Combining Systemic Therapy With Radiation: Head and Neck Cancer Treatments in an Era of Targeted Agents and Immunotherapy

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ABSTRACT

The addition of chemotherapy to radiation therapy (RT) has been established for decades to improve outcomes in patients with head and neck cancer (HNC). Concurrent chemoradiation increases both local control and overall survival but at the cost of significant toxicity, motivating extensive investigations to optimize the balance of clinical efficacy and adverse effects. This review discusses the rationale and seminal studies underlying the concurrent chemoradiation treatment paradigm in HNC, and describes attempts to better tailor systemic therapy beyond standard-of-care cisplatin, such as the use of alternate cytotoxic agents and nonstandard dosing regimens. Modern efforts to incorporate targeted therapies and immunotherapy are then summarized, particularly for patients unable to receive standard cytotoxic chemotherapy. Finally, mechanisms through which RT and systemic therapy cooperate to improve the therapeutic ratio are discussed, with a focus on the interaction between immunotherapy and RT, a rapidly emerging treatment paradigm. With increasing application of novel diagnostic and therapeutic approaches, determining the optimal concurrent systemic program to maximize RT efficacy will continue to evolve. Identification of patient- and tumor-specific factors will offer a unique opportunity to implement personalized oncologic care.

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The pillars of cancer treatment are surgery, radiation therapy (RT), and chemotherapy, and multimodality treatment integrating multiple approaches is a well-established paradigm. During the past decades, the combinatorial use of systemic agents and RT has demonstrated improved outcomes in lung cancer,¹ gastrointestinal malignancies,^{2–4} glioblastoma,⁵ bladder cancer,⁶ and HNC.^{7,8} Broadly, numerous mechanisms underlie the interactions observed between these 2 treatment modalities, including simple additivity, cytotoxic enhancement leading to a globally enhanced tumor response, biologic cooperation comprising alleviation of radioresistance by concurrent systemic therapy within distinct tumor subpopulations, and temporal modulation regulating classic radiobiologic determinants of the therapeutic index, such as DNA repair, tumor reoxygenation, cell cycle redistribution, and malignant cell repopulation. Various classes of systemic agents demonstrate clinically significant synergistic effects, including antimetabolites such as 5-FU, classic alkylating agents such as mitomycin C, DNA-damaging platins, and microtubule inhibitors such as taxanes. Thus, there is a rich tradition of improved patient outcomes with combined modality therapy across a range of disease sites and systemic drugs.

For HNC, concurrent chemoradiation (CRT) constitutes the standard of care for locoregionally advanced disease.⁹ Seminal studies demonstrated significantly improved locoregional control and overall survival (OS) with the addition of concurrent chemotherapy to RT alone,^{7,10} and a subsequent meta-analysis showed an OS benefit with concurrent CRT,⁸ thus establishing the modern treatment paradigm. However, although these pioneering trials consistently reveal a benefit to concurrent CRT, the choice and dose of systemic therapy differed, underscoring the lack of consensus regarding an optimal treatment regimen. Adding to this ambiguity, direct prospective comparisons of different regimens are limited. Furthermore, the benefits of concurrent CRT are

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associated with significantly enhanced toxicity, with up to 89% of patients in early studies experiencing grade 3–5 toxicity,⁷ affecting the ability to complete an uninterrupted RT course. Although improvements in supportive care and radiation technique have increased compliance, treatment-related toxicity remains a clinically meaningful hardship for many patients with HNC undergoing CRT. Taken together, these observations highlight the need for optimization and individualization of systemic therapy regimens.

This review critically evaluates the role of concurrent systemic therapy with RT in HNC. Of note, we do not discuss the role of induction therapy, which merits its own comprehensive treatment. We examine different cisplatin regimens and alternatives for cisplatin-ineligible patients. We then discuss challenges in treatment deintensification through the use of alternate systemic agents such as the epidermal growth factor receptor (EGFR) inhibitor cetuximab or immunotherapy, and consider the option of omitting concurrent chemotherapy altogether in low-risk patients. Finally, we summarize a biologic framework through which to study the mechanisms underlying interactions between RT and systemic therapy, with a focus on immunotherapy. In conclusion, ongoing clinical protocols and novel scientific advances will shift both standard treatment paradigms and criteria to personalize CRT regimens over the next several years.

