Radiation Therapy for Oropharyngeal Squamous Cell Carcinoma: An ASTRO Evidence Based Clinical Practice Guideline

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Conflict of Interest Disclosure Statement

The guideline panelists were required to complete disclosure statements before initiating work on this project. These statements are maintained at the American Society for Radiation Oncology (ASTRO) Headquarters in Arlington, VA, and pertinent disclosures are published within this report. The ASTRO Conflict of Interest Disclosure Statement seeks to provide a broad disclosure of outside interests. The guideline panel chairs (AE and DJS), in concert with the ASTRO COI review committee, ASTRO legal counsel, and ASTRO guidelines subcommittee chair and vice-chair, reviewed these disclosures and approved the participation of all task force members for all key questions.

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The Oropharyngeal Squamous Cell Carcinoma Guideline (OPSCC) panel, created by the Guidelines Subcommittee of the Clinical Affairs and Quality Committee (CAQC) of ASTRO, prepared this document. ASTRO guidelines present scientific, health, and safety information and may to some extent reflect scientific or medical opinion. They are made available to ASTRO members and to the public for educational and informational purposes only. Commercial use of any content in this guideline without the prior written consent of ASTRO is strictly prohibited.

Adherence to this guideline will not ensure successful treatment in every situation. Furthermore, this guideline should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The physician must make the ultimate judgment regarding the propriety of any specific therapy in light of all the circumstances presented by the individual patient. ASTRO assumes no liability for the information, conclusions, and findings contained in its guidelines. In addition, this guideline cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved treatments are needed or are being explored.

The guideline panel recommends that providers discuss with patients’ shortly after diagnosis what to expect regarding symptoms, treatment-related toxicities, outcomes including risk of recurrence, and effects of the disease and the treatments on quality of life.

This guideline was prepared on the basis of information available at the time the panel was conducting its research and discussions on this topic. There may be new developments that are not reflected in this guideline and that may, over time, be a basis for ASTRO to consider revisiting and updating the guideline.

Introduction
The oropharynx is an anatomic site within the head and neck that includes the tonsils, base of tongue, soft palate, and the upper lateral and posterior pharyngeal walls. It is lined by squamous epithelium, and thus squamous cell carcinoma composes the vast majority of malignancies that arise from the oropharynx. The epidemiology and prognosis of OPSCC has changed dramatically over the past 30 years, such that its treatment and expected outcomes are vastly improved from a generation ago.

Indeed, HPV associated cancers of the oropharynx are now widely recognized as a distinct clinical disease with regard to risk factor profiles, clinical and molecular characteristics, treatment response and prognosis. Human papillomavirus associated cancers arise from the lingual and palatine tonsils within the oropharynx, are poorly differentiated and present with early T stage and advanced N stage. When compared to patients with HPV-negative disease, patients with HPV-positive tumors are more frequently male, young, and possess a favorable performance status. The incidence of HPV-positive OPSCC has increased by over 200% between 1988 and 2004, whereas the incidence of HPV-negative OPSCC declined by half over that same era. Individuals with HPV-driven oropharynx cancers have an estimated 50% reduction in risk of death when compared to patients with HPV-negative tumors. The recognition of this powerful prognostic and predictive influence of HPV has generated a wide array of treatment paradigms for OPSCC, and the panel firmly believes that patients should be actively encouraged to enroll on prospective clinical trials to answer pressing questions in the management of this disease. Moreover, the diverse spectrum of treatment options highlights the importance of evidence-based medicine to guide standard clinical practice.

The options for curative management of OPSCC include surgery with or without adjuvant RT (with concurrent chemotherapy in selected cases), and primary RT with or without concurrent systemic therapy. The role of primary surgery is in evolution with increasing use of transoral approaches, particularly in the T1 and T2 setting with minimal soft palate or base of tongue involvement, permitting tumor resection with the possibility of clear margins, minimal surgical morbidity, and the avoidance or deintensification of adjuvant treatment. Studies such as Eastern Cooperative Oncology Group (ECOG) 3311 are underway investigating the combination of transoral approaches with reduced dose postoperative radiation in selected cases as an overall treatment de-intensification strategy. The most frequently employed strategy for the curative management of OPSCC remains primary RT (with or without concurrent systemic therapy), which is the intended focus of these guidelines. These guidelines also address the use of adjuvant RT and chemoradiation (CRT) for those patients selected for primary surgical
management. Specific recommendations as to the selection of the primary treatment modality (surgical vs non-surgical approaches) are beyond the scope of these guidelines.

