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The Role of Systemic Treatment Before, During, and After Definitive Treatment

Kathryn A. Gold, M.D., Michele Neskey, P.A., and William N. William, M.D.¹

Department of Thoracic / Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas

Introduction

In local-regionally advanced head and neck squamous cell carcinomas, outcomes using single modality therapy are usually poor. Head and neck cancers are chemosensitive malignancies, with response rates as high as 90% described with chemotherapy in treatment-naïve patients.¹ Though chemotherapy alone is not considered a curative therapy, the addition of chemotherapy to other modalities can lead to improved outcomes. Discussed here is the use of chemotherapy for oropharyngeal and/or oral cavity squamous cell carcinomas in three settings:

1. in combination with radiation as definitive therapy
2. as induction treatment prior to definitive therapy
3. in combination with radiation therapy as adjuvant treatment following surgical resection

We also discuss the role of the targeted agent cetuximab in combination with radiation therapy for locally advanced disease.

Concurrent Chemoradiation Therapy

Definitive radiation treatment for patients with unresectable or locoregionally advanced head and neck cancer has been associated with high rates of both locoregional failure and distant recurrence. The addition of chemotherapy to radiation therapy has been studied in an attempt to improve cure rates and functional outcomes, as well as survival rates.

Locally advanced oropharyngeal cancer

For patients with locally advanced oropharyngeal cancer, a pivotal randomized phase III trial by the French GORTEC group was designed to compare radiotherapy alone to radiotherapy and concomitant chemotherapy.²

- Both groups received identical radiation therapy with conventional fractionation of 70Gy in 35 fractions.

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¹Corresponding author. **Address:** William N. William Jr., M.D., Department of Thoracic / Head and Neck Medical Oncology, The University of Texas M. D., Anderson Cancer Center, 1515 Holcombe Blvd., Unit 432, Houston, TX, 77030, USA, **Phone:** +1-713-7926363, **FAX:** +1-713-7921220, wnwillia@mdanderson.org.

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- Patients in the chemotherapy arm received a 4-day chemotherapy regimen consisting of carboplatin (70mg/m² per day) and 5-flourouracil (600mg/m² per day) by continuous infusion for the duration of radiotherapy.

Results yielded:

- an improvement in both progression-free survival and overall survival for patients receiving combined modality therapy (42% and 51%) versus radiation therapy alone (20% and 31%).
- improvement in locoregional control rates in the chemoradiation arm (66%) versus radiation therapy alone (42%).
- similar rates of distant metastases in both arms (11%)
- higher hematologic toxicities and incidence of grade 3 and 4 mucositis in the chemotherapy arm, leading to a need for a temporary feeding tube more frequently when compared to the radiation therapy alone arm.

These results suggest that the addition of chemotherapy concurrently to radiation therapy improves locoregional control, which translates into both an overall and progression-free survival benefit for these patients, at the expense of more acute toxicities. Long-term follow-up of this study confirms the results in favor of the concurrent chemoradiation therapy arm, with an improvement in overall survival primarily secondary to a reduced incidence of locoregional failure.³

Resectable or unresectable head and neck cancer

To better assess the impact of chemotherapy on the treatment of head and neck cancer and overall survival, an updated meta-analysis of 87 randomized trials between 1965 and 2000 was performed.

The Meta-Analysis of Chemotherapy in Head and Neck Cancer (MAHC-NC) pooled data from clinical trials in which patients with resectable or unresectable disease were randomized to receive definitive local therapy (surgery or radiation) or definitive local therapy plus chemotherapy.^{4,5} Trials included patients who had received chemotherapy in the induction, concurrent or adjuvant setting, and had a diagnosis of oral cavity, oropharynx, hypopharynx or larynx cancer.

Results yielded:

- Addition of chemotherapy in any setting had a statistically significant overall absolute survival benefit of 4.5% at 5 years, and an even greater benefit of 6.5% at 5 years in the concurrent chemoradiation trials.
- As in the GORTEC trial, the improvement in survival was primarily due to an impact of concurrent chemotherapy on locoregional control, with an absolute reduction of cumulative rate of locoregional recurrence of 9.3% in the concurrent group at 5 years.
- Concurrent chemotherapy also reduced the cumulative rate of distant metastases, but to a lesser extent (absolute reduction of 2.5% at 5 years).⁵ This analysis did not define an optimal concurrent chemotherapy regimen but found a greater benefit of platinum-based chemotherapy. Multi-drug regimens including 5-flourouracil had similar benefit when compared to single agent cisplatin; however, monotherapy with a drug other than cisplatin yielded inferior results.