Concurrent Cytotoxic Chemotherapy: Platins, Platins, and More Platins

Cisplatin is the most commonly used agent for concurrent CRT in HNC. The classic schedule of 3 cycles of concurrent cisplatin given at a dose of 100 mg/m² every 3 weeks^{7,11,12} remains the most commonly recommended regimen of choice.⁹ However, the high rate of adverse effects associated with this “bolus” regimen limits treatment compliance and completion, motivating interest in trialing alternate cisplatin schedules to balance efficacy and toxicity. The therapeutic effect of cisplatin may be related to the cumulative dose received, with a potential threshold seen at only 2 cycles (corresponding to a total dose of 200 mg/m²)¹³ when given in conjunction with moderately accelerated radiation. Furthermore, retrospective analysis did not clearly demonstrate substantial differences in survival between patients given the “bolus” regimen in 3-week cycles and those given 40 mg/m² of cisplatin weekly,¹⁴ consistent with earlier meta-analysis suggesting no difference in outcome between high-dose (3 doses of cisplatin at >100 mg/m²) and low-dose regimens (≥6 doses of cisplatin at <50 mg/m²).¹⁵ However, it should be noted that both of these analyses demonstrated improved toxicity profiles with the lower-dose cisplatin regimen, highlighting a potential benefit to

such a treatment approach. In contrast, a prospective randomized phase III study demonstrated that among patients with locally advanced HNC given 100 mg/m² cisplatin every 3 weeks versus 30 mg/m² cisplatin every week, locoregional control, but not survival, was improved in those receiving the high-dose regimen.¹⁶ In this trial, the dosing of cisplatin was at 30 mg/m² weekly (rather than the more commonly used 40 mg/m² weekly dose) and most patients had oral cavity primary tumors treated with adjuvant rather than concurrent CRT, calling into question the generalizability of these findings. A second prospective study randomized patients with oral cavity cancer to 100 mg/m² of cisplatin every 3 weeks versus 40 mg/m² weekly; this study only enrolled 50 patients at interim report, closing early as a result of slow accrual, and did not identify a significant benefit to the bolus cisplatin regimen.¹⁷ With regard to adverse effects, although weekly cisplatin is often selected for improved tolerability, the relative toxicity profiles of these 2 cisplatin regimens is also in question, as the Tsan et al¹⁷ study demonstrated improved quality-of-life metrics with the bolus regimen. In addition, early results were reported from a randomized phase III study of patients with nasopharyngeal cancer and showed higher hematologic toxicity (neutropenia) in those receiving weekly dosing.¹⁸

In summary, although there is no clear evidence that a weekly regimen compromises efficacy when given concurrently with RT, it likewise remains unclear whether a weekly regimen results in decreased toxicity. Thus, we conclude that high-dose bolus cisplatin remains the standard-of-care concurrent regimen. There are likely numerous complex factors at work balancing efficacy and toxicity, which may be related to the specific population in question. Further work to rigorously evaluate the factors that regulate this balance, such as the total cumulative dose of cisplatin, details of RT, and patient and tumor characteristics, will be important to guide more precise treatment regimens for individual patients.

Alternatives to Cisplatin: Second-Line Cytotoxic Therapies, Targeted Agents, and Immunotherapy

Despite the established value of concurrent cisplatin and RT compared with RT alone, such cisplatin-based regimens often come with prohibitive toxicity profiles, particularly in patients with poor performance status or disqualifying medical comorbidities, such as renal dysfunction. Furthermore, in patients with advanced age regardless of medical comorbidities, the benefits from cisplatin may be attenuated.¹⁹ Thus, in patients ineligible for cisplatin, the development of alternate concurrent regimens represents a key clinical need.

One second-line cytotoxic regimen is weekly carboplatin, to which 5-FU or paclitaxel may be added. Carboplatin and 5-FU comprise a standard concurrent HNC regimen for the Groupe d'Oncologie Radiothérapie Tête Et Cou (GORTEC) cooperative group²⁰; carboplatin and paclitaxel are commonly given concurrently with RT for non-small cell lung cancer.²¹ There are few direct prospective comparisons of carboplatin-based regimens versus cisplatin in the nonmetastatic setting. In patients with nasopharyngeal carcinoma, one prospective trial compared concurrent cisplatin at 100 mg/m² every 3 weeks versus concurrent carboplatin at 100 mg/m² weekly, with both arms receiving additional adjuvant chemotherapy; in this noninferiority design, the 2 regimens were not statistically different with regard to outcome.²² In contrast, a randomized phase III trial for non-nasopharyngeal HNC demonstrated improved outcomes with concurrent cisplatin compared with concurrent carboplatin or RT alone.²³ However, although carboplatin-based combinations may be less acutely emetogenic, carboplatin remains a potent myelosuppressive agent and often incurs similar issues of hematologic tolerability, potentially offering its own set of unique toxicities. Thus, investigators continue to seek agents to decrease treatment-related toxicity without compromising efficacy.

