Eur Arch Otorhinolaryngol (2009) 266:1845–1855
DOI 10.1007/s00405-009-1109-2

REVIEW ARTICLE

Current trends in initial management of oropharyngeal cancer: the declining use of open surgery

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Received: 3 August 2009 / Accepted: 17 September 2009 / Published online: 27 September 2009

Abstract The widespread availability of novel primary treatment approaches against oropharyngeal cancers has provided several potentially curative surgical and nonsurgical treatment options for patients, generating both hope and controversy. As treatment is usually curative in intent, management considerations must include consideration of primary tumor and nodal disease control as well as long-term toxicities and functional outcomes. Anatomical and functional organ preservation (speech and deglutition) remains of paramount importance to patients with oropharyngeal cancer and the physicians involved in their care, accounting for the growing popularity of chemoradiotherapy and transoral surgical techniques for this indication. These novel approaches have greatly diminished the role of open surgery as initial therapy for oropharyngeal cancers. Open surgery which is often reserved for salvage on relapse, may still be an appropriate therapy for certain early stage primary lesions. The growing treatment armamentarium requires careful consideration for optimal individualized care. The identification of oncogenic human papillomavirus as a predictive and prognostic marker in patients with oropharyngeal cancer has great potential to further optimize the choice of treatment. In this review, novel primary therapies against oropharyngeal squamous cell carcinoma are presented in the context of anatomical, quality of life, and emerging biological considerations.

Keywords Oropharyngeal cancer · Oropharynx · Squamous cell carcinoma · Treatment · Human papillomavirus

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Introduction

Due to recent advances in epidemiology, molecular biology as well as in therapeutic approaches, the management of cancer of the oropharynx is in a period of great transition [1]. Oropharyngeal cancers comprise only a small subset of squamous cell carcinomas of the head and neck, with approximately 5,000 new cases each year in the United States [2, 3]. The most common sites for oropharyngeal cancer are the tongue base and tonsillar regions, while cancers of the soft palate and posterior pharyngeal wall are less common.

Aside from tobacco and alcohol use, long-known major risk factors for this disease, a recently growing body of evidence has demonstrated an association of oncogenic human papillomavirus (specifically HPV 16) infection with development of oropharyngeal malignancies. The virus is notably present in 50% of tonsillar cancers [4–7]. Oral HPV infection is the principal cause of a distinct form of oropharyngeal cancer that has been rising in incidence in the United States since 1973, particularly among young men [8]. A high lifetime number of sexual partners (both vaginal as well as oral) appears to be correlated with HPV-associated oropharyngeal cancer [7, 9]. Over the past 30 years, the proportion of potentially HPV-related oral cancer in the United States has increased; an increase possibly related to changing sexual behaviors [10]. The molecular biology of HPV-associated oropharyngeal cancer appears to be distinct from non-HPV associated head and neck cancer [11–13]. Furthermore, HPV-related oropharyngeal cancer appears to be linked to better clinical outcomes and improved patient survival [10, 14–16]. The presence of HPV DNA in oropharyngeal squamous cell carcinoma has been found to be an independent favorable prognostic factor for overall and disease-specific survival [17]. However, non-smoking patients with HPV-positive tumors have a remarkably better disease-specific survival rate compared with those with HPV-negative tumors but also compared with smoking patients with HPV-positive tumors [18]. Due to differences in biology as well as patient prognosis, HPV-associated oropharyngeal cancer has been proposed to be a distinct malignancy which should be targeted [16].

Patients with oropharyngeal cancers are often treated with curative intent despite frequent presentation with advanced-stage disease, an intent which must be balanced with the potential for long-term morbidity following aggressive local and regional therapies. Oropharyngeal cancers are classified as either "resectable" or technically "unresectable" due to regional invasion of critical structures; while "unresectable" tumors are often best treated with chemoradiotherapy, several curative-intent treatment options currently exist for resectable tumors. Besides the classification of "resectable" versus "unresectable," "functional inoperability" may also be a consideration for the choice of treatment. However, the definition of "functional inoperability" is vague and may differ among surgeons [19]. In practice, the expected chances of cure and morbidities of the different treatment options are weighted against each other, often resulting in non-surgical treatment for the more advanced cancers if (severe) functional impairment is expected from surgical treatment.

Driven by curability and functional organ preservation, continued advances have been made in modern surgical and nonsurgical therapies. In particular, these concerns have led to the current popularity of curative-intent radiotherapy protocols in combination with chemotherapy and biological therapies. Furthermore, the transoral accessibility of the oropharynx has recently been exploited by the development of novel "minimally invasive" therapies which offer the prospect of effective oncological treatment with the goal of decreased morbidity compared with traditional open surgical procedures. As a result, these novel approaches have greatly diminished the role of open surgery as initial therapy for oropharyngeal cancers. The widespread availability of advanced radiation technologies as well as transoral laser and robotic surgeries has transformed the management of oropharyngeal cancers. Appropriate future patient selection for these therapeutic modalities will need to be based on anatomical, functional, and, given the association of HPV infection with oropharyngeal cancer, biological considerations.

Surgical options for initial management of oropharyngeal cancer

The advantages of surgery as primary therapy include complete pathological staging for determination of patient prognosis as well as the potential for sparing some patients subsequent radiotherapy with or without chemotherapy with its attendant toxicity. However, possible disadvantages of primary surgery include morbidity of the procedure, postoperative functional impairment, or, when the patient is not able to avoid postoperative treatment, the toxicity of both surgical and subsequent adjuvant therapy.

Surgery for early stage primary lesions

As noted above, although most patients with oropharyngeal cancer are treated with definitive radiotherapy either with or without concurrent chemotherapy, some early-stage primary lesions may be amenable to surgical extirpation, offering the potential for avoiding other therapeutic modalities, with their associated toxicities in selected patients. In support of this approach, the French Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC)—sponsored multicenter study of T1–T2, N0 oropharyngeal cancer patients treated exclusively with surgery produced a disease-specific survival rate of 100% [20]. Moncrieff et al. [21] recently reported a retrospective series of 92 patients who had early primary (T1 or T2) stage, any N-stage, M0, largely lateral oropharyngeal cancers treated with primary surgery at a single institution. Wide local excision of the primary lesion was achieved by a transoral approach in 52%, and via a lip-split with mandibulotomy in the remaining 48% of cases. A cervical lymphadenectomy was

performed in 76% of cases, with bilateral dissections in only one case. Based on pathological results, postoperative radiotherapy (without chemotherapy) was administered to 62% of cases. An 87% overall 5-year local control rate was observed, associated with a 5-year disease-specific survival of 83%. Local–regional recurrence was seen in 19% and distant metastases were observed in 8%. While the above results of primary surgery indicate good outcomes for selected patients, limitations of these surgical procedures include the relatively high number of patients requiring postoperative radiotherapy and the lack of toxicity and quality of life data that are critical for generalizing this approach to patients with resectable oropharyngeal cancers.

