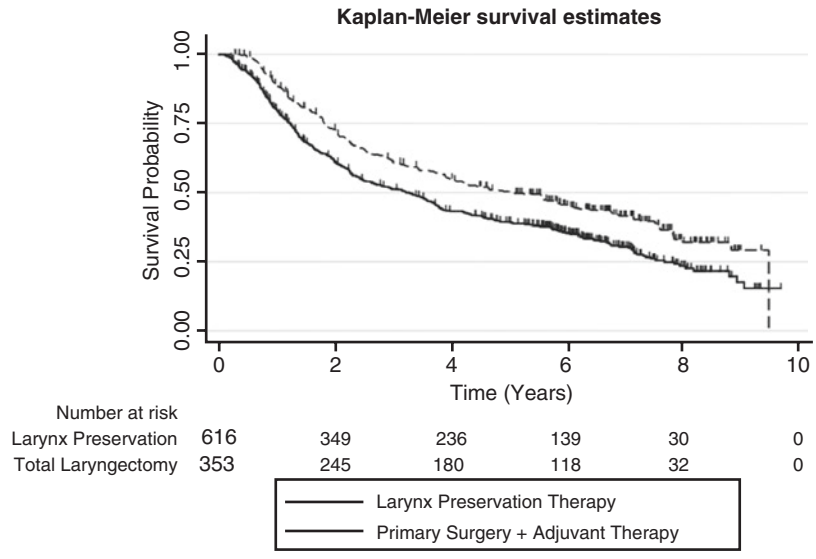

Fig. 6 Kaplan–Meier overall survival comparing laryngectomy and adjuvant therapy to laryngeal preservation in T4a tumors. Figure courtesy of Grover et al. Int J Radiat Biol Phys Oncol 2015;92: p 599 (Grover et al. 2015)

evaluated patterns of care and outcomes of 969 larynx cancer patients with T4a disease using the National Cancer database (Grover et al. 2015). Although national guidelines recommend upfront laryngectomy for T4a larynx cancer, this review found most (64%) patients being offered larynx preservation therapy. Interestingly, at "high case volume" facilities, patients were more likely to be treated with laryngectomy. For these patients with locally advanced tumors, survival was significantly better if they were treated with upfront laryngectomy (Fig. 6). Median survival was 61 months after laryngectomy compared with 39 months after upfront laryngeal preservation ($p < 0.001$). While trying to preserve the larynx, we must consider how our treatment choice may affect overall survival. Again, appropriate patient selection is vital.

6 Supportive Care

Technological advances such as image guided radiotherapy, intensity-modulated radiotherapy, and adaptive radiotherapy have had a profound effect on head and neck radiotherapy delivery.

While this has certainly had an impact on acute and chronic adverse events, treatment related morbidity continues to persist. We continue to search for agents to help mitigate the acute and chronic side effects of head and neck radiotherapy and attempt to optimize supportive care and treatment approaches.

6.1 Xerostomia

Xerostomia and mucositis are common adverse effects of head and neck radiation therapy. Ionizing radiation results in the formation of free radicals that damage the DNA. Thiol-containing agents, such as cysteine, are well known to have radioprotective activity (Patt et al. 1949). The necessity to provide preferential protection to normal tissue leads to the development of amifostine (WR-2721) (Kouvaris et al. 2007). Amifostine is a pro-drug that needs to be activated by membrane bound alkaline phosphatase to scavenge free radicals. Concentration of alkaline phosphatase is low in tumors, which provides a selective mechanism for normal tissue protection. Amifostine is also preferentially taken up in the salivary glands and kidneys (Rasey et al. 1986) and has been investigated in normal tissue protection for radiation and chemotherapy.

Brizel et al. reported on a phase III, multi-institutional, randomized trial of the addition of amifostine to post-operative head and neck radiotherapy in which greater than 75% of the both parotids were planned to receive at least 40 Gy. Amifostine reduced grade two and greater acute xerostomia from 78% to 51% and grade two and greater chronic xerostomia from 57% to 34%. Median saliva production was greater with amifostine, 0.26 g v 0.10 g. The use of amifostine had no deleterious effect on tumor control or survival (Brizel et al. 2000). Amifostine use in combination chemoradiotherapy is even more controversial with some trials showing benefit (Vacha et al. 2003; Antonadou et al. 2002), and others failing to do so (Buentzel et al. 2006; Haddad et al. 2009). In addition to the conflicting results from clinical studies, amifostine has other barriers to its routine clinical use. Amifostine is logistically challenging to dose as it has a relatively short bioavailability and must be delivered within a short time before daily radiotherapy. In addition to the financial cost of this medication, it is associated with significant side effects including nausea and hypotension. The benefit of amifostine in reducing radiation xerostomia is further challenged in the IMRT era where salivary gland sparing is routine (Nutting et al. 2011; Kam et al. 2007). In fact, Rudat et al. have retrospectively compared parotid function using quantitative salivary gland scintigraphy in those patients receiving conventional non-salivary sparing radiotherapy with amifostine versus IMRT with salivary sparing technique. In their review, the ability for IMRT to spare long-term parotid function was greater than that seen with amifostine using conventional radiation techniques (Rudat et al. 2008).

Cholinergic agonists (e.g., pilocarpine, cevimeline) have effects on exocrine glands to stimulate secretions such as sweat and saliva. These agents are FDA approved for the treatment of radiation-induced xerostomia. They have displayed benefits in salivary flow over multiple randomized, double-blind, placebo-controlled, multi-institutional trials (LeVeque et al. 1993; Johnson et al. 1993). The benefit of their use during radiotherapy is less clear. However, a recent meta-analysis of the randomized, controlled data supports its concurrent use in improving non-stimulated salivary flow (Yang et al. 2016). Still, the cholinergic side effects (e.g., sweating, palpations) can be challenging for patients to tolerate. Given these side effects, there has developed an interest in non-pharmaceutical approaches, including acupuncture. Acupuncture has been studied as a therapy to prevent radiation-induced xerostomia in multiple randomized control trials (Pfister et al. 2010; Cho et al. 2008; Blom et al. 1996; Meng et al. 2012). These results are limited with mixed results and small study populations. Individual patients report subjective benefit from acupuncture with little to no morbidity reported in any series.