Cetuximab, an EGFR inhibitor, is the best studied nonplatinum concurrent therapy in HNC. EGFR is overexpressed across epithelial malignancies²⁴ and has long been known to be associated with poor outcomes in HNC.²⁵ A randomized phase III trial comparing RT + concurrent cetuximab versus RT only demonstrated significantly improved outcomes with concurrent cetuximab while showing decreased toxicity in the cetuximab arm, except for a predictive acneiform rash and infusion reactions.²⁶ However, subgroup analysis indicated that this survival benefit was restricted to patients aged >65 years or with Karnofsky performance score <90, suggesting that cetuximab may not benefit fit patients with fewer competing comorbidities. Furthermore, the control arm lacked any concurrent chemotherapy, leaving open the question of whether cetuximab should be considered appropriate for platinum-eligible patients. Directly addressing these shortcomings, a comparator phase II study of concurrent cisplatin versus cetuximab and a phase III study of concurrent cisplatin versus panitumumab (with altered fractionation in the panitumumab arm) both failed to show superiority or noninferiority of the EGFR inhibitor-containing arm, and the phase II study showed significantly higher toxicities associated with cetuximab.^{27,28} Focusing specifically on patients with HPV-positive oropharyngeal

cancer who may be prime candidates for deescalation, 2 large phase III randomized trials (NRG-RT0G 1016²⁹ and De-ESCALaTE HPV³⁰) compared concurrent cetuximab and RT versus concurrent cisplatin and RT. The HPV-positive oropharyngeal cancer population was thought to be optimal for treatment deintensification given the positive prognostic value of HPV status for survival, but both of these trials demonstrated increased disease recurrence and reduced OS in the concurrent cetuximab arm.^{29,30} Furthermore, the toxicities incurred by cetuximab were comparable to those of cisplatin. The final results of TROG 12.01 (ClinicalTrials.gov identifier: NCT01855451), which compared concurrent weekly cetuximab versus weekly cisplatin in patients with RT-treated HPV-positive oropharyngeal cancer, are awaited.

Given the potential for synergy between cetuximab and platinum agents as observed in the metastatic setting,³¹ there was significant interest in determining whether cetuximab could improve oncologic outcomes when combined with CRT as part of primary treatment. However, a phase III randomized trial in patients with HNC receiving definitive RT showed that the addition of cetuximab to concurrent cisplatin and RT did not significantly improve any oncologic outcomes, and there was no observed synergistic benefit to EGFR inhibition in combination with cisplatin and RT.³² In contrast, in another randomized phase III trial, RT with cetuximab + carboplatin and 5-FU demonstrated improved progression-free survival and locoregional control (without an OS benefit) compared with RT + cetuximab. However, given that there was no arm with CRT alone, it is not possible to know whether concurrent cetuximab results in an additive benefit compared with standard CRT.³³ Taken together, these data suggest that concurrent EGFR inhibition is not a replacement for platinum-based regimens in an HPV-positive population, and more generally, that adding cetuximab does not convey additional benefit in combination with CRT in HNC. Nonetheless, in patients who are not eligible for platinum-based therapy, cetuximab appears to be a major current alternative standard in the United States, whereas internationally, RT alone is more heavily favored. However, the shortcomings of concurrent cetuximab as outlined earlier have motivated investigation into other regimens as alternatives to platinum-based therapy.

