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Chemotherapy regimens and treatment protocols for laryngeal cancer

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Importance of the field: Laryngeal cancer has been the model of curative-intent organ-preserving therapies in clinical oncology. Although the optimal care of patients with laryngeal cancer is truly multidisciplinary, with progressive advances in surgical, radiation, and medical oncology, the development of effective systemic therapies has been a major component of the therapeutic arsenal against laryngeal cancer.
Areas covered in this review: This review will discuss the rapidly evolving roles of chemotherapy in the management of locally advanced and metastatic laryngeal cancer.
What the reader will gain: The reader will gain a historical perspective on this evolution in treatment and will appreciate current treatment challenges and promising future directions in optimizing therapeutic efficacy in functional larynx preservation and in patient survival.
Take home message: The treatment of most patients with laryngeal cancer with systemic therapy represents an opportunity to positively impact functional outcomes with an anatomically and functionally preserved larynx. Future challenges include identification of novel therapies and optimizing therapy protocols for individualized patient care.

Keywords: cancer, chemoradiotherapy, chemotherapy, laryngeal cancer, larynx, molecular targeted therapy, treatment

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1. Introduction

As a result of several landmark studies of innovative therapies, the multidisciplinary treatment of laryngeal cancer has become the model for organ-preserving and curative non-surgical therapies in clinical oncology. With the goals of cure, improved survival and improvement in the quality of life of patients with preserved larynx functionality, the primary management for most locally advanced disease has moved away from total laryngectomy to opportunities for larynx preservation, with particular progress made in non-surgical therapies. This report presents an overview of the evolving chemotherapy regimens and treatment protocols employed for laryngeal cancer.

1.1 Treatment goals for laryngeal cancer and definitions

The intent of therapy must always be the primary consideration for treatment decisions. Cancer of the larynx, as in other sites of the head and neck, tends to metastasize first to regional lymph nodes and subsequently to distant organs. When the extent of the disease is confined to the neck, even in the setting of locoregionally advanced (stage III and IV) disease, it can be treated with initial (primary) curative-intent surgical or radiotherapy-based interventions. However, disease

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Article highlights.

- Laryngeal cancer is the model for organ-preserving therapies in clinical oncology, in which systemic therapy has greatly contributed to modern management plans.
- The observation that previously untreated laryngeal cancer is a remarkably chemosensitive disease led to the landmark VA Laryngeal Cancer Study, which demonstrated effectiveness of this initial curative-intent non-surgical treatment paradigm in laryngeal preservation.
- The radiosensitizing properties of chemotherapy have been exploited in modern concurrent chemotherapy and radiotherapy protocols for locally advanced laryngeal cancer, which provide improved laryngeal preservation rates when compared to the induction chemotherapy protocol (RTOG 91-11 Intergroup Study).
- Sequential chemoradiotherapy (induction chemotherapy followed by concurrent chemoradiotherapy) is a novel curative-intent treatment protocol exploiting both systemic disease control and radiosensitization properties of chemotherapy which has been associated with outstanding clinical outcomes in early studies. Randomized studies of this approach compared to standard concurrent chemoradiotherapy approaches in head and neck cancer are in progress.
- In an era of molecular targeted therapies in clinical oncology, cetuximab is the first targeted agent to have demonstrated clinical evidence of radiosensitization in patients with locally advanced head and neck cancer. The optimal combination of this therapy with traditional chemotherapy and radiation therapy is an active area of clinical research.
- The study and management of laryngeal cancer continues to evolve with a focus on functional organ preservation. Investigations of intra-arterial chemoradiotherapy, 'chemoselection', and even chemotherapy alone present promising opportunities for further advances in this field.

This box summarizes key points contained in the article.

presenting as either distant metastatic disease or unresectable local recurrence after definitive primary radiotherapy is generally considered incurable.

The role of chemotherapy for patients with laryngeal cancer, initially applied only to palliative settings, has evolved into curative management plans. In the case of laryngeal cancer, administration of chemotherapy potentially offers: i) systemic disease cytoreduction; and/or ii) locoregional radiosensitization. While successful achievement of these therapeutic objectives is often dependent on preservation of patient functional status and minimizing toxicities during therapy, considerable advances in supportive care have been made to ameliorate the morbidity of disease and the toxicities associated with cancer therapy, which are not the focus of this review. Rather, this article focuses on the role of chemotherapy as a component of curative-intent interventions.

In discussing treatment protocols, is necessary to define common terms used in cancer management plans. 'Neoadjuvant (induction) therapy' is treatment (often chemotherapy) administered before a definitive locoregional therapy (surgery, radiation, or chemoradiotherapy). 'Adjuvant therapy' is treatment administered following a definitive treatment intervention, with the intent of treating micrometastatic disease remaining after the primary therapy, thereby preventing disease recurrence and improving survival. Evidence of response to systemic therapy is currently defined by the Response Evaluation Criteria in Solid Tumors (RECIST) as complete response (CR, the disappearance of all targeted lesions) or partial response (PR, at least a 30% decrease in the sum of the largest diameters of targeted lesions) [1]. Prolonged disease stabilization (stable disease, SD), however, may possibly be another measure of therapeutic activity in patients with incurable disease. Complete responses following chemotherapy have been observed in laryngeal cancers, and this observation has led to several curative-intent, non-surgical therapies for this disease. However, only in very rare and currently experimental exceptions is systemic therapy alone a possibly curative intervention (see Section 4). Definitive therapy with concurrent radiation is therefore necessary to achieve final local and regional control.

2. Roles of chemotherapy and molecular targeted therapies in primary, curative-intent treatment

As noted above, the role of chemotherapy in the management of laryngeal cancer has evolved from only palliative therapy of incurable disease to an important therapeutic component in curative-intent management. Systemic disease control and radiosensitization properties of chemotherapy and molecular targeted therapies have been exploited in current management plans.

2.1 Induction (neoadjuvant) chemotherapy followed by radiotherapy

Neoadjuvant, or induction chemotherapy, given prior to definitive irradiation or surgery provides a number of theoretical advantages including the possible eradication of systemic micrometastases, the ability to deliver therapy to a tumor bed with blood supply unaltered by prior surgery or irradiation, and possibly altered tumor kinetics in the region targeted for subsequent irradiation. Response to neoadjuvant treatment may also predict the response to subsequent radiation therapy, as will be discussed.

Clinical research of induction chemotherapy in laryngeal cancer has revolutionized the treatment of this disease. In 1975, the feasibility of neoadjuvant chemotherapy was first established by Tarpley *et al.* [2], using preoperative methotrexate. The concept was further explored in several subsequent clinical trials [3-10]. The largest of these, the Head and Neck Contracts Program, showed that 3% of patients with resectable stage III or IV cancer of the oral cavity, larynx and hypopharynx achieved a pathologic CR (complete eradication of the tumor at the time of surgery) after only one cycle of

preoperative cisplatin and bleomycin chemotherapy; however, the neoadjuvant chemotherapy failed to demonstrate a benefit in terms of survival [4]. Cisplatin and 5-fluorouracil (PF) regimens also produced high response rates in patients with previously untreated disease. Thirty to 50% of patients achieved clinical CRs, with pathologic complete response confirmed in approximately two-thirds of the complete responders [11]. A significant survival advantage was demonstrated among patients who achieved complete clinical and pathological response following PF chemotherapy, and there was a trend toward improved outcomes even among partially responding patients as compared with non-responders [8,12-14]. Jacobs *et al.* [15] and Karp *et al.* [16] were the first to incorporate these observations into a treatment paradigm that used response to preoperative chemotherapy as a means to select patients for non-surgical definitive treatment.