6.2 Mucositis

Mucositis is a challenging adverse side effect during radiotherapy for head and neck cancer. This can be very painful and limit patients' ability for proper oral intake.

Palifermin is a humanized keratinocyte growth factor that stimulates the growth of cells that line the mouth and intestinal tract. It has an established role in limiting mucositis in patients undergoing hematopoietic stem cell transplantation (Stiff et al. 2006). Its use for prevention of mucositis in head and neck cancer has been investigated in two randomized controlled trials (Henke et al. 2011; Le et al. 2011). Physician quantified mucositis was reduced in both trials; however, patient reported outcomes remained unchanged. There is currently an ongoing phase II multi-institution trial evaluating a superoxide dismutase mimetic agent to reduce mucositis from head and neck chemoradiation. This utilizes pre-radiotherapy infusion of a small molecule that selectively targets the superoxide pathway accelerating conversion of superoxide to hydrogen peroxide. This mechanism is believed to block the large "burst" of superoxide caused by ionizing radiation which is felt to be the initial step in the development of mucositis [https://clinicaltrials.gov/show/NCT02508389. Accessed June 26, 2016].

6.3 Osteoradionecrosis

Osteoradionecrosis (ORN) of the mandible is a painful complication of head and neck radiotherapy that can range from self-limiting mucosal regression and mandible exposure to necrosis of the jaw with fracture requiring surgical intervention. The pathophysiology is poorly understood, but is felt to be caused by radiation fibrosis of the microvasculature (Marx 1983; Delanian and Lefaix 2002). A standard treatment has not been defined and optimal management remains controversial. Agents including pentoxifylline, vitamin E, and clodronate have been studied as therapy. Hyperbaric oxygen therapy has also been evaluated.

Pentoxifylline is a drug developed initially to treat claudication in peripheral artery disease. It has multiple effects on the body including vasodilation and increasing plasticity of red blood cells. It also further inhibits TNF-alpha and human dermal fibroblast production/proliferation and increases collagenase activity. This activity may reduce radiation fibrosis (Delanian et al. 1999). Pentoxifylline has been investigated in combination with vitamin E, an antioxidate that stops production of reactive oxygen species. This combination, along with clodronate, a bisphosphonate, has shown to be safe and effective in a phase II trial (Delanian et al. 2011). The pentoxifylline-tocopherol-clodronate combination (PENTOCLO) was found to be helpful improving refractory ORN in 54 patients treated with prior radiation. However, randomized data on the benefit of these agents is lacking.

Hyperbaric oxygen therapy (HBOT) has been shown to be clinically useful in diabetic ulcers and burn patients. HBOT increases partial pressure of oxygen in the blood, increasing the delivery of oxygen to hypoxic tissue. This increase in oxygen concentration is thought to stimulate capillary angiogenesis (Clarke et al. 2008; Abidia et al. 2003; Gothard et al. 2004). HBOT has been shown to lower the incidence of ORN after dental extractions and has been used as an adjunct to surgical intervention of established ORN in small series (Dhanda et al. 2016; Marx et al. 1985). However, data from ORN96, a prospective, multicenter, randomized, double blind, placebo-controlled trial failed to show a benefit of HBOT. In this study conducted at 12 university hospitals in France, 68 patients with overt osteoradionecrosis of the mandible were randomized to HBOT or placebo with the primary end point 1-year recovery rate from osteoradionecrosis. The study was stopped early due to worse outcome in the HBOT arm (Annane et al. 2004). This study was criticized for the use of controversial inclusion criteria, lack of stratification, and unusual HBOT twice daily regimen (Dhanda et al. 2016). Further, three-quarters of the HBOT patients failed to reach optimal oxygen concentration.

Two randomized prospective multicenter clinical trials (HOPON and DAHANCA-21) in the UK will hopefully provide a more definitive answer regarding the role of hyperbaric oxygen in the management of ORN (Shaw et al. 2011).

6.4 Feeding Tubes: Prophylactic Vs. Reactive PEG Placement

Despite all our improvements in patient care with increased survival and approaches to decrease treatment intensity and radiation volumes, one fact remains clear: head and neck chemoradiation is *HARD*! Many of our patients will require feeding tube placement to get through and subsequently recover from our therapy. So is it better to place percutaneous endoscopic gastrostomy (PEG) tubes in all of our chemoradiation patients upfront or to place selectively only if and when they are required? PEG placement is associated with complications including infection and bleeding. Still, patients often need PEG support urgently at times when they may be neutropenic or thrombocytopenic from therapy.

Fortunately, even if patients need feeding tube placement for support, long-term dependence on gastrostomy tubes appears to be an unusual occurrence in the IMRT era. Setton et al. performed a pooled analysis of gastrostomy tube dependence in oropharynx cancer patients treated with IMRT (Setton et al. 2015). In this multi-institutional review of 2,315 patients, 1,459 received a gastrostomy tube (63%). Of these patients, 52% had prophylactic placement and 48% had "reactive" placement with tubes placed only as needed. Overall, gastrostomy tube dependence was 7% at 1 year and only 3.7% at 2 years. The risk of gastrostomy tube dependence increased with stage of disease: 5.2% for T1–T2, N0–N2 patients compared with 10.1% for T3–T4 or N3 tumors. Advanced age, increased number of smoking pack years, higher nodal stage, and addition of chemotherapy all increased the risk of gastrostomy tube dependence at 1 year (Fig. 7).

Salas led a small (39 patients) randomized trial of prophylactic PEG compared with no prophylactic PEG in patients receiving chemoradiation for unresectable head and neck cancer (Salas et al. 2009). Quality of life was measured using EORTC QLQ-C30 and EORTC H&N 35 questionnaires. These authors found that placing gastrostomy tubes prophylactically improved post-chemoradiation quality of life especially in terms of reducing "speech problems."

