ASCO special article abstract

Role of Treatment Deintensification in the Management of p16+ Oropharyngeal Cancer: ASCO Provisional Clinical Opinion

David J. Adelstein, MD[1]; Nofisat Ismaila, MD[2]; Jamie A. Ku, MD[1]; Barbara Burtness, MD[3]; Paul L. Swiecicki, MD[4]; Loren Mell, MD[5]; Jonathan J. Beitler, MD, MBA[6]; Neil Gross, MD[7]; Christopher U. Jones, MD[8]; Marnie Kaufman[9]; Quynh-Thu Le, MD[10]; Thomas J. Semrad, MD, MAS[11]; Lillian L. Siu, MD[12]; and John A. Ridge, MD, PhD[13]

PURPOSE An ASCO provisional clinical opinion offers timely clinical direction to ASCO's membership after publication or presentation of potentially practice-changing data from major studies. This provisional clinical opinion addresses the role of treatment deintensification in the management of p16+ oropharyngeal cancer (OPC).

CLINICAL CONTEXT For patients with p16+ OPC, current treatment approaches are well established. In the good-prognosis subset of nonsmoking p16+ patients with early-stage disease, these treatments have been highly successful, albeit with significant associated acute and late toxicity. Deintensification of surgical, radiation, and medical treatment in an effort to reduce toxicity while preserving high survival rates is an appropriate therapeutic objective currently being explored in patients who are experiencing the best treatment results. However, careful delineation of this good-risk subset is essential. While the current eighth edition of the American Joint Committee on Cancer staging system is prognostically robust, it should not be interpreted as reason to alter therapeutic decisions or justify treatment deintensification. The development of transoral surgical techniques and the adoption of intensity-modulated radiation therapy planning have been transformative in disease management and suggest potentially beneficial approaches. Recent advances in systemic treatments have been notable. The optimal integration and modification of these modalities to ameliorate toxicity has not been defined and remains an important focus of current investigation.

PROVISIONAL CLINICAL OPINION The hypothesis that de-escalation of treatment intensity for patients with p16+ OPC can reduce long-term toxicity without compromising survival is compelling and necessitates careful study and the analysis of well-designed clinical trials before changing current treatment standards. Treatment deintensification for these patients should only be undertaken in a clinical trial.

Additional information is available at www.asco.org/head-neck-cancer-guidelines.

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INTRODUCTION

ASCO has established a rigorous, evidence-based approach—the provisional clinical opinion (PCO)—to offer a rapid response to emerging data in clinical oncology. The PCO is intended to offer timely clinical direction to ASCO's oncologists after publication or presentation of potentially practice-changing data from major studies. This PCO addresses the rationale for and evidence supporting treatment deintensification in the management of p16+ oropharyngeal cancer (OPC).

STATEMENT OF THE CLINICAL ISSUE

The human papillomavirus (HPV) has been identified as the etiologic agent in the majority of patients with squamous cell carcinoma of the oropharynx (tonsil and base of tongue) in North America and northern Europe.[1] Unlike tobacco-induced squamous cell cancer, which represents most cancers at other head and neck subsites, HPV-mediated OPC is increasing in frequency. These cancers tend to occur in a younger, healthier population with less tobacco exposure. Furthermore, the prognosis of HPV-mediated cancer is significantly better than that of the tobacco-induced malignancies. Historically, single-modality surgery and radiation have been appropriate and highly effective treatment options for patients with stage I or II head and neck cancer. Transoral surgical approaches and intensity-modulated radiation have been rapidly incorporated into treatment standards and have proven to be successful in limiting morbidity.

For more advanced disease, recent multimodality treatment standards used for oropharynx squamous cell cancer have generally used concurrent cisplatin-based chemoradiotherapy, administered either definitively or as a postoperative adjuvant treatment.[2,3] These treatments

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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THE BOTTOM LINE

Role of Treatment Deintensification in the Management of p16+ Oropharyngeal Cancer: ASCO Provisional Clinical Opinion

Research Question

Have deintensified treatment approaches become an acceptable treatment standard in patients with p16+ oropharyngeal cancer (OPC)?

Target Population

Patients with p16+ OPC

Target Audience

Medical oncologists, radiation oncologists, surgeons, primary care physicians, dentists, nurses, speech pathologists, oncology pharmacists, and patients

Methods

An Expert Panel was convened to develop provisional clinical opinions based on a systematic review of the medical literature and informal expert consensus.

Provisional Clinical Opinion

- The statement that de-escalation of treatment intensity for patients with p16+ OPC can reduce long-term toxicity without compromising survival is a hypothesis that requires appropriate testing.
- Despite the identification of good-prognosis patient subsets, the promising early results of treatment deintensified regimens, and the fact that many formerly advanced-stage p16+ cancers are now considered to be early-stage disease, current treatment recommendations have not changed.
- The standard of care for the definitive nonoperative management of cisplatin-eligible patients with advanced disease is concurrent chemoradiation with high-dose cisplatin given every 3 weeks. For patients undergoing initial surgical resection, adjuvant chemoradiation with concurrent high-dose cisplatin given every 3 weeks is recommended for patients with positive margins and/or extranodal tumor extension.
- Deintensification of treatment of patients with p16+ oropharynx cancer should only be undertaken in a clinical trial.