As a result of this work, the first randomized study of organ-preservation therapy for laryngeal cancer was conducted by the Department of Veterans Affairs (VA) Laryngeal Cancer Study Group, with results published in 1991 [17]. Starting in 1985, a total of 332 patients with either stage III or stage IV laryngeal cancer (57% with laryngeal fixation, and 63% supraglottic tumors) were randomly assigned to one of two treatment strategies: total laryngectomy followed by radiation (then the sole standard treatment) vs chemotherapy followed by either radiotherapy in responding patients or surgery in non-responders. The experimental arm included three cycles of induction chemotherapy consisting of intravenous cisplatin at 100 mg/m^2 on day 1 and 5-fluorouracil at 1000 mg/m^2/day over 24 h for five consecutive days. Three clinical response assessments were performed, the first after two cycles of induction chemotherapy. If there was not at least a 50% reduction in primary tumor size and at least stable disease in the neck, chemotherapy was stopped and surgery was performed, followed by postoperative radiotherapy. If at least a partial response (> 50% shrinkage) was noted after two cycles, patients received a third cycle of induction chemotherapy followed by a second tumor assessment and primary site biopsy. This was followed by definitive radiotherapy (66 – 76 Gy). Twelve weeks after the completion of radiotherapy, a third tumor assessment by direct laryngoscopy was performed. If biopsy-proven cancer was found, a salvage laryngectomy was performed. If not, the patient entered a standardized follow-up schedule. Although 5-year survival for the two arms of the study was equivalent, larynx preservation was noted in nearly two-thirds of surviving patients randomized to the induction chemotherapy arm. There was also a trend toward reduced distant metastasis, although this was not statistically significant. The 1991 publication did not compare functional quality of life issues between the two arms. The study was subsequently analyzed in 1998 for swallowing and voice functions. Whereas voice preservation was significantly higher in the larynx preservation group, the same incidence of swallowing abnormalities, even up to 2 years after treatment, was observed in the two treatment arms [18]. Nevertheless, non-surgical therapy became a standard of care for the treatment of locally advanced laryngeal cancer.

The second randomized induction therapy trial for larynx preservation was conducted by EORTC (the European Organisation for Research and Treatment of Cancer) in patients with pyriform sinus (78%) and lateral epilaryngeal cancers (22%) [19]. A total of 194 patients were randomized to standard total laryngectomy and partial pharyngectomy followed by radiotherapy or to induction PF chemotherapy followed by radiotherapy in complete responders. The rate of complete clinical response to induction chemotherapy was 54%. Although survival was similar between the study arms, the functional larynx preservation rate was 48% at 3 years.

A third randomized study involving 68 patients by the GETTEC (Groupe d'Etude des Tumeurs de la Tête et du Cou) specifically in T3 laryngeal cancer also supported the concept of larynx preservation [20]. In this study, patient selection was more restrictive than in the VA trial, because all patients had larynx fixation, but only 31% had a supraglottic tumor. Two-year survival was significantly higher in the surgery group than in the chemotherapy group (84 vs 69%), but 15 of 36 patients (42%) in the chemotherapy group avoided a total laryngectomy. A meta-analysis of chemotherapy in head and neck cancer (MACH-NC) in these three studies (n = 602) found no significant difference in survival, with larynx preservation in 58% of the surviving patients at 5 years [21].

Recently, Pointreau *et al.* [22] compared the effect of three cycles of induction PF with induction TPF (docetaxel–cisplatin–fluorouracil) in a larynx-preservation study of 213 laryngeal and hypopharyngeal cancer patients who otherwise required total laryngectomy. The TPF induction regimen consisted of three planned cycles of intravenous docetaxel at 75 mg/m^2 on day 1, cisplatin at 75 mg/m^2 on day 1, and 5-fluorouracil at 750 mg/m^2/day as a 24-h continuous infusion for 5 days, with each cycle administered at intervals of 21 days. Patients responding to induction chemotherapy received radiotherapy (70 Gy to the tumor volume) with or without additional chemotherapy (per institutional practice) and non-responders underwent total laryngectomy followed by radiotherapy with or without additional chemotherapy. At 3 years, the laryngeal preservation rate in the taxane (docetaxel) group was significantly higher (70.3 vs 57.5%, p = 0.03) and the response rate was higher in the taxane group (80 vs 59.2%, p = 0.002), but there was no differences in overall survival.

2.2 Concurrent chemoradiotherapy

The rationale for concurrent chemoradiotherapy (chemotherapy delivered during a radiotherapy course) results from the concept of radiosensitization of tumor cells, which remains theoretical. One hypothesis accounting for radiosensitization is that chemotherapy can synchronize cancer cells in the cell cycle to promote radiation sensitivity (the G2 phase). Concurrent chemotherapy may additionally impair DNA

repair mechanisms following damage induced by radiotherapy. Another hypothesis is that chemotherapy delivered concurrently can have antiangiogenic effects. Finally, concurrent chemotherapy combats tumor cell repopulation associated with resistance to radiation [23-26]. Clinical evidence supporting this treatment approach has been demonstrated by several trials in head and neck cancer resulting in improved patient survival [27-31]. Although the potential for eradication of micrometastatic distant disease may be exploited in concurrent chemoradiotherapy regimens, the local toxicity and tolerance of chemoradiotherapy are worse than for radiotherapy [24]. As a result, the doses of chemotherapy prescribed in the absence of radiotherapy are frequently decreased in concurrent regimens to improve tolerance and compliance.

Following the VA trial, the RTOG (Radiation Therapy Oncology Group) 91-11 Intergroup randomized trial was the next landmark study in patients with locally advanced laryngeal cancer, published in 2003 [32]. This study randomized 547 patients with stage III and stage IV larynx cancer (although only data for 497 were analyzed) to two experimental arms as compared to induction PF chemotherapy followed by definitive radiotherapy in responders (the identical protocol as in the VA study). Patients with stage T1 primary tumor or patients with large-volume T4 disease (defined as tumor penetrating through the cartilage or extending more than 1 cm into the base of the tongue) were not eligible for study participation. Of participating patients, 68% had supraglottic tumors and 65% had laryngeal fixation. The first experimental arm consisted of radiotherapy alone, and the second experimental arm was concurrent chemoradiotherapy with single agent cisplatin at a dose of 100 mg/m^2 given on days 1, 22, and 43 during radiotherapy. The radiotherapy regimens in all treatment arms were identical, planned as 35 once-daily radiotherapy fractions to a total dose of 70 Gy to the primary site.