High-dose cisplatin concurrent with radiation therapy

High-dose cisplatin administered at 100mg/m² on days 1, 22, and 43 concurrent with radiation therapy has been associated with an improvement in overall survival and has been considered the preferred regimen for definitive treatment.^{6,7} Due to both acute and late toxicities, it is reserved for patients with a good performance status and limited comorbidities. Alternative schedules and dosing of cisplatin including daily and weekly treatment have demonstrated improvements in both locoregional control and survival, but have not been directly compared with high dose cisplatin.^{8,9} Due to a more tolerable side effect profile, specifically, less nephrotoxicity, ototoxicity, and neurotoxicity, carboplatin has also been investigated as an alternative option, though it has not been directly compared as a single agent against cisplatin. However, when carboplatin is used in combination with another agent such as 5-fluorouracil, there is a survival benefit when compared to radiation therapy alone.² Definitive radiation therapy with carboplatin monotherapy is occasionally used for patients with a poor performance status, multiple comorbidities, or a contraindication to cisplatin therapy.

Accelerated radiation therapy and hyperfractionation

The impact of altered radiation schedules with concurrent chemotherapy on overall survival and locoregional control has also been studied. Accelerated radiation which delivers the same dose as conventional therapy over a shorter period of time, and hyperfractionation, which gives higher doses of radiation therapy via multiple small fractions, were developed to help improve locoregional control rates. For patients receiving radiation therapy alone, studies have shown hyperfractionation to have an 8% absolute benefit in 5-year overall survival.¹⁰ When combined with chemotherapy, the value of these techniques remains unclear. In a comparison of conventional radiation with three cycles of standard high-dose cisplatin to accelerated boost radiation with two cycles of high-dose cisplatin, there was no statistically significant difference in overall survival, locoregional failure, progression free survival or development of distant metastases between the two chemoradiation schedules.¹¹

Radiation with Concurrent Cetuximab

The use of targeted therapies for the treatment of head and neck cancer has been of high interest due to, potentially, a more favorable side effect profile than platinum-based therapies. Cetuximab is a monoclonal antibody against the epidermal growth factor receptor (EGFR) and is the only targeted agent currently approved for management of locally advanced and/or recurrent and metastatic head and neck squamous cell carcinomas.^{12–14} Pre-clinically, EGFR-targeted agents have been demonstrated to reduce cancer cell proliferation, increase apoptosis, inhibit invasiveness and metastatic potential, and augment sensitivity to chemotherapy and radiation therapy.¹⁵

In a multinational study, weekly cetuximab in combination with radiation therapy was compared to radiation therapy alone.

- Eligibility criteria included: previously untreated stage III or IV non-metastatic cancer of the oropharynx, larynx or hypopharynx and a Karnofsky performance score of at least 60.
- Three radiotherapy schedules were allowed and chosen by the investigators before patient registration (70.0 Gy in once-daily fractions, 72.0 to 76.8 Gy in twice daily fractions, or 72 Gy in once-daily fractions with concomitant twice-daily boost in the last 2.4 weeks of treatment).
- In the experimental arm, cetuximab was added to the elected radiotherapy treatment, given at a loading dose of 400 mg/m² (starting one week prior to

radiation) followed by weekly 250 mg/m² maintenance dose for the duration of radiotherapy.

- Patients were stratified according to performance status, nodal involvement, tumor stage and radiation-fractionation regimen.