The purpose of this clinical practice guideline is to systematically review the evidence for effective treatment of OPSCC with definitive or adjuvant RT. The panel acknowledges the interest in and established literature on the value of brachytherapy in OPSCC, but the purview of this guideline was restricted to the use of external beam radiation therapy. Recommendation statements are independent of HPV and smoking status. Although it is clear that these factors strongly influence the prognosis of patients with oropharyngeal cancer,\textsuperscript{6} such outcomes have been achieved with standard therapies; in the absence of convincing high-level, high-quality data confirming similarly favorable outcomes with de-intensified therapy, the panel makes treatment recommendations agnostic of cancer etiology. The panel used a formalized literature review process, complemented by expert opinion where appropriate, to make recommendations on the use of concurrent systemic therapy in the primary and post-operative settings, adjuvant RT following curative surgery, neoadjuvant chemotherapy prior to RT, and dose, fractionation and neck volume decisions faced in the management of this disease. It is well recognized that the treatment of OPSCC leads to acute, chronic, and potentially lifelong complications that significantly impair patient quality-of-life. As the disease burden continues to shift to a younger population with an improved prognosis, the balance of toxicity with efficacy takes on an even greater priority. The development of evidence-based recommendations on the prevention and management of these side effects was not within the charge of this panel. However, the panel carefully considered the therapeutic ratio in the generation of these guidelines, requiring the demonstration of efficacy to recommend a therapy associated with increased morbidity.

This guideline is endorsed by the American Society of Clinical Oncology and the European Society for Radiotherapy & Oncology.

**Methods and Materials**

**Process**

In accordance with established ASTRO policy, the Guidelines Subcommittee recruited a guideline panel of recognized experts in oropharyngeal cancer, including radiation oncologists, medical oncologists, otolaryngologists, and a patient advocate. Panel members were drawn from academic settings, private practice, and residency. Four specific key questions (KQs) were proposed, which addressed: (KQ1) the addition of concurrent systemic therapy to
RT, (KQ2) the delivery of PORT with and without systemic therapy following primary surgery, (KQ3) the use of IC, and (KQ4) the optimal dose-fractionation regimens with and without systemic therapy, as well as nodal volumes for primary tonsillar cancer. In September 2014, the ASTRO Board of Directors approved the proposal and panel membership.

Through a series of communications by conference calls and emails between December 2014 and February 2016, the guideline panel, with ASTRO staff support, completed the systematic review, created literature tables, and formulated the recommendation statements and narratives for the guideline. The members of the task force were divided into four writing groups by KQs, according to their areas of expertise. The initial draft of the manuscript was reviewed by three expert reviewers (see Acknowledgements) and ASTRO legal counsel. A revised draft was placed on the ASTRO Web site in April 2016 for a six-week period of public comment. Following integration of the feedback, the document was submitted for approval to the ASTRO Board of Directors in September 2016. The ASTRO Guidelines Subcommittee intends to monitor this guideline and initiate an update when appropriate, according to existing ASTRO policies.

**Literature Review**

A systematic review of the literature was performed in early 2015 to form the basis of the guideline. An analytic framework incorporating the population, interventions, comparators, and outcomes (PICO) was first used to develop and refine search strategies for each KQ. The searches were conducted in MEDLINE PubMed and designed to identify studies published in English between January 1990 and December 2014 that evaluated adults with OPSCC who were treated with primary RT, adjuvant RT, or RT with concurrent systemic therapy. Both MeSH terms and text words were utilized and terms common to all searches included: *oropharyngeal neoplasms*, *carcinoma squamous cell*, and *radiotherapy*. Additional terms specific to each KQ were also incorporated. The outcomes of interest were overall and progression-free survival, recurrence rates, toxicity, and quality of life. The electronic searches were supplemented by hand searches.