Primary neck dissection

The presentation of small primary tumors with bulky nodal metastasis is not uncommon in patients with oropharyngeal squamous cell carcinomas. Indeed, many cases that were reported in the past as having "unknown primary site" malignancies (presenting with metastatic cervical lymphadenopathy), have been found, more recently, to originate in the oropharynx, particularly the tongue base or tonsil. Investigators at the Johns Hopkins University Medical Center have reported an analysis of a cohort of 16 patients with small primary (T1–2 stage) oropharynx cancer with extensive cervical metastasis (N2 or greater disease) treated with primary neck dissection followed by radiotherapy or chemoradiotherapy [22]. Nearly all (15 of 16 patients) had a base of tongue primary lesion. With a median follow-up time of 33 months, disease-free survival in this stage IV patient population was 93.75%. Although this series is small, this approach appears to be feasible and is associated with excellent outcomes.

Transoral laser microsurgery

Transoral laser microsurgery (TLM) is a minimally invasive endoscopic surgical technique which offers a local therapy alternative to traditional surgical procedures and is associated with rapid recovery and a low long-term toxicity profile. As indications for TLM are similar to those of other surgical techniques limited by endoscopic accessibility, evaluation of this therapeutic modality should be based on disease control and on organ functionality. When applied to a series of 59 previously untreated base of tongue cancers (any T stage, any N stage, M0 disease) with appropriate neck dissections in 49 patients (83%), and adjuvant postoperative radiotherapy in 28 patients (47%), the respective 2- and 5-year overall survival estimates were 91 and 69%, with a 5-year local control estimate of 90% [23]. Rich et al. [24] recently reported a series of 84 patients with advanced stage (stages III and IV) oropharyngeal cancers (not limited to base of tongue cancers) treated with TLM with or without neck dissections and chemoradiotherapy, and observed a 5-year overall survival of 88% and disease-specific survival of 92%. Higher T-stage and positive margins were associated with worse survival, and positive p16 immunohistochemical status (a sensitive surrogate marker of HPV infection) was associated with improved survival. Of note, 6% of patients experienced major surgical complications, but without observed mortality. The rate of gastrostomy tube use was 3.4% of living patients at 3 years.

Transoral robotic surgery

As robotic urological and cardiac surgeries are becoming widely accepted, minimally invasive treatment modalities for prostate cancer and management of cardiac valvular disease with good outcomes, several investigators have demonstrated that transoral robotic surgery (TORS) using the *da Vinci* Surgical Robot (Intuitive Surgical, Inc., Sunnyvale, CA, USA) holds great potential for minimally invasive extirpation of oropharyngeal cancers [25–28]. O'Malley et al. [25] were the first to demonstrate the utility and safety of TORS. Subsequently, several reports have shown that TORS provides excellent three-dimensional visualization and the unique ability to manipulate and perform reconstruction of the oropharynx, an area that heretofore could only be accessed via open surgical approaches [29].

The ability to extirpate tumors of the oropharynx and perform reconstruction through minimally invasive approaches such as TORS has prompted consideration for de-escalation of adjuvant therapy. In those patients where complete tumor resection can be achieved by TORS and where is no evidence of poor prognostic factors such as extracapsular spread, perineural invasion or angioinvasion, it may be feasible to reduce the dose of radiotherapy in an attempt to achieve local–regional control with less morbidity. While current non-surgical methods for the management of oropharynx cancer achieve acceptable control rates, the morbidity associated with therapy can be rather significant. The combination of minimally invasive surgical techniques and de-escalation of adjuvant therapy may hold the potential for excellent control rates with a reduction in post-therapy morbidity. This may be particularly true for HPV-associated disease. However, all of these hypotheses are still under investigation.

Sentinel lymph node biopsy for cancer staging

Accurate staging of cervical lymph nodes is critical in patients with oropharyngeal cancers. Extensively studied for management of oral cavity cancers, sentinel lymph node biopsy has also received considerable attention for

oropharyngeal cancers. In those cases of early oropharyngeal cancer that are surgically treated and are staged N0, sentinel lymph node biopsy seems to be a promising alternative to elective neck dissection with comparable regional control rates [30].

Advances in radiotherapy for oropharyngeal cancer

Advances in radiotherapy have focused on improved cancer control as well as normal tissue-sparing techniques. Intensity modulated radiation therapy (IMRT) technology, altered fractionation schedules, and brachytherapy techniques have contributed to state-of-the-art definitive therapy for oropharyngeal cancers.

Intensity modulated radiation therapy (IMRT)

Early in its history, IMRT was found to be an effective therapeutic modality for locally advanced oropharyngeal cancer, offering the prospect of high local–regional control with salivary gland sparing [31–34]. In a recently published Stanford University series of IMRT with or without concurrent chemotherapy or cetuximab applied to 107 patients with locally advanced oropharyngeal cancers, the 3-year local–regional control, freedom from distant metastasis, overall survival, and disease-free survival rates were 92, 92, 83, and 81%, respectively [35]. No marginal failures were observed. Although local–regional control was excellent, the observed major failure pattern was distant; seven patients developed distant metastasis as the first site of failure. A similar observation of excellent local–regional control but with high distant failure was noted for oropharyngeal cancer patients treated with IMRT at the University of Iowa [34].

A recently reported series of 34 patients specifically with tongue base cancers treated with accelerated IMRT and definitive chemotherapy at Emory University had 24-month actuarial overall survival and local control of 90 and 92%, respectively [36]. Esophageal stricture or stenosis was noted in 15% of patients.

A nonrandomized, retrospective comparison of IMRT with accelerated fractionation with concomitant boost and three-dimensional conformal radiotherapy techniques at the University of Wisconsin for patients with locally advanced oropharyngeal cancer was recently reported [37]. While local–regional control and survival outcomes were generally similar between the three patient cohorts, IMRT was associated with reduced skin and mucosal toxicity compared with accelerated fractionation with concomitant boost and also was associated with the lowest incidence of xerostomia. Similar observations were found in the comparison of IMRT with accelerated concomitant boost radiotherapy at the Memorial Sloan Kettering Cancer Center [38].