Although the survival curves for all treatment arms were identical, a slightly – but significantly – lower rate of distant metastasis was observed for patients treated with induction chemotherapy than those treated with radiotherapy. With 2-year results, the rate of larynx preservation in the induction chemotherapy arm was 71%, similar to that of the VA Study, and was not statistically different from the 64% laryngeal preservation in the radiotherapy arm, also comparable to rates of earlier studies of radiotherapy alone [33-37]. However, the rate of larynx preservation of the concurrent chemotherapy arm was significantly greater, at 81% ($p = 0.005$). With 5-year follow up, although laryngeal preservation and locoregional control remained superior for the concurrent chemoradiotherapy arm, laryngectomy-free survival was significantly better with either induction chemotherapy (44.6%, $p = 0.011$) or concurrent chemoradiotherapy (46.6%, $p = 0.011$) than with radiotherapy alone (33.9%) [38].

This study thus demonstrated an advantage with concurrent chemoradiotherapy in the treatment of locally advanced laryngeal cancer, which consequently supplanted induction chemotherapy regimens. The radiosensitization afforded by concurrent chemoradiotherapy was also apparent, however, in the increased rate of serious (grade 3 or grade 4) mucositis, which was nearly twice as frequent as the mucosal toxicity of the control arm. Finally, one European trial (EORTC 24954) compared alternating chemoradiotherapy and induction chemotherapy with no significant difference between arms in terms of survival or larynx preservation [39].

In terms of survival, a recent update of the MACH-NC meta-analysis [40] demonstrated a statistically significant effect of concurrent platinum-based chemotherapy on improving survival associated with locoregional therapy. Concurrent chemoradiotherapy was shown to improve overall survival, event-free survival, and locoregional failure significantly more than induction chemotherapy, with an absolute benefit in overall survival of 3.5% at 5 years.

2.3 Sequential chemoradiotherapy

Although no significant improvement in survival to date has been observed in specific laryngeal cancer trials, platinum-based chemotherapy has been shown in a meta-analysis to improve survival [40]. Because of the separate potential benefits of induction chemotherapy and concurrent chemoradiotherapy, several investigators have examined sequential regimens (involving both treatments). The theoretical advantages of this approach include administration of full-dose systemic chemotherapy upfront to a previously untreated tumor and upfront aggressive treatment of potential micrometastatic distant disease. Of concern is the added treatment time with neoadjuvant chemotherapy and the potential for delay of definitive treatment resulting from either toxicity or non-compliance.

Sequential therapy has been studied in the context of several series and Phase II trials in head and neck cancer, with remarkably encouraging results [41-45], now supported by larger studies [46,47]. TAX 324, a randomized Phase III trial of two induction chemotherapy regimens in a sequential protocol, confirmed these observations and demonstrated superiority of TPF over PF as the optimal induction chemotherapy regimen for future trials [47]. In this protocol, induction TPF consisted of three planned cycles of intravenous docetaxel at 75 mg/m^2 on day 1, cisplatin at 100 mg/m^2 on day 1, and 5-fluorouracil at 1000 mg/m^2/day as a 24-h continuous infusion administered over 4 days. The concurrent chemoradiotherapy regimen consisted of carboplatin at area under the curve (AUC) of 1.5 administered once a week during the radiotherapy course. In a recent subset analysis of 166 participating patients with locally advanced laryngeal and hypopharyngeal cancer, sequential therapy with induction TPF was associated with improved survival and, in operable patients, with laryngectomy-free survival [48]. The recently published results demonstrating superiority of TPF over PF as induction chemotherapy in a specific laryngeal preservation protocol confirm these observations, although improved survival was not observed [22].

Preliminary results of sequential therapy for locally advanced disease show a 3-year survival rate of over 60%. The concept is being tested in at least three large, randomized Phase III trials in locally advanced, non-site-specific head and neck cancer, compared with concurrent chemoradiotherapy. In addition to examining traditional outcomes of survival and disease control, these trials are prospectively studying measures of patient quality of life and functional issues (speech and swallowing).

2.4 Bioradiotherapy

The development of active molecular targeted therapies for head and neck cancer has led to studies integrating these relatively less toxic agents with radiotherapy regimens with intent to cure (bioradiotherapy). The molecular targeted therapy most successfully combined with radiation to date is cetuximab, a monoclonal antibody with high affinity for the epidermal growth factor receptor (EGFR), blocking the binding of its ligands and inducing receptor internalization and down-regulation. Preclinical studies showed cetuximab-induced enhancement of the cytotoxic effects of radiotherapy in squamous cell carcinomas [49]. Encouraging results from early clinical feasibility studies led to the first randomized study of bioradiotherapy in head and neck cancer, initially published in 2006 [50] (with updated 5-year survival results in 2009 [51]), which included a total of 424 patients with untreated, stage III and stage IV head and neck cancer who were randomly assigned to definitive radiotherapy or radiotherapy with cetuximab. Cetuximab was administered intravenously starting 1 week before radiotherapy as a 400 mg/m^2 loading dose, followed by weekly infusions of 250 mg/m^2 for the duration of the radiotherapy. The median duration of locoregional control and progression free survival was significantly higher with concurrent cetuximab treatment, as was the median survival (49 months vs 29.3 months, $p = 0.03$). Treatment with cetuximab was well tolerated, associated with frequent acneiform rash and development of potentially serious but rare infusion-related allergic reactions. However, incidence of other serious (grade 3 or greater) toxicities, including mucositis, did not differ significantly. Additionally, patient quality of life (evaluated by EORTC QLQ-C30 and the EORTC QLQ Head and Neck Cancer-Specific Module) was not adversely affected with the addition of cetuximab [52].

Although this study did not include a chemoradiotherapy arm, it represents the first clinical demonstration of radiosensitization of head and neck cancers induced by molecular targeted therapies, an observation likely to be duplicated with other future molecular targeted therapies. It is important to note that on subset analysis, the patient population that appeared to have greatest survival benefit for cetuximab in combination with radiotherapy was in oropharyngeal cancer, which comprised 60% of the study population [hazard ratio (HR) 0.62]; the survival benefit for cetuximab in laryngeal cancer (about 25% of the study population) was less (HR = 0.87). Therefore, the role of cetuximab with radiotherapy in the curative management of locoregionally advanced laryngeal cancer remains poorly defined. Currently, several clinical trials are investigating the incorporation of cetuximab in concurrent and sequential chemoradiotherapy regimens.