A total of 2615 abstracts were retrieved. The articles were then reviewed by ASTRO staff, the co-chairs of the guideline, and the writing groups for each KQ. During the first round of screening, 2452 articles were eliminated based on the inclusion and exclusion criteria. The inclusion criteria were: patients ≥18 years or older, all stages of oropharyngeal cancer, and publication date 1990 to 2014. Included treatments were: primary RT, primary
chemoradiation, primary surgery with adjuvant RT with or without systemic therapy, or IC followed by radiation therapy or CRT. The exclusion criteria were: pre-clinical or non-human studies, case reports/series, non-English language, available in abstract only, pediatric patients, distant metastasis, non-squamous cell carcinoma, and otherwise not clinically relevant to the key clinical questions. The panelists on KQ 1, 3 and 4 generally only considered articles in which the percentage of OPSCC patients was greater than 50%; the panelists on KQ2 did not have an absolute threshold because OPSCC patients typically comprise a minority of individuals in post-operative studies. Ultimately, 119 full-text articles were chosen for inclusion and abstracted into detailed literature tables to provide supporting evidence for the clinical guideline recommendations.

Because expression of the p16 protein is typically used as a surrogate for HPV infection, the two words – p16-positive and HPV-positive – are sometimes used interchangeably (and incorrectly). However, throughout this guideline, the mention of p16 will be reserved for clinical studies in which its status was assessed and reported. In addition, all Tumor-Node-Metastasis stages are derived from the American Joint Commission on Cancer version 7 staging system, since the data driving these recommendations are based on the older, HPV-agnostic staging system.

Grading of Evidence and Recommendations and Consensus Methodology

Guideline recommendation statements were generated from this literature review, with high-quality evidence forming the basis of the statements whenever possible, in accordance with Institute of Medicine (IOM) standards; expert opinion supplemented the evidence base if high-level data were not available. The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methodology was followed in the construction and assessment of the recommendation statements. GRADE is an explicit, systematic approach to defining the recommendation strength and quality of evidence.

Recommendation strengths were dichotomized as “strong” or “conditional.” Strong recommendations were made when the panel was very confident that the benefits of the intervention clearly outweighed the harms; conditional recommendations were made when the ratio between risks and benefits was more balanced. Per the GRADE formalism, a “strong” recommendation implies that the panelists believe “all or almost all informed people would make the recommended choice for or against an intervention.” A “conditional” recommendation implies that “most informed people would choose the recommended course of action, but a substantial number would not.”
to devote more time to the process of shared decision making by which they ensure that the informed choice reflects individual values and preferences." The importance of patient preferences and shared decision-making was highlighted in each conditional recommendation statement.

The GRADE methodology defines “quality of evidence” as a rating that indicates “the extent of our confidence that the estimates of an effect are adequate to support a particular decision or recommendation.” The quality of evidence underlying each recommendation statement was categorized as either high, moderate, low. Although GRADE does provide for a “very low” quality, the panel did not consider this rating for consistency with prior ASTRO guidelines. Descriptions of each quality level are below:

- High: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

The degree of consensus among the panelists on each recommendation statement was evaluated through a modified Delphi approach. A survey was sent by ASTRO staff to the panel members, who rated their agreement with each recommendation on a five-point Likert scale, ranging from strongly disagree to strongly agree (higher score corresponds with stronger agreement). A pre-specified threshold of ≥ 75% of raters was determined to indicate when consensus was achieved. If a recommendation statement did not meet this threshold, it was modified and resurveyed, or excluded from the guideline. The final set of recommendation statements were achieved after 2 surveys. The guideline statements, along with the corresponding ratings of recommendation strength, quality of evidence, and level of consensus, are listed in Table 1.

Results

Key Question 1: When is it appropriate to add systemic therapy to definitive radiotherapy in the treatment of oropharyngeal squamous cell carcinoma (OPSCC)?

In the scenario of stage IVA-B disease?

Statement KQ1A: Concurrent high-dose intermittent cisplatin should be delivered to patients with stage IVA-B oropharyngeal squamous cell carcinoma receiving definitive radiotherapy.

- Recommendation strength: Strong
• Quality of evidence: High

Statement KQ1B: Concurrent cetuximab or carboplatin-fluorouracil should be delivered to patients with stage IVA-B oropharyngeal squamous cell carcinoma receiving definitive radiotherapy who are not medically fit for high-dose cisplatin.
  • Recommendation strength: Strong
  • Quality of evidence: High

Statement KQ1C: Concurrent weekly cisplatin may be delivered to patients with stage IVA-B oropharyngeal squamous cell carcinoma receiving definitive radiotherapy who are not medically fit for high-dose cisplatin, after a careful discussion of patient preferences and the limited prospective data supporting this regimen.
  • Recommendation strength: Conditional
  • Quality of evidence: Low

Statement KQ1D: Concurrent cetuximab should not be delivered in combination with chemotherapy to patients with stage IVA-B oropharyngeal squamous cell carcinoma receiving definitive radiotherapy.
  • Recommendation strength: Strong
  • Quality of evidence: High