Garden et al. [39] initially demonstrated efficacy of IMRT in small primary (<4 cm) lesions of the oropharynx. Of 51 patients treated (all but one with bilateral neck irradiation), 95% had a mean radiation dose of <30 Gy to at least one parotid gland. A Radiation Therapy Oncology Group (RTOG)-sponsored multicenter study of IMRT as a single treatment modality for early stage (T1–2, N0–1, M0) oropharyngeal cancer was recently published [40]. The study listed 69 patients requiring bilateral neck radiotherapy. With prescribed radiotherapy doses to primary tumor and involved nodes of 66 Gy at 2.2 Gy/fraction over 6 weeks, the 2-year local–regional failure rate was 9%. Of note, all cases of local–regional failure, metastasis, or second primary cancer occurred among patients who were current or former smokers, and none occurred among patients who never smoked. This phenomenon may be explained by different biology of smoking-related and HPV associated cancers [18]. Although xerostomia was reportedly less common for IMRT than with historical RTOG data, it was still common. Grade ≥ 2 xerostomia was observed in 55% of patients at 6 months but reduced to 25 and 16% at 12 and 24 months of follow-up, respectively.

Altered fractionation schedules

In an effort to improve local–regional tumor control, altered fractionation radiotherapy schedules have been examined to target accelerated tumor repopulation. Based on promising single-institution studies, the RTOG conducted a randomized trial (RTOG-90-03) comparing leading altered fractionation radiotherapy schedules for patients with mostly locally advanced head and neck cancer: conventional fractionation (2 Gy daily, 5 days a week to 70 Gy over 7 weeks); split course accelerated fractionation (1.6 Gy BID to 67.2 Gy over 6 weeks with a planned 2-week break at 38.4 Gy); accelerated concomitant boost (daily 1.8 Gy treatments with 1.8 Gy afternoon treatments during the last 12 days of therapy, total dose 72 Gy over 6 weeks); and hyperfractionation (1.2 Gy twice daily to a dose of 81.6 Gy over 7 weeks) [41]. Although most major head and neck anatomical sites were included in the study, approximately 60% of the 1,073 listed patients had oropharyngeal primaries. Although there was no statistically significant survival benefit observed, patients treated with hyperfractionation and accelerated fractionation with concomitant boost had significantly better local–regional control than those treated with standard fractionation. All three altered fractionation groups had significantly greater acute treatment-related morbidity compared with standard fractionation. However, there was no significant increase of late effects.

The European Organization for Research and Treatment of Cancer (EORTC) conducted a randomized trial (EORTC 22791) of a hyperfractionation regimen compared with conventional radiotherapy in 356 patients with T2–3, N0–1 oropharyngeal cancers excluding the base of tongue [42]. Hyperfractionation resulted in improved actuarial 5-year local–regional control compared with conventional radiotherapy (59 vs. 40%, respectively, $P = 0.02$), which was associated with a trend toward improved survival. Of note, the benefit in local–regional control was limited to T3 tumors. No differences in late toxicities were observed.

Brachytherapy

Interstitial brachytherapy, which permits localized delivery of a radiotherapy source to tumor tissues for focal delivery of radiotherapy, has been commonly employed in conjunction with external beam radiotherapy for curative-intent treatment of oropharyngeal malignancies for many years [43–50]. In current practice, brachytherapy is frequently administered for base of tongue lesions following external beam radiotherapy with or without chemotherapy [51, 52]. In a recent analysis of 90 patients with oropharyngeal cancer treated with interstitial brachytherapy from 1984 to 2001 at the University of Utah, 5-year local control, disease-free survival, and overall survival of this patient series were 76, 61, and 55%, respectively [53]. Severe complications occurred in 13 patients, including two treatment-related deaths. Although the data supporting brachytherapy indicate it is effective as a treatment modality, the reports are limited to case series from single institutions, and no randomized data exist comparing the value of brachytherapy implants with modern conformal IMRT techniques.

Concomitant chemoradiotherapy

Several randomized studies have demonstrated improved local–regional control rates and also improved overall survival with concurrent administration of chemotherapy with radiotherapy for patients with locally advanced (stages III and IV) squamous cell carcinoma of the head and neck (recently reviewed by Forastiere [54]). While most of the randomized study literature consists of non-anatomical site-specific studies, there is one randomized controlled trial limited to patients with oropharyngeal cancer.

The Groupe d'Oncologie Radiotherapie Tete et Cou (GORTEC) conducted a randomized, controlled trial of radiotherapy alone (70 Gy) compared with concomitant carboplatin and infusional 5-fluorouracil chemotherapy and conventional fractionation radiotherapy (70 Gy) in patients with locally advanced (stages III and IV) oropharyngeal cancer [55, 56]. Five-year overall survival, specific disease-free survival, and local–regional control rates associated with concurrent chemoradiotherapy, and radiotherapy alone were 22 and 16% (log-rank $P = 0.05$), 27 and 15% ($P = 0.01$), and 48 and 25% ($P = 0.002$), respectively. However, the addition of systemic chemotherapy failed to prevent distant recurrence.

Although this trial provides convincing clinical evidence supporting chemotherapy-induced radiosensitization of oropharyngeal cancers, the optimal chemotherapeutic regimen and radiotherapy protocol against oropharyngeal cancer is not known. In addition to platinum-based chemotherapy, taxane-based chemotherapy has also been employed effectively for induction and concomitant treatment of oropharyngeal carcinoma. In 2007, Cmelak et al. [57] reported the results of an Eastern Cooperative Oncology Group (ECOG 2399) phase II study of chemoradiotherapy in patients with resectable stages III/IV laryngeal and oropharyngeal cancers. The cohort of 111 patients, which included 69 patients with oropharyngeal carcinoma, were treated with induction paclitaxel 175 mg/m^2 and carboplatin AUC 6 for two cycles every 21 days followed by concurrent paclitaxel 30 mg/m^2 every 7 days in association with 70 Gy of radiotherapy. "Organ preservation" (defined in the manuscript as freedom from either local recurrence or need for salvage surgery at the primary site) was achieved in 84% of the patients with oropharyngeal cancer. Eighty-three percent of the oropharynx group survived 2 years. Toxicity was low, and induction chemotherapy did not preclude delivery of concurrent chemoradiotherapy. In a subsequent publication, Fakhry et al. [16] demonstrated presence of oncogenic HPV genomic DNA in 40% of tumor cell nuclei of ECOG 2399 study patients and found a survival advantage associated with HPV infection in this prospective clinical trial. Compared with patients with HPV-negative tumors, patients with HPV-positive tumors had higher response rates after induction chemotherapy and chemoradiation treatment, as well as improved 2-year overall survival (95 vs. 62%, $P = 0.005$). Current areas of research are focusing on the role of other sequential therapy (aggressive systemic chemotherapy doses followed by concurrent chemoradiotherapy) regimens [58] as well as the role of bioradiotherapy, as discussed below.