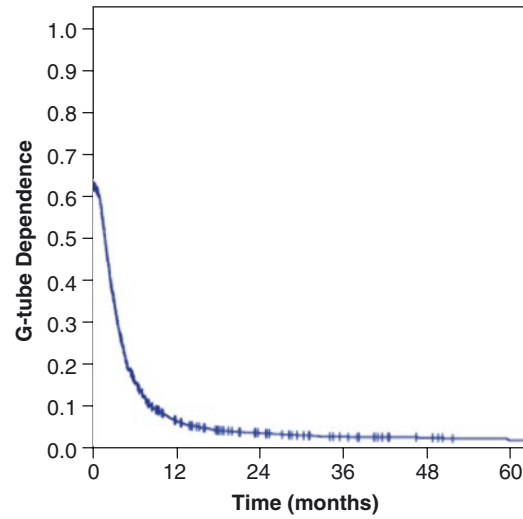

Fig. 7 Gastrostomy tube dependence over time among stage III and IV patients treated with concurrent chemotherapy. Figure courtesy of Setton et al. Cancer 2015;121:294–301 (Setton et al. 2015)

However, prophylactic placement has been associated with greater long-term PEG dependence. In a review of 104 patients receiving chemoradiation for head and neck cancer, Pohar et al. found a higher rate of PEG tube dependence at 1 year (Pohar et al. 2015). Further, 25% of the prophylactic PEG tube patients subsequently required dilation for stricture compared with 13% of the patients who started off eating by mouth. Locher has led a call for a more comprehensive review using evidence-based results on the use of prophylactic PEG tube placement in head and neck cancer (Locher et al. 2011). Her team calls for "more research to inform physician behavior on whether prophylactic PEG tube placement is warranted in the treatment of head and neck cancer." Perhaps, upfront PEG tube placement should be limited to those patients suffering significant pre-treatment weight loss or those patients presenting with severe dysphagia

or odynophagia caused by their cancers. In any case, close involvement of speech therapy early on and throughout treatment is warranted in head and neck cancer patients receiving chemoradiation. These patients should also undergo evaluation and be followed by a registered dietician.

7 Particle Therapies

Particle therapy is a form of external beam radiotherapy that uses beams of energetic ions for cancer treatment. Electrons are small negatively charged particles that can be accelerated close to the speed of light by a standard linear accelerator (Linac) and can be used therapeutically to treat superficial lesions since they have relatively shallow penetration. Electrons are commonly used in daily clinical practice in head and neck cancers, especially when treating skin cancers and superficial neck nodes, and will not be discussed in detail in this chapter. On the other hand, protons and other heavy particles require specialized and more costly machines (e.g., a cyclotron) that have only become commercially available in the last few decades, limiting the experience that exists in treating head and neck cancers. Particles have potential physical properties that can improve conformality of radiation delivery and may increase tumor kill defined as relative biologic effect (RBE).

7.1 Proton Radiotherapy

There is convincing biological and physical evidence to support the use of particle therapy (e.g., protons, neutrons, and heavy ions) in radiation oncology. Proponents of charged particle therapy tout the potential to improve local control while sparing adjacent normal tissue. This is due to the deposition of the maximum amount of energy near the end of an ion track, termed the Bragg peak, which can be used to spare critical excessive radiation dose to nearby organs-at-risk (e.g., for treatment of skull base tumors in close proximity to the optic apparatus or brainstem) (Fig. 8) (Kosaki et al. 2012). Protons or carbon ions stop immediately following this peak of energy deposition limiting the radiation dose to distal structures, in comparison to photons which continue to travel through the body and deposit energy distal to a target. Proton therapy has been used in the treatment of cancer since the 1950s. However, with recent increased interest, and with the help of modern technology, construction of many facilities across the USA has increased the number of patients being treated and the clinical experience treating head and neck cancer is rapidly expanding.

Proton beam RBE is traditionally reported as 1.1, which is about 10% greater biological effectiveness than photon therapy. However, there is experimental data showing proton RBE is

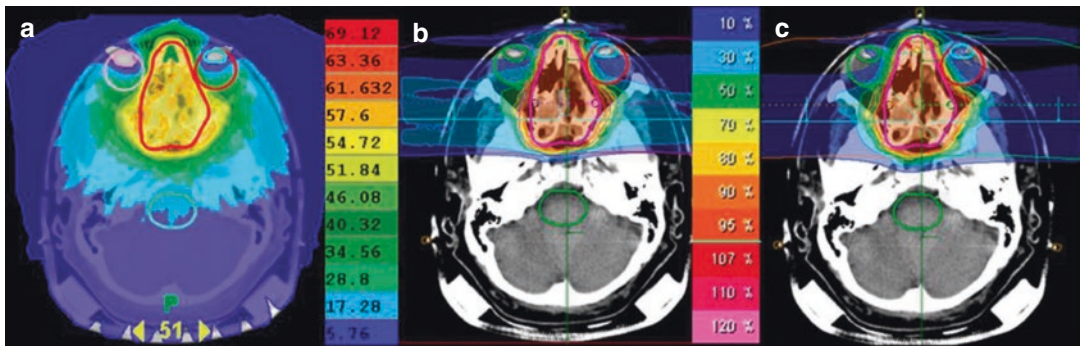

Fig. 8 Dose distributions in transverse plane for (**a**) photon IMRT, (**b**) carbon ion and (**c**) proton treatment planning techniques for a patient with a skull base meningioma. The same beam arrangements were used for carbon ion and proton plans. These plans consisted of two lateral beams and one cranial–caudal beam. Particle radiotherapy (**b**, **c**) spares the brainstem and cochlea from low-dose radiation (light and *dark blue* volumes). Figure courtesy of Kosaki et al. Radiation Oncology 2012;7:44 (Kosaki et al. 2012)

dependent on various factors including dose per fraction, depth of spread out Bragg peak, and the alpha/beta ratio of target tissue (Gerweck and Kozin 1999). Still, this slight advantage in RBE is not the driving force behind the recent interest in proton therapy. Rather, it is the steep dose distribution found with protons, particularly the sharp beam penumbra and lack of exit dose. These physical properties improve therapeutic ratio by lowering dose to normal tissues and allowing dose escalation to tumors.

