ELSEVIER

Seminars in
RADIATION
ONCOLOGY

Successes and Failures of Combined Modality Therapies in Head and Neck Cancer

Daniel W. Bowles, MD,[*,†] Eric Deutsch, MD, PhD, MD,[‡] and David Raben, MD[§]

The paradigms for treating head and neck squamous cell carcinoma are changing as new subgroups are defined. The technical successes of improved radiation therapy are many; however, the success of novel combined therapies are few. With the emergence of human papillomavirus and the development of immunooncology agents, such as checkpoint inhibitors, are we ready to reevaluate how we use radiation and chemotherapy for locally advanced and metastatic disease—will we remain the fire or become the fire starter?
Semin Radiat Oncol 26:299-306 © 2016 Published by Elsevier Inc.

Introduction

Success or failure in the management of head and neck squamous cell carcinoma (HNSCC) over the past several decades is in the eye of the beholder as well as in the results of phase 3 trials. After establishing the role of combined cisplatin-based combined chemotherapy and radiation more than 3 decades ago,[1,2] the acute and long-term side effects of curative-intent therapy remain problematic and 5-year overall survival (OS) for non—human papillomavirus (HPV)-driven HNSCC remains poor.[3,4] New sensitizers, such as the taxanes and anti-epidermal growth factor receptor (EGFR) antibodies, are being employed with hopes that they may improve outcomes.[5] Similarly, functional outcomes have improved as radiation techniques have advanced over the past 15 years, yet much more needs to be done. We are now entering a new world with advanced radigation techniques, novel small molecule inhibitors such DNA repair inhibitors, PI3K inhibitors, mTOR inhibitors, and now the burgeoning world of immunooncology. Will these new agents and techniques lead to the success we are looking for and will our view of combined modality therapy shift? To help us decide the best way forward in definitive HNSCC management, this article would review select recent successes and failures in combined modality therapy and provide some thoughts for the future.

*Division of Medical Oncology, University of Colorado School of Medicine, Aurora, CO.
†Department of Medicine, Denver Veterans Affairs Medical Center, Denver, CO.
‡Department of Radiotherapy, INSERM 1030 molecular radiotherapy, Université Paris-Sud, Université Paris-Saclay.
§Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, CO.
Conflict of interest: None. David Raben consulted for AstraZeneca during 2015-2016.
Address reprint requests to David Raben, MD, Department of Radiation Oncology, University of Colorado Health, Mail Stop F706, 1665 Aurora Court, Suite 1032, Aurora CO80045. E-mail: david.raben@ucdenver.edu

It's Technical: Radiation Success With Improved Planning and Delivery Capabilities

Dramatic improvements in radiation software and hardware have enabled radiation oncologists to make the shift from a 3-dimensional to a more elegant intensity modulated radiation therapy (IMRT) world. Although not the focus of the review, we would be remiss not to mention how the adoption of IMRT has improved functional outcomes for patients with HNSCC. For instance, sparing of the constrictor muscles, mylo or geniohyoid complex and the esophageal inlet, and understanding that reducing the volume of normal tissue exposed to doses greater than 60 Gy reduces long-term dysphagia, has been an important achievement.[6-8] We continue to explore a variety of delivery techniques such as volumetric-modulated arc therapy or TOMOtherapy to maximize normal tissue sparing while sending homogenous doses of radiation to the intended targets. Salivary function and quality of life continue to improve as radiation oncologists use parotid and submandibular sparing techniques with no decrease in safety.[9-11] Beyond decreasing long-term side effects, IMRT-based approaches may also improve cancer specific survival.[12] Novel radiation techniques may push the envelope further with regards to efficacy and toxicity. For instance, will proton beam radiation therapy take us further down the reduced toxicity pathway? Proton beam radiation therapy reduces acute toxicity

http://dx.doi.org/10.1016/j.semradonc.2016.05.004
1053-4296/© 2016 Published by Elsevier Inc.

compared with IMRT for head and neck tumors that require ipsilateral radiation, but its effect on long-term toxicities are unknown.[13,14] Stereotactic body radiation therapy may allow for more rapid and safe delivery of radiation to the head and neck area similar to what we have achieved in other sites like prostate and pancreas. Time and rigorous comparisons between proton and photon therapy in HNSCC treatment will determine whether protons will be a future success story.

The Failure of Neoadjuvant Chemotherapy: Revisiting the Past to See the Future

Our goal in this section is not to belabor the failures of neoadjuvant or induction chemotherapy but to drive home the point that this strategy has been investigated extensively in both the organ preservation and preoperative settings, yet no clear improvements in patient outcomes have been demonstrated. The central theory of neoadjuvant chemotherapy, also referred to as sequential or induction chemotherapy, is that multiagent chemotherapy given at the beginning of curative-intent therapy can improve OS by improving local-regional control (LRC) and decreasing distant metastatic recurrence.