Bioradiotherapy

The most thoroughly studied biologic therapy combined with radiation for patients with head and neck cancer to date is cetuximab, a monoclonal antibody which has high affinity for the EGFR, preventing ligand binding to the EGFR and inducing receptor downregulation. Preclinical evidence suggested cetuximab-induced enhancement of cytotoxic effects of radiotherapy in squamous cell carcinomas [59], and early clinical feasibility studies suggested

that the regimen was well tolerated and active [60]. These encouraging results led to the first randomized study of bioradiotherapy in head and neck cancer, reported by Bonner et al. [61]. A total of 424 patients with untreated, local–regionally advanced, stages III and IV head and neck cancer were randomly assigned to treatment with definitive radiotherapy or to radiotherapy with cetuximab. Cetuximab was administered 1 week prior to radiotherapy as a 400 mg/m^2 IV loading dose, followed by weekly infusions at 250 mg/m^2 for the duration of radiotherapy. The median duration of local–regional disease control and progression-free survival was significantly greater in the cetuximab arm, and the median survival of patients was nearly doubled [49 vs. 29.3 months, HR = 0.74 (CI 0.57–0.97), $P = 0.03$). Of particular interest is the fact that the subset of patients with oropharyngeal cancer (representing approximately 60% of the study population) appeared to experience the greatest benefit from cetuximab (local–regional disease control: HR = 0.61; overall survival: HR = 0.62). The relationship of this observed benefit to cetuximab-based radiotherapy with HPV infection status is presently unknown. Cetuximab therapy was not associated with increased in-field toxic effects associated with curative radiotherapy doses to the head and neck (e.g., mucositis, xerostomia, dysphagia, radiation dermatitis). Additionally, patient quality of life was not adversely affected with the addition of cetuximab [62]. Although these initial results clearly demonstrate the potential of cetuximab as a radiosensitizing agent, the optimal role of cetuximab in curative settings is undefined given the extensive body of evidence supporting more traditional chemoradiotherapy approaches. Several clinical trials adding cetuximab to chemoradiotherapy regimens are in progress.

Chemotherapy alone or as a modulator of therapy

The observation that previously untreated head and neck cancer is a highly chemosensitive disease is exploited in modern induction and sequential chemoradiotherapy protocols. Although the standard approach of curative-intent therapy for head and neck cancers involves definitive local and regional therapy, with chemotherapy employed as a means to augment the efficacy of radiotherapy, recent evidence suggests that chemotherapy as a single treatment modality may be appropriate for highly selected patients with laryngeal cancer in the context of a clinical trial [63, 64].

Holsinger et al. [63] recently published long-term follow-up of a series of patients treated exclusively with platin/fluorouracil-based chemotherapy at the University of Paris V. From 1981 to 2004, 2,271 patients with previously untreated, invasive squamous cell carcinomas of the larynx or pharynx (excluding the nasopharynx and velum palati) were managed with an induction chemotherapy regimen. Of these patients, 23.9% (545 of 2271) achieved a clinical complete response with induction chemotherapy, and chemotherapy was the sole treatment modality in 26.1% (142 of 545) of patients experiencing complete clinical response. These 142 patients included 123 patients with laryngeal or hypopharyngeal cancer and 19 patients with oropharyngeal cancer, 87% of whom had N0 disease. The 5-year Kaplan–Meier actuarial survival and local control estimates of this cohort were 61.2 and 50.7%, respectively. In multivariate analysis, patients with primary tumor arising from the glottic larynx had improved survival compared with patients who had tumors arising in other sites ($P < 0.0001$). Holsinger et al. [64] confirmed these findings in a prospective clinical trial of chemotherapy in selected patients with laryngeal cancer conducted at the MD Anderson Cancer Center.

The data supporting chemotherapy alone as a treatment modality for oropharyngeal cancers are therefore premature. However, using frequent induction chemotherapy, Laccourreye et al. [65] demonstrated effective management of 166 patients with T1–3, N0–3 tonsillar cancer with subsequent transoral lateral oropharyngectomy with or without neck dissection. It is notable that only 31% of patients in this series required adjuvant radiotherapy. The true role of primary chemotherapy in oropharyngeal cancer requires further research.

Quality of life following curative intent therapy

The several primary treatment options discussed above, while clearly effective in tumor control and patient survival, are indeed of questionable value if patients experience excessive treatment-related toxicity and subsequent morbidity. In 2002, Parsons et al. [66] reviewed all North American published series for the treatment of oropharyngeal cancer. Although tumor control rates were similar for either surgery ± radiotherapy or radiotherapy ± neck dissection, the rates of severe complications were significantly greater for the surgery ± radiotherapy patients. The available data on functional consequences of treatment suggested superiority of radiotherapy ± neck dissection.

Mowry et al. [67] examined patient-perceived quality of life after either chemoradiation or primary surgery and radiation for advanced-stage oropharyngeal cancer. In a cohort of 35 patients (17 treated with chemoradiation, 18 treated with primary surgery) responding by mail using the University of Washington quality-of-life instrument version 4 at an average of 25 months after treatment, there was no significant difference between the two groups in pain, appearance, swallowing, chewing, speech, saliva, or mood. Global

long-term quality of life was also similar, with most respondents having good quality of life after treatment.

Allal et al. [68] examined the functional outcome of 60 patients with oropharyngeal cancer who had been free of disease at least 1 year following management by either accelerated concomitant boost radiotherapy with or without concurrent chemotherapy (40 patients), or radical surgery followed by radiotherapy (20 patients), using the subjective Performance Status Scale for Head and Neck cancer (PSSHN) and the EORTC Core Quality of Life questionnaire (EORTC QLQ-C30). Although quality of life was generally similar between the two primary treatment modalities for patients with early-stage primary tumors, improvements in quality of life were noted for patients with T3–4 stage disease treated with radiotherapy.

Denis et al. [69] reported the 5-year long-term toxicity data for the randomized GORTEC trial which established superiority of concurrent chemoradiotherapy over radiotherapy alone for oropharyngeal cancers. All of the patients treated with combined modality therapy developed one or more late complications versus 94% in the radiotherapy-alone arm. Concurrent chemoradiotherapy for oropharyngeal cancer, while not associated with higher rates of long-term toxicity, was clearly associated with increased (grades 1–4) toxicity in several organs including salivary glands, skin, teeth, and mandible.