Additional Resources

More information, including a Data Supplement, slide sets, and clinical tools and resources, is available at www.asco.org/head-neck-cancer-guidelines. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

are rigorous and produce considerable acute and late toxicity.[4,5]

Appreciating the improved prognosis of patients with HPV-mediated OPC, there has been increasing interest in amelioration of this toxicity. In 2008, the National Cancer Institute convened a State of the Science meeting on this topic. Among the conclusions was the observation that treatment deintensification was a reasonable investigational strategy to pursue in the HPV-mediated cancers with the best prognosis, with the goal of reducing short- and long-term toxicity without compromising outcomes.[6] Using recursive partitioning analysis, it has since been possible to refine the criteria of a good-prognosis cohort, and patients with HPV-mediated OPC and a limited smoking history can anticipate a greater than 80% cure rate with combined-modality treatment, even when presenting with advanced nodal disease and/or large primary tumors.[7-9]

Since promulgating this recommendation, many retrospective series have been reported and prospective clinical trials conducted exploring possible deintensification approaches for these patients. Highly encouraging preliminary reports have been published (or presented) suggesting that toxicity may be reduced without significant decline in survival. There is legitimate concern, however, that initial reports in patients with an excellent overall prognosis may result in an unjustified change in the treatments used by the oncologic community.

The problem has been compounded by widespread misunderstanding of the recently revised American Joint Committee on Cancer (AJCC) staging system. The AJCC eighth edition staging system appropriately distinguishes the staging for patients with p16-positive (p16+; HPV-mediated) OPC from the other p16-negative head and neck cancers.[10] p16+ OPC is defined as a distinct disease. Earlier staging systems, most recently the AJCC sixth and

seventh editions, did not reflect the gratifying survival rates for p16+ disease derived from modern treatment regimens.[11] Hence, many patients once considered to have stage III and IV disease have now been classified as having stage I or II disease. While this has markedly improved the prognostic utility of the AJCC eighth edition, it has engendered some confusion surrounding treatment planning. Historically, excellent results have been achieved using single-modality treatment of most patients with stage I and II head and neck cancers. Reassigning p16+ cancers from stage IV (AJCC sixth and seventh editions) to stage I or II (AJCC eighth edition) does not mean that the treatments appropriate for patients with stage I and II disease according to the AJCC sixth and seventh edition staging systems are suddenly correct for patients with stage I or II p16+ cancer according to the AJCC eighth edition staging system. The AJCC eighth edition does not justify treatment deintensification. The low stages assigned reflect the success achieved from aggressive treatments originally designed for patients with stage III or IV cancers, regardless of HPV mediation.

In this monograph, in keeping with the AJCC eighth edition, HPV-mediated cancers of the oropharynx will be described as p16+. The AJCC chose p16 overexpression as the defining identifier of this disease in the oropharynx because of the low cost, universal applicability, and ease of interpretation of the test (as opposed to other HPV-mediated signatures). While p16 positivity is an excellent surrogate for HPV-mediated disease in the oropharynx, it is not interchangeable with HPV positivity in other anatomic subsites.[12] When specific trials use HPV signifiers other than p16, they will be described as such.

METHODS

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and ASCO guidelines staff with health research methodology expertise. All funding for the administration of the project was provided by ASCO. The members of the Expert Panel on the role of treatment deintensification in the management of p16+ OPC are listed in Appendix Table A1 (online only). Additional information about ASCO PCO methodology is available in the ASCO Guidelines Methodology Manual (www.asco.org/guideline-methodology).

PCO Development Process

This PCO was informed by a systematic review of available evidence (search dates, January 2008 to December 2018), informal consensus, and clinical experience. Articles were selected for inclusion in the systematic review of the evidence based on the following criteria:

- Population: patients with HPV-positive and p16+ OPC
- Interventions: transoral surgery (TOS), radiation (dose reduction, field reduction), concurrent chemoradiotherapy, induction chemotherapy, targeted therapy, and immunotherapy
- Study designs: systematic reviews, meta-analyses, randomized controlled trials, prospective cohort reports, retrospective observational studies, and relevant meeting abstracts

Articles were excluded from the systematic review if they were editorials, commentaries, letters, news articles, case reports, or narrative reviews and if they were published in a non-English language.

Guideline Disclaimer

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PCO and Conflict of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and

other relationships. In accordance with the Policy, the majority of the members of the Panel did not disclose any relationships constituting a conflict under the Policy.

ASCO PCO

Patient Selection

Accurate identification of patients who are at low risk for death when approached with current treatment paradigms is essential in defining those most likely to benefit from treatment deintensification without compromising overall survival. Several publications have helped to describe low-risk cohorts.

