Curr. Treat. Options in Oncol. (2019) 20: 89
DOI 10.1007/s11864-019-0688-4

Head and Neck Cancer (CP Rodriguez, Section Editor)

Current Standards for Organ Preservation in Locoregionally Advanced Non-nasopharyngeal Head and Neck Cancer and Evolving Strategies for Favorable-Risk and Platinum-Ineligible Populations

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Published online: 4 December 2019

This article is part of the Topical Collection on *Head and Neck Cancer*

Keywords Locoregionally advanced head and neck cancer · Organ preservation · Cisplatin-ineligible · HPV deintensification

Opinion statement

Standard-of-care treatment for the majority of patients with locoregionally advanced squamous cell carcinoma of the head and neck (SCCHN) is either upfront surgery followed by adjuvant treatment as indicated by intraoperative or pathologic findings or concurrent chemoradiation reserving surgical salvage for non-responsive disease. An attempt at upfront complete resection should be pursued if feasible in patients with oral cavity or paranasal sinus primary tumors. Given multimodality treatment paradigms, patients with locoregionally advanced SCCHN should be managed in a multidisciplinary setting. Modern radiation therapy, whether postoperative or definitive in intent, is based on target delineation guided by high-quality imaging, using an intensity-modulated radiation technique to spare organs at risk. In select groups of low-risk patients, most notably

those with HPV-associated oropharyngeal SCC (OPSCC), several treatment deintensification approaches are currently under investigation. Major experimental strategies within this non-surgical organ preservation domain include reductions in the intensity of the chemotherapy or radiation therapy components of the chemoradiation program, use of induction chemotherapy, or imaging-based selection of patients eligible for deintensified radiation-based treatment. Of note, recent efforts to substitute cetuximab for cisplatin in low-risk HPV-associated OPSCC have demonstrated the inferiority of cetuximab to cisplatin in cisplatin-eligible patients, re-confirming cisplatin as the standard systemic therapy of choice in HNSCC. In patients who are not candidates for any type of cisplatin administration, carboplatin-based therapy or cetuximab remain options, and other non-cisplatin therapies are under investigation. Altered fractionation may be considered in patients who are not candidates for any type of systemic therapy. The role of immunotherapy in the management of locoregional SCCHN remains investigational.

Introduction

Treatment of locoregionally advanced squamous cell carcinoma of the head and neck (SCCHN) is a complex, multidisciplinary pursuit that has become increasingly nuanced with advances in imaging, identification of patients with more favorable-risk disease, and refinements of surgical and radiation therapy techniques and systemic agents. In this review, we highlight standard-of-care non-surgical approaches within the organ preservation domain in patients with locoregionally advanced non-nasopharyngeal SCCHN. We also outline major deintensification strategies in this domain for low-risk HPV-associated oropharyngeal SCC (OPSCC) and describe investigations in the treatment of cisplatin-ineligible patients.

Standard-of-care treatment for locoregionally advanced SSCHN

Treatment with surgery alone for locoregionally advanced disease has traditionally been associated with a high rate of recurrence [1, 2]. However, when supplemented with adjuvant radiation-based therapy, surgical outcomes are similar to those achieved with concurrent chemoradiation (CRT). Though limited by sample size, the only randomized trial comparing surgery and adjuvant radiation with definitive CRT in patients with advanced resectable SCCHN demonstrated no significant differences in overall survival (OS) or disease-specific survival (DSS), even at 10 years of follow-up [3]. On subset analysis, clear exceptions to this finding were patients with SCC of the oral cavity or maxillary sinus. These patients had improvement in their 5-year DSS when treated with a primary surgical resection.

After surgery, level I evidence supports delivery of adjuvant CRT to patients with high-risk features such as extranodal extension or positive margins [4]. In patients with tumors arising outside the oral cavity or paranasal sinuses who are at high risk for having these adverse pathologic features, concurrent CRT is often preferred due to the increased toxicities associated with trimodality therapy. However, these general indications mandating postoperative CRT have been questioned in relation to HPV-associated OPSCC and are now being re-tested in

prospective trials in this population (e.g., ECOG E3311 [NCT01898494], PATHOS [NCT02215265], ADEPT [NCT01687413]) which may refine or rebut these criteria. For patients who are not candidates for surgery, CRT generally produces better outcomes than radiation alone [5], although this contention has likewise been challenged for select subpopulations with very limited primary and nodal disease burden.

Trials evaluating the addition of induction chemotherapy to definitive CRT have demonstrated conflicting results. One phase II–III study demonstrated improved progression-free survival (PFS), locoregional control (LRC), and OS with induction docetaxel, cisplatin, and 5-fluorouracil (TPF) followed by cisplatin-based CRT [6] as compared to CRT alone, but three phase III trials (one of which also utilized concurrent cisplatin during CRT) did not confirm local control or survival advantages [7–9]. Thus, in the absence of more consistent results, induction chemotherapy should be reserved for use on trial, or to precede subsequent radiation-based larynx preservation in patients with SCC of the larynx [10, 11] or hypopharynx [12], as no reduction in OS has been demonstrated in these patients when induction has been used prior to radiation therapy. Ad hoc systemic therapy programs have been used in clinical practice, outside of oncologic indications, as a temporizing strategy when a definitive-intent program cannot be initiated due to insurmountable medical or logistical barriers; these are not intentional induction programs but rather should be considered as an unavoidable delay of indicated treatment.