Although not specific for oropharyngeal cancers, the bioradiotherapy study by Bonner et al. [61] was notable for demonstrating that concurrent cetuximab therapy was not associated with increased in field toxic effects associated with curative radiotherapy doses to the head and neck (e.g., mucositis, xerostomia, dysphagia, radiation dermatitis). Additionally, patient quality of life (evaluated by EORTC QLQ-C30 and the EORTC QLQ Head and Neck Cancer-Specific Module) was not adversely affected by the addition of cetuximab [62]. It is notable, however, that this study did not have a chemoradiotherapy treatment arm for comparison of activity and toxicity with a more traditional approach, and current trials are adding cetuximab with existing chemoradiotherapy regimens. The optimal chemoradiotherapy regimen for oropharyngeal cancer patients remains undefined. Quality of life and survivorship issues have not been sufficiently studied and need to be addressed in future clinical trials in oropharyngeal cancer management.

Salvage therapy

While the role of "planned" neck dissections following chemoradiotherapy has been traditionally controversial (particularly for ≥N2 nodal disease), observed improvements in local–regional disease control from modern chemoradiotherapy regimens have been such that patients who achieve complete clinical (including radiologic) response have a low rate of isolated neck failure and will therefore not benefit from "planned" neck dissection [70]. Advances in diagnostic technology will continue to permit improved selection of patients for medically appropriate neck dissections for suspicious or proven disease persistence ("salvage" neck dissections) following primary nonsurgical therapy [71, 72].

Despite advances in primary therapy, however, disease relapse or development of second primary malignancies are the cause of death of most patients with a head and neck cancer diagnosis. While relapse is most commonly local and regional, recent evidence noted above has suggested that advances in aggressive local primary therapies for oropharyngeal cancers may be changing the pattern of failure from local–regional to distant [34, 35]. Management of distant recurrence outside of modest results for metastatectomy for solitary lung lesions [73–75] or for unresectable local–regional recurrence is generally palliative and often involves chemotherapy as a single therapeutic modality. While recent advances in chemotherapy have been made in this setting [76], the disease remains incurable. However, the potential for cure with local therapies applied as salvage therapy for persistent disease as well as local and regional recurrence and second primary head and neck cancers is the only hope for patients afflicted with this condition, and has stimulated interest in the study of novel local therapies.

Surgical salvage is therefore the gold standard for comparison (reviewed by Lee et al. [77]). Goodwin [78] prospectively examined the question of efficacy and value of salvage surgery in head and neck cancer patients and observed that the 2-year disease-free survival of patients was most strongly associated with stage of recurrence, with benefit in approximately 70% of patients who are treated for an early-stage (stage I/II) recurrence and in 25% of patients who have surgery for a late-stage (stage III/IV) recurrence. Salvage surgical procedures for base of tongue cancers (glossectomy with or without total laryngectomy) are associated with crude local control rates of 47–57% and survival rates of 16–28% [79–81]. The decision to undergo salvage therapy for patients is often difficult, considering low chances of cure and likely high long-term morbidity following surgical salvage.

TLM has also been examined in persistent, recurrent, and second primary base of tongue cancers [82, 83]. In limited series of select patients, this approach has resulted in favorable local–regional control and survival while avoiding common salvage and reconstructive surgical complications associated with impaired wound healing (fistulas, flap failure and infection).

Reirradiation (with external beam or brachytherapy implants) may also be an alternative to salvage surgery in

patients with previously treated oropharyngeal cancer, particularly for patients with surgically unresectable disease for which radioresistance is not suspected and normal tissue tolerability is acceptable. In one series, Iridium-192 brachytherapy implantation controlled the primary tumor in 4 of 17 patients with recurrent oropharyngeal cancer [84]. Clinical trials of reirradiation may serve as a reasonable platform to investigate the tolerability and efficacy of novel radiosensitizing agents. Another (experimental) modality under investigation that may be considered in recurrent (or second primary) oropharyngeal cancers is photodynamic therapy, or interstitial photodynamic therapy for deeper infiltrating tumors, using photosensitizing agents and subsequent laser illumination of the tumor [85]. However, these modalities will usually be considered in a more palliative setting.

Conclusions

The study of oropharyngeal cancer is currently in dynamic evolution. The emerging science of HPV not only provides a deeper understanding of non-tobacco related oropharyngeal carcinogenesis, but also provides opportunities for future direct targeting of HPV-infected cancer cells in this setting. Given the differences in biology and patient prognosis, the ideal treatment protocol for HPV-associated malignancies will likely be different from non-HPV related oropharyngeal cancers. These differences may be explained by differences in carcinogenesis pathways that are involved depending on the presence or absence of HPV, with an absence of p53 disruptive mutations in HPV 16 positive tumors [13]. However, this description is perhaps simplistic, as mechanistic interactions of HPV-associated carcinogenesis with tobacco carcinogen exposure are poorly understood. Given the observed improved survival of patients with HPV-associated cancers seen with existing therapies, one real concern is the possibility of current overtreatment of this subset of patients, leading to increased risk of long-term toxicities following (chemo)radiotherapy. Furthermore, while advances in oropharyngeal cancer management at the local-regional level with chemoradiotherapy have resulted in improved survival outcomes for patients, the observed increased distant failure patterns demand attention for improved systemic therapies against this disease.

The management of oropharyngeal cancer is also in transformation, with development of exciting local therapies that limit the use of traditional open procedures. The controversy of choice of primary therapy that should be offered to patients is unsettled, with nonsurgical modalities presently being considered a therapeutic standard. Although the novel surgical therapies presented in this review have had outstanding results, they were small, uncontrolled series. Multicenter, randomized studies comparing these techniques to primary (chemo)radiotherapy for patients with resectable disease are required. Obviously, important challenges to this consideration include the choice of local surgical therapy studied (standard surgical procedures versus transoral laser microdissection versus transoral robotic approach) with predefined neck dissection criteria and postoperative chemoradiotherapy recommendations as well as the choice of primary chemoradiotherapy or bioradiotherapy protocols with appropriate follow up.

In the future, optimal treatment recommendations based on biological considerations will likely result in individualized management of oropharyngeal cancer patients. While translational research in identification and validation of prognostic and predictive molecular markers is in progress, the need to stratify patients by HPV status (by p16 immunohistochemical stains and other sensitive assays for HPV) is of critical importance in current clinical trials, given the different pathobiology and improved prognosis associated with HPV infection.