In an unplanned multivariable subgroup analysis of patients with OPC treated on the Radiation Therapy Oncology Group (RTOG) 0129 trial, the conventional anatomic T and N categories, as well as the nonanatomic factors of age, race, performance status, tobacco smoking history, and HPV status, proved to be significant determinants of overall survival.[8] Recursive partitioning analysis identified HPV status as the feature most predictive of overall survival, followed by the smoking history pack-years (selecting a cut point of 10 pack-years), N category (for HPV-positive tumors), and T category (for HPV-negative tumors). In the low-risk group (defined as patients with HPV-positive tumors and either a smoking history of 10 or fewer pack-years or a greater than 10 pack-year smoking history and AJCC seventh edition N0-2a disease), the 3-year survival rate was 93%. In a similar fashion, the Princess Margaret Cancer Centre group defined a good-risk cohort that included patients with p16+ oropharynx cancer, AJCC seventh edition T1-3N0-2c disease, and a smoking history of 20 or fewer pack-years. Such patients had a 5-year overall survival rate of 89%.[7]

Based on the superior survival of patients with HPV-mediated OPC compared with stage-matched patients with non–HPV-mediated OPC and the lack of survival discrimination between the AJCC seventh edition clinical stages in HPV-mediated patients, the International Collaboration on Oropharyngeal Cancer Network for Staging (ICON-S) study sought to define a clinical staging system for HPV-mediated, p16+ OPC.[11] Using data from multiple centers, the authors redefined N1 disease to include the AJCC seventh edition N1, N2a, and N2b categories. They then articulated a validated staging system in which patients with T1-2N0-1 tumors were considered to have stage I cancer. Those patients experienced a 5-year overall survival rate of 88%. Using the National Cancer Database, the Yale group further validated the ICON-S staging, in both patients treated with primary surgery and patients treated with primary radiation. Based on this analysis, additional refinements were proposed.[13]

The ICON-S definitions formed the basis of the eighth edition of the AJCC staging system, which distinguishes p16+ and p16-negative OPCs, with a distinct staging system for p16+ cancers. In the AJCC eighth edition, T1-2N0-1 tumors (which span stages I to IV in the AJCC seventh edition) are all now considered stage I.[10]

It is noteworthy that the ICON-S and AJCC eighth edition definitions are anatomic. They do not incorporate nonanatomic factors (most notably, smoking history) that may, in the future, prove important in defining a good-prognosis patient cohort. Final delineation of the patient population most appropriate for treatment deintensification may well require consideration of both types of determinants.

The AJCC eighth edition represents a significant improvement. Integrating nonanatomic patient-specific parameters into prognostic group definitions is a work in progress. Optimal cut points for smoking history are not well defined and vary across reports. The importance of other nonanatomic factors is unclear.[14,15] Ascertainment of their significance and identification of potential molecular markers of prognostic importance will be essential in the exploration of treatment deintensification.

End Points

Maintaining the excellent survival outcomes resulting from modern, highly morbid, multimodality treatments is critical to the success of any treatment deintensification approach. However, demonstrating the equivalence of treatments is difficult when standard interventions result in 2-year survival rates greater than 90%. Traditional phase III noninferiority trials, which are designed to provide the highest level of evidence, require large numbers of both patients and events. They demand significant resources. Other study designs may suffice, but they must be carefully constructed with appropriate statistical power, acceptable CIs, and adequate follow-up. Such trials will take time to design and execute. Ideally, they will be explicitly embraced by the therapeutic community before they are launched.

If survival equivalence can be demonstrated, then the end points of interest will be the acute and, more importantly, late toxicities of treatment. Conventional toxicity grading systems may lack the necessary sensitivity to identify meaningful improvements. Validated quality-of-life and patient-reported outcome tools are available and should be used, but the ability to demonstrate the clinical importance of small changes using these metrics is unclear and differences may take several years to emerge.

Cost will be an additional end point of concern. Many of the potential interventions being considered for deintensification (eg, transoral robotic surgery, particle radiation therapy, immunotherapy) may add significant cost to patient management. How to reduce toxicity with acceptable cost and without compromising treatment outcomes is decidedly uncertain.

Surgical Approaches

Until recently, surgery for most OPCs entailed an open transcervical approach, often with mandibulotomy. This

frequently resulted in substantial functional and some cosmetic morbidity.[16] TOS was generally limited to patients with small tonsil cancers and was usually undertaken in specialty centers.[17] The development of newer technologies, such as transoral robotic surgery, has greatly increased the enthusiasm for surgical therapy of OPC. The increasing incidence of HPV-mediated OPC, which often presents with small primary tumors and seems to tolerate more limited resection margins, has increased the number of patients eligible for less morbid resection. Current TOS techniques permit improved three-dimensional definition of the tumor-host interface and achieve excellent oncologic outcomes in selected patients.[18,19] Reports from experienced centers have demonstrated a lower complication rate, faster postoperative recovery, and a more limited functional and cosmetic impact compared with traditional transcervical approaches.[20-22]

The increased acceptance and apparent success of TOS has reinvigorated the debate surrounding whether surgery or radiation is the optimal single-modality treatment of early-stage OPC. While not strictly limited to patients with HPV-mediated disease, deriving acceptable oncologic and functional outcomes after treatment demands appropriate patient selection and is frequently motivated by institutional biases and expertise. Decisions about surgery should involve not only technical feasibility (based on factors such as tumor size, location, and accessibility), but also the anticipated functional outcomes, extent and necessary treatment of nodal disease, and likely need for adjuvant therapy. Currently, there is a paucity of data directly comparing these two strategies. The European Organisation for Research and Treatment of Cancer (EORTC) 1420 trial (ClinicalTrials.gov identifier: NCT02984410), an active phase III trial, is directly comparing primary radiation therapy (66 to 70 Gy) to TOS for patients with either p16+ or p16-negative T1-2N0 OPC (AJCC seventh edition). The primary outcome measure is a functional one, the change in the MD Anderson Dysphagia Inventory score.