2.5 Intra-arterial chemoradiotherapy

Patients with locally advanced laryngeal cancer with bone or thyroid cartilage invasion generally have a poor prognosis, are best managed by primary total laryngectomy, and have therefore been excluded from randomized clinical trials of organ preservation. Intra-arterial chemotherapy administration has been explored in many head and neck anatomical sites as a means to administer supradose cisplatin chemotherapy (doses up to 150 mg/m^2 weekly) directly into the tumor blood flow, followed by rapid systemic detoxification with intravenous sodium thiosulfate [53-56]. For laryngeal cancers, intra-arterial therapy poses vascular access problems to isolate vessels that adequately perfuse the tumor and involved lymph nodes, but advances in radiologically guided catheterization have improved access to these vessels. Robbins *et al.* [57] have employed superselective arterial infusions of cisplatin combined with radiation as part of an organ-preservation strategy. Samant *et al.* [58,59] observed high rates of response and organ preservation when this treatment protocol was applied to advanced pyriform sinus cancers and head and neck cancers with bone or cartilage involvement. Although this approach requires new expertise, this intensive treatment regimen (RADPLAT) has been feasible in multi-institutional settings [60]. Staton *et al.* [61] reviewed 45 laryngeal cancer patients treated with RADPLAT in terms of risk factors resulting in a poor functional outcome following successful disease control (defined as the persistent need for a feeding tube and/or tracheostomy at 6 months after therapy). Regression analysis of all pretreatment factors indicated vocal cord fixation as being the strongest predictor of a poor functional outcome. Among the 27 patients in this subset, 15 (56%) had a poor functional outcome. By contrast, only 1 (6%) of 18 patients without vocal cord fixation had poor laryngeal function. Randomized clinical trials will be needed to determine the optimal use of this treatment approach, and as with all laryngeal organ preservation studies, function and quality of life issues need to be assessed.

2.6 Treatment decisions based on response to neoadjuvant chemotherapy

Since the introduction of induction chemotherapy, researchers had hoped to select future therapy based on the response to induction chemotherapy. This theory is based on the similarities of the cytotoxic effects of chemotherapy and radiotherapy and on the complete response to induction chemotherapy being predictive of local control with radiotherapy in the VA study discussed above.

Along these lines, Urba *et al.* [62] have recently introduced a protocol for selecting patients with laryngeal cancer for subsequent chemoradiotherapy by extent of response to only one cycle of induction chemotherapy. Using the same induction chemotherapy regimen as employed in the VA larynx preservation study (PF), patients who achieved a < 50% response to the initial chemotherapy cycle underwent total laryngectomy, while good or complete responders underwent subsequent concurrent chemoradiotherapy with cisplatin. On completion of chemoradiotherapy, two adjuvant cycles of PF were then offered to complete responders. Of 97 eligible patients, including patients with bulky or deeply invasive T4 disease for whom total laryngectomy remains standard, 75% achieved > 50% response to one cycle of induction chemotherapy, leading to an altered therapeutic plan with an overall survival rate at 3 years of 85% and a 70% laryngeal preservation rate. A retrospective analysis of patients with T4 disease with cartilage invasion from this trial and a subsequent study demonstrated that 'chemoselection', even for such patients, may be a feasible organ-preservation alternative to standard primary total laryngectomy [63]. Although the survival and larynx preservation rates in these studies are encouraging, additional research is required to determine the exact role of induction chemotherapy in selecting patients for subsequent locoregional therapy, comparing this approach to primary chemoradiotherapy, sequential protocols, and regimens including bioradiotherapy.

3. Roles of chemotherapy in the adjuvant (post-definitive treatment) setting

Locoregional therapies, namely surgery and radiotherapy, have been the traditional mainstay of curative-intent therapy of laryngeal and other head and neck cancers. However, the observation of both regional and systemic disease recurrence following curative-intent primary therapy has driven investigations of adjuvant therapy to improve disease-specific survival.

3.1 Adjuvant chemotherapy

The Head and Neck Contracts Program, initiated in 1978, was a three-arm study of 462 patients with stage III/IV cancer of the oral cavity, larynx or hypopharynx comparing single-course preoperative cisplatin and bleomycin chemotherapy followed by surgery and postoperative radiotherapy with the same treatment followed by six cycles of monthly cisplatin. The third arm was the control arm with conventional surgery and radiotherapy [4]. No benefit was demonstrated with neoadjuvant chemotherapy, although detailed analysis of various subsets of patients suggested that induction chemotherapy plus maintenance may have had a beneficial effect in patients with oral cavity cancer, small primaries (T1–T2) or neck disease (N1–N2). However, the group of patients receiving adjuvant chemotherapy showed a delay in the appearance of distant metastases. One important limitation of this study is that only 27% of patients enrolled on the adjuvant therapy arm received three or more cycles of adjuvant chemotherapy and nearly half never received any at all. Other investigators have consistently observed incomplete delivery of planned adjuvant chemotherapy regimens following primary chemoradiotherapy [29,62,64]. Tolerance and adherence to a planned adjuvant therapy course is required for it to be effective. For now, this approach with conventional chemotherapy does not play a role in the management of patients with laryngeal cancer.

The goal of prolonged, maintenance therapy for control of distant metastases may be attained in the future using molecular targeted agents, which may be better tolerated than traditional cytotoxic chemotherapies. Gefitinib, an orally bioavailable EGFR tyrosine kinase inhibitor, has been successfully administered as daily dose to head and neck cancer patients both during and following curative-intent chemoradiotherapy for up to 2 years [65]. The oncological effects and patient quality of life experienced in this type of approach need further confirmation.

3.2 Postoperative chemoradiotherapy

Head and neck cancer patients continue to undergo primary surgical resection with low morbidity. This is due to patient selection and modern surgical techniques, including transoral laser or robotic-assisted resection with or without reconstruction. Primary total laryngectomy also remains a standard treatment for deeply infiltrating T4 cancers with loss of laryngeal function. As meta-analyses of randomized controlled trials have shown that concurrent chemoradiotherapy offers a small but significant survival advantage over radiotherapy for the treatment of primary disease [40], this concept has been applied to the postoperative setting.

Two randomized clinical trials (sponsored by the EORTC and RTOG) address this issue, both published in 2004 [66,67]. Both studies included patients with adequate organ function and performance status following surgical resection of squamous-cell carcinomas of the oral cavity, oropharynx, larynx, and hypopharynx. High-risk patients in the RTOG study were defined as having positive margins, extracapsular extension of lymph node metastases, or involvement of two or more lymph nodes [67]. The EORTC study included only pT3-4Nx disease (except pT3N0 larynx cancer), pT1-2N0-1-staged tumors with high-risk features, or oral cavity/oropharynx cancer with involvement of level IV/V lymph nodes [66]. Although the two studies employed slightly different radiotherapy regimens (EORTC: 60 Gy in 30 fractions, with a 6 Gy boost to high-risk sites; RTOG: 54 Gy in 27 fractions with a 12 Gy boost to high-risk sites), the concurrent chemotherapy regimens were identical, with single-agent cisplatin administered at 100 mg/m^2 on days 1, 22, and 43 of the radiotherapy course.

Although improved locoregional control and progression-free survival was observed with adjuvant postoperative chemoradiotherapy in both the RTOG and EORTC studies, only the EORTC study demonstrated a significant survival advantage

with chemoradiotherapy [EORTC: HR = 0.70, confidence interval (CI) 0.52 – 0.95, p = 0.02 vs RTOG: HR = 0.84, CI 0.65 – 1.09, p = 0.19]. No improvement in distant recurrence was observed in either study. Additionally, the toxicities of the approach were considerable, with a higher rate of serious acute toxicity observed in the chemoradiotherapy regimens of both studies, particularly in mucositis; however, there was no significant difference in late toxicities. Four patients died in the chemoradiotherapy arm of the RTOG study and one patient died from treatment-related toxicity in each arm of the EORTC study. Postoperative adjuvant chemoradiotherapy should therefore be considered for high-risk patients who are able to tolerate aggressive treatment.