Results yielded:

- The three-year rates of locoregional control (the study's primary endpoint) were significantly higher for the cetuximab-radiotherapy arm as compared to the radiotherapy alone arm (47% versus 34%, respectively, $P<0.01$).
- Median progression-free survival was 17.1 months versus 12.4 months for the experimental and control arms, respectively ($P=0.006$).
- Three-year overall survival was 55% among patients treated with the combined modality versus 45% among those given radiation only ($P=0.03$).
- Response rates were significantly higher for the experimental group as compared to control patients (74 versus 64%, respectively, $P=0.02$).
- The cumulative rates of distant metastases were similar between the two groups. Grade 3 to 5 mucositis and dermatitis occurred in 56 and 23% of the experimental group versus 52 and 18% of the control group.
- Other toxicities were similar between the arms, except for acneiform rash (17% in the cetuximab arm versus 1% in the radiation alone arm, $P<0.001$) and infusion-related side effects (3% for cetuximab).

Taken together, this study demonstrates that cetuximab increases survival and locoregional control rates without significant additional toxicity.¹⁴

Long-term followup

On long-term follow-up, the survival benefits of cetuximab added to radiation therapy remained (overall survival of 46% and 36% at 5 years for the experimental and control arms, respectively). Subgroup analysis demonstrated more pronounced improvement in survival by the addition of cetuximab in the following cohorts: patients with oropharyngeal cancers (compared to larynx or hypopharynx), T1–3 primary tumor (versus T4), N1–N3 nodal status (versus N0), treatment in the USA, use of concomitant boost radiotherapy, Karnofsky performance status of 90 to 100, male gender, and younger age (<65 years). These results should be interpreted with caution, given the low number of patients in each group and the exploratory nature of the analysis.¹⁶

Though this study showed a benefit of concurrent cetuximab versus radiation alone, there has been no head-to-head comparison to concurrent cisplatin with radiation therapy, the standard of care, and it is unknown which patients would derive greater benefits from one approach versus the other.

The follow-up study to the trial of Bonner et al., RTOG 0522, randomized patients to cisplatin chemoradiation therapy with or without cetuximab. The combination with cetuximab did not improve progression-free or overall survival and increased adverse events when compared to cisplatin and radiation, and this strategy should not be used.¹⁷

Unfortunately, despite extensive efforts, no predictive biomarkers of efficacy of cetuximab have been identified to date. The demographics of the patients who had improved survival in the study by Bonner et al. suggest that patients with HPV-positive oropharyngeal tumors could be appropriate candidates for this therapy, as they typically present at a younger age,

with a low T primary tumor and more advanced nodal stage. Nonetheless, exploratory analysis of a recent trial in the recurrent/metastatic setting evaluating chemotherapy +/- panitumumab (another anti-EGFR antibody), demonstrated a survival benefit of the targeted agent in the HPV-negative group only.¹⁸ It is unknown whether these results hold true in the setting of locally advanced disease, using cetuximab combined with radiation therapy. Currently, the RTOG1016 study is evaluating cetuximab and radiation therapy versus cisplatin and radiation therapy in locally advanced, HPV-positive oropharyngeal squamous cell carcinomas, using a non-inferiority phase III trial design (NCT01302834).

Induction Chemotherapy

Induction chemotherapy in locally advanced head and neck cancer offers a number of theoretical benefits:^{19,20}

- It allows for administration of more intensified chemotherapy than with concurrent therapy, with a potential for reducing the risk of distant metastases by treatment of micrometastatic disease.
- It can be used to reduce tumor bulk prior to a definitive approach to therapy and has been used to select patients for organ preservation.

Despite these advantages, clinical trial data have not definitively shown a survival benefit of induction chemotherapy, and its use remains controversial.

Early induction chemotherapy studies

In the 1970s, a number of groups studied cisplatin-based combinations with methotrexate, bleomycin or vinca alkaloids in the induction setting, prior to either surgery or radiation therapy.^{21–23} They found that these regimens were feasible and active. The combination of cisplatin and fluorouracil was first studied in a phase II pilot trial by a group at Wayne State University.¹ Cisplatin (100 mg/m² IV on day 1) followed by a 5 day infusion of fluorouracil (1000 mg/m²/day) resulted in a response rate of 93% and a complete response rate of 54%. All patients went on to receive surgery and/or radiation, and median survival was not reached after 18 months of follow-up. With these promising efficacy data, this regimen became the basis for many other trials.