Radiation target delineation and treatment technique

Increasingly, the focus of organ preservation in the treatment of SCCHN has been not only structural, but also functional with particular emphasis on speech and swallowing. Improved imaging with high-resolution cross-sectional imaging and combined positron emission tomography/computed tomography (PET/CT), along with anatomically and evidence-based radiation treatment planning should be employed to best preserve function.

Multiple imaging modalities are fused to the radiation planning CT to guide target volume delineation. As diagnostic scans are acquired at different points in time, with different patient alignment compared to the radiation planning CT scan, diagnostic images should be used to localize and guide volume delineation, but not be presumed to be exactly accurate.

While diagnostic CT images are sufficient to delineate organ-at-risk (OAR) volumes and calculate radiation dose, use of CT scans alone can result in significant inter-observer variability even among experts [13]. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET has slightly higher sensitivity and specificity for nodal disease as compared to CT [14] and is superior in the identification of occult primaries or metastatic disease [15]. For target delineation, PET should be used in conjunction with anatomical imaging and clinical exam. While PET-guided delineation may result in smaller and more consistent target volumes among observers [16], PET is unreliable for determining the extent of mucosally spreading, edematous, or necrotic tumor which is best appreciated from comprehensive clinical synthesis [17, 18]. PET uptake is also less reliable for disease identification in lymph nodes less than 1 cm in size [19].

MRI sequences may be able to supplement CT and PET in the identification of pathologic lymph nodes. Diffusion-weighted imaging has been shown to have high sensitivity and specificity for pathologic nodal involvement, although results are still unreliable for small-size or necrotic nodes [20]. At the skull base or within deep and complex soft tissue regions, MRI has superior resolution over CT and is considered a necessity for visualization and target delineation.

Intensity-modulated radiotherapy (IMRT) is now the standard treatment modality for radiation of SCCHN. Phase III trials have associated an improved quality of life with IMRT as compared to older conformal radiation techniques. IMRT produces improvements in xerostomia [21–23], dysphagia, and aspiration risk [24] in both early-stage and locally advanced disease without reductions in local control or overall survival [25].

In patients with very bulky nodal disease or advanced primary tumors, or in patients who experience large-scale anatomic changes during the radiation course, adaptive replanning may be considered to spare OARs [26–28] while simultaneously improving target coverage and possibly locoregional control [29–31].

Treatment deintensification in human papilloma virus-associated squamous cell carcinoma of the oropharynx (HPV-SCCOP)

The proper execution of treatment deintensification is contingent on identification of an appropriately low-risk patient population. In patients with OPSCC, survival is doubled in those with HPV-driven tumors compared to those with tumors associated with tobacco and alcohol use [32, 33]. This may be due in part to increased sensitivity of HPV-OPSCC to chemotherapy and radiation [34], or because this tends to be a younger and healthier patient population with fewer competing causes of mortality. The improved prognosis for HPV-OPSCC is reflected in the updated AJCC 8th edition staging system and has been discussed extensively elsewhere [35, 36]. However, with these favorable outcomes also comes an increased relative burden of both acute [37] and late [38] toxicity for patients with HPV-OPSCC after multimodality treatment, which has inspired a variety of treatment deintensification strategies.

Major current strategies for treatment deintensification in the setting of organ preservation for patients with locoregionally advanced disease include (1) modifications of systemic therapy within a CRT program; (2) reductions in radiation dose or volume within a CRT program; (3) induction chemotherapy to select patients with a good treatment response to guide a reduction in subsequent treatment; or (4) imaging-based selection of patients with a good treatment response to guide a reduction in subsequent treatment.

Modifications of systemic therapy

The longstanding standard of care for locoregionally advanced HNSCC is concurrent radiation therapy to a dose of 70 Gy to gross disease combined with high-dose cisplatin (100 mg/m^2 administered on days 1, 22, and 43), which was shown to improve LRC and OS compared to radiation alone in

cisplatin-eligible patients [5]. Furthermore, the MACH-NC meta-analysis confirmed that the addition of concurrent platinum-based chemotherapy to radiation therapy conferred an absolute benefit of 6.5% in OS at 5 years [5].

A few large retrospective series have nonetheless documented successful outcomes of radiation alone (including some patients treated with altered fractionation) in patients with locoregionally advanced HPV-OPSCC, finding encouraging LRC and OS results despite the omission of chemotherapy [39], particularly for patients with small primary tumors [40]. At the Princess Margaret Cancer Center, patients undergoing radiation alone for HPV-OPSCC tended to be older or have medical contraindications for chemotherapy yet demonstrated a 3-year cancer-specific survival of 92% and a local control rate of 95%. In patients with low-risk (AJCC 7th edition T1–3, N0–2b) HPV-OPSCC, chemoradiation did not appear to reduce the distant metastasis rate compared to standard or accelerated radiation therapy alone [41, 42].