In patients with more advanced disease, there are widely accepted indications and recommendations for postoperative radiation therapy to both the primary site and the neck.[2,3,23,24] The addition of concurrent chemotherapy to adjuvant radiation was tested by RTOG 9501 and EORTC 22931, two landmark trials published in 2004 comparing postoperative adjuvant radiation with adjuvant cisplatin chemoradiation.[25,26] Eligibility criteria for these two studies differed, and the overall results were not entirely consistent. However, an unplanned retrospective subgroup analysis of pooled data from these two trials demonstrated that locoregional control and survival outcomes were improved with chemoradiation for patients with involved surgical margins and/or extranodal extension (ENE),[27] leading to adoption of intensified therapy in this patient subset as a treatment standard.[2,3]

It is not known, however, whether these adjuvant guidelines, established from a cohort of mostly non-OPC HPV-agnostic patients, should apply to the p16+ good-prognosis population and whether TOS may offer potential for treatment deintensification. Are these good-prognosis patients being overtreated, or are the excellent outcomes that have been achieved the result of appropriately aggressive protocols? If TOS results in minimal and acceptable morbidity, deintensification would revolve around the need for and necessary toxicity of adjuvant postoperative therapy. Whether primary TOS followed by appropriate adjuvant treatment results in survival and functional outcomes equivalent to (or better than) standard chemoradiotherapy is the larger question.

The most frequently cited advantage of initial resection is the ability to determine the pathologic stage and appropriate adjuvant therapy, instead of basing nonsurgical management on clinical staging. In a recent retrospective multi-institutional report, using AJCC eighth edition staging, clinical overstaging was identified in 10% of patients with p16+ OPC treated surgically.[28] For such clinically overstaged patients, the added information may permit treatment deintensification. If initial TOS and neck dissection can be executed with low enough morbidity and if this approach allows for less intensive postoperative adjuvant therapy, there may be diminished late toxicity when compared with definitive full-dose radiation or chemoradiation. However, if TOS with pathologic staging does not reduce the morbidity of the subsequent nonsurgical treatment, then deintensification cannot be accomplished, and overall toxicity may increase.

One possible approach to the deintensification of postoperative adjuvant therapy is reducing the adjuvant radiation dose, a modification that holds promise for reducing late radiation-induced toxicity. The Eastern Cooperative Oncology Group (ECOG) 3311 trial, a phase II study that has completed accrual, addressed this question. Surgeon-selected patients with stage III or IV (AJCC seventh edition) p16+ OPC amenable to TOS (irrespective of smoking history and prognostic group) all underwent TOS and neck dissection. Subsequent adjuvant management was based on the pathologic findings and respective risk group allocation (termed low, intermediate, or high risk). Low-risk patients (T1-2N0-1 with 3-mm or greater margins and without ENE, perineural invasion, or lymphovascular invasion) were treated with surgery alone. High-risk patients (positive surgical margins, greater than 1 mm ENE, or five or more metastatic lymph nodes) received postoperative radiation (66 Gy) with concurrent weekly cisplatin. Patients who fell into the intermediate-risk category, defined by close margins (less than 3 mm), minimal ENE (1 mm or less), N2a-b disease, or perineural invasion or lymphovascular invasion, were randomly assigned to either 50 or 60 Gy of adjuvant radiation alone. Primary objectives included both the feasibility of a large

multi-institutional TOS trial (which has now been demonstrated) and the 2-year progression-free survival rate, which is pending. Secondary outcomes included toxicity, swallowing function, patient-reported outcomes, and the risk group distribution of these surgeon-selected patients for inclusion.

Pathologically based risk stratification after TOS with radiation dose reduction in selected patients is also being explored in the Sinai Robotic Surgery (SIRS) trial (ClinicalTrials.gov identifier: NCT02072148) from Mt Sinai Hospital in New York and the Postoperative Adjuvant Treatment for HPV-Positive Tumors (PATHOS) trial (ClinicalTrials.gov identifier: NCT02215265), a multi-institutional effort from the United Kingdom. Both studies continue to accrue patients and should add to our understanding of the survival and functional outcomes that result from this strategy.

Retrospective reports from several institutions have questioned the prognostic magnitude of ENE in patients with p16+ oropharynx cancer[29,30] and suggested a lack of benefit from the addition of adjuvant chemotherapy.[31] However, larger series from multiple institutions and analysis of the National Cancer Database seem to confirm the importance of ENE.[32-34] Furthermore, the implications of the pathologic extent of ENE and concerns about significant intra- and interobserver variability in ENE assessment cloud the issue.[35,36]

Although there is significant and reasonable concern about the applicability of the RTOG 9501 and EORTC 22931 results to the population with HPV-mediated OPC and, in particular, the good-prognosis p16+ patients, these two protocols provide the best available evidence. Outside of a trial setting, it is premature to alter standards of care by reducing dose or omitting chemotherapy. The Washington University group has completed accrual to a small prospective trial addressing this issue by comparing adjuvant radiation alone to adjuvant radiation with weekly cisplatin in patients with p16+ OPC who have undergone TOS and a neck dissection demonstrating ENE (Adjuvant De-escalation, Extracapsular Spread, p16+, Transoral [ADEPT] trial; ClinicalTrials.gov identifier: NCT01687413). However, the study may not be large enough to provide definitive information.