Paccagnella et al randomized patients with locally advanced squamous cell carcinoma of the oropharynx, oral cavity, hypopharynx, and paranasal sinus to either induction chemotherapy followed by loco-regional treatment or loco-regional treatment alone.²⁴ A significant reduction in the rate of distant metastases was seen with induction chemotherapy (15% vs 36% at 2 years). For patients deemed inoperable, induction chemotherapy led to improved local control and overall survival. This survival benefit persisted with longer follow-up.²⁵ Another trial with a similar design enrolled only patients with oropharyngeal cancer.²⁶ This trial demonstrated an improvement in overall survival with induction chemotherapy (median overall survival 5.1 years vs 3.3 years, p=0.03).

The MACH-NC also summarized the experience with induction chemotherapy added to combination with loco-regional therapy.^{4,5} The hazard ratio for death with induction chemotherapy was 0.96 (95% confidence interval 0.90 to 1.02), translating into an absolute improvement in survival at 5 years of 2.4%. This figure compares unfavorably to the benefits in survival seen with concurrent chemoradiation therapy (absolute improvement in survival of 6.5% at 5 years). As a result, induction chemotherapy failed to be considered the standard regimen for management of locally advanced head and neck cancers. Nonetheless, a more detailed analysis of the data presented by the MACH-HN collaborative group demonstrated that when only trials utilizing platinum/fluorouracil induction regimens were

considered, the hazard ratio for death was 0.90 (95% confidence interval 0.82 to 0.99) in favor of induction treatment.⁵ Furthermore, induction chemotherapy led to an absolute reduction in the cumulative rate of distant metastases of 4.3%, while the absolute reduction in the rate of locoregional failure was only 1.0% at 5 years. Taken together, these results demonstrate that there might be a role for induction chemotherapy, especially when treatment goals are to reduce the risk of distant metastases. However, the benefits in locoregional failure and overall survival are marginal, and less striking than what is observed with concurrent chemoradiation therapy regimens.

Induction chemotherapy with taxane-containing regimens

In hopes of improving outcomes with induction chemotherapy, several groups studied the addition of docetaxel to cisplatin and fluorouracil. Docetaxel was known to be an active agent in squamous cell carcinoma of the head and neck, with single agent activity in recurrent or metastatic disease.²⁷ Two initial phase III trials used docetaxel in combination with cisplatin and fluorouracil (TPF) as induction chemotherapy.

In the TAX 324 study, 501 patients with locally advanced head and neck cancer were randomized to receive three cycles of induction chemotherapy with either TPF (docetaxel 75 mg/m², cisplatin 100 mg/m², and infusional fluorouracil 1000 mg/m²/day for 4 days every three weeks) or PF (cisplatin 100 mg/m² and fluorouracil 1000 mg/m²/day for 5 days), followed by concurrent chemoradiation with weekly carboplatin (AUC 1.5).

Results of the TAX 324 study yielded:

- Median overall survival was significantly prolonged in the group receiving TPF (71 vs 40 months, $p=0.0006$).
- Rates of locoregional recurrence were decreased with TPF, but the rate of distant metastatic disease was not significantly different between the groups.²⁸
- Results remained similar on long-term follow-up, demonstrating a 5-year overall survival rate of 52% for TPF, compared to 42% for PF, $p=0.014$.²⁹

The TAX 323 study had a similar design, with patients randomized to induction chemotherapy with either TPF or PF followed by radiation therapy alone. The TPF regimen used (docetaxel 75 mg/m², cisplatin 75 mg/m², and infusional fluorouracil 750 mg/m²/day for 5 days every three weeks) was slightly different than that used in the TAX 324 study.

Results of the TAX 323 study yielded:

- Median overall survival was significantly improved with TPF (18.8 vs 14.5 months, $p=0.02$).³⁰ Patient selection criteria for these trials were different, perhaps accounting for the differences in overall survival seen between the two studies, though the use of concurrent carboplatin in the TAX 324 study compared to radiation alone in TAX 323 might also contribute to the differences.

Though these studies were able to show conclusively that TPF is superior to PF as an induction chemotherapy regimen, they did not address what the optimal concurrent treatment following induction chemotherapy is, or whether concurrent chemoradiation with cisplatin upfront is superior to an induction approach. Several recent studies have attempted to address these questions.