4. Chemotherapy alone as an investigational curative-intent therapy

In the VA Laryngeal Cancer Study, low T stage (T1–3 disease vs T4 disease) was found to be the best predictor of response to induction chemotherapy [68]. In 1996, Laccourreye *et al.* [69] published results of an investigation of chemotherapy as a single treatment modality in patients with early to intermediate stage glottic cancer, with the intent of providing curative treatment and preserving organ function. Although the initial study in laryngeal cancer was small and retrospective in nature, this hypothesis has been confirmed in recent publications [70-73]. In 2009, Holsinger *et al.* [72] reported results of a prospective study at the M.D. Anderson Cancer Center, University of Texas, involving 31 previously untreated patients with laryngeal cancer (T2–4, N0–1, M0) with tumors considered for conservation laryngeal surgery. Patients received three or four cycles of paclitaxel, ifosfamide, and cisplatin (TIP), with histopathological assessment of response. Patients achieving a complete pathologic response (pCR) received an additional three cycles of TIP and no other treatment. With chemotherapy alone, 11 patients (37%) achieved pCR, 10 of whom (33% of total) remained alive with no evidence of recurrence over a median follow-up time of 5 years.

In the most recent report from the University of Paris, Holsinger *et al.* [73] reviewed all patients treated with chemotherapy alone resulting in a much larger cohort of 142 patients, out of 2271 patients initially treated with induction chemotherapy over 23 years. No deaths were attributable to chemotherapy. The authors reported a 5-year survival rate of 61.2%, with metachronous second primaries and intercurrent disease being the main causes of death. The 5-year local control rate was 50.7%, with salvage therapy resulting in a 93% overall local control rate (97.2% in patients with glottic cancer). Chemotherapy decreased the need for or the extent of local therapy in 54.9% of patients. It is notable that the results of this study were achieved with platinum-based chemotherapy regimens that did not include taxanes or molecular targeted therapies. The authors concluded that for selected patients, chemotherapy alone may provide long-term disease control. Additionally, in the event of relapse after chemotherapy, this approach permits effective salvage and maintains function in a majority of patients.

As a result of these studies, laryngeal cancer joins the ranks of those select malignancies potentially curable with chemotherapy alone [74]. Supporting these results, intra-arterial chemotherapy has recently demonstrated efficacy as primary therapy for laryngeal verrucous carcinoma [75]. To date, chemotherapy alone generally has best addressed early-stage disease, however, for which local single-modality treatments using surgery or radiotherapy provide excellent oncological results. Indeed, a recent publication from the University of Michigan demonstrated that patients with locoregionally advanced (stage III or IVA) laryngeal or hypopharyngeal cancer do not seem to benefit from a chemotherapy alone protocol, even when complete histological response is confirmed at the primary site [76]. Further studies are needed to compare chemotherapy alone with traditional curative treatment modalities in terms of oncological results, toxicity and quality of life before chemotherapy alone can be advocated as a curative intervention for laryngeal carcinoma [74,77].

5. Chemotherapy and molecular targeted therapy as palliative treatment for laryngeal cancer

Despite advances in primary therapy, disease relapse or development of second primary malignancies are frequent causes of death in patients with head and neck cancer, even when complete locoregional control has been achieved. Improvements in locoregional control with advances in primary therapies may ultimately change the pattern of failure from locoregional to distant disease. Management of distant or locoregionally unresectable recurrent disease is often achieved with palliative chemotherapy as a single treatment modality. Whereas previously untreated laryngeal cancer is highly chemosensitive, patients with unresectable recurrence often have median survival duration of 6 – 8 months. Although the single-agent activity of cetuximab for incurable disease is quite modest (associated with a response rate of 13% in patients with disease progression on platinum-based therapy) [78], the combination of cetuximab with platinum-based combination chemotherapy has led to survival benefit in this setting in a recently published randomized Phase III trial [79]. Whether this survival benefit observed with cetuximab is limited to its combination with chemotherapy or is maintained when administered as a single agent, as it is for colorectal cancer, is unknown. Additionally, aside from cetuximab and other EGFR-targeted therapies, a host of biological agents targeting relevant signaling pathways and carcinogenesis mechanisms are under clinical investigation. Further clinical research on systemic therapy in this setting will not only have implications for patients with incurable disease but also serve as an evidence-based platform for future neoadjuvant/sequential therapies or even in curative-intent chemotherapy/molecular targeted therapy protocols.

6. Conclusions

This article reviews the evolving roles of chemotherapy and molecular targeted therapies in the management of laryngeal cancer. Chemotherapy, once considered as only a palliative therapy for incurable disease, has now come to the forefront as an integral component of multidisciplinary curative treatment plans. This process has resulted from a stepwise progression of results from landmark trials in clinical oncology, which have challenged traditional surgical oncological principles, from the induction chemotherapy protocol in the VA Laryngeal Cancer Study to modern standards including concurrent and sequential chemoradiotherapy and bioradiotherapy regimens. However, it must be made clear that no larynx-preservation approach offers a survival advantage with respect to total laryngectomy and appropriate adjuvant therapy. Postoperative concurrent chemoradiotherapy is now a standard of care for high-risk patients who are able to tolerate aggressive therapy after primary surgery. Intra-arterial chemoradiotherapy remains investigational, as is the role of chemotherapy as a sole treatment modality for highly selected patients. There is no doubt that clinical research has shifted the paradigms in the treatment of laryngeal cancer leading to a declining use of surgery [80]. It is in this environment of innovative multidisciplinary research where continued advances are expected to be made in laryngeal preservation, patient survival and quality of life, and in cancer prevention.

7. Expert opinion

The treatment of laryngeal cancer has truly been shaped by groundbreaking clinical research documenting logical advances in multidisciplinary management. The primary therapy for most locally advanced disease has moved away from total laryngectomy to novel surgical and, increasingly non-surgical, opportunities for functional larynx preservation. Furthermore, recent evidence now places laryngeal cancer among the ranks of those select malignancies potentially curable with chemotherapy alone. However, although great therapeutic advances have been made, many concerns still require future research attention.

In an era of several effective treatment regimens, identification of an optimal treatment protocol for locally advanced laryngeal cancer remains a future challenge. Current clinical research in this field consists of large number of small, non-site-specific and non-randomized studies with widely varied chemotherapy regimens (now in combination with molecular targeted therapies), and available radiation regimens have also become increasingly complex [e.g., altered radiation fractionation schedules, intensity modulated radiation therapy (IMRT)]. Results from randomized Phase III clinical trials, the highest level of scientific evidence supporting therapeutic interventions, are limited for head and neck cancers. Only recently are randomized trials in progress comparing modern chemoradiotherapy protocols. As in these trials, future studies of chemoradiotherapy should prospectively examine quality of life and assess the functionality of the anatomically preserved larynx.