Nonsurgical Approaches

The standard of care for definitive nonoperative treatment of OPC is radiation therapy to a dose of 70 Gy for gross disease and 50 to 66 Gy to the elective and high-risk regions of the neck, administered in daily fractions over 7 weeks or in one of several altered fractionation regimens.[37] For patients with AJCC sixth or seventh edition stage IV and advanced stage III disease, concurrent high-dose intermittent cisplatin is recommended. For patients receiving conventional radiation treatment over 7 weeks, three doses of cisplatin 100 mg/m^2 are administered. A schedule using two doses of cisplatin 100 mg/m^2 concurrent with accelerated fractionation radiation in a 6-week course has been demonstrated to be equivalent in the RTOG 0129 trial.[8,38] The use of concurrent cetuximab or carboplatin plus fluorouracil has been considered an acceptable alternative for patients considered unfit for cisplatin.[2,3] While the acute toxicity from systemic cisplatin-based chemoradiotherapy can be significant, oncologists have become adept at its management. Of greater concern is the late toxicity resulting from multimodality treatment.[5] Most of these adverse effects can be attributed to the radiation therapy, although they are augmented by the concurrent use of chemotherapy. The amount of normal tissue radiated, the tissue targeted, and the total radiation dose are all believed to contribute to this late toxicity. It assumes greater importance in view of the younger demographic and high survival rate of patients with good-prognosis p16+ disease and their potential for long-term morbidity associated with successful treatment.

While not specifically designed for deintensification, several radiation therapy strategies have been successfully used to ameliorate this late toxicity. The rapid and widespread adoption of intensity-modulated radiation therapy in place of older two- or three-dimensional planning techniques has reduced late treatment-related complications including xerostomia.[39] Reduction of elective neck volume treated in well-selected patients is now generally accepted as another effective strategy to reduce treatment-related morbidity. Well-lateralized p16+ tonsil cancers involving only the primary site and ipsilateral side of the neck, for example, can be safely treated without radiation to the clinically uninvolved contralateral side of the neck.[40] Altered fractionation regimens and proton therapy are also being tested.

Reduction of chemotherapy toxicity has largely focused on the acute toxicity produced by the well-tested high-dose cisplatin regimen of 100 mg/m^2 given in a standard every-3-week schedule with radiation. It has been hypothesized that weekly treatment with cisplatin 30 to 40 mg/m^2 will result in less acute injury, more drug delivery, and equivalent survival outcomes. Small retrospective reports of definitive chemoradiotherapy[41] and adjuvant chemoradiotherapy[42] have suggested that overall survival times with either schedule are similar in p16+ patients. However, there are few published randomized comparative trials of weekly versus every-3-week cisplatin for head and neck cancer in general[43,44] and none in p16+ OPC. Results are mixed, and it remains unclear whether the regimens are equivalent in outcome or whether the toxicity profile is improved with weekly administration.[45,46] In p16+ OPC, randomized prospective evidence does not exist to support the use of cisplatin given weekly at 30 to 40 mg/m^2, instead of every 3 weeks at 100 mg/m^2, irrespective of the radiation fractionation schedule.

Retrospective analyses have also suggested that a threshold total cisplatin dose of 200 mg/m^2 is required and perhaps sufficient.[47,48] This arbitrary cut point is in large

part reflective of the toxicity-related practical difficulty often encountered in administering the third planned cisplatin dose to achieve the recommended total cisplatin dose of 300 mg/m^2. It is noteworthy that, although a total cisplatin dose of 200 mg/m^2 is an established standard when delivered concurrently with accelerated fractionation radiation, no randomized prospective evidence supports the use of this lower dose in patients being treated with conventional radiation.

Nonetheless, because of the putative toxicity advantages, weekly cisplatin schedules have frequently been used in treatment deintensification regimens. Ongoing work from Chera et al[49,50] has explored radiation dose reduction using only 60 Gy with concurrent weekly cisplatin (30 mg/m^2/wk) for patients with non-T4, less than N3 (AJCC seventh edition), p16+ OPC with minimal smoking history. Encouraging survival and quality-of-life outcomes have been reported, but this is a single-arm experience without concurrent controls.[49,50]

Similarly, the NRG Oncology group has completed the two-arm phase II HN002 trial testing the same reduced radiation dose of 60 Gy with concurrent weekly cisplatin at 40 mg/m^2 versus 60 Gy of accelerated radiation alone without chemotherapy in a good-prognosis subset (AJCC seventh edition non-T4 and less than N2c disease and smoking history of 10 or fewer pack-years) of patients with p16+ OPC. Quality-of-life data are being collected. The statistical design of this trial defined an expected 2-year progression-free survival rate of 91%, with a type I error rate of 10% and 80% power to reject either arm should the 2-year progression-free survival rate be less than 85%. Results from this study are pending, and long-term outcomes will not be available for years.