7.1.1 Skull Base Chordoma/ Chondrosarcoma

One of the first clinical uses of proton therapy was for treatment of chordomas and chondrosarcomas of the base of skull; base of skull location makes these tumors very challenging to resect and they are known to locally recur when a gross total resection is not performed. Multiple single institutional retrospective data have reported local control rates of 54–100% with proton beam radiotherapy (Rombi et al. 2013; Ares et al. 2009; Rutz et al. 2008; Noel et al. 2005; Munzenrider and Liebsch 1999; Pommier et al. 2006); this is a significant improvement compared to historical controls treated with photon external beam radiotherapy with control rates of less than 25% (Catton et al. 1996; Zorlu et al. 2000). The largest of these series, Munzenrider and Liebsch (1999) reported outcomes on 519 patients with skull base chordoma and chondrosarcoma treated with 66–82 cobalt Gray equivalent proton–photon mixed radiation with reports of locoregional failure free survival of 73% at 5 years. However, this dose escalation with proton beam therapy was not without significant toxicity as three patients died of brainstem injury and eight patients had temporal lobe injury, as well as reports of hearing loss, cranial neuropathy, and endocrinopathies (Munzenrider and Liebsch 1999).

7.1.2 Nasal Cavity/Paranasal Sinuses

The typical treatment paradigm for paranasal sinus and nasal cavity cancers includes large surgical resections followed by adjuvant radiation or chemoradiation. Resto et al. (2008) published the largest reported retrospective review of 102 patients with locally advanced sinonasal cancers treated with proton beam or mixed proton–photon beam at Massachusetts General Hospital (MGH) between 1991 and 2002. Five year local control rates were excellent regardless of extent of resection: 95% (complete resection), 82% (partial resection), and 87% (biopsy only) (Resto et al. 2008); compared to single institution reports of external beam photon radiotherapy with control rates of 56–78% at 5 years (Myers et al. 2002; Jansen et al. 2000; Jiang et al. 1991). However, this excellent local control seen with proton beam radiotherapy didn't translate to better disease-free survival as patients with partial resection and biopsy only had a 5-year disease-free survival of 49% and 39%, respectively. Patients undergoing complete resection had an excellent 5-year disease-free survival of 90% (Resto et al. 2008).

7.1.3 Nasopharynx

Very limited data exists regarding the use of proton therapy for nasopharyngeal cancer outside of reports of re-irradiation from Loma Linda (Lin et al. 1999) and Lawrence Berkeley National Laboratory (Feehan et al. 1992). These small series report outcomes on 16 and 11 patients, respectively; with local control rates of 45–50%. Two abstracts from MGH have been presented on proton therapy in nasopharynx cancer, however, neither has yet to be formally published (Chan et al. 2004, 2012). Chan et al. reported the use of proton/photon therapy with chemotherapy to treat 17 patients with T4 nasopharynx carcinoma at the 2004 American Society of Clinical Oncology meeting. Three year locoregional control was 92%. These authors later reported on the use of proton/photon chemoradiation to treat 23 patients with stage III–IVB primary nasopharynx cancer at 2012 American Society for Radiation Oncology (ASTRO). At a median follow-up of 28 months, they reported no local or regional failures. MD Anderson has reported a single institution series of nine patients treated with intensity-modulated proton therapy with 2-year locoregional control of 100% and 2 year overall survival of 88.9%. This report also observed a dosimetric advantage of protons compared to

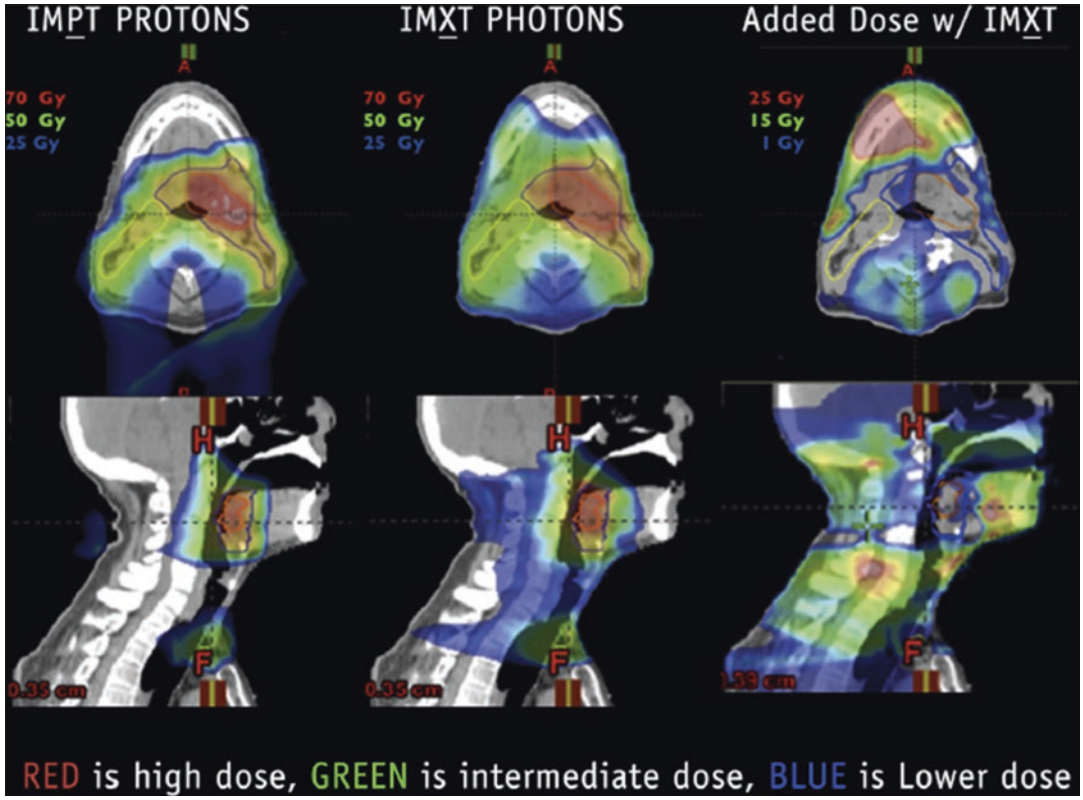

Fig. 9 Oropharyngeal cancer patient with intensity-modulated proton (*left*) and photon (*middle*) plans. The excess from the photon plan is shown in the plan on the *right*. Figure courtesy: Frank IJROBP 2016;95:37–39 (Frank 2016)

IMRT photon plans generated for the same patients (Lewis et al. 2016). However, it is unknown if this translates into clinically meaningful reduced toxicity.