Here, we must stress that the true objective of organ preservation is function preservation, not the avoidance of surgery *per se.* In fact, surgery is a crucial component of the function preservation paradigm. For example, local treatment for early glottic cancer provides excellent oncological and functional results, without the toxicity involved with chemotherapy. Also, primary non-surgical therapy may not be optimal for some locally advanced laryngeal cancers, where chemoradiotherapy could result in a non-functional larynx with chronic aspiration, cervical esophageal stricture, and/or permanent tracheotomy, leaving a patient without effective speech or swallowing. In this disease where cure is the primary goal of patient care, quality of life and survivorship concerns will need to be more effectively addressed.

Although efforts at laryngeal preservation have been successful for most patients with locally advanced laryngeal cancer, improved survival has been an elusive objective in clinical research to date. Randomized studies of modern chemoradiotherapy regimens in other site- and non-site-specific head and neck cancers have demonstrated survival improvements when compared to radiotherapy, but this benefit has not been observed in laryngeal cancer studies. Perhaps this is due to the technical feasibility and therapeutic efficacy of surgical salvage on locoregional failure. However, demonstration of a primary therapy offering a survival advantage will be the ultimate objective.

We are certain that no single treatment approach will be applicable to all patients. Until now, response to induction chemotherapy has been the primary method in directing subsequent locoregional management of patients with locally advanced laryngeal cancer. Although clearly effective, it is crude given the extent of our growing knowledge of cancer biology. In the future, we expect it will be possible to predict best patient response, prognosis, and quality of life associated with various available treatments (surgery, radiation alone, various chemoradiotherapy regimens, even chemotherapy alone) prior to initiating treatment. Optimizing patient selection will then spare a subset of patients from toxicities of unnecessary therapies and will also identify high-risk patients warranting treatment intensification. Identification of specific patient populations with good prognosis will additionally have an impact on patient survival. The hope of individualized treatment depends on the extent to which tumor biology and patient characteristics interact and contribute to treatment outcomes. The application of current scientific technology (including DNA microarray technology, genomics, and proteomics) in clinical research will therefore be critical for the development of future treatment plans.

The number of molecular targets for anticancer therapies is rapidly growing, and defining the roles of novel targeted therapies for laryngeal cancer will require additional research in palliative and curative settings, and possibly in

cancer prevention. The curative potential of chemotherapy alone as a treatment modality in laryngeal cancer supports the development of non-toxic systemic therapies for the prevention of head and neck cancer. Identification of appropriate biomarkers of disease that can be targeted with specific therapies will hopefully result in an effective chemoprevention strategy. Ongoing studies of maintenance targeted therapies, studied following curative-intent treatment of primary disease, may lead to the next generation of chemoprevention research.

These concerns will be addressed only in the context of well-designed and innovative clinical trials. The addition of translational research to clinical research will certainly provide a biological rationale for patient and treatment selection as well. The multidisciplinary approach to patient care and research in laryngeal cancer has led to therapies which have revolutionized its treatment. Future research in laryngeal cancer will require continued active collaboration, investment, and effort from all members of the medical community. As in the past, advances made in the study of laryngeal cancer are expected to transform the management of this disease.

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Bibliography

Papers of special note have been highlighted as either of especial interest (•) or of considerable interest (••) to the reader.

1. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205-16
2. Tarpley JL, Chretien PB, Alexander JC Jr, et al. High dose methotrexate as a preoperative adjuvant in the treatment of epidermoid carcinoma of the head and neck. A feasibility study and clinical trial. Am J Surg 1975;130:481-6
3. Kun LE, Toohill RJ, Holoye PY, et al. A randomized study of adjuvant chemotherapy for cancer of the upper aerodigestive tract. Int J Radiat Oncol Biol Phys 1986;12:173-8
4. Adjuvant chemotherapy for advanced head and neck squamous carcinoma. Final report of the Head and Neck Contracts Program. Cancer 1987;60:301-11
5. Toohill RJ, Duncavage JA, Grossmam TW, et al. The effects of delay in standard treatment due to induction chemotherapy in two randomized prospective studies. Laryngoscope 1987;97:407-12
6. Schuller DE, Metch B, Stein DW, et al. Preoperative chemotherapy in advanced resectable head and neck cancer: final report of the Southwest Oncology Group. Laryngoscope 1988;98:1205-11
7. Gehanno P, Depondt J, Peynegre R, et al. Neoadjuvant combination of carboplatin and 5-FU in head and neck cancer: a randomized study. Ann Oncol 1992;3(Suppl 3):43-6
8. Jaulerry C, Rodriguez J, Brunin F, et al. Induction chemotherapy in advanced head and neck tumors: results of two randomized trials. Int J Radiat Oncol Biol Phys 1992;23:483-9
9. Mazeron JJ, Martin M, Brun B, et al. Induction chemotherapy in head and neck cancer: results of a phase III trial. Head Neck 1992;14:85-91
10. Paccagnella A, Orlando A, Marchiori C, et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: a study by the Gruppo di Studio sui Tumori della Testa e del Collo. J Natl Cancer Inst 1994;86:265-72
11. Al-Sarraf M. Chemotherapeutic management of head and neck cancer. Cancer Metastasis Rev 1987;6:181-98
12. Ensley JF, Jacobs JR, Weaver A, et al. Correlation between response to cisplatinum-combination chemotherapy and subsequent radiotherapy in previously untreated patients with advanced squamous cell cancers of the head and neck. Cancer 1984;54:811-4
13. Glick JH, Marcial V, Richter M, Velez-Garcia E. The adjuvant treatment of inoperable stage III and IV epidermoid carcinoma of the head and neck with platinum and bleomycin infusions prior to definitive radiotherapy: an RTOG pilot study. Cancer 1980;46:1919-24
14. Hong WK, Bromer RH, Amato DA, et al. Patterns of relapse in locally advanced head and neck cancer patients who achieved complete remission after combined modality therapy. Cancer 1985;56:1242-5
15. Jacobs C, Goffinet DR, Goffinet L, et al. Chemotherapy as a substitute for surgery in the treatment advanced resectable head and neck cancer. A report from the Northern California Oncology Group. Cancer 1987;60:1178-83
16. Karp DD, Vaughan CW, Carter R, et al. Larynx preservation using induction chemotherapy plus radiation therapy as an alternative to laryngectomy in advanced head and neck cancer. A long-term follow-up report. Am J Clin Oncol 1991;14:273-9
17. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med 1991;324:1685-90

•• **This landmark study demonstrated the efficacy of an induction chemotherapy approach as a curative-intent, non-surgical organ-preservation regimen for locally advanced laryngeal cancer.**

18. Hillman RE, Walsh MJ, Wolf GT, et al. Functional outcomes following treatment for advanced laryngeal cancer. Part I–Voice preservation in advanced laryngeal cancer. Part II–Laryngectomy rehabilitation: the state of the art in the

VA System. Research Speech-Language Pathologists. Department of Veterans Affairs Laryngeal Cancer Study Group. Ann Otol Rhinol Laryngol Suppl 1998;172:1-27