Recognizing the association between chemotherapy responsiveness and locoregional control,[51,52] a potentially fruitful approach is the use of induction chemotherapy as a tool to identify patients responding to chemotherapy who, with significant reduction of their disease burden, might then be strong candidates for the use of smaller radiation doses or treatment fields. Several groups have explored this paradigm, most notably ECOG and the American College of Radiology Imaging Network in the E1308 trial.[53] Ninety patients with p16+ and/or HPV-positive stage III or IV OPC were treated with three cycles of induction cisplatin, paclitaxel, and cetuximab chemotherapy. Patients with clinical complete responses at the primary site then received concurrent cetuximab and a substantially reduced dose of primary site radiation (54 Gy), whereas patients with less than a complete response were treated with cetuximab and a full radiation dose (69.3 Gy). Late toxicity and functional outcomes were recorded. Fifty-one patients achieved a clinical complete response to induction, received the reduced dose of radiation, and experienced a 2-year progression-free survival rate of 80%. However, when the analysis of patients who achieved a complete primary site response to induction was limited to a good-prognosis subset of 27 nonsmoking patients with less than T4 tumors and ipsilateral nodes smaller than 6 cm, the 2-year progression-free survival rate was 96%. This supports the importance of careful patient selection for treatment deintensification approaches. The 15-Gy reduction in radiation dose seemed to improve measured swallowing outcomes and nutritional status.

A similar tactic was reported in a 45-patient study by Chen et al,[54] who used the same radiation dose reduction to 54 Gy in patients achieving a complete or partial response to carboplatin and paclitaxel induction chemotherapy, whereas patients who achieved less than a partial response were treated with 60 Gy. A concurrent chemotherapy regimen of paclitaxel 30 mg/m^2/wk, first explored in the ECOG E2399 trial,[55] was administered to all patients. Overall survival outcomes were encouraging, but using the University of Washington Quality of Life Questionnaire and the Functional Assessment of Cancer Therapy–Head and Neck, no long-term improvement resulted from the 6-Gy radiation dose reduction.[56]

The Nab-paclitaxel and Carboplatin Followed by Response-Based Local Therapy in Treating Patients With Stage III or IV HPV-Related Oropharyngeal Cancer (OPTIMA) trial was a single-arm phase II trial in 62 patients with both low-risk (AJCC seventh edition T0-3N0-2b disease and a smoking history of 10 or fewer pack-years) and high-risk (all others) p16+ OPC.[57] The treatment consisted of induction carboplatin and nanoparticle albumin-bound paclitaxel for three cycles, followed by a response-based deintensification of radiation dose, volume, and the use of concurrent chemotherapy. Low-risk patients with a favorable (50% or greater) response received 50 Gy of radiotherapy alone; low-risk patients with a 30% to 50% response and high-risk patients with a 50% or greater response received 45 Gy of radiotherapy with concurrent chemotherapy; and all other patients received 75 Gy of radiotherapy and concurrent chemotherapy. Concurrent chemoradiotherapy was given as 5-day, alternate-week regimens of 1.5 Gy of radiation twice daily with paclitaxel, fluorouracil, and hydroxyurea. Elective neck radiation volumes were limited to the first echelon of uninvolved nodes. A surgical evaluation, including neck dissection and/or biopsy or primary site excision, was planned for all patients and was performed in 84% of patients after radiation. The 2-year progression-free survival rate was 95% in the 28 low-risk patients and 94% in the 34 high-risk patients. There was less acute toxicity in the deintensified arms. Late toxicity was not reported. Treatment deintensification proved to be possible in 81% of the patients enrolled, but only 32% of patients avoided concurrent chemotherapy. Although deemed a de-escalation trial, the overall intensity of the trimodality induction, concurrent chemoradiotherapy, and surgery is of concern, and

interpretation is limited without randomized comparisons to standard treatments.

Early results of trials exploring even more aggressive radiation dose reduction have also been reported. The Mayo Clinic group is testing a postoperative adjuvant dose of 30 to 36 Gy with weekly docetaxel in good-prognosis p16+ patients.[58] Investigators at Memorial Sloan Kettering Cancer Center have reported results from a trial of definitive concurrent chemotherapy and radiation that was truncated after 30 Gy in patients without fluoromisonidazole positron emission tomography–demonstrated hypoxia at that time.[59] Siegel et al[60] tested the possibility of eliminating radiation entirely after induction chemotherapy followed by TOS in a small trial from George Washington University. All such approaches should be considered investigational, however, and their application should be limited to clinical trials.

The experience with programmed cell death 1 blockade in patients with metastatic disease has demonstrated durable long-term remissions in a small number of patients.[61-63] Due to the relatively limited toxicity of these agents, their potential use as part of a treatment deintensification strategy in p16+ patients is intriguing but will require appropriate testing.

The best studied deintensification approach was based on the phase III evidence that the addition of concurrent cetuximab to definitive radiation improves survival compared with radiation alone in squamous cell head and neck cancer[64,65] and the prospect that cetuximab might be a less toxic systemic intervention than cisplatin. Therefore, the possibility of treatment deintensification by substituting cetuximab for the cisplatin seemed compelling for patients with p16+ OPC.