Because of the interest in reducing toxicities of CRT and the possibility of a lesser contribution of cisplatin in HPV-OPSCC, major trials were launched investigating the substitution of cisplatin with cetuximab. Cetuximab, a monoclonal antibody binding the epidermal growth factor receptor (EGFR), was shown to confer improved LRC and OS when given in combination with radiotherapy over radiotherapy alone [43]. The approved schedule for concurrent cetuximab was 400 mg/m^2 loading dose followed by weekly administration of 250 mg/m^2. However, two randomized phase III trials, RTOG 1016 and De-ESCALaTE, both failed to demonstrate the equivalence of this concurrent cetuximab regimen to high-dose cisplatin among HPV-OPSCC patients [44••, 45••]. RTOG 1016 randomized 987 patients with HPV-OPSCC to concurrent radiotherapy (70 Gy in 35 fractions over 6 weeks, at 6 fractions per week) plus cetuximab (400 mg/m^2 loading dose then 250 mg/m^2 weekly) or radiotherapy plus cisplatin (100 mg/m^2 days 1 and 22). The trial results demonstrated significantly lower PFS and OS in the cetuximab group (67% vs. 78% for 5-year PFS, 78% vs. 85% for 5-year OS); as cetuximab did not meet non-inferiority criteria, cisplatin should remain the standard of care for HPV-OPCC in medically eligible patients [45••]. De-ESCALaTE randomized 334 patients with locally advanced, low-risk HPV-OPSCC to intensity-modulated radiotherapy (70 Gy in 35 fractions) plus concurrent cetuximab (400 mg/m^2 loading dose followed by 7 weekly infusions of 250 mg/m^2) or concurrent cisplatin (100 mg/m^2 on days 1, 22, and 43) [44••]. The primary endpoint was the number of high-grade toxicity events at 2 years, which did not differ between arms. However, there was a significant difference in 2-year overall survival (97.5% in the cisplatin arm, 89.4% in the cetuximab arm), locoregional recurrence (3% in the cisplatin arm, 12% in the cetuximab arm), and distant metastases (3% with cisplatin, 9% with cetuximab), all favoring concurrent cisplatin [44••]. A third trial, TROG 12.01, compares standard radiation given with either cetuximab or cisplatin at 40 mg/m^2 weekly, with a primary endpoint of symptom severity. TROG 12.01 has completed accrual but has not yet been reported (NCT01855451).

It should be noted that the precise identification of patients best suited for treatment deintensification remains challenging and in the design of clinical trials for these patients, the inclusion criteria should be rigorously determined. Recursive partitioning analysis of patients enrolled in RTOG 0129 (a randomized phase III trial which tested accelerated or standard radiation in

combination with cisplatin) suggested that there were three distinct OPSCC risk groups that could be separated based on p16/HPV status, smoking history, and extent of nodal disease [32]. When applied to a later cohort of patients treated in RTOG 0522 (a randomized phase III trial which tested accelerated radiation in combination with cisplatin with or without cetuximab), similar trends persisted but notably there was a lower progression-free survival rate in the HPV-associated OPSCC low-risk group (73% vs. 80%) [46], suggesting that risk stratification and patient selection require further refinement and validation. Continued follow-up in these patients is also important, as distant failures may occur later than seen with non-HPV-associated cancers [42] and in less common sites [47], and the long-term functional outcomes of standard versus deintensified programs need better characterization.

Reductions in radiation dose or volume

Alternative approaches to deintensification have centered around reductions in radiation dose or volume. In a two-institution phase II feasibility trial, 44 patients with p16+ OPSCC (T0–T3, N0–N2c) and low-level or remote smoking history were treated to 60 Gy in 30 fractions (54 Gy was given to areas at risk of subclinical disease) concurrent with weekly cisplatin at 30 mg/m^2, followed by biopsy of the primary site and dissection of pre-treatment involved neck levels [48•]. A pathologic complete response was seen in 86% of patients, with 6 patients having only microscopic residual disease. At 3-year follow-up, all patients had achieved disease control with LRC and OS rates of 100% and 95% [48•].

The randomized phase II cooperative group trial, NRG-HN002, assigned 306 patients with p16+ OPSCC (T1–T2/N1–N2b or T3N0–N2b by 7th edition staging) with ≤ 10 pack-year smoking history to either dose-reduced chemoradiation (60 Gy in 30 fractions over 6 weeks, concurrent with weekly cisplatin at 40 mg/m^2) or accelerated radiation therapy alone (60 Gy in 30 fractions over 5 weeks, given at 6 fractions per week). The hypothesis was that one or both of these arms would produce a 2-year progression-free survival ≥ 85%; these results are maturing.

NRG-HN002 also mandated ipsilateral radiation in patients with well-lateralized tonsil primaries with a single involved lymph node [49], with the option of ipsilateral radiation in patients with multiple lymph nodes confined to level 2 of the neck without extranodal extension. This reduction in radiation target volumes is supported by several notable single-institution series. A recent meta-analysis of these series including over 1100 patients with OPSCC treated with ipsilateral radiation suggests that the incidence of contralateral failure is quite low, averaging 2.4% and associated with midline involvement [50]. Furthermore, several series of patients treated with surgery and adjuvant ipsilateral RT (with chemotherapy reserved for high-risk features) have demonstrated an absence of contralateral failures at follow-up durations of over 5 years [51–53]. It must be stressed that informed patient selection is critical to the success of the ipsilateral treatment approach, and in addition to detailed physical examination, careful analysis of surgical notes and cross-sectional imaging is advisable [54]. Single-institution series have suggested a superior negative predictive value of PET/CT over CT and MRI [55], which is supported by the results of ACRIN 6685 suggesting a high negative predictive value of PET/

CT for the pathologically N0 neck of 92% [56].