Immunotherapy broadly comprises methods to augment the host immune system to effectively detect and destroy cancer cells. Currently, the most common FDA-approved agents relieve negative inhibition of the host immune system by tumors and are thus termed *checkpoint inhibitors* because they release inhibitory signals to increase cancer cell destruction by the host

immune system.³⁴ Checkpoint inhibitors include agents such as durvalumab, which blocks interactions between host T lymphocytes and PD-L1 expressed on host antigen-presenting cells as well as tumors, and pembrolizumab and nivolumab, which block interactions with PD-1. CTLA-4 antagonists such as ipilimumab and tremelimumab are also commonly used immunotherapy agents. KEYNOTE-048 enrolled patients with recurrent or metastatic HNC, randomizing them to pembrolizumab monotherapy, pembrolizumab with a platinum agent + 5-FU, or cetuximab with a platinum agent + 5-FU. Interim analysis showed improved outcomes with pembrolizumab + chemotherapy compared with cetuximab + chemotherapy, and perhaps most interestingly, pembrolizumab monotherapy was associated with improved outcomes compared with cetuximab + multiagent chemotherapy in the subpopulation with a high PD-L1 score and was noninferior across all patients.³⁵ Thus, checkpoint inhibition appears to display activity in HNC. These results raise the intriguing possibility that immunotherapy may be superior to cetuximab and potentially competitive to platinum-based chemotherapy with less toxicity, laying the foundation for a number of ongoing investigations, such as JAVELIN Head and Neck 100 (NCT02952586) and KEYNOTE-412 (NCT03040999), into the role of immunotherapy within the traditional paradigm of CRT for the definitive management of HNC.

For patients unable to tolerate concurrent cisplatin, immunotherapy may be an important option in improving outcomes. In that regard, GORTEC 2015-01 ("PembroRad") is a randomized phase II trial studying the efficacy and tolerance of cetuximab and RT versus pembrolizumab and RT in patients with locoregionally advanced HNC (ClinicalTrials.gov identifier: NCT02707588). Meanwhile, in a more selective manner, other trials are investigating immunotherapy in cisplatin-ineligible or HPV-positive populations. NRG-HN004 is a phase II/III study randomizing patients with locally advanced HNC who are cisplatin-ineligible to either concurrent durvalumab and RT or concurrent cetuximab and RT (NCT03258554). A preliminary report of the lead-in phase showed that durvalumab given concurrently with RT was safe, with high compliance and minimal toxicity.³⁶ Canadian Cancer Trials Group (CCTG) HN9 is an ongoing randomized phase II study testing cisplatin and RT versus durvalumab and RT in patients with intermediate-risk HPV-positive oropharyngeal cancer, defined as those with either a >10 pack-year smoking history or bilateral neck disease (NCT03410615). NRG-HN005 is an immunotherapy trial addressing deintensification of RT in patients with p16-positive oropharyngeal cancer (NCT03952585). This trial is comparing concurrent cisplatin combined with either mildly accelerated RT (70 Gy over 6 weeks, 6

days per week) or deintensified RT (60 Gy over 6 weeks, 5 days per week) versus concurrent nivolumab and deintensified RT (60 Gy over 6 weeks, 5 days per week). The combination of cetuximab with immunotherapy remains intriguing, and this combination has not yet been tested against standard-of-care RT-based regimens. One randomized phase III study (GORTEC "REACH") will include 688 patients who have locoregionally advanced HNC. Stratified cohorts will include both patients who are fit and unfit for high-dose cisplatin, with the objective of demonstrating that avelumab in combination with cetuximab and RT is superior to cisplatin/RT or cetuximab/RT in one or more of these subgroups (NCT02999087). These ongoing studies will provide key information on the efficacy of concurrent immunotherapy in various distinct populations of patients with HNC and define the direction of this research.

Numerous other protocols are evaluating how to appropriately deintensify treatment using risk-adapted approaches based on molecular features. Most notably, p16 positivity as a surrogate for HPV status is a well-validated positive prognostic feature in oropharyngeal cancer.³⁷ Accordingly, NRG-HN002 evaluated deintensification regimens for patients with p16+ oropharyngeal cancer, randomizing patients to dose-reduced RT of 60 Gy over 5 weeks with or without concurrent cisplatin. The preliminary report demonstrated 2 key conclusions: concurrent cisplatin was required to meet the prespecified acceptability benchmarks, and treatment to 60 Gy with cisplatin did not appear to compromise 2-year progression-free survival or swallowing-related quality-of-life measures compared with historical benchmarks.³⁸ Moving forward, the development of methods to measure serum HPV DNA as a potential liquid biomarker of disease status represents another viable approach to risk-stratify patients.³⁹ These efforts illustrate the interest in identifying and validating alternate or deintensified regimens in both RT and systemic therapy to improve patient compliance and optimize the balance between treatment efficacy and adverse effects.