The widespread adoption of neoadjuvant chemotherapy followed by radiation can be traced to the landmark Department of Veterans Affairs Larynx Preservation trial published 25 years ago, which demonstrated that neoadjuvant chemotherapy with cisplatin and 5-fluorouracil [FU] (PF) followed by radiation, yielded similar survival to laryngectomy followed by radiation in select patients with larynx cancer but with improved organ preservation.[15] RTOG 91-11 subsequently demonstrated that concurrent chemoradiation therapy (CRT) improved organ preservation rates but not OS compared to neoadjuvant chemotherapy followed by RT, however, and concurrent CRT became the standard of care.[16] Introduction of taxanes into the neoadjuvant regimens renewed enthusiasm in the mid-2000s when TAX323 and TAX324 were published. These 2 randomized, phase 3 trials demonstrated that the addition of a taxane (docetaxel) to neoadjuvant cisplatin, and 5-FU (TPF) followed by either RT alone or concurrent low dose, weekly carboplatin plus RT yielded superior LRC, progression free survival (PFS), and OS compared to neoadjuvant PF in oropharynx, larynx, and hypopharynx cancers.[17,18] The GORTEC trial subsequently demonstrated TPF's superiority over PF followed by RT in larynx cancers and a large meta-analysis confirmed that TPF is a superior neoadjuvant regimen compared to PF.[19,20]

Neoadjuvant Chemotherapy Before Standard of Care Definitive Therapy

Did we achieve any success when we compared the above regimen to CRT or surgery followed by RT? "No" is the unfortunate answer. Several randomized trials have been published comparing neoadjuvant chemotherapy followed by standard of care definitive therapy (Table 1). A study from China administered TPF before surgical resection for oral cavity SCC vs surgery upfront and found that, while a complete response (CR) to TPF predicted improved OS, there was no OS difference between the entire TPF and non-TPF groups.[21] A 2 US-based phase 3 trials, DeCIDE and PARADIGM, failed to demonstrate a clear benefit to neoadjuvant chemotherapy compared to concurrent CRT (Table 1).[22,23] Both of these studies randomized patients to CRT or CRT preceded by neoadjuvant TPF. In both studies there was no difference in OS between the 2 groups (hazard ratio [HR] = 0.91; 95% CI: 0.59-1.91; $P = 0.68$ in the DeCIDE trial; HR = 1.09; 95% CI: 0.59-2.03; $P = 0.77$ in the PARADIGM trial) and no specific subgroup has experienced an OS benefit from neoadjuvant TPF. Adding to the lack of survival success was consistently higher toxicity in the neoadjuvant arms. A phase 3 study from Spain with a similar treatment plan to PARADIGM also failed to demonstrate an improvement in OS with neoadjuvant chemotherapy at the cost of excess toxicity (Table 1). Although these studies lacked the statistical power to demonstrate improved OS because of poor accrual and longer than expected survival in the control group, the results were disappointing and point to neoadjuvant chemotherapy's shortcomings.[24]

Are There Any Neoadjuvant Success Stories?

The only randomized study to report an OS advantage to neoadjuvant chemotherapy was an ambitious 2 × 2 trial from Italy.[25] Patients were randomized to 4 arms: (1) concurrent PF and standard fraction RT; (2) cetuximab and concurrent RT; (3) TPF ×3 cycles followed by concurrent PF-RT; and (4) TPF followed by cetuximab-RT. For the initial analysis, the 2 neoadjuvant arms were combined and compared to the 2 concurrent CRT arms, demonstrating an improvement in 3-year PFS (HR = 0.73; 95% CI: 0.57-0.94; $P = 0.015$) and OS (HR = 0.72; 95% CI: 0.55-0.96; $P = 0.025$) for neoadjuvant chemotherapy. A subgroup analysis suggested TPF followed by cetuximab-RT may be superior to the other regimens (HR = 0.57; 95% CI: 0.34-0.93); however, the power to make this conclusion was limited. Toxicity did not differ significantly between all 4 arms. Although the results of this study are provocative, it should be noted that this has only been presented in abstract form. The French GORTEC trials (NCT01233843) will address this topic further; however, at this point neoadjuvant chemotherapy should not be routinely given for patients with locally advanced HNSCC.

Accelerated Chemoradiation Therapy: A Bridge to Far?

There was excitement that accelerated radiation (RTOG 9003) combined with concurrent chemotherapy would improve LRC and OS. The phase 3 RTOG 0129 and the GORTEC 99-02 studies attempted to answer this question, comparing conventional cisplatin-RT to accelerated cisplatin-radiation (or accelerated radiation alone in GORTEC). Unfortunately, neither trial demonstrated any improvements in LRC, PFS, or OS.[26,27] As a result, new studies looking at accelerated CRT are limited. Let us emphasize to our readers that accelerated