7.1.4 Oropharynx

There is currently no published data outside of re-irradiation with proton therapy in oropharyngeal cancer. The theoretical advantages are in limiting the integral dose to non-target organs at risk; this is represented well in Fig. 9, which shows a visual comparison of an intensity-modulated proton beam therapy (IMPT) and IMRT photon plans in the same oropharyngeal cancer patient (Frank 2016).

MD Anderson Cancer Center is currently enrolling oropharyngeal patients in a phase II/III randomized trial comparing IMPT to IMRT [NCT01893307]. This trial will treat both groups to 70 Gy equivalent in 33 fractions, with the primary endpoint being the development of chronic grade 3 or higher toxicity during the first 2 years after completion of radiation therapy (Frank 2016) [http://clinicaltrials.gov/show/NCT01893307. Accessed May 21, 2016].

7.2 Heavy Ion Radiotherapy

Heavy ion therapy, most commonly carbon ion therapy, uses particles with more mass than neutrons or protons. Heavy ions have the steep dose distribution of protons while having a much higher RBE; which has the potential to have the greatest impact in radioresistant tumors. Carbon ions are generally used as a boost to photon therapy for head and neck cancers and data is limited to a few institutions (Mizoe et al. 2004, 2012; Schulz-Ertner et al. 2003; Kamada et al. 2015; Rieken et al. 2011). A phase I/II trial evaluating

carbon ion radiotherapy in recurrent nasopharyngeal carcinoma is ongoing in Japan to determine optimal dosing and efficacy (Kong et al. 2016). As of June 2016, there are currently no carbon ion centers in the USA.

7.3 Neutron Radiotherapy

Neutrons have high relative biological effectiveness (RBE) that may offer an advantage compared to photon radiotherapy, especially in known radioresistant and hypoxic tumors. This theoretical advantage is from high linear energy transfer (in the range of 200 KeV/μm for 2 MV neutrons) which is about 200-fold that of photons. With an RBE in the range of 2–8, a single Gray of fast neutron therapy has the killing effect of 2–7 Gy of photons (Schmid et al. 2003; Battermann et al. 1981). Neutrons also have a low oxygen enhancement ratio (OER), giving a theoretical advantage over photons in hypoxic tumors. It is these biological and physical advantages which drove fast neutron therapy into the limelight in the 1970s to the mid-1980s. However, neutrons were mostly abandoned in the late 1980s due to unacceptable side effects including soft tissue fibrosis and necrosis. Few randomized trials comparing photons and neutrons exist for cancer therapy. Still, a randomized trial comparing the two was performed in salivary gland tumors (Laramore et al. 1993). This trial was performed by Radiation Therapy Oncology Group (RTOG) in the USA and the Medical Research Council (MRC) in Great Britain and randomized inoperable primary or recurrent salivary gland malignancies to fast neutron radiotherapy versus conventional photon and/or electron radiotherapy. With poor prior results at that time with conventional radiotherapy and the often superficial location of salivary gland malignancies, it was felt to be an ideal tumor model for early neutron studies. The initial RBE calculation of neutron therapy in treating adenoid cystic salivary gland cancer was 8.0, while the RBE of neutrons on normal tissue in those same studies was only 3–3.5 (Battermann et al. 1981). This meant a dose of 20 neutron Gy to a parotid tumor had the biological effect of 60–70 Gy on normal tissue while delivering a biologic effect on the tumor equivalent to 160 Gy, a therapeutic gain of 2.3–2.6. This radiobiologic rational was the basis for the RTOG/MRC trial. Only 32 patients were ultimately enrolled with 25 eligible and evaluable, at four institutions: Fermi Laboratory, Edinburgh, Scotland, University of Pennsylvania, and the University of Washington. Neutron dosing was scaled according to the RBE of the individual facility over 12 fractions in 4 weeks, with the control photon arm receiving 70 Gy over 7.5 weeks. Locoregional control was 67% for the neutron group compared to 17% ($p < 0.005$) for the photon group at 2 years. Two-year overall survival was 62% for the neutron group versus 25% in the photon group ($p = 0.1$) (Koh et al. 1989). This study was closed early given the dramatic differences in locoregional control. Ten-year follow-up shows locoregional control of 56% in the neutron group versus 17% in the photon group, which remains significant. However, the apparent survival benefit seen at 2 years was lost by 10 years: 15% for the neutron patients versus 25% for the photon patients. Study limitations include small sample size and unbalanced treatment arms. Neutrons resulted in a higher incidence of severe morbidity compared to photons (Table 1).

At the peak of neutrons' use, there were eight active centers in the USA. In 2015, due to diminishing demand and closure of all but the University of Washington facility, the NCCN

Table 1 Grade 3 and greater toxicities as reported in RTOG/MRC neutron trial (Laramore et al. 1993)

	Photons	Neutrons
Hoarseness	0	1
Dysphagia	1	2
Dehydration	1	2
Malnutrition	1	2
Pain	0	3
Mucosal	1	3
Skin	2	2
Fibrosis	1	2
Necrosis	0	3
Xerostomia	2	1
Impaired taste	1	4
Other	0	1

guidelines have removed recommendations for neutron therapy for salivary gland cancers from their primary pathway. Neutron therapy is still listed as footnote for selected patients (Pfister et al. 2015). The toxicity concerns, cost, and lack of randomized data (only salivary gland malignancies) have resulted in the diminished use of neutron therapy over time.

With the current lack of data supporting clear indications for the use of proton beam and heavy ion therapy in head and neck cancers, as well as the limited number of patients who have potential access to the few facilities, current NCCN Guidelines limit any specific recommendations for their use in head and neck cancers (Pfister et al. 2015). In the modern, cost-centered healthcare era, although proton beam and heavy ion therapy sport advantageous physical and hypothetical benefits, it is unlikely their use will be adopted until supportive clinical data exists.