Biologic Mechanisms Underlying Synergy Between RT and Systemic Therapy

Given the interest in how best to use multimodality therapy to improve patient outcomes, understanding the mechanisms through which concurrent treatment exerts its effects on tumor cells and normal tissues is critical. Broadly, the goal of combining systemic therapy and RT is to improve the therapeutic index in order to maximize efficacy and minimize toxicity. Ideally, this would result from a synergistic effect on efficacy that is greater than that derived from the addition of each modality alone. Such interactions can be further conceptualized as

mechanisms through which systemic therapy improves effects of RT (eg, classic radiosensitizers) or mechanisms through which RT accentuates effects of systemic therapy (eg, the abscopal effect).

Classically, 4 mechanisms were proposed to underlie improved responses due to CRT: spatial cooperation, toxicity independence, normal tissue protection, and enhancement of tumor response.⁴⁰ Spatial cooperation encapsulates the notion that RT and systemic therapy act on distinct anatomic compartments; this explanation is often invoked to explain improvements in distant metastasis control by concurrent cytotoxic chemotherapy.⁸ The same principle further forms the basis for ongoing efforts to risk-stratify patients for additional adjuvant therapy, such as in nasopharyngeal carcinoma.⁴¹ Toxicity independence refers to combining 2 anticancer treatments without requiring a dose reduction in either modality. In practice, this approach has generally been applied to avoid treatment modalities with overlapping toxicities, a principle that is unfortunately of limited utility in CRT for HNC.

Normal tissue protection is of particular importance in HNC given the relationship between radiation dose, treatment completion, and patient outcomes.^{42,43} It is critical that fundamental issues of RT dose, technique, and volume remain in the forefront as basic mediators of combinational toxicity. In terms of administered agents, amifostine was investigated as a potential radioprotective agent for xerostomia; however, randomized prospective data demonstrate unclear benefit.⁴⁴ Recently, a phase II randomized trial showed that avasopasem manganese (GC4419) significantly reduced oral mucositis in HNC,⁴⁵ and a number of novel agents are being tested as methods to improve toxicities associated with concurrent therapy. As additional trials with exciting new systemic therapies are designed, it will remain important to maintain focus on how to optimize normal tissue protection to derive maximal benefit from RT.

Enhancement of tumor response is perhaps the most intuitive and often-invoked framework to describe interactions between systemic therapy and RT, encompassing situations in which an increased effect is observed when combining 2 agents compared with the use of either agent alone. We will now specifically highlight the interaction between immunotherapy and RT, an expanding treatment paradigm that remains biologically exciting yet poorly understood. The conceptual basis for synergy between RT and immunotherapy is straightforward: RT results in tumor cell death and release of tumor antigens, priming immune activation to improve both local and distant control.⁴⁶ Such interplay can be divided into 2 scenarios of clinical benefit: increasing the magnitude of immunotherapy response in partial responders (with regard to sites or

duration of response), or conversion of nonresponders to responders. Indeed, among the most interesting phenomena is the often-cited abscopal effect in which RT may induce T-cell-mediated responses at distant tumor sites away from the treatment field.⁴⁷ Mechanistically, RT improves antigen visibility and thus generates an increased diversity and volume of neoantigens both through direct cell kill leading to greater tumor cell phagocytosis and antigen presentation as well as by inducing changes in the tumor microenvironment to relieve tumor-mediated immunosuppression.⁴⁸ Thus, RT may serve as a critical component of generating and maintaining responses to immunotherapy both at the primary tumor site as well as across metastases. However, many challenges remain, including optimizing the relative timings of such treatments, identifying safe yet effective radiation dose and fractionation schemes within this context, and developing prognostic methods to identify patients most likely to benefit or at highest risk of toxicity, the latter of which remains an area of active concern, particularly when combining immunotherapy with other targeted agents such as EGFR inhibitors.⁴⁹

Conclusions

This review emphasizes the premise that the standard-of-care concurrent chemotherapy with RT in HNC remains cisplatin. Alternative options for patients unwilling or unable to complete this treatment include other cytotoxic chemotherapy combinations such as carboplatin as well as targeted agents such as cetuximab and experimental approaches involving immunotherapy. We concluded by evaluating opportunities for deintensification by focusing on ongoing clinical approaches as well as mechanistic frameworks underlying the interplay between systemic therapy and RT. We anticipate that the upcoming decade will witness numerous opportunities to develop improved prognostic approaches to personalizing RT and concurrent therapy for each patient, leading to individualized selection of the optimal sequence and combination of cytotoxic chemotherapy, targeted agents, and immunotherapy to maximize benefit and minimize toxicity based on clinical, pathologic, and molecular characteristics unique to each patient and tumor.