Unlike other deintensification proposals, however, this proposition has undergone phase III testing in the RTOG 1016 trial, and the recently published results are instructive.[66] This was a randomized, noninferiority, multicenter study undertaken to test the hypothesis that for patients with p16+ OPC, the treatment-related toxicity from the RTOG altered fractionation chemoradiation schedule (70 Gy in 35 fractions over 6 weeks with two doses of concurrent cisplatin) could be reduced by replacement of cisplatin with cetuximab, without compromising outcome. Overall survival was the primary end point. The RTOG accrued 849 patients with locoregionally advanced p16+ OPC to this trial between June 2011 and July 2014. Importantly, entry was not restricted to a good-prognosis subset, and 38% of the patients had a smoking history of greater than 10 pack-years. With a median follow-up time of 4.5 years, the estimated 5-year overall survival rates were 77.9% for the cetuximab group and 84.5% for the cisplatin group (P = .02). The cetuximab arm did not meet the predefined noninferiority criteria. Progression-free survival and locoregional control were also significantly better for patients treated with high-dose cisplatin, although several measures of acute, but not late, toxicity suggested that the cetuximab was better tolerated.

The smaller 334-patient randomized phase III De-ESCALaTE HPV (Determination of Epidermal Growth Factor Receptor Inhibitor [Cetuximab] Versus Standard Chemotherapy [Cisplatin] Early and Late Toxicity Events in Human Papillomavirus-Positive Oropharyngeal Squamous Cell Carcinoma) trial was similarly designed and came to similar conclusions.[67] A control arm of conventionally fractionated radiation (70 Gy in 35 fractions over 7 weeks) and three planned doses of concurrent cisplatin was compared with the same radiation with weekly concurrent cetuximab. Outcomes on the cetuximab arm were inferior to those on the concurrent chemoradiotherapy with cisplatin arm. Although the experienced adverse effects differed, the overall toxicity burden was equivalent between the two treatment arms. Unlike the RTOG 1016 trial, however, eligibility was restricted to patients with a smoking history of less than 10 pack-years. It is also noteworthy that the follow-up was considerably shorter than for the RTOG 1016 trial and that the study was not powered to show a survival difference. It was, instead, designed to assess differences in toxicity with the assumption that survival would be equivalent. The Trans-Tasman Radiation Oncology Group 12.01 trial (ClinicalTrials.gov identifier: NCT01855451), using a similar design, has completed accrual of 189 patients. Toxicity, not survival, is the primary end point of this study, and preliminary results are anticipated soon.

These findings demonstrate that the modification or elimination of systemic therapy in an effort to reduce overall chemoradiation toxicity will be problematic. The most widely adopted and well-studied of the alternative systemic treatments, concurrent cetuximab, was less effective than concurrent, high-dose cisplatin, the current treatment standard. Elaboration of other approaches seeking to modify systemic treatments will require careful consideration and appropriate patient selection.

Furthermore, testing deintensification in an unselected population of patients with p16+ OPC has proven shortsighted. This echoes the experience of the E1308 trial, which suggested that a reduction in radiation dose in complete responders after induction chemotherapy was of greatest benefit only in the best-prognosis patients. Deintensification strategies should initially be explored solely in favorable-risk patients. Inclusion of patients with a less than excellent prognosis in deintensification trials may compromise treatment outcomes and obscure potential benefit in more appropriate patients.

CONCLUSION

Advances in single-modality surgical and radiotherapeutic techniques have been highly successful in maintaining efficacy and limiting morbidity in patients with head and

neck cancer with limited disease (T0-2 primary lesions and either no nodes or a single node smaller than 3 cm in size). Treatment deintensification for good-prognosis patients with p16+ OPC with more advanced disease justifiably attracts interest in the therapeutic community. A number of promising approaches are currently under investigation, including concurrent chemotherapy with radiation dose reduction or field size limitation, with or without the use of a response to induction chemotherapy to better identify patients most appropriate for such modifications. Integration of TOS into treatment algorithms is also being studied and may allow for more appropriate and less intensive pathologically based adjuvant treatment. These strategies merit continued investigation. Careful patient selection is essential, however, and impeccable study design will be needed.

Despite the identification of a good-prognosis patient subset, the encouraging early results of treatment deintensification approaches, and the reassignment of many advanced p16+ cancers to stage I and II, current treatment guidelines for p16+ OPC have not changed.[2,3] The standard of care for the definitive nonoperative management of cisplatin-eligible patients with advanced disease is concurrent chemoradiation with high-dose cisplatin given every 3 weeks. For patients undergoing initial surgical resection, adjuvant chemoradiation with concurrent high-dose cisplatin given every 3 weeks is recommended for those with positive surgical margins and/or extranodal tumor extension. Adoption of other approaches must await the results of well-conducted randomized clinical trials.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[68-71] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities, which may be a particular problem in OPC, where multidisciplinary coordination can improve efficiency and completeness of care.[72] Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCCs)—is challenging. Patients with MCCs are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as p16+ OPC, is often from clinical trials with study selection criteria that exclude these patients to avoid potential interaction effects or confounding of results associated with MCCs. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

Because many patients for whom guideline recommendations apply present with MCCs, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCCs, which highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

ADDITIONAL RESOURCES

More information, including a Data Supplement, slide sets, and clinical tools and resources, is available at www.asco.org/head-neck-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Integration of Palliative Care Into Standard Oncology Care[73] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[74] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Human Papillomavirus Testing in Head and Neck Carcinomas[12] (http://ascopubs.org/doi/10.1200/JCO.18.00684)
- Use of Larynx-Preservation Strategies in the Treatment of Laryngeal Cancer Update[75] (http://ascopubs.org/doi/10.1200/JCO.2017.75.7385)
- Radiation Therapy for Oropharyngeal Squamous Cell Carcinoma[3] (http://ascopubs.org/doi/10.1200/JCO.2017.73.8633)
- Head and Neck Cancer Survivorship Care Guideline[76] (http://ascopubs.org/doi/10.1200/JCO.2016.71.8478)