Conclusion

Radiotherapy for head and neck cancer continues to improve with advances in technology. Treatment planning techniques and protons have improved our ability to deliver radiotherapy more precisely. With the increase in HPV-associated oropharyngeal cancer, we are facing a new disease entity which is fortunately responsive to radiation and chemotherapy. This radiosensitive disease combined with our improvements in technology has led to questions regarding reduction in radiation dose and volumes. While we seek to reduce the considerable morbidities of our therapy, we hope to improve our control and ultimately our cure of head and neck cancer.

References

Abidia A, Laden G, Kuhan G et al (2003) The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. Eur J Vasc Endovasc Surg 25:513–518

Ang KK, Harris J, Wheeler R et al (2010) Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 363:24–35

Annane D, Depondt J, Aubert P et al (2004) Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized, placebo-controlled, double-blind trial from the ORN96 study group. J Clin Oncol 22:4893–4900

Antonadou D, Pepelassi M, Synodinou M et al (2002) Prophylactic use of amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer. Int J Radiat Oncol Biol Phys 52:739–747

Ares C, Hug EB, Lomax AJ et al (2009) Effectiveness and safety of spot scanning proton radiation therapy for chordomas and chondrosarcomas of the skull base: first long-term report. Int J Radiat Oncol Biol Phys 75:1111–1118

Battermann JJ, Breur K, Hart GA et al (1981) Observations on pulmonary metastases in patients after single doses and multiple fractions of fast neutrons and cobalt-60 gamma rays. Eur J Cancer 17:539–548

Blom M, Dawidson I, Fernberg JO et al (1996) Acupuncture treatment of patients with radiation-induced xerostomia. Eur J Cancer B Oral Oncol 32b:182–190

Brizel DM, Wasserman TH, Henke M et al (2000) Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. J Clin Oncol 18:3339–3345

Buentzel J, Micke O, Adamietz IA et al (2006) Intravenous amifostine during chemoradiotherapy for head-and-neck cancer: a randomized placebo-controlled phase III study. Int J Radiat Oncol Biol Phys 64:684–691

Catton C, O'Sullivan B, Bell R et al (1996) Chordoma: long-term follow-up after radical photon irradiation. Radiother Oncol 41:67–72

Chan AW, Liebsch LJ, Deschler DG, Adams JA, Vrishali LV, McIntyre JF, Pommier P, Fabian RL, Busse PM (2004) Proton radiotherapy for T4 nasopharyngeal carcinoma. J Clin Oncol 22:5574

Chan A, Adams JA, Weyman E et al (2012) A phase II trial of proton radiation therapy with chemotherapy for nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 84:S151–S152

Chera BS, Amdur RJ, Tepper J et al (2015) Phase 2 trial of de-intensified chemoradiation therapy for favorable-risk human papillomavirus-associated oropharyngeal squamous cell carcinoma. Int J Radiat Oncol Biol Phys 93:976–985

Cho JH, Chung WK, Kang W et al (2008) Manual acupuncture improved quality of life in cancer patients with radiation-induced xerostomia. J Altern Complement Med 14:523–526

Chronowski GM, Garden AS, Morrison WH et al (2012) Unilateral radiotherapy for the treatment of tonsil cancer. Int J Radiat Oncol Biol Phys 83:204–209

Clarke RE, Tenorio LM, Hussey JR et al (2008) Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. Int J Radiat Oncol Biol Phys 72:134–143

Cmelak A, Li S, Marur S, Zhao W, Westra WH, Chung CH, Gillison ML, Gilbert J, Bauman JE, Wagner LI,

Ferris RL, Trevarthen DR, Dimitrios Colevas A, Jahagirdar BN, Burtness B (2014) E1308: reduced-dose IMRT in human papillomavirus (HPV)-associated resectable oropharyngeal squamous carcinomas (OPSCC) after clinical complete response (CCR) to induction chemotherapy (IC). J Clin Oncol 32:LBA6006

Cohen EE, Karrison TG, Kocherginsky M et al (2014) Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. J Clin Oncol 32:2735–2743

Delanian S, Lefaix JL (2002) Radionécrose de l'os mature: connaissance physiopathologique récente motrice d'une thérapeutique médicale innovante. Cancer/Radiothérapie 6:1–9

Delanian S, Balla-Mekias S, Lefaix JL (1999) Striking regression of chronic radiotherapy damage in a clinical trial of combined pentoxifylline and tocopherol. J Clin Oncol 17:3283–3290

Delanian S, Chatel C, Porcher R et al (2011) Complete restoration of refractory mandibular osteoradionecrosis by prolonged treatment with a pentoxifylline-tocopherol-clodronate combination (PENTOCLO): a phase ii trial. Int J Radiat Oncol Biol Phys 80:832–839

Dhanda J, Pasquier D, Newman L et al (2016) Current concepts in osteoradionecrosis after head and neck radiotherapy. Clin Oncol (R Coll Radiol) 28:459–466

Feehan PE, Castro JR, Phillips TL et al (1992) Recurrent locally advanced nasopharyngeal carcinoma treated with heavy charged particle irradiation. Int J Radiat Oncol Biol Phys 23:881–884

Forastiere AA, Zhang Q, Weber RS et al (2013) Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. J Clin Oncol 31:845–852

Frank SJ (2016) Intensity modulated proton therapy for head and neck tumors: gilding the lily or holy grail? Int J Radiat Oncol Biol Phys 95:37–39

Gerweck LE, Kozin SV (1999) Relative biological effectiveness of proton beams in clinical therapy. Radiother Oncol 50:135–142

Gillison ML, Koch WM, Capone RB et al (2000) Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst 92:709–720

Gothard L, Stanton A, MacLaren J et al (2004) Non-randomised phase ii trial of hyperbaric oxygen therapy in patients with chronic arm lymphoedema and tissue fibrosis after radiotherapy for early breast cancer. Radiother Oncol 70:217–224

Grover S, Swisher-McClure S, Mitra N et al (2015) Total laryngectomy versus larynx preservation for T4a larynx cancer: patterns of care and survival outcomes. Int J Radiat Oncol Biol Phys 92:594–601

Haddad R, Sonis S, Posner M et al (2009) Randomized phase 2 study of concomitant chemoradiotherapy using weekly carboplatin/paclitaxel with or without daily subcutaneous amifostine in patients with locally advanced head and neck cancer. Cancer 115:4514–4523