Finally, exclusive focus on traditional disease endpoints in clinical trials to date has unfortunately hindered optimal clinical management of oropharyngeal cancer. As reported survival outcomes are high for these treatment modalities, careful attention must be given to toxicities and validated quality of life measures as primary study endpoints. These questions will only be answered with well-designed clinical trials with translational studies and quality of life endpoints, and patient participation should be strongly encouraged. As a result of current scientific knowledge and an expanded therapeutic arsenal, we expect a future of exciting clinical research in oropharyngeal cancer biology and management.

References

1. Cohan DM, Popat S, Kaplan SE, Rigual N, Loree T, Hicks WL Jr (2009) Oropharyngeal cancer: current understanding and management. Curr Opin Otolaryngol Head Neck Surg 17(2):88–94
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ (2009) Cancer statistics, 2009. CA Cancer J Clin 59(4):225–249
3. National Cancer Institute, Surveillance, Epidemiology and End Results (SEER) Program. http://www.seer.cancer.gov/
4. Puscas L (2005) The role of human papilloma virus infection in the etiology of oropharyngeal carcinoma. Curr Opin Otolaryngol Head Neck Surg 13(4):212–216
5. Mork J, Lie AK, Glattre E, Hallmans G, Jellum E, Koskela P et al (2001) Human papillomavirus infection as a risk factor for squamous-cell carcinoma of the head and neck. N Engl J Med 344(15):1125–1131
6. Herrero R, Castellsague X, Pawlita M, Lissowska J, Kee F, Balaram P et al (2003) Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst 95(23):1772–1783
7. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM et al (2007) Case–control study of human papillomavirus and oropharyngeal cancer. N Engl J Med 356(19):1944–1956

8. Gillison ML (2009) Oropharyngeal cancer: a potential consequence of concomitant HPV and HIV infection. Curr Opin Oncol 21:439–444
9. Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S et al (2008) Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst 100(6):407–420
10. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML (2008) Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. J Clin Oncol 26(4):612–619
11. Braakhuis BJ, Snijders PJ, Keune WJ, Meijer CJ, Ruijter-Schippers HJ, Leemans CR et al (2004) Genetic patterns in head and neck cancers that contain or lack transcriptionally active human papillomavirus. J Natl Cancer Inst 96(13):998–1006
12. Pyeon D, Newton MA, Lambert PF, den Boon JA, Sengupta S, Marsit CJ et al (2007) Fundamental differences in cell cycle deregulation in human papillomavirus-positive and human papillomavirus-negative head/neck and cervical cancers. Cancer Res 67(10):4605–4619
13. Westra WH, Taube JM, Poeta ML, Begum S, Sidransky D, Koch WM (2008) Inverse relationship between human papillomavirus-16 infection and disruptive p53 gene mutations in squamous cell carcinoma of the head and neck. Clin Cancer Res 14(2):366–369
14. Ritchie JM, Smith EM, Summersgill KF, Hoffman HT, Wang D, Klussmann JP et al (2003) Human papillomavirus infection as a prognostic factor in carcinomas of the oral cavity and oropharynx. Int J Cancer 104(3):336–344
15. Kumar B, Cordell KG, Lee JS, Prince ME, Tran HH, Wolf GT et al (2007) Response to therapy and outcomes in oropharyngeal cancer are associated with biomarkers including human papillomavirus, epidermal growth factor receptor, gender, and smoking. Int J Radiat Oncol Biol Phys 69(2 Suppl):S109–S111
16. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H et al (2008) Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 100(4):261–269
17. Klozar J, Kratochvil V, Salakova M, Smahelova J, Vesela E, Hamsikova E et al (2008) HPV status and regional metastasis in the prognosis of oral and oropharyngeal cancer. Eur Arch Otorhinolaryngol 265(Suppl 1):S75–S82
18. Hafkamp HC, Manni JJ, Haesevoets A, Voogd AC, Schepers M, Bot FJ et al (2008) Marked differences in survival rate between smokers and nonsmokers with HPV 16-associated tonsillar carcinomas. Int J Cancer 122(12):2656–2664
19. Kreeft A, Tan IB, van den Brekel MW, Hilgers FJ, Balm AJ (2009) The surgical dilemma of 'functional inoperability' in oral and oropharyngeal cancer: current consensus on operability with regard to functional results. Clin Otolaryngol 34(2):140–146
20. Cosmidis A, Rame JP, Dassonville O, Temam S, Massip F, Poissonnet G et al (2004) T1-T2 NO oropharyngeal cancers treated with surgery alone. A GETTEC study. Eur Arch Otorhinolaryngol 261(5):276–281
21. Moncrieff M, Sandilla J, Clark J, Clifford A, Shannon K, Gao K et al (2009) Outcomes of primary surgical treatment of T1 and T2 carcinomas of the oropharynx. Laryngoscope 119(2):307–311
22. Reddy AN, Eisele DW, Forastiere AA, Lee DJ, Westra WH, Califano JA (2005) Neck dissection followed by radiotherapy or chemoradiotherapy for small primary oropharynx carcinoma with cervical metastasis. Laryngoscope 115(7):1196–1200
23. Grant DG, Salassa JR, Hinni ML, Pearson BW, Perry WC (2006) Carcinoma of the tongue base treated by transoral laser microsurgery, part one: Untreated tumors, a prospective analysis of oncologic and functional outcomes. Laryngoscope 116(12):2150–2155
24. Rich JT, Milov S, Lewis JS, Jr, Thorstad WL, Adkins DR, Haughey BH (2009) Transoral laser microsurgery (TLM) ± adjuvant therapy for advanced stage oropharyngeal cancer: outcomes and prognostic factors. Laryngoscope 119:1709–1719
25. O'Malley BW Jr, Weinstein GS, Snyder W, Hockstein NG (2006) Transoral robotic surgery (TORS) for base of tongue neoplasms. Laryngoscope 116(8):1465–1472
26. Genden EM, Desai S, Sung CK (2009) Transoral robotic surgery for the management of head and neck cancer: a preliminary experience. Head Neck 31(3):283–289
27. Moore EJ, Henstrom DK, Olsen KD, Kasperbauer JL, McGree ME (2009) Transoral resection of tonsillar squamous cell carcinoma. Laryngoscope 119(3):508–515
28. Park YM, Lee JG, Lee WS, Choi EC, Chung SM, Kim SH (2009) Feasibility of transoral lateral oropharyngectomy using a robotic surgical system for tonsillar cancer. Oral Oncol 45(8):e62–e66
29. Mukhija VK, Sung CK, Desai SC, Wanna G, Genden EM (2009) Transoral robotic assisted free flap reconstruction. Otolaryngol Head Neck Surg 140(1):124–125
30. Stoeckli SJ, Alkureishi LW, Ross GL (2009) Sentinel node biopsy for early oral and oropharyngeal squamous cell carcinoma. Eur Arch Otorhinolaryngol 266(6):787–793
31. Chao KS, Majhail N, Huang CJ, Simpson JR, Perez CA, Haughey B et al (2001) Intensity-modulated radiation therapy reduces late salivary toxicity without compromising tumor control in patients with oropharyngeal carcinoma: a comparison with conventional techniques. Radiother Oncol 61(3):275–280
32. Chao KS, Ozyigit G, Blanco AI, Thorstad WL, Deasy JO, Haughey BH et al (2004) Intensity-modulated radiation therapy for oropharyngeal carcinoma: impact of tumor volume. Int J Radiat Oncol Biol Phys 59(1):43–50
33. de Arruda FF, Puri DR, Zhung J, Narayana A, Wolden S, Hunt M et al (2006) Intensity-modulated radiation therapy for the treatment of oropharyngeal carcinoma: the Memorial Sloan-Kettering Cancer Center experience. Int J Radiat Oncol Biol Phys 64(2):363–373
34. Yao M, Nguyen T, Buatti JM, Dornfeld KJ, Tan H, Wacha J et al (2006) Changing failure patterns in oropharyngeal squamous cell carcinoma treated with intensity modulated radiotherapy and implications for future research. Am J Clin Oncol 29(6):606–612
35. Daly ME, Le QT, Maxim PG, Loo BW Jr, Kaplan MJ, Fischbein NJ et al (2009) Intensity-modulated radiotherapy in the treatment of oropharyngeal cancer: clinical outcomes and patterns of failure. Int J Radiat Oncol Biol Phys [Epub ahead of print]
36. Lawson JD, Otto K, Chen A, Shin DM, Davis L, Johnstone PA (2008) Concurrent platinum-based chemotherapy and simultaneous modulated accelerated radiation therapy for locally advanced squamous cell carcinoma of the tongue base. Head Neck 30(3):327–335
37. Rusthoven KE, Raben D, Ballonoff A, Kane M, Song JI, Chen C (2008) Effect of radiation techniques in treatment of oropharynx cancer. Laryngoscope 118(4):635–639
38. Lee NY, de Arruda FF, Puri DR, Wolden SL, Narayana A, Mechalakos J et al (2006) A comparison of intensity-modulated radiation therapy and concomitant boost radiotherapy in the setting of concurrent chemotherapy for locally advanced oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys 66(4):966–974
39. Garden AS, Morrison WH, Wong PF, Tung SS, Rosenthal DI, Dong L et al (2007) Disease-control rates following intensity-modulated radiation therapy for small primary oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys 67(2):438–444
40. Eisbruch A, Harris J, Garden AS, Chao CK, Straube W, Harari PM, et al (2009) Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). Int J Radiat Oncol Biol Phys [Epub ahead of print]
41. Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, Phillips TL et al (2000) A Radiation Therapy Oncology Group (RTOG) phase