A phase II, single arm Southwest Oncology Group study, S0216, treated patients with two cycles of induction TPF, followed by concurrent chemoradiation, with cisplatin 100 mg/m² on days 1 and 22.³¹ There were 74 patients enrolled for this study; 61 patients were able to complete induction and begin concurrent chemoradiation. Four deaths occurred during

treatment, and 50 patients were able to complete all planned treatment. 85% and 91% of patients had at least grade 3 toxicity during induction chemotherapy and concurrent chemoradiation, respectively.

Results of the Southwest Oncology Group study:

- Suggest that high dose cisplatin following induction TPF leads to excessive toxicity, and should be reserved for carefully selected patients.
- Demonstrates that sequential therapy, with induction chemotherapy followed by concurrent chemoradiation, may compromise administration of concurrent therapy.

Two recently reported studies compared a sequential approach, with induction chemotherapy followed by concurrent chemoradiation, to concurrent chemoradiation alone.

In the PARADIGM trial, patients with locally advanced head and neck cancer were randomized to concurrent chemoradiation with cisplatin or induction chemotherapy with three cycles of TPF followed by chemoradiation with either weekly carboplatin (for patients with a complete response to induction treatment) or weekly docetaxel (for patients with less than a complete response to induction treatment).³² Planned accrual was 300 patients, but because of slow enrollment, only 145 patients were treated on study. There were no clear survival differences between the arms, with a three-year survival of 73% with induction chemotherapy and 78% with concurrent therapy.

In the DeCIDE trial, patients were randomized to receive either concurrent chemoradiation with docetaxel, fluorouracil, and hydroxyurea with or without induction chemotherapy with two cycles of TPF.³³ Three year overall survival was similar between the arms (75% with induction therapy vs 73% with concurrent therapy only, $p=0.70$), though the induction arm had a lower risk of distant failure (10% vs 19%, $p=0.025$).

Induction chemotherapy versus concurrent chemoradiation trial results

DeCIDE and PARADIGM were limited by the small sample size, and a reduced power to detect survival differences between the arms, as the outcomes in both studies (three-year overall survival greater than 70% in all arms) outperformed original estimations. While these studies cannot definitely exclude a benefit from TPF induction chemotherapy prior to chemoradiation therapy, they illustrate that the magnitude of improvement in survival in an unselected patient population is marginal, at best, especially in an era when a significant proportion of patients are alive and disease-free following non-surgical treatment of head and neck cancers. Almost certainly the increased incidence of HPV-positive oropharyngeal cancers is contributing to the improvement in prognosis seen in recent studies. Patients with HPV-positive cancers have high survival rates when treated with induction chemotherapy,^{34,35} but it is yet to be determined if HPV status serves as a predictive marker of benefit from induction treatment.

In summary, to date, no trials have shown a clear survival benefit for induction chemotherapy over concurrent chemoradiation, and concurrent chemoradiation with cisplatin is still considered the standard of care for most patients with locally advanced squamous cell carcinoma of the head and neck. As locoregional treatment improves, distant metastatic failure is becoming a more frequent cause of treatment failure. Induction chemotherapy may reduce this risk; however, we do not yet know which patients may derive a benefit. Induction chemotherapy should be used only following multidisciplinary discussion between medical oncologists, radiation oncologists, and head and neck surgeons. Preferably, induction chemotherapy should be used in the setting of a clinical trial.

Newer approaches to induction chemotherapy include regimens containing targeted agents like cetuximab,³⁶ selection of patients for organ preservation approaches following only one cycle of induction therapy,³⁷ and the use of chemotherapy alone as definitive treatment in carefully selected, closely monitored patients.³⁸

Adjuvant Concurrent Chemoradiation Therapy

The risk of recurrence for locally advanced squamous cell carcinomas of the head and neck following surgical resection is high. For patients with adverse features like perineural invasion, multiple positive lymph nodes, and T3 or T4 tumors, post-operative radiation therapy has long been known to provide benefit.³⁹ Even with radiotherapy, however, tumors frequently recur. Since chemotherapy can act as a radiation sensitizer, combined chemoradiation has been studied as adjuvant treatment for surgically treated tumors.