In another cooperative group trial, NRG-HN005, an additional deintensification strategy combining accelerated radiation with the PD-1 inhibitor nivolumab is being explored. NRG-HN005 is a randomized phase II/III trial comparing the chemoradiation arm of RTOG 1016 (70 Gy of radiation therapy given in 6 weeks, with 2 cycles of cisplatin at 100 mg/m^2 on days 1 and 22) against two experimental arms: (1) 60 Gy of radiation therapy in 6 weeks with the same schedule of concurrent cisplatin and (2) 60 Gy of radiation in 5 weeks with 6 cycles of nivolumab at 240 mg every 2 weeks starting 1 week prior to radiation (NCT03952585). If one or both of the experimental arms meet the phase II criteria for progression-free survival and patient-reported swallowing (M.D. Anderson Dysphagia Inventory), the trial will continue to a phase III randomization.

Induction chemotherapy-based selection

The use of response to induction chemotherapy to select patients for subsequent reduced-intensity radiation-based treatment was first explored in an ECOG-ACRIN Cancer Research Group Phase II trial (ECOG E1308) [57•]. Eighty patients with stage III–IV OPSCC received three cycles of induction chemotherapy every 21 days; the regimen was cisplatin (75 mg/m^2 on day 1), paclitaxel (90 mg/m^2 on days 1, 8, and 15), and cetuximab (loading dose of 400 mg/m^2 day 1 followed by 250 mg/m^2 weekly). A complete response at the primary site was defined as no evidence of disease on exam and fiber-optic endoscopy. Primary or nodal regions with a complete response were treated to 54 Gy in 27 fractions using an IMRT technique. In regions without a complete response, the radiation dose was 69.3 Gy in 33 fractions. Uninvolved neck nodal regions were treated to 51.3 Gy in 27 fractions. Radiation was given with weekly cetuximab (continued at 250 mg/m^2). In patients with a complete response at the primary site receiving 54 Gy, the overall 2-year PFS was 80%. Among those with a complete response at the primary site as well as highly favorable clinical features (< T4, < N2c, ≤ 10 pack-year smoking history), the 2-year PFS and OS rates were both 96%, confirming the prognostic robustness of clinical staging and smoking history.

Another phase II single-arm study conducted at 2 institutions (NCT 02048020, NCT01716195) evaluated response-based radiation dose reduction following 2 cycles of induction carboplatin (AUC 6) and paclitaxel (175 mg/m^2) given 21 days apart [58•]. Radiation was delivered using an IMRT technique to 54 Gy in those with a complete or partial response ($n = 24$) and 60 Gy in those with a minor response or stable disease ($n = 20$). Radiation was given with concurrent weekly paclitaxel (30 mg/m^2). The 2-year PFS was 92% [58•]. At 3 months post-treatment, there was no decrease in patients' mean overall quality of life as measured using the University of Washington Quality of Life Scale [59].

In addition to explorations of reduced radiation dose, there have been a series of phase II trials investigating response-adapted volume and dose reduction. The first trial of Response-Adapted Volume De-escalation (RAVD) following induction chemotherapy with cisplatin, paclitaxel, and cetuximab (everolimus was dropped from this regimen after an interim analysis) found that in patients with a good response, treatment with paclitaxel, fluorouracil, hydroxyurea, and concurrent hyperfractionated radiation at 1.5 Gy BID to a total dose of 75 Gy to a limited volume targeting gross disease plus a margin resulted in a 2-year PFS of 87% [60•]. This study was followed by the OPTIMA I trial, which

used an induction regimen of carboplatin and nab-paclitaxel [61, 62]. In the OPTIMA I patients, radiation volumes were reduced to encompass only the first echelon of uninvolved nodes. Low-risk patients who had a good response received radiotherapy alone to 50 Gy, while low-risk patients with a moderate response or high-risk patients with a good response received chemoradiation to 45 Gy with paclitaxel, 5-FU, hydroxyurea, and abraxane. Patients with a poor response received combined chemoradiation to 75 Gy; in this study, all chemoradiation was given with BID fractionation, week-on week-off [61]. Though follow-up is limited, the 2-year PFS has been reported to be 100% and 94% for low- and high-risk patients, respectively, with one in-field failure in a high-risk patient that was surgically salvaged [62]. Despite the reduction in radiation volumes, there were no failures in the omitted regions (data presented at ASTRO 2017).

Imaging-based selection

Hypoxic conditions limit the repair of radiation-induced DNA double-strand-breaks and may also limit the delivery of chemotherapeutic agents, together rendering tumors more resistant to treatment [63]. Measuring hypoxia has historically been through use of needle electrodes placed in accessible tumors or measurement of endogenous markers such as hypoxia-inducible factor 1a (HIF-1α), vascular endothelial growth factor (VEGF), or serum osteopontin (OPN); these have been shown to be prognostic in SCCHN [64, 65]. Now, with increasing availability of non-invasive hypoxia imaging techniques, "biologically based" radiation dose reduction has increasingly been another area of interest. Imaging agents that are the most developed at present include the FDA-approved hypoxic tracer ^{18}F-FMISO (fluoromisonidazole) as well ^{64}Cu-ATSM and single-photon emission CT with ^{111}IN/^{89}Zr-labeled antibodies to hypoxia-related markers.