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References

- Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992;327:1618-1624.
- Cooper JS, Guo MD, Herskovic A, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). *JAMA* 1999;281:1623-1627.
- Bartelink H, Roelofsens F, Eschwege F, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol* 1997;15:2040-2049.
- Wolmark N, Wieand HS, Hyams DM, et al. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02. *J Natl Cancer Inst* 2000;92:388-396.
- Stupp, Weller M, Fisher B, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;352:987-996.
- James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. *N Engl J Med* 2012;366:1477-1488.
- Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol* 2003;21:92-98.
- Pignon JP, Bourhis J, Domenge C, et al. 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;355:949-955.
- Pfister DG, Spencer S, Adelstein D, et al. NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers. Accessed May 28, 2020. To view the most recent version, visit NCCN.org.
- 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;91:2081-2086.
- Al-Sarraf M, LeBlanc M, Giri PGS, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol* 1998;16:1310-1317.
- Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol* 2013;31:845-852.
- Nguyen-Tan PF, Zhang Q, Ang KK, et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. *J Clin Oncol* 2014;32:3858-3866.
- Baum JM, Vinnakota R, Anna Park YH, et al. Cisplatin every 3 weeks versus weekly with definitive concurrent radiotherapy for squamous cell carcinoma of the head and neck. *J Natl Cancer Inst* 2019;111:490-497.
- Szturc P, Wouters K, Kiyota N, et al. Weekly low-dose versus three-weekly high-dose cisplatin for concurrent chemoradiation in locoregionally advanced non-nasopharyngeal head and neck cancer: a systematic review and meta-analysis of aggregate data. *Oncologist* 2017;22:1056-1066.
- Noronha V, Joshi A, Patil VM, et al. Once-a-week versus once-every-3-weeks cisplatin chemoradiation for locally advanced head and neck cancer: a phase III randomized noninferiority trial. *J Clin Oncol* 2018;36:1064-1072.
- Tsan DL, Lin CY, Kang CJ, et al. The comparison between weekly and three-weekly cisplatin delivered concurrently with radiotherapy for patients with postoperative high-risk squamous cell carcinoma of the oral cavity. *Radiat Oncol* 2012;7:215.
- Liang H, Xia WX, Lv X, et al. Concurrent chemoradiotherapy with 3-weekly versus weekly cisplatin in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial (ChiCTR-TRC-12001979) [abstract]. *J Clin Oncol* 2017;35(Suppl):Abstract 6006.
- Kish JA, Zhang Q, Langer CJ, et al. The effect of age on outcome in prospective, phase III NRG Oncology/RTOG trials of radiotherapy (XRT) +/- chemotherapy in locally advanced (LA) head and neck cancer (HNC) [abstract]. *J Clin Oncol* 2015;33(Suppl):Abstract 6003.
- Bourhis J, Sire C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. *Lancet Oncol* 2012;13:145-153.
- Santana-Davila R, Devisetty K, Szabo A, et al. Cisplatin and etoposide versus carboplatin and paclitaxel with concurrent radiotherapy for stage III non-small-cell lung cancer: an analysis of Veterans Health Administration data. *J Clin Oncol* 2015;33:567-574.
- Chitapanarux I, Lovidhaya V, Kamnerdsupaphon P, et al. Chemoradiation comparing cisplatin versus carboplatin in locally advanced nasopharyngeal cancer: randomised, non-inferiority, open trial. *Eur J Cancer* 2007;43:1399-1406.
- Fountzilas G, Ciuleanu E, Dafni U, et al. Concomitant radiochemotherapy vs radiotherapy alone in patients with head and neck cancer: a Hellenic Cooperative Oncology Group phase III study. *Med Oncol* 2004;21:95-107.
- Hynes NE, Lane HA. ERBB receptors and cancer: the complexity of targeted inhibitors. *Nat Rev Cancer* 2005;5:341-354.
- Dassonville O, Formento JL, Francoual M, et al. Expression of epidermal growth factor receptor and survival in upper aerodigestive tract cancer. *J Clin Oncol* 1993;11:1873-1878.
- 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;354:567-578.
- Magrini S, Bulgione M, Corvo R, et al. Cetuximab and radiotherapy versus cisplatin and radiotherapy for locally advanced head and neck cancer: a randomized phase II trial. *J Clin Oncol* 2016;34:427-435.
- Siu LL, Waldron JN, Chen BE, et al. Effect of standard radiotherapy with cisplatin vs accelerated radiotherapy with panitumumab in locoregionally advanced squamous cell head and neck carcinoma a randomized clinical trial. *JAMA Oncol* 2017;3:220-226.
- Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. *Lancet* 2019;393:40-50.
- Mehanna H, Robinson M, Hartley A, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. *Lancet* 2019;393:51-60.
- Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008;359:1116-1127.
- Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. *J Clin Oncol* 2014;32:2940-2950.
- Tao Y, Auperin A, Sire C, et al. Improved outcome by adding concurrent chemotherapy to cetuximab and radiotherapy for locally advanced head and neck carcinomas: results of the GORTEC 2007-01 phase III randomized trial. *J Clin Oncol* 2018;36:JCO2017762518.
- Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;12:252-264.
- Burtress B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet* 2019;394:1915-1928.
- Mell LK, Torres-Saavedra PA, Wong SJ, et al. Safety of radiotherapy with concurrent and adjuvant MEDI4736 (durvalumab) in patients with locoregionally advanced head and neck cancer with a contraindication to cisplatin: NRG-HN004 [abstract]. *J Clin Oncol* 2019;37(Suppl):Abstract 6065.
- Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;363:24-35.
- Yom SS, Torres-Saavedra P, Caudell JJ, et al. NRG-HN002: a randomized phase II trial for patients with p16-positive, non-smoking-associated, locoregionally advanced oropharyngeal cancer. *Int J Radiat Oncol* 2019;105:684-685.