III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. Int J Radiat Oncol Biol Phys 48(1):7–16
42. Horiot JC, Le Fur R, N'Guyen T, Chenal C, Schraub S, Alfonsi S et al (1992) Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother Oncol 25(4):231–241
43. Goffinet DR, Fee WE Jr, Wells J, Austin-Seymour M, Clarke D, Mariscal JM et al (1985) 192Ir pharyngoepiglottic fold interstitial implants. The key to successful treatment of base tongue carcinoma by radiation therapy. Cancer 55(5):941–948
44. Housset M, Baillet F, Dessard-Diana B, Martin D, Miglianico L (1987) A retrospective study of three treatment techniques for T1–T2 base of tongue lesions: surgery plus postoperative radiation, external radiation plus interstitial implantation and external radiation alone. Int J Radiat Oncol Biol Phys 13(4):511–516
45. Leborgne JH, Leborgne F, Barlocci LA, Ortega B (1986) The place of brachytherapy in the treatment of carcinoma of the tonsil with lingual extension. Int J Radiat Oncol Biol Phys 12(10):1787–1792
46. Esche BA, Haie CM, Gerbaulet AP, Eschwege F, Richard JM, Chassagne D (1988) Interstitial and external radiotherapy in carcinoma of the soft palate and uvula. Int J Radiat Oncol Biol Phys 15(3):619–625
47. Pernot M, Malissard L, Taghian A, Hoffstetter S, Luporsi E, Forcard JJ et al (1992) Velotonsillar squamous cell carcinoma: 277 cases treated by combined external irradiation and brachytherapy—results according to extension, localization, and dose rate. Int J Radiat Oncol Biol Phys 23(4):715–723
48. Mazeron JJ, Belkacemi Y, Simon JM, Le Pechoux C, Martin M, Haddad E et al (1993) Place of Iridium 192 implantation in definitive irradiation of faucial arch squamous cell carcinomas. Int J Radiat Oncol Biol Phys 27(2):251–257
49. Levendag PC, Schmitz PI, Jansen PP, Senan S, Eijkenboom WM, Sipkema D et al (1997) Fractionated high-dose-rate and pulsed-dose-rate brachytherapy: first clinical experience in squamous cell carcinoma of the tonsillar fossa and soft palate. Int J Radiat Oncol Biol Phys 38(3):497–506
50. Rudoltz MS, Perkins RS, Luthmann RW, Fracke TD, Green TM, Moye L et al (1999) High-dose-rate brachytherapy for primary carcinomas of the oral cavity and oropharynx. Laryngoscope 109(12):1967–1973
51. Quon H, Harrison LB (2002) Brachytherapy in the treatment of head and neck cancer. Oncology (Williston Park) 16(10):1379–1393; discussion 1393, 1395–1376
52. Mazeron JJ, Ardiet JM, Haie-Meder C, Kovacs G, Levendag P, Peiffert D et al (2009) GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinomas. Radiother Oncol 91(2):150–156
53. Chen J, Pappas L, Moeller JH, Rankin J, Sharma PK, Bentz BG et al (2007) Treatment of oropharyngeal squamous cell carcinoma with external beam radiation combined with interstitial brachytherapy. Head Neck 29(4):362–369
54. Forastiere AA (2008) Chemotherapy in the treatment of locally advanced head and neck cancer. J Surg Oncol 97(8):701–707
55. Calais G, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot P et al (1999) Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. J Natl Cancer Inst 91(24):2081–2086
56. Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T et al (2004) Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 22(1):69–76
57. Cmelak AJ, Li S, Goldwasser MA, Murphy B, Cannon M, Pinto H et al (2007) Phase II trial of chemoradiation for organ preservation in resectable stage III or IV squamous cell carcinomas of the larynx or oropharynx: results of Eastern Cooperative Oncology Group Study E2399. J Clin Oncol 25(25):3971–3977
58. Posner M, Vermorken JB (2008) Induction therapy in the modern era of combined-modality therapy for locally advanced head and neck cancer. Semin Oncol 35(3):221–228
59. Huang SM, Bock JM, Harari PM (1999) Epidermal growth factor receptor blockade with C225 modulates proliferation, apoptosis, and radiosensitivity in squamous cell carcinomas of the head and neck. Cancer Res 59(8):1935–1940
60. Robert F, Ezekiel MP, Spencer SA, Meredith RF, Bonner JA, Khazaeli MB et al (2001) Phase I study of anti-epidermal growth factor receptor antibody cetuximab in combination with radiation therapy in patients with advanced head and neck cancer. J Clin Oncol 19(13):3234–3243
61. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB et al (2006) Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354(6):567–578
62. Curran D, Giralt J, Harari PM, Ang KK, Cohen RB, Kies MS et al (2007) Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab. J Clin Oncol 25(16):2191–2197
63. Holsinger FC, Lin HY, Bassot V, Laccourreye O (2009) Platin-based exclusive chemotherapy for selected patients with squamous cell carcinoma of the larynx and pharynx. Cancer 115:3909–3918
64. Holsinger FC, Kies MS, Diaz EM, Jr, Gillenwater AM, Lewin JS, Ginsberg LE et al (2009) Durable long-term remission with chemotherapy alone for stage II to IV laryngeal cancer. J Clin Oncol 27:1976–1982
65. Laccourreye O, Hans S, Menard M, Garcia D, Brasnu D, Holsinger FC (2005) Transoral lateral oropharyngectomy for squamous cell carcinoma of the tonsillar region: II. An analysis of the incidence, related variables, and consequences of local recurrence. Arch Otolaryngol Head Neck Surg 131(7):592–599
66. Parsons JT, Mendenhall WM, Stringer SP, Amdur RJ, Hinerman RW, Villaret DB et al (2002) Squamous cell carcinoma of the oropharynx: surgery, radiation therapy, or both. Cancer 94(11):2967–2980
67. Mowry SE, Ho A, Lotempio MM, Sadeghi A, Blackwell KE, Wang MB (2006) Quality of life in advanced oropharyngeal carcinoma after chemoradiation versus surgery and radiation. Laryngoscope 116(9):1589–1593
68. Allal AS, Nicoucar K, Mach N, Dulguerov P (2003) Quality of life in patients with oropharynx carcinomas: assessment after accelerated radiotherapy with or without chemotherapy versus radical surgery and postoperative radiotherapy. Head Neck 25(10):833–839; discussion 839–840
69. Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T et al (2003) Late toxicity results of the GORTEC 94-01 randomized trial comparing radiotherapy with concomitant radiochemotherapy for advanced-stage oropharynx carcinoma: comparison of LENT/SOMA, RTOG/EORTC, and NCI-CTC scoring systems. Int J Radiat Oncol Biol Phys 55(1):93–98
70. Ferlito A, Corry J, Silver CE, Shaha AR, Thomas Robbins K, Rinaldo A (2009) Planned neck dissection for patients with complete response to chemoradiotherapy: a concept approaching obsolescence. Head Neck [Epub ahead of print]
71. Yao M, Buatti JM, Dornfeld KJ, Graham MM, Smith RB, Funk GF et al (2005) Can post-RT FDG PET accurately predict the pathologic status in neck dissection after radiation for locally advanced head and neck cancer? In regard to Rogers et al. (Int J Radiat Oncol Biol Phys. 2004;58:694–697). Int J Radiat Oncol Biol Phys 61(1):306–307; author reply 307