In a very small feasibility study, ^{18}F-FMISO PET was used to identify normoxic nodes prior to treatment as well as to detect resolution of hypoxia in nodes after 1 week of chemoradiation. Hypoxic nodes which had resolved were dose-reduced by 10 to 60 Gy; the primary tumor was still treated to a total dose of 70 Gy [66]. Using this approach, 10 of 33 patients were able to receive reduced-dose radiation to involved nodes. At a median follow-up of 32 months, the 2-year LRC was 100%. Further dose reduction was reported in another small cohort of patients who underwent resection of their primary tumor [67]. ^{18}F-FMISO PET was similarly used to identify normoxic cervical lymph nodes in 14 patients after 1 week of treatment; these nodes were treated to a dose of 30 Gy with concurrent cisplatin then removed with neck dissection 3–4 months later. Eleven of 14 patients had a pathologic complete response and the remaining 3 patients were felt to have residual but non-viable disease [67] (data presented at ASTRO 2017).

Systemic treatment in cisplatin-ineligible patients

Treatment regimens supported by level I evidence that may be considered for cisplatin-ineligible patients include concurrent carboplatin/5-FU [68] and concurrent cetuximab [69]. GORTEC 94-01 randomized 226 patients to radiation alone (70 Gy in 35 fractions) or with 3 cycles of concurrent carboplatin

(70 mg/m^2/day for 4 days) and fluorouracil (600 mg/m^2/day for 4 days), demonstrating improved 5-year LRC (48% vs. 25%) and 5-year OS (22% vs. 16%) in favor of concurrent chemoradiation [68]. Bonner et al. randomized 424 patients to radiotherapy with one of three regimens (once-daily treatment, twice-daily fractionation, or concomitant boost) alone or with concurrent cetuximab (400 mg/m^2 loading dose, then 250 mg/m^2 weekly) [69]. The median overall survival was significantly longer in patients who received concurrent cetuximab, at 49 months compared to 29 months in patients who received radiation alone. However, neither of these studies was specifically designed for cisplatin-ineligible patients and it is unknown whether outcomes would differ in a cisplatin-ineligible population.

Identification of alternative concurrent systemic agents specifically for cisplatin-ineligible patients is the subject of NRG-HN004 (NCT03258554), a phase II/III trial randomizing patients with locally advanced SCCHN (excluding p16+ OPSCC or unknown primary T0–3, N0–N2b with ≤ 10 pack-year smoking history) to radiation therapy with either cetuximab for up to 8 cycles or the PD-L1 inhibitor durvalumab for up to 7 cycles. This trial is currently open and accruing. Other alternatives to cisplatin that have been explored include panitumumab, a fully humanized anti-EGFR monoclonal antibody, which was tested in a Canadian phase III cooperative group trial in combination with accelerated radiation and did not demonstrate non-inferiority compared to standard chemoradiation with cisplatin [70]. Additional trials are evaluating radiation with concurrent immunotherapy agents, such as pembrolizumab (NCT03383094, NCT03040999), durvalumab and cetuximab (NCT03051906), durvalumab and tremelimumab (NCT NCT03426657), ipilimumab and/or nivolumab (NCT03799445, NCT03349710), and avelumab with cetuximab (NCT02999087).

Despite the continuing search for optimal systemic agents to offer to this group of patients, the role of altered fractionation should not be forgotten. A recent update of the MARCH meta-analysis demonstrated improved survival with hyperfractionation compared to conventionally fractionated radiotherapy, conferring an absolute advantage in OS of 8.1% at 5 years and 3.9% at 10 years [71]. A relatively more convenient schedule of 6 fractions per week (BID once weekly) tested by the Danish Head and Neck Cancer Group resulted in a 7% disease-specific survival improvement and 10% improvement in locoregional control at 5 years [72].

Conclusion

Although locoregionally advanced SCCHN is a heterogeneous disease involving complicated treatment nuances based on site and stage, several themes can be summarized. The first is that with the exception of patients with primary SCC of the paranasal sinuses or oral cavity, in whom there is clear benefit to local resection, organ-preserving chemoradiation in patients with acceptable performance status is a dominant standard of care. For all patients with locoregionally advanced SCCHN, there is an ongoing emphasis on decreasing the morbidity of treatment, and in planning IMRT, precise target delineation informed by advanced imaging should be standard.

Identification of favorable-risk subgroups of patients, most notably among the HPV-OPSCC population, has led to a number of differing deintensification approaches, ranging from modifications of concurrent chemotherapy to reductions in radiation dose and volume and use of induction chemotherapy or imaging to select patients manifesting an early treatment response. No conclusive level I evidence yet exists comparing a deintensification regimen to a standard chemoradiation program, and treatment deintensification in individual patients at present should be pursued only on a clinical trial.

As the population ages, it is likely that an increasing proportion of patients will be chronologically or functionally older, with accompanying medical comorbidities that limit systemic therapy options. Adjustments to cisplatin or use of carboplatin-based regimens may be options for borderline patients. Both the addition of cetuximab and altered fractionation radiation schedules have been demonstrated to be superior to conventional radiation alone. Numerous trials are ongoing evaluating the role of immunotherapy in the treatment of SCCHN.