39. Chera BS, Kumar S, Beaty BT, et al. Rapid clearance profile of plasma circulating tumor HPV type 16 DNA during chemoradiotherapy correlates with disease control in HPV-associated oropharyngeal cancer. *Clin Cancer Res* 2019;25:4682–4690.
40. Steel GG, Peckham MJ. Exploitable mechanisms in combined radiotherapy-chemotherapy: the concept of additivity. *Int J Radiat Oncol Biol Phys* 1979;5:85–91.
41. Chan KCA, Woo JKS, King A, et al. Analysis of plasma Epstein-Barr virus DNA to screen for nasopharyngeal cancer. *N Engl J Med* 2017;377:513–522.
42. Peters LJ, Goepfert H, Ang KK, et al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. *Int J Radiat Oncol Biol Phys* 1993;26:3–11.
43. Ang KK, Trotti A, Brown BW, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2001;51:571–578.
44. Buentzel J, Micke O, Adamietz IA, et al. Intravenous amifostine during chemoradiotherapy for head-and-neck cancer: a randomized placebo-controlled phase III study. *Int J Radiat Oncol Biol Phys* 2006;64:684–691.
45. Anderson CM, Lee CM, Saunders DP, et al. Phase IIb, randomized, double-blind trial of GC4419 versus placebo to reduce severe oral mucositis due to concurrent radiotherapy and cisplatin for head and neck cancer. *J Clin Oncol* 2019;37:3256–3265.
46. Weichselbaum RR, Liang H, Deng L, et al. Radiotherapy and immunotherapy: a beneficial liaison? *Nat Rev Clin Oncol* 2017;14:365–379.
47. Demaria S, Ng B, Devitt ML, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. *Int J Radiat Oncol Biol Phys* 2004;58:862–870.
48. Jiang W, Chan CK, Weissman IL, et al. Immune priming of the tumor microenvironment by radiation. *Trends Cancer* 2016;2:638–645.
49. Oshima Y, Tanimoto T, Yuji K, et al. EGFR-TKI-associated interstitial pneumonitis in nivolumab-treated patients with non-small cell lung cancer. *JAMA Oncol* 2018;4:1112–1115.

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We're excited to launch a new resource designed to help keep oncology APs up to date about managing the cardiac effects of the treatments their patients are receiving.

CLASS CATEGORIES

Immune Checkpoint
Inhibitors

Novel Immunotherapies
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Kinase Inhibitors

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