In EORTC 22931, patients with surgically resected head and neck cancer were randomized to postoperative irradiation alone or with concurrent chemotherapy (cisplatin 100 mg/m² on days 1, 22, and 43).⁴⁰ Eligible patients had tumor stage T3 or T4, or nodal stage N2 or N3. Patients with earlier stage tumors but unfavorable pathology (extracapsular extension, positive margins, perineural involvement or vascular emboli) were also eligible.

Results yielded:

- Progression-free survival was significantly greater in the group that received chemotherapy (55 months with chemoradiation vs. 23 months with radiation alone, $p=0.04$)
- Overall survival was significantly greater in the chemotherapy group (72 months vs. 32 months, $p=0.02$), though at the cost of increased grade 3 or higher adverse effects (41% vs 21%, $p=0.001$).

RTOG 9501 had a very similar design, though with slightly different inclusion criteria.⁴¹ Patients with extracapsular extension, positive margins, and two or more involved lymph nodes were eligible. Both studies used an identical chemotherapy schedule – cisplatin 100 mg/m² IV on days 1, 22, and 43 of radiation.

Results yielded:

- Significantly improved locoregional control (hazard ratio 0.61 with chemoradiation, $p=0.01$) and disease-free survival with concurrent chemoradiation (hazard ratio 0.78, $p=0.04$)
- In contrast to the EORTC trial, there was no significant increase in overall survival (hazard ratio for death 0.84, $p=0.19$)

Since there are significant side effects of concurrent chemoradiation, efforts have been made to identify which patients might derive the greatest benefit from this approach. The data from the two studies described, EORTC 22931 and RTOG 9501, were included in a collaborative comparative analysis.⁴² The criteria that predicted an improved outcome with the addition of chemotherapy to radiation therapy were positive surgical margins and extracapsular extension. The other criteria used in these studies to identify patients as high risk for recurrence – vascular emboli, perineural invasion, stage III or IV disease, and 2 or more involved lymph nodes – were not associated with a significant benefit from chemotherapy.

Conclusions

For many patients with locally advanced head and neck cancer, chemotherapy represents a key component of optimal multimodality therapy. Cisplatin administered concurrently with radiation has been shown to improve outcomes when compared to radiation alone, and is considered the standard of care for many patients with squamous cell carcinomas of the oropharynx, hypopharynx, or larynx. Radiation therapy with cetuximab is also superior to radiation therapy alone, and is a viable treatment option, though for most patients that are candidates for concurrent cytotoxic therapy, cisplatin remains the standard of care.

Induction chemotherapy has the potential to improve outcomes by reducing disease burden prior to definitive treatment and by reducing the risk of distant metastatic disease, but at the cost of increased adverse events and reduction in the intensity of subsequent therapy. However, its use is controversial, and it is not yet known which patients may derive benefit from this approach. Prior to use of induction chemotherapy, patients should be evaluated and discussed by a multidisciplinary group. This treatment approach is best utilized at a tertiary care center, and clinical trials should always be considered.

Following surgical resection, adjuvant concurrent chemoradiation improves disease free and overall survival in selected patients. The greatest benefit is in those with positive surgical margins or extracapsular extension. High dose cisplatin is the most widely studied regimen in this setting.

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Key Points

- Patients with squamous cell carcinoma of the head and neck frequently present with locally advanced disease. In this setting, outcomes can be improved by the incorporation of multi-modality treatment, often with chemotherapy.
- In locally advanced oropharyngeal squamous cell carcinomas, concurrent chemoradiation with cisplatin is the standard of care, and improves outcomes compared to radiation alone.
- In patients with oropharyngeal squamous cell carcinomas, radiation with concurrent cetuximab improves disease-free and overall survival compared to radiation alone, and is another treatment option for patients with locally advanced disease.
- Use of induction chemotherapy prior to definitive radiation has been extensively studied and may improve outcomes in certain groups. Its use, however, remains controversial.
- Following surgical resection, adjuvant concurrent chemoradiation with cisplatin improves outcomes for patients with nodal extracapsular extension or positive margins on surgical pathology.