Compliance with Ethical Standards

Conflict of Interest

Susan Y. Wu declares that she has no conflict of interest.

Sue S. Yom has received research funding for clinical trials from Genentech, Bristol-Myers Squibb, Merck, and BioMimetix JV; has received royalties from Springer and UpToDate; and has received compensation from Galera Therapeutics for serving on a Data Safety Monitoring Committee.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Peters LJ, Goepfert H, Ang KK, Byers RM, Maor MH, Guillamondegui O, et al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. IJROBP. 1993;26:3–11.
2. Fletcher GH, Evers WT. Radiotherapeutic management of surgical recurrences and postoperative residuals in tumors of the head and neck. Radiology. 1970;95:185–8.
3. Iyer NG, Tan DSW, Tan VKM, Wang W, Hwang J, Tan NC, et al. Randomized trial comparing surgery and adjuvant radiotherapy versus concurrent chemoradiotherapy in patients with advanced, nonmetastatic squamous cell carcinoma of the head and neck: 10-year update and subset analysis. Cancer. 2015;121:1599–607.
4. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005;27:843–50.

5. Pignon J-P, Le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group. 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.
6. Ghi MG, Paccagnella A, Ferrari D, et al. Induction TPF followed by concomitant treatment versus concomitant treatment alone in locally advanced head and neck cancer. A phase II-III trial. Ann Oncol. 2017;28:2206–12.
7. Haddad R, O'Neill A, Rabinowits G, Tishler R, Khuri F, Adkins D, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. The Lancet Oncology. 2013;14:257–64.
8. Hitt R, Grau JJ, López-Pousa A, et al. A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. Ann Oncol. 2013;25:216–25.
9. Cohen EEW, Karrison TG, Kocherginsky M, Mueller J, Egan R, Huang CH, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. J Clin Oncol. 2014;32:2735–43.
10. Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF, 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;31:845–52.
11. Group TDOVALCS. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. N Engl J Med. 1991;324:1685–90.
12. Janoray G, Pointreau Y, Garaud P, Chapet S, Alfonsi M, Sire C, et al. Long-term results of a multicenter randomized phase III trial of induction chemotherapy with cisplatin, 5-fluorouracil, ± docetaxel for larynx preservation. J Natl Cancer Inst. 2016. https://doi.org/10.1093/jnci/djv368.
13. Cooper JS, Mukherji SK, Toledano AY, et al. An evaluation of the variability of tumor-shape definition derived by experienced observers from CT images of supraglottic carcinomas (ACRIN protocol 6658). IJROBP. 2007;67:972–5.
14. Kyzas PA, Evangelou E, Denaxa-Kyza D, Ioannidis JPA. 18F-fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: a meta-analysis. J Natl Cancer Inst. 2008;100:712–20.
15. Lee JR, Kim JS, Roh J-L, Lee JH, Baek JH, Cho K-J, et al. Detection of occult primary tumors in patients with cervical metastases of unknown primary tumors: comparison of (18)F FDG PET/CT with contrast-enhanced CT or CT/MR imaging-prospective study. Radiology. 2015;274:764–71.
16. Leclerc M, Lartigau E, Lacornerie T, Daisne J-F, Kramar A, Gregoire V. Primary tumor delineation based on (18)FDG PET for locally advanced head and neck cancer treated by chemo-radiotherapy. Radiother Oncol. 2015;116:87–93.
17. Thiagarajan A, Caria N, Schöder H, Iyer NG, Wolden S, Wong RJ, et al. Target volume delineation in oropharyngeal cancer: impact of PET, MRI, and physical examination. Int J Radiat Oncol Biol Phys. 2012;83:220–7.
18. Daisne J-F, Duprez T, Weynand B, Lonneux M, Hamoir M, Reychler H, et al. Tumor volume in pharyngolaryngeal squamous cell carcinoma: comparison at CT, MR imaging, and FDG PET and validation with surgical specimen. Radiology. 2004;233:93–100.
19. Murakami R, Uozumi H, Hirai T, et al. Impact of FDG-PET/CT imaging on nodal staging for head-and-neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2007;68:377–82.
20. Lee M-C, Tsai H-Y, Chuang K-S, Liu C-K, Chen M-K. Prediction of nodal metastasis in head and neck cancer using a 3T MRI ADC map. AJNR Am J Neuroradiol. 2013;34:864–9.
21. Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. The Lancet Oncology. 2011;12:127–36.
22. Lee N, Xia P, Quivey JM, Sultanem K, Poon I, Akazawa C, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. Int J Radiat Oncol Biol Phys. 2002;53:12–22.
23. Lee N, Harris J, Garden AS, Straube W, Glisson B, Xia P, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. J Clin Oncol. 2009;27:3684–90.
24. Eisbruch A, Schwartz M, Rasch C, Vineberg K, Damen E, Van As CJ, et al. Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT? Int J Radiat Oncol Biol Phys. 2004;60:1425–39.
25. Eisbruch A, Harris J, Garden AS, Chao CKS, Straube W, Harari PM, et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). Int J Radiat Oncol Biol Phys. 2010;76:1333–8.
26. Geets X, Tomsej M, Lee JA, Duprez T, Coche E, Cosnard G, et al. Adaptive biological image-guided IMRT with anatomic and functional imaging in pharyngo-laryngeal tumors: impact on target volume delineation and dose distribution using helical tomotherapy. Radiother Oncol. 2007;85:105–15.