Haddad R, O'Neill A, Rabinowits G et al (2013) Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (paradigm): a randomised phase 3 trial. Lancet Oncol 14:257–264

Henke M, Alfonsi M, Foa P et al (2011) Palifermin decreases severe oral mucositis of patients undergoing postoperative radiochemotherapy for head and neck cancer: a randomized, placebo-controlled trial. J Clin Oncol 29:2815–2820

Jackson SM, Hay JH, Flores AD et al (1999) Cancer of the tonsil: the results of ipsilateral radiation treatment. Radiother Oncol 51:123–128

Jansen EP, Keus RB, Hilgers FJ et al (2000) Does the combination of radiotherapy and debulking surgery favor survival in paranasal sinus carcinoma? Int J Radiat Oncol Biol Phys 48:27–35

Jiang GL, Ang KK, Peters LJ et al (1991) Maxillary sinus carcinomas: natural history and results of postoperative radiotherapy. Radiother Oncol 21:193–200

Johnson JT, Ferretti GA, Nethery WJ et al (1993) Oral pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. N Engl J Med 329:390–395

Kaczmar JM, Tan KS, Heitjan DF et al (2016) HPV-related oropharyngeal cancer: risk factors for treatment failure in patients managed with primary transoral robotic surgery. Head Neck 38:59–65

Kam MK, Leung SF, Zee B et al (2007) Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol 25:4873–4879

Kamada T, Tsujii H, Blakely EA et al (2015) Carbon ion radiotherapy in Japan: an assessment of 20 years of clinical experience. Lancet Oncol 16:e93–e100

Kjems J, Gothelf AB, Hakansson K et al (2016) Elective nodal irradiation and patterns of failure in head and neck cancer after primary radiation therapy. Int J Radiat Oncol Biol Phys 94:775–782

Koh WJ, Laramore G, Griffin T et al (1989) Fast neutron radiation for inoperable and recurrent salivary gland cancers. Am J Clin Oncol 12:316–319

Kong L, Hu J, Guan X et al (2016) Phase I/II trial evaluating carbon ion radiotherapy for salvaging treatment of locally recurrent nasopharyngeal carcinoma. J Cancer 7:774–783

Kosaki K, Ecker S, Habermehl D et al (2012) Comparison of intensity modulated radiotherapy (IMRT) with intensity modulated particle therapy (IMPT) using fixed beams or an ion gantry for the treatment of patients with skull base meningiomas. Radiat Oncol 7:44

Kouvaris JR, Kouloulias VE, Vlahos LJ (2007) Amifostine: the first selective-target and broad-spectrum radioprotector. Oncologist 12:738–747

Laramore GE, Krall JM, Griffin TW et al (1993) Neutron versus photon irradiation for unresectable salivary gland tumors: final report of an rtog-mrc randomized clinical trial. Radiation therapy oncology group. Medical research council. Int J Radiat Oncol Biol Phys 27:235–240

Le QT, Kim HE, Schneider CJ et al (2011) Palifermin reduces severe mucositis in definitive chemoradiotherapy of locally advanced head and neck cancer: a randomized, placebo-controlled study. J Clin Oncol 29:2808–2814

Lefebvre JL, Andry G, Chevalier D et al (2012) Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891. Ann Oncol 23:2708–2714

LeVeque FG, Montgomery M, Potter D et al (1993) A multicenter, randomized, double-blind, placebo-controlled, dose-titration study of oral pilocarpine for treatment of radiation-induced xerostomia in head and neck cancer patients. J Clin Oncol 11:1124–1131

Lewis GD, Holliday EB, Kocak-Uzel E et al (2016) Intensity-modulated proton therapy for nasopharyngeal carcinoma: decreased radiation dose to normal structures and encouraging clinical outcomes. Head Neck 38(Suppl 1):E1886–E1895

Lin R, Slater JD, Yonemoto LT et al (1999) Nasopharyngeal carcinoma: repeat treatment with conformal proton therapy: dose-volume histogram analysis. Radiology 213:489–494

Locher JL, Bonner JA, Carroll WR et al (2011) Prophylactic percutaneous endoscopic gastrostomy tube placement in treatment of head and neck cancer: a comprehensive review and call for evidence-based medicine. JPEN J Parenter Enteral Nutr 35:365–374

Marx RE (1983) Osteoradionecrosis: a new concept of its pathophysiology. J Oral Maxillofac Surg 41:283–288

Marx RE, Johnson RP, Kline SN (1985) Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin. J Am Dent Assoc 111:49–54

Meng Z, Garcia MK, Hu C et al (2012) Randomized controlled trial of acupuncture for prevention of radiation-induced xerostomia among patients with nasopharyngeal carcinoma. Cancer 118:3337–3344

Mizoe JE, Tsujii H, Kamada T et al (2004) Dose escalation study of carbon ion radiotherapy for locally advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 60:358–364

Mizoe JE, Hasegawa A, Jingu K et al (2012) Results of carbon ion radiotherapy for head and neck cancer. Radiother Oncol 103:32–37

Munzenrider JE, Liebsch NJ (1999) Proton therapy for tumors of the skull base. Strahlenther Onkol 175(Suppl 2):57–63

Murdoch-Kinch CA, Kim HM, Vineberg KA et al (2008) Dose-effect relationships for the submandibular salivary glands and implications for their sparing by intensity modulated radiotherapy. Int J Radiat Oncol Biol Phys 72:373–382

Murthy AK, Hendrickson FR (1980) Is contralateral neck treatment necessary in early carcinoma of the tonsil? Int J Radiat Oncol Biol Phys 6:91–94

Myers LL, Nussenbaum B, Bradford CR et al (2002) Paranasal sinus malignancies: an 18-year single institution experience. Laryngoscope 112:1964–1969

Noel G, Feuvret L, Calugaru V et al (2005) Chordomas of the base of the skull and upper cervical spine. One hundred patients irradiated by a 3D conformal technique combining photon and proton beams. Acta Oncol 44:700–708

Nutting CM, Morden JP, Harrington KJ et al (2011) Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (parsport): a phase 3 multicentre randomised controlled trial. Lancet Oncol 12:127–136