Statement KQ1D: Intra-arterial chemotherapy should not be delivered to patients with stage IVA-B oropharyngeal squamous cell carcinoma receiving definitive radiotherapy.
  • Recommendation strength: Strong
  • Quality of evidence: High

Narrative

The role of concurrent cytotoxic chemotherapy combined with radiotherapy

Several phase III trials have randomized patients with locally advanced, non-metastatic head and neck squamous cell carcinoma to treatment with conventionally or altered fractionated (AltFX) RT alone versus treatment with concurrent CRT (Table 2). All of the studies in this systematic review were predominantly composed of patients with oropharynx cancer, and the clear majority of patients presented with stage IV disease. In the six studies that directly compared standard fractionation (SFX) RT to combined concurrent CRT, dose and fractionation schemes were relatively uniform, with total delivered doses approaching 66-70.2 Gy in 1.8-2 Gy fractions.12-16 The chemotherapy regimens were variable, including bolus cisplatin12, weekly cisplatin,16 carboplatin-fluorouracil,17,18 daily carboplatin,14 and bleomycin-mitomycin.14

The five trials comparing AltFX (3 accelerated fractionation [AccFX], 2 hyperfractionation) with and without concurrent chemotherapy also employed a variety of systemic therapy regimens, including carboplatin-fluorouracil,19 daily cisplatin,20 cisplatin-fluorouracil,21 high-intensity cisplatin-fluorouracil (bolus cisplatin every 2 weeks),22 and fluorouracil-mitomycin.23,24 However, as opposed to the conventionally fractionated trials, in which
the RT was standardized between the two arms, two of these studies\textsuperscript{22,23} used different RT schemes for the RT-alone arm. The ARO 95-06 trial\textsuperscript{12} treated patients to a total dose of 77.6 Gy without chemotherapy and 70.6 Gy with chemotherapy, and the Groupe d’Oncologie Radiothérapie Tête et Cou (GORTEC) trial\textsuperscript{25} delivered 64 Gy in 5 weeks with chemotherapy and the same dose in 3 weeks without chemotherapy.

\textit{Impact on overall survival}

In all but two of the 7 studies of conventionally fractionated radiation therapy, CRT significantly improved overall survival\textsuperscript{12-18}. Most of these studies reported the statistically significant improvement in overall survival (OS) at 3 years, with the absolute benefit of CRT ranging between 14\% and 24\%.\textsuperscript{13,14,26} The few studies with longer follow-up showed a persistent but smaller survival advantage to concurrent chemotherapy. For example, the 5-year OS difference in GORTEC 94-01\textsuperscript{27} was 6\% (22\% vs. 16\%, \textit{p}=0.05), whereas in the AIRO study\textsuperscript{14} using daily carboplatin, the 5-year survival difference was less than 3\%. In contrast, neither the Mumbai trial\textsuperscript{16} (weekly cisplatin) nor the ORO 93-01\textsuperscript{28} (carboplatin-fluorouracil) showed an OS advantage with concurrent chemotherapy, although disease-free survival was significantly improved with chemotherapy in both studies; it is notable that both of these trials included a third arm of AltFX alone, and so the total numbers of patients in each arm were less than 70, likely under powering the studies for an OS endpoint.

Among the five studies of CRT with AltFX, three of them showed an absolute OS advantage with the addition of concurrent chemotherapy, ranging from 5\%\textsuperscript{22} (5-year ARO 95-06, fluorouracil and mitomycin) to 9.8\%\textsuperscript{29} (5-year, Semrau et al, carboplatin and fluorouracil) to 24\%\textsuperscript{21} (3-year, Wendt et al, cisplatin and fluorouracil). Among the other two trials, concurrent daily cisplatin improved cancer-specific survival in Swiss Group for Clinical Cancer Research trial (SAKK 10/94)\textsuperscript{20} by an absolute 12\% at 10 years, and concurrent carboplatin-fluorouracil with VeryAccFX in Bourhis et al.\textsuperscript{25} reduced the risk of any cancer progression by nearly 25\%, but toxic deaths precluded a survival benefit.