27. Schwartz DL, Garden AS, Shah SJ, et al. Adaptive radiotherapy for head and neck cancer—dosimetric results from a prospective clinical trial. Radiother Oncol. 2013;106:80–4.
28. Olteanu LAM, Berwouts D, Madani I, De Gersem W, Vercauteren T, Duprez F, et al. Comparative dosimetry of three-phase adaptive and non-adaptive dose-painting IMRT for head-and-neck cancer. Radiother Oncol. 2014;111:348–53.
29. Surucu M, Shah KK, Roeske JC, Choi M, Small W Jr, Emami B. Adaptive radiotherapy for head and neck cancer. Technol Cancer Res Treat. 2016;16:218–23.
30. Hansen EK, Bucci MK, Quivey JM, Weinberg V, Xia P. Repeat CT imaging and replanning during the course of IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2006;64:355–62.
31. Chen AM, Daly ME, Cui J, Mathai M, Benedict S, Purdy JA. Clinical outcomes among patients with head and neck cancer treated by intensity-modulated radiotherapy with and without adaptive replanning. Head Neck. 2014;36:1541–6.
32. 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.
33. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008;100:261–9.
34. Cleary C, Leeman JE, Higginson DS, Katabi N, Sherman E, Morris L, et al. Biological features of human papillomavirus-related head and neck cancers contributing to improved response. Clin Oncol (R Coll Radiol). 2016;28:467–74.
35. Lydiatt W, O'Sullivan B, Patel S. Major changes in head and neck staging for 2018. Am Soc Clin Oncol Educ Book. 2018;38:505–14.
36. O'Sullivan B, Huang SH, Su J, et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal Cancer Network for Staging (ICON-S): a multicentre cohort study. The Lancet Oncology. 2016;17:440–51.
37. Trotti A, Pajak TF, Gwede CK, Paulus R, Cooper J, Forastiere A, et al. TAME: development of a new method for summarising adverse events of cancer treatment by the Radiation Therapy Oncology Group. Lancet Oncol. 2007;8:613–24.
38. Machtay M, Moughan J, Trotti A, Garden AS, Weber RS, Cooper JS, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J Clin Oncol. 2008;26:3582–9.
39. O'Sullivan B, Huang SH, Perez-Ordonez B, et al. Outcomes of HPV-related oropharyngeal cancer patients treated by radiotherapy alone using altered fractionation. Radiother Oncol. 2012;103:49–56.
40. Garden AS, Kies MS, Morrison WH, et al. Outcomes and patterns of care of patients with locally advanced oropharyngeal carcinoma treated in the early 21st century. Radiat Oncol. 2013;8:21.
41. Hall SF, Griffiths RJ, O'Sullivan B, Liu F-F. The addition of chemotherapy to radiotherapy did not reduce the rate of distant metastases in low-risk HPV-related oropharyngeal cancer in a real-world setting. Head Neck. 2019;41:2271–6.
42. O'Sullivan B, Huang SH, Siu LL, et al. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. J Clin Oncol. 2013;31:543–50.
43. Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, 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.
44.•• 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;393:51–6.

This randomized controlled clinical trial demonstrated similar overall toxicity and worsened oncologic outcomes with concurrent cetuximab as compared to cisplatin.

45.•• 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;393:40–5.

This randomized controlled clinical trial demonstrated similar late toxicity and worsened oncologic outcomes with concurrent cetuximab as compared to cisplatin.

46. Fakhry C, Zhang Q, Gillison ML, et al. Validation of NRG oncology/RTOG-0129 risk groups for HPV-positive and HPV-negative oropharyngeal squamous cell cancer: implications for risk-based therapeutic intensity trials. Cancer. 2019;125:2027–38.
47. Trosman SJ, Koyfman SA, Ward MC, al-Khudari S, Nwizu T, Greskovich JF, et al. Effect of human papillomavirus on patterns of distant metastatic failure in oropharyngeal squamous cell carcinoma treated with chemoradiotherapy. JAMA Otolaryngol Head Neck Surg. 2015;141:457–62.
48.• Chera BS, Amdur RJ, Tepper JE, et al. Mature results of a prospective study of deintensified chemoradiotherapy for low-risk human papillomavirus-associated oropharyngeal squamous cell carcinoma. Cancer. 2018;124:2347–54.

This phase II clinical trial demonstrated promising oncologic outcomes with reduced-dose radiation treatment combined with reduced-dose cisplatin.

49. Yeung AR, Amdur RJ, Morris CG, Morgan LS, Mendenhall WM. Long-term outcome after radiotherapy for FIGO stage IIIB and IVA carcinoma of the cervix. Int J Radiat Oncol Biol Phys. 2007;67:1445–50.