O'Sullivan B, Warde P, Grice B et al (2001) The benefits and pitfalls of ipsilateral radiotherapy in carcinoma of the tonsillar region. Int J Radiat Oncol Biol Phys 51:332–343

O'Sullivan B, Huang SH, Siu LL et al (2013) Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. J Clin Oncol 31:543–550

Olsen KD (2010) Reexamining the treatment of advanced laryngeal cancer. Head Neck 32:1–7

Patt HM, Tyree EB, Straube RL et al (1949) Cysteine protection against X irradiation. Science (New York, NY) 110:213–214

Pfister DG, Cassileth BR, Deng GE et al (2010) Acupuncture for pain and dysfunction after neck dissection: results of a randomized controlled trial. J Clin Oncol 28:2565–2570

Pfister DG, Spencer S, Brizel DM et al (2015) Head and neck cancers, version 1.2015. J Natl Compr Cancer Netw 13:847–855. quiz 856

Pohar S, Demarcantonio M, Whiting P et al (2015) Percutaneous endoscopic gastrostomy tube dependence following chemoradiation in head and neck cancer patients. Laryngoscope 125:1366–1371

Pommier P, Liebsch NJ, Deschler DG et al (2006) Proton beam radiation therapy for skull base adenoid cystic carcinoma. Arch Otolaryngol Head Neck Surg 132:1242–1249

Posner MR, Hershock DM, Blajman CR et al (2007) Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 357:1705–1715

Rasey JS, Krohn KA, Menard TW et al (1986) Comparative biodistribution and radioprotection studies with three radioprotective drugs in mouse tumors. Int J Radiat Oncol Biol Phys 12:1487–1490

Resto VA, Chan AW, Deschler DG et al (2008) Extent of surgery in the management of locally advanced sinonasal malignancies. Head Neck 30:222–229

Rieken S, Habermehl D, Nikoghosyan A et al (2011) Assessment of early toxicity and response in patients treated with proton and carbon ion therapy at the Heidelberg ion therapy center using the raster scanning technique. Int J Radiat Oncol Biol Phys 81:e793–e801

Rombi B, Ares C, Hug EB et al (2013) Spot-scanning proton radiation therapy for pediatric chordoma and chondrosarcoma: clinical outcome of 26 patients treated at Paul Scherrer Institute. Int J Radiat Oncol Biol Phys 86:578–584

Rosenzweig KE, Sim SE, Mychalczak B et al (2001) Elective nodal irradiation in the treatment of non-small-cell lung cancer with three-dimensional conformal radiation therapy. Int J Radiat Oncol Biol Phys 50:681–685

Rudat V, Munter M, Rades D et al (2008) The effect of amifostine or imrt to preserve the parotid function after radiotherapy of the head and neck region measured by quantitative salivary gland scintigraphy. Radiother Oncol 89:71–80

Rutz HP, Weber DC, Goitein G et al (2008) Postoperative spot-scanning proton radiation therapy for chordoma and chondrosarcoma in children and adolescents: initial experience at Paul Scherrer Institute. Int J Radiat Oncol Biol Phys 71:220–225

Salas S, Baumstarck-Barrau K, Alfonsi M et al (2009) Impact of the prophylactic gastrostomy for unresectable squamous cell head and neck carcinomas treated with radio-chemotherapy on quality of life: prospective randomized trial. Radiother Oncol 93:503–509

Schmid E, Schlegel D, Guldbakke S et al (2003) RBE of nearly monoenergetic neutrons at energies of 36 keV-14.6 MeV for induction of dicentrics in human lymphocytes. Radiat Environ Biophys 42:87–94

Schulz-Ertner D, Nikoghosyan A, Jakel O et al (2003) Feasibility and toxicity of combined photon and carbon ion radiotherapy for locally advanced adenoid cystic carcinomas. Int J Radiat Oncol Biol Phys 56:391–398

Setton J, Lee NY, Riaz N et al (2015) A multi-institution pooled analysis of gastrostomy tube dependence in patients with oropharyngeal cancer treated with definitive intensity-modulated radiotherapy. Cancer 121:294–301

Shaw R, Forner L, Butterworth C et al (2011) Randomised controlled trials in HBO: "a call to arms" for HOPON & DAHANCA-21. Br J Oral Maxillofac Surg 49:76–77

Stiff PJ, Emmanouilides C, Bensinger WI et al (2006) Palifermin reduces patient-reported mouth and throat soreness and improves patient functioning in the hematopoietic stem-cell transplantation setting. J Clin Oncol 24:5186–5193

Vacha P, Fehlauer F, Mahlmann B et al (2003) Randomized phase iii trial of postoperative radiochemotherapy +/– amifostine in head and neck cancer. Is there evidence for radioprotection? Strahlenther Onkol 179:385–389

Villaflor VM, Melotek JM, Karrison TG et al (2016) Response-adapted volume de-escalation (RAVD) in locally advanced head and neck cancer. Ann Oncol 27:908–913

Vlashi E, Chen AM, Boyrie S et al (2016) Radiation-induced dedifferentiation of head and neck cancer cells into cancer stem cells depends on human papillomavirus status. Int J Radiat Oncol Biol Phys 94:1198–1206

Wolf GT, Hong WK, Fisher SG, Urba S, Endicott JW, Fisher SR, Toohill RJ, Karp D, Miller DM, Cheung NK, Weaver A, Hillel AD, Spauldine M, Chang BK, Dougherty B, Deconti R, Garewal H, Fye C (1991) Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The department of veterans affairs laryngeal cancer study group. N Engl J Med 324:1685–1690

Yang WF, Liao GQ, Hakim SG et al (2016) Is pilocarpine effective in preventing radiation-induced xerostomia? A systematic review and meta-analysis. Int J Radiat Oncol Biol Phys 94:503–511

Yeung AR, Garg MK, Lawson J et al (2012) ACR appropriateness criteria(r) ipsilateral radiation for squamous cell carcinoma of the tonsil. Head Neck 34:613–616

Zorlu F, Gurkaynak M, Yildiz F et al (2000) Conventional external radiotherapy in the management of clivus chordomas with overt residual disease. Neurol Sci 21:203–207