AFFILIATIONS

[1]Cleveland Clinic, Cleveland, OH
[2]American Society of Clinical Oncology, Alexandria, VA
[3]Yale Cancer Center, New Haven, CT
[4]University of Michigan, Ann Arbor, MI
[5]University of California San Diego, La Jolla, CA
[6]Emory University Hospital, Atlanta, GA
[7]The University of Texas MD Anderson Cancer Center, Houston, TX
[8]Sutter Health, Roseville, CA
[9]Adenoid Cystic Carcinoma Research Foundation, Needham, MA
[10]Stanford University, Palo Alto, CA
[11]Gene Upshaw Memorial Tahoe Forest Cancer Center, Truckee, CA
[12]Princess Margaret Cancer Centre, Toronto, Ontario, Canada
[13]Fox Chase Cancer Center, Philadelphia, PA

CORRESPONDING AUTHOR

American Society of Clinical Oncology, 2318 Mill Rd, Ste 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

D.J.A. and J.A.R. were Expert Panel co-chairs.

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Editor's note: This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/head-neck-cancer-guidelines.

Reprint Requests: 2318 Mill Rd, Ste 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHOR CONTRIBUTIONS

Conception and design: David J. Adelstein, Jamie A. Ku, Marnie Kaufman, John A. Ridge
Administrative support: Quynh-Thu Le
Provision of study material or patients: Lillian L. Siu
Collection and assembly of data: David J. Adelstein, Nofisat Ismaila, Jamie A. Ku, Paul L. Swiecicki, Christopher U. Jones, John A. Ridge
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Role of Treatment Deintensification in the Management of p16+ Oropharyngeal Cancer: ASCO Provisional Clinical Opinion

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Barbara Burtness
Consulting or Advisory Role: Merck, MedImmune, Boehringer Ingelheim, Amgen, Debiopharm Group, VentiRx, AstraZeneca, Bristol-Myers Squibb, Alligator Biosciences, Genentech, Aduro Biotech

Paul L. Swiecicki
Research Funding: Pfizer, Ascentage Pharma Group

Loren Mell
Honoraria: Varian Medical Systems, Nanobiotix
Consulting or Advisory Role: Bristol-Myers Squibb
Research Funding: Merck, AstraZeneca
Travel, Accommodations, Expenses: Bristol-Myers Squibb

Neil Gross
Honoraria: Intuitive Surgical
Consulting or Advisory Role: PDS Biotechnology, Verb Surgical (Inst)
Research Funding: Regeneron, MedImmune (Inst), Genentech (Inst)

Quynh-Thu Le
Stock and Other Ownership Interests: Aldea
Consulting or Advisory Role: GRAIL
Travel, Accommodations, Expenses: Genentech

Thomas J. Semrad
Consulting or Advisory Role: Genentech, Celgene

Lillian L. Siu
Leadership: Agios (I)
Stock and Other Ownership Interests: Agios (I)
Consulting or Advisory Role: Merck, AstraZeneca/MedImmune, MorphoSys, Symphony Evolution, Roche, Loxo
Research Funding: Bristol-Myers Squibb (Inst), Genentech (Inst), GlaxoSmithKline (Inst), Merck (Inst), Novartis (Inst), Pfizer (Inst), MedImmune (Inst), AstraZeneca (Inst), Boehringer Ingelheim (Inst), Bayer (Inst), Amgen (Inst), Symphony Evolution (Inst), Astellas Pharma (Inst)

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Treatment Deintensification in p16+ Oropharyngeal Cancer Expert Panel Membership

Name	Affiliation or Institution	Role or Area of Expertise
David J. Adelstein, MD (co-chair)	Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH	Medical oncology
John A. Ridge, MD (co-chair)	Fox Chase Cancer Center, Philadelphia, PA	Surgical oncology
Lillian L. Siu, MD	Princess Margaret Cancer Centre, Toronto, CA	Medical oncology
Paul L. Swiecicki, MD	Rogel Cancer Center, University of Michigan, Ann Arbor, MI	Medical oncology
Barbara Burtness, MD	Yale Cancer Center, New Haven, CT	Medical oncology
Quynh-Thu Le, MD	Stanford University, Palo Alto, CA	Radiation oncology
Jonathan J. Beitler, MD	Emory University Hospital, Atlanta, GA	Radiation oncology
Loren Mell, MD	University of California San Diego, La Jolla, CA	Radiation oncology
Christopher U. Jones, MD	Sutter Health, Roseville, CA	Radiation oncology
Jamie A. Ku, MD	Head and Neck Institute, Cleveland Clinic, Cleveland, OH	Surgical oncology
Neil Gross, MD	The University of Texas MD Anderson Cancer Center, Houston, TX	Surgical oncology
Marnie Kaufman	Adenoid Cystic Carcinoma Research Foundation, Needham, MA	Patient representative
Thomas J. Semrad, MD	Gene Upshaw Memorial Tahoe Forest Cancer Center, Truckee, CA	PGIN representative
Nofisat Ismaila, MD	ASCO, Alexandria, VA	Practice guideline staff (health research methods)

Abbreviation: PGIN, Practice Guideline Implementation Network.