50. Al-Mamgani A, van Werkhoven E, Navran A, Karakullukcu B, Hamming-Vrieze O, Machiels M, et al. Contralateral regional recurrence after elective unilateral neck irradiation in oropharyngeal carcinoma: a literature-based critical review. Cancer Treat Rev. 2017;59:102–8.
51. Chin R-I, Rao YJ, Hwang MY, et al. Comparison of unilateral versus bilateral intensity-modulated radiotherapy for surgically treated squamous cell carcinoma of the palatine tonsil. Cancer. 2017;123:4594–607.
52. Rackley TP, Namelo WC, Palaniappan N, Cole N, Owens DMJ, Evans M. Unilateral radiotherapy for surgically resected lateralized squamous cell carcinoma of the tonsil. Head Neck. 2017;39:17–23.
53. Huang SH, Waldron J, Bratman SV, et al. Re-evaluation of ipsilateral radiation for T1-T2N0-N2b tonsil carcinoma at the Princess Margaret Hospital in the human papillomavirus era, 25 years later. Int J Radiat Oncol Biol Phys. 2017;98:159–69.
54. Castelijns JA, van den Brekel MWM. Imaging of lymphadenopathy in the neck. Eur Radiol. 2002;12:727–38.
55. Nguyen A, Luginbuhl A, Cognetti D, Van Abel K, Bar-Ad V, Intenzo C, et al. Effectiveness of PET/CT in the preoperative evaluation of neck disease. Laryngoscope. 2014;124:159–64.
56. Stack BC, Duan F, Sicks J, Romanoff J, Opanowski A, Horng D, et al. The negative predictive value (NPV) of FDG-PET/CT in the head and neck squamous cell carcinoma (HNSCC) N0 patient, the first report of the ACRIN 6685 trial. J Clin Oncol. 2017. https://doi.org/10.1200/JCO.2017.35.15_suppl.6041.
57.• Marur S, Li S, Cmelak AJ, et al. E1308: phase II trial of induction chemotherapy followed by reduced-dose radiation and weekly cetuximab in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx—ECOG-ACRIN Cancer Research Group. J Clin Oncol. 2017;35:490–7.
This phase II clinical trial demonstrated promising oncologic outcomes with induction chemotherapy used to select patients showing good response for subsequent reduced-dose radiation treatment combined with cetuximab.
58.• Chen AM, Felix C, Wang P-C, et al. Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: a single-arm, phase 2 study. The Lancet Oncology. 2017;18:803–11.
This phase II clinical trial demonstrated promising oncologic outcomes with induction chemotherapy used to select patients showing good response for subsequent reduced-dose radiation treatment combined with paclitaxel.
59. Hegde JV, Shaverdian N, Daly ME, Felix C, Wong DL, Rosove MH, et al. Patient-reported quality-of-life outcomes after de-escalated chemoradiation for human papillomavirus-positive oropharyngeal carcinoma: findings from a phase 2 trial. Cancer. 2018;124:521–9.
60.• Villaflor VM, Melotek JM, Karrison TG, et al. Response-adapted volume de-escalation (RAVD) in locally advanced head and neck cancer. Ann Oncol. 2016;27:908–13.
This phase II clinical trial demonstrated promising oncologic outcomes with induction chemotherapy used to select patients showing good response for subsequent reduced-volume radiation treatment combined with paclitaxel, fluorouracil, and hydroxyurea.
61. Melotek JM, Seiwert TY, Blair EA, et al. A phase 2 dose and volume de-escalation trial for high- and low-risk HPV+ oropharynx cancer: efficacy, toxicity, and dosimetric analyses. Int J Radiat Oncol Biol Phys. 2017;99:S135.
62. Seiwert T, Melotek JM, Foster CC, et al. OPTIMA—a phase 2 trial of induction chemotherapy response-stratified radiation therapy dose and volume de-escalation for HPV+ oropharyngeal cancer: efficacy, toxicity, and HPV subtype analysis. Int J Radiat Oncol Biol Phys. 2018;100:1309.
63. Bristow RG, Hill RP. Hypoxia, DNA repair and genetic instability. Nat Rev Cancer. 2008;8:180–92.
64. Brizel DM, Sibley GS, Prosnitz LR, Scher RL, Dewhirst MW. Tumor hypoxia adversely affects the prognosis of carcinoma of the head and neck. Int J Radiat Oncol Biol Phys. 1997;38:285–9.
65. Göttgens E-L, Ostheimer C, Span PN, Bussink J, Hammond EM. HPV, hypoxia and radiation response in head and neck cancer. Br J Radiol. 2018;20180047.
66. Lee N, Schöder H, Beattie B, et al. Strategy of using intratreatment hypoxia imaging to selectively and safely guide radiation dose de-escalation concurrent with chemotherapy for locoregionally advanced human papillomavirus-related oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys. 2016;96:9–17.
67. Riaz N, Sherman E, Katabi N, et al. A personalized approach using hypoxia resolution to guide curative-intent radiation therapy dose-reduction to 30 Gy: a novel de-escalation paradigm for HPV-associated oropharynx cancers treated with concurrent chemoradiation therapy. Int J Radiat Oncol Biol Phys. 2017;99:S136.
68. Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group Randomized Trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol. 2003;22:69–76.
69. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006;354:567–78.
70. 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;3:220–6.
71. Lacas B, Bourhis J, Overgaard J, Zhang Q, Grégoire V, Nankivell M, et al. Role of radiotherapy fractionation in head and neck cancers

(MARCH): an updated meta-analysis. The Lancet Oncology. 2017;18:1221–37.
72. Overgaard J, Hansen HS, Specht L, Overgaard M, Grau C, Andersen E, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet. 2003;362:933–40.

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