72. Brkovich VS, Miller FR, Karnad AB, Hussey DH, McGuff HS, Otto RA (2006) The role of positron emission tomography scans in the management of the N-positive neck in head and neck squamous cell carcinoma after chemoradiotherapy. Laryngoscope 116(6):855–858
73. Winter H, Meimarakis G, Hoffmann G, Hummel M, Ruttinger D, Zilbauer A et al (2008) Does surgical resection of pulmonary metastases of head and neck cancer improve survival? Ann Surg Oncol 15(10):2915–2926
74. Liu D, Labow DM, Dang N, Martini N, Bains M, Burt M et al (1999) Pulmonary metastasectomy for head and neck cancers. Ann Surg Oncol 6(6):572–578
75. Wedman J, Balm AJ, Hart AA, Loftus BM, Hilgers FJ, Gregor RT et al (1996) Value of resection of pulmonary metastases in head and neck cancer patients. Head Neck 18(4):311–316
76. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S et al (2008) Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 359(11):1116–1127
77. Lee SC, Shores CG, Weissler MC (2008) Salvage surgery after failed primary concomitant chemoradiation. Curr Opin Otolaryngol Head Neck Surg 16(2):135–140
78. Goodwin WJ, Jr (2000) Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? Laryngoscope 110(3 Pt 2 Suppl 93):1–18
79. Pradhan SA, Rajpal RM, Kothary PM (1980) Surgical management of postradiation residual/recurrent cancer of the base of the tongue. J Surg Oncol 14(3):201–206
80. Rodriguez R, Perry C, Soo KC, Shaw HJ (1987) Total glossectomy. Am J Surg 154(4):415–418
81. Barry B, Baujat B, Albert S, Nallet E, Depondt J, Guedon C et al (2003) Total glossectomy without laryngectomy as first-line or salvage therapy. Laryngoscope 113(2):373–376
82. Grant DG, Salassa JR, Hinni ML, Pearson BW, Perry WC (2006) Carcinoma of the tongue base treated by transoral laser microsurgery, part two: Persistent, recurrent and second primary tumors. Laryngoscope 116(12):2156–2161
83. Grant DG, Salassa JR, Hinni ML, Pearson BW, Hayden RE, Perry WC (2008) Transoral laser microsurgery for recurrent laryngeal and pharyngeal cancer. Otolaryngol Head Neck Surg 138(5):606–613
84. Regueiro CA, de la Torre A, Valcarcel FJ, Magallon R, Aragon G (1995) Salvage brachytherapy and salvage surgery for recurrent oropharyngeal carcinoma following radiotherapy. J Laryngol Otol 109(1):45–48
85. Copper MP, Triesscheijn M, Tan IB, Ruevekamp MC, Stewart FA (2007) Photodynamic therapy in the treatment of multiple primary tumours in the head and neck, located to the oral cavity and oropharynx. Clin Otolaryngol 32(3):185–189