• **This study analyzed functional outcomes of patients in the VA study.**

19. Lefebvre JL, Chevalier D, Luboinski B, et al. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. J Natl Cancer Inst 1996;88:890-9

•• **This randomized study demonstrated the efficacy of an induction chemotherapy regimen for larynx preservation in pyriform sinus and lateral epilaryngeal cancers.**

20. Richard JM, Sancho-Garnier H, Pessey JJ, et al. Randomized trial of induction chemotherapy in larynx carcinoma. Oral Oncol 1998;34:224-8

21. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-analysis of chemotherapy on head and neck cancer. Lancet 2000;355:949-55

• **This is the first published meta-analysis of chemotherapy in head and neck cancer (MACH-NC), which demonstrated a small but significant survival benefit associated with chemotherapy when added to locoregional treatment.**

22. Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst 2009;101:498-506

•• **This randomized study of TPF vs. PF induction chemotherapy in a larynx preservation protocol demonstrated improved response rate and larynx preservation with induction chemotherapy including docetaxel (TPF).**

23. Bourhis J, Wilson G, Wibault P, et al. Rapid tumor cell proliferation after induction chemotherapy in oropharyngeal cancer. Laryngoscope 1994;104:468-72

24. Duncan W, MacDougall RH, Kerr GR, Downing D. Adverse effect of treatment gaps in the outcome of radiotherapy for laryngeal cancer. Radiother Oncol 1996;41:203-7

25. Peters LJ, Withers HR. Applying radiobiological principles to combined modality treatment of head and neck cancer–the time factor. Int J Radiat Oncol Biol Phys 1997;39:831-6

26. Withers HR, Maciejewski B, Taylor JM, Hliniak A. Accelerated repopulation in head and neck cancer. Front Radiat Ther Oncol 1988;22:105-10

27. Adelstein DJ, Sharan VM, Earle AS, et al. Simultaneous versus sequential combined technique therapy for squamous cell head and neck cancer. Cancer 1990;65:1685-91

28. Merlano M, Benasso M, Corvo R, et al. Five-year update of a randomized trial of alternating radiotherapy and chemotherapy compared with radiotherapy alone in treatment of unresectable squamous cell carcinoma of the head and neck. J Natl Cancer Inst 1996;88:583-9

29. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. J Clin Oncol 1998;16:1310-7

30. Wendt TG, Grabenbauer GG, Rodel CM, et al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: a randomized multicenter study. J Clin Oncol 1998;16:1318-24

31. Calais G, Alfonsi M, Bardet E, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. J Natl Cancer Inst 1999;91:2081-6

32. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003;349:2091-8

•• **This study demonstrated the superiority of concurrent chemoradiotherapy over induction chemotherapy as an organ-preservation strategy for locally advanced laryngeal cancer.**

33. Goepfert H, Jesse RH, Fletcher GH, Hamberger A. Optimal treatment for the technically resectable squamous cell carcinoma of the supraglottic larynx. Laryngoscope 1975;85:14-32

34. Harwood AR, Hawkins NV, Beale FA, et al. Management of advanced glottic cancer. A 10 year review of the Toronto experience. Int J Radiat Oncol Biol Phys 1979;5:899-904

35. Harwood AR, Bryce DP, Rider WD. Management of T3 glottic cancer. Arch Otolaryngol 1980;106:697-9

36. Harwood AR, Beale FA, Cummings BJ, et al. Supraglottic laryngeal carcinoma: an analysis of dose-time-volume factors in 410 patients. Int J Radiat Oncol Biol Phys 1983;9:311-9

37. Croll GA, Gerritsen GJ, Tiwari RM, Snow GB. Primary radiotherapy with surgery in reserve for advanced laryngeal carcinoma. Results and complications. Eur J Surg Oncol 1989;15:350-6

38. Forastiere AA, Maor M, Weber RS, et al. Long-term results of Intergroup RTOG 91-11: a phase III trial to preserve the larynx–Induction cisplatin/5-FU and radiation therapy versus concurrent cisplatin and radiation therapy versus radiation therapy [abstract]. 2006 ASCO Annual Meeting Proceedings Part I. J Clin Oncol 2006;24:5517

39. Lefebvre JL, Rolland F, Tesselaar M, et al. Phase 3 randomized trial on larynx preservation comparing sequential vs alternating chemotherapy and radiotherapy. J Natl Cancer Inst 2009;101:142-52

40. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4-14

• **This recently updated meta-analysis of chemotherapy in head and neck cancer (MACH-NC) confirmed a survival benefit associated with concurrent chemoradiotherapy regimens that is greater than that of induction chemotherapy regimens.**

41. Vokes EE, Kies M, Haraf DJ, et al. Induction chemotherapy followed by concomitant chemoradiotherapy for advanced head and neck cancer: impact on the natural history of the disease. J Clin Oncol 1995;13:876-83

42. Kies MS, Haraf DJ, Athanasiadis I, et al. Induction chemotherapy followed by concurrent chemoradiation for advanced

head and neck cancer: improved disease control and survival. J Clin Oncol 1998;16:2715-21

43. Mantz CA, Vokes EE, Kies MS, et al. Sequential induction chemotherapy and concomitant chemoradiotherapy in the management of locoregionally advanced laryngeal cancer. Ann Oncol 2001;12:343-7

44. Machtay M, Rosenthal DI, Hershock D, et al. Organ preservation therapy using induction plus concurrent chemoradiation for advanced resectable oropharyngeal carcinoma: a University of Pennsylvania Phase II Trial. J Clin Oncol 2002;20:3964-71

45. Guadagnolo BA, Haddad RI, Posner MR, et al. Organ preservation and treatment toxicity with induction chemotherapy followed by radiation therapy or chemoradiation for advanced laryngeal cancer. Am J Clin Oncol 2005;28:371-8

46. Hitt R, Lopez-Pousa A, Martinez-Trufero J, et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. J Clin Oncol 2005;23:8636-45

47. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357:1705-15

•• **This randomized phase III study demonstrated the superiority of TPF over PF as induction therapy in head and neck cancers and demonstrated excellent clinical outcomes associated with this sequential chemoradiotherapy protocol.**

48. Posner MR, Norris CM, Wirth LJ, et al. Sequential therapy for the locally advanced larynx and hypopharynx cancer subgroup in TAX 324: survival, surgery, and organ preservation. Ann Oncol 2009;20:921-7

• **This paper presents a subset analysis of the TAX 324 study for laryngeal and hypopharyngeal cancers.**

49. Huang SM, Bock JM, Harari PM. Epidermal growth factor receptor blockade with C225 modulates proliferation, apoptosis, and radiosensitivity in squamous cell carcinomas of the head and neck. Cancer Res 1999;59:1935-40

50. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567-78

•• **This is the first randomized trial of a molecular targeted agent combined with curative-intent radiotherapy (bioradiotherapy) which demonstrated improved outcomes over primary radiotherapy for locally advanced head and neck cancer.**

51. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010;11:21-8

• **This recent paper presented updated, 5-year results of the above study.**

52. Curran D, Giralt J, Harari PM, et al. Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab. J Clin Oncol 2007;25:2191-7

53. Forastiere AA, Takasugi BJ, Baker SR, et al. High-dose cisplatin in advanced head and neck cancer. Cancer Chemother Pharmacol 1987;19:155-8

54. Forastiere AA, Baker SR, Wheeler R, Medvec BR. Intra-arterial cisplatin and FUDR in advanced malignancies confined to the head and neck. J Clin Oncol 1987;5:1601-6

55. Mortimer JE, Taylor ME, Schulman S, et al. Feasibility and efficacy of weekly intraarterial cisplatin in locally advanced (stage III and IV) head and neck cancers. J Clin Oncol 1988;6:969-75

56. Robbins KT, Kumar P, Regine WF, et al. Efficacy of targeted supradose cisplatin and concomitant radiation therapy for advanced head and neck cancer: the Memphis experience. Int J Radiat Oncol Biol Phys 1997;38:263-71

57. Robbins KT, Fontanesi J, Wong FS, et al. A novel organ preservation protocol for advanced carcinoma of the larynx and pharynx. Arch Otolaryngol Head Neck Surg 1996;122:853-7

58. Samant S, Kumar P, Wan J, et al. Concomitant radiation therapy and targeted cisplatin chemotherapy for the treatment of advanced pyriform sinus carcinoma: disease control and preservation of organ function. Head Neck 1999;21:595-601

59. Samant S, Robbins KT, Kumar P, et al. Bone or cartilage invasion by advanced head and neck cancer: intra-arterial supradose cisplatin chemotherapy and concomitant radiotherapy for organ preservation. Arch Otolaryngol Head Neck Surg 2001;127:1451-6

60. Robbins KT, Kumar P, Harris J, et al. Supradose intra-arterial cisplatin and concurrent radiation therapy for the treatment of stage IV head and neck squamous cell carcinoma is feasible and efficacious in a multi-institutional setting: results of Radiation Therapy Oncology Group Trial 9615. J Clin Oncol 2005;23:1447-54

• **This study demonstrates the multi-institutional feasibility and efficacy of intra-arterial cisplatin and concurrent radiation therapy as a novel treatment approach for locally advanced head and neck cancers.**

61. Staton J, Robbins KT, Newman L, et al. Factors predictive of poor functional outcome after chemoradiation for advanced laryngeal cancer. Otolaryngol Head Neck Surg 2002;127:43-7

62. Urba S, Wolf G, Eisbruch A, et al. Single-cycle induction chemotherapy selects patients with advanced laryngeal cancer for combined chemoradiation: a new treatment paradigm. J Clin Oncol 2006;24:593-8

• **This paper presented initial excellent results of a novel treatment protocol that employs tumor response following a single cycle of induction chemotherapy in the selection of subsequent curative-intent therapy for locally advanced laryngeal cancer.**

63. Worden FP, Moyer J, Lee JS, et al. Chemoselection as a strategy for organ preservation in patients with T4 laryngeal squamous cell carcinoma with cartilage invasion. Laryngoscope 2009;119:1510-7

64. Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med 1998;338:1798-804

65. Chen C, Kane M, Song J, et al. Phase I trial of gefitinib in combination with radiation or chemoradiation for patients with locally advanced squamous

cell head and neck cancer. J Clin Oncol 2007;25:4880-6

66. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945-52

•• **This paper reported the results of the EORTC trial, which demonstrated superior locoregional control and survival with postoperative concurrent chemoradiotherapy over postoperative radiotherapy alone.**

67. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 2004;350:1937-44

•• **This paper reported the results of the RTOG trial of postoperative chemoradiotherapy, demonstrating improved locoregional control compared to radiotherapy for head and neck cancer patients at high-risk for disease recurrence.**

68. Bradford CR, Wolf GT, Carey TE, et al. Predictive markers for response to chemotherapy, organ preservation, and survival in patients with advanced laryngeal carcinoma. Otolaryngol Head Neck Surg 1999;121:534-8

69. Laccourreye O, Brasnu D, Bassot V, et al. Cisplatin-fluorouracil exclusive chemotherapy for T1-T3N0 glottic squamous cell carcinoma complete clinical responders: five-year results. J Clin Oncol 1996;14:2331-6

• **This paper was the initial report of exclusive chemotherapy in glottic cancers for disease control, a hypothesis confirmed in subsequent publications.**

70. Laccourreye O, Veivers D, Bassot V, et al. Analysis of local recurrence in patients with selected T1-3N0M0 squamous cell carcinoma of the true vocal cord managed with a platinum-based chemotherapy-alone regimen for cure. Ann Otol Rhinol Laryngol 2002;111:315-21; discussion 21-2

71. Bonfils P, Trotoux J, Bassot V. Chemotherapy alone in laryngeal squamous cell carcinoma. J Laryngol Otol 2007;121:143-8

72. Holsinger FC, Kies MS, Diaz EM Jr, et al. Durable long-term remission with chemotherapy alone for stage II to IV laryngeal cancer. J Clin Oncol 2009;27:1976-82

• **This was the first prospective clinical trial providing evidence of long-term disease control with chemotherapy alone for highly selected patients with laryngeal cancer.**

73. Holsinger FC, Lin HY, Bassot V, Laccourreye O. Platin-based exclusive chemotherapy for selected patients with squamous cell carcinoma of the larynx and pharynx. Cancer 2009;115:3909-18

• **This recent publication reported the 23-year, University of Paris experience of platin-based exclusive chemotherapy for head and neck cancer.**

74. Haigentz M Jr, Silver CE, Rinaldo A, Ferlito A. Definitive chemotherapy: a new frontier in the fight against laryngeal cancer [editorial]. Eur Arch Otorhinolaryngol 2010;267:1-4

75. Strojan P, Ferlito A, Wu CF, Rinaldo A. Intraarterial chemotherapy: a valid option in the treatment of verrucous carcinoma? Eur Arch Otorhinolaryngol 2009: published online 27 December 2009, doi: 10.1007/s00405-009-1178-2

76. Divi V, Worden FP, Prince ME, et al. Chemotherapy alone for organ preservation in advanced laryngeal cancer. Head Neck 2009: published online 1 December 2009, doi: 10.1002/hed.21285

• **This recent publication presented results suggesting that patients with locoregionally advanced (stage III or IVA) laryngeal or hypopharyngeal cancer do not seem to benefit from a chemotherapy alone protocol.**

77. Hartl DM, Brasnu DF. Chemotherapy alone for glottic carcinoma: a need for higher-level evidence. Ann Otol Rhinol Laryngol 2009;118:543-5

78. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol 2007;25:2171-7

79. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-27

•• **This is the first report of survival improvement for patients with incurable recurrent or metastatic disease with molecular targeted therapy (cetuximab) in combination with chemotherapy.**

80. Silver CE, Beitler JJ, Shaha AR, et al. Current trends in initial management of laryngeal cancer: the declining use of open surgery. Eur Arch Otorhinolaryngol 2009;266:1333-52

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