The data from the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC Meta-analysis)\textsuperscript{30} corroborated the conclusions drawn from these individual phase III randomized trials. In the most recent update from this group, Blanchard et al.\textsuperscript{30} analyzed over 5800 patients with oropharynx cancer and showed that the concomitant addition of chemotherapy to RT resulted in an 8.1\% absolute benefit in OS at 5 years\textsuperscript{31}, translating into a relative 22\% reduction in overall mortality. By contrast, adjuvant or neoadjuvant chemotherapy administration
was not associated with a survival benefit. There was no significant heterogeneity in chemotherapy treatment effect by fractionation regimen, although only the use of platinum-fluorouracil (HR 0.83, 95% CI 0.75-0.91) or platinum monotherapy (HR 0.70, 95% CI 0.59-0.84) was significantly associated with survival. Additional univariable analyses suggested that the survival benefit with concurrent chemotherapy was largely restricted to younger patients (HR for 61 years or older, 0.97, 95% CI 0.87-1.08) and patients with stage IV disease (HR for stage III disease, 1.01, 95% CI 0.88-1.14). However, multivariable analysis showed that only favorable performance status and type of chemotherapy (i.e. platinum-based chemotherapy with or without 5-FU) were significantly associated with overall survival.

**Impact on locoregional control**

The three trials of conventionally fractionated RT that reported locoregional control (LRC) outcomes showed a statistically significant improvement in patients receiving concurrent chemotherapy. Calais et al. and Ruo Redda et al.\(^{13,14}\) demonstrated an absolute 3-year LRC benefit with concurrent chemotherapy of 24% and 6.7%, respectively, although notably, the LRC difference in Ruo Redda et al.\(^{14}\) was only statistically significant among stage IV patients. Ghosh-Laskar\(^{16}\) found that weekly cisplatin improved LRC by an absolute 17% at 5 years. The four studies of concurrent chemotherapy with AltFX that presented distinct LRC probabilities consistently found that concomitant treatment significantly reduced locoregional failure, with the absolute benefits of 8% (10-year, SAKK 10/94),\(^{20,29}\) 12% (5-year, Semrau et al.),\(^{29}\) 19% (3-year, Wendt et al.),\(^ {21}\) and 13% (3-year, Budach et al.).\(^ {24,29}\)

In the recent MACH-NC meta-analysis\(^ {32}\) that did not distinguish by tumor site, Pignon and colleagues showed that concurrent CRT significantly improved LRC, with an absolute improvement of 9.3% and 13.5% among all studies and those with platinum-fluorouracil, respectively. These absolute improvements translated into hazard reductions of 0.74 and 0.66 for all studies and those with platinum-fluorouracil, respectively (p<0.0001).

**Impact on distant metastases**

One of the challenges in interpreting the impact of chemotherapy on distant metastasis is the inability of trials to distinguish between metastasis arising from a first locoregional failure versus metastasis as the first site of failure. That said, none of the randomized studies of concurrent chemotherapy in conventionally fractionated RT found an improvement in distant control with systemic therapy, and of the five trials of AltFX, only the SAKK
trial\textsuperscript{20} of daily cisplatin showed an improvement in distant metastasis-free survival. In this study, concurrent chemotherapy improved 10-year distant metastasis free survival by 15\% at 10 years, but only 9 total patients in the entire study developed an isolated metastasis without prior locoregional failure; thus, one may assume that this presumptive improvement in distant control was a function of reduced locoregional recurrence.

In contrast, the MACH-NC meta-analysis\textsuperscript{32}, which benefitted from the increased power of thousands of patients, showed a small but statistically significant improvement in distant control with concurrent treatment; the absolute improvement was 2.5\% for all patients, with a relative improvement of 0.88 (95\% CI 0.77-1.0, p=0.04). As stated above, this reduction in distant metastasis with concurrent systemic treatment may reflect less propagation from fewer locoregional recurrences.

\textit{Complications}

While most of these phase III randomized studies show that adding chemotherapy to RT improves survival, the combination clearly increased the risk of severe, acute toxicities. For example, Adelstein et al.\textsuperscript{26} reported that patients receiving SFX RT with or without concurrent cisplatin had an overall grade 3 to 5 incidence of 85\% and 51\%, respectively, of which leukopenia, anemia, and renal toxicities were the most significant. In this Intergroup trial,\textsuperscript{12} approximately 15\% of patients treated with bolus cisplatin did not complete treatment, and delivering three cycles of bolus cisplatin has been consistently challenging. For example, in Radiation Therapy Oncology group (RTOG) 0129,\textsuperscript{33} which compared AccFX versus conventional RT with concurrent bolus cisplatin in both arms, only 69\% of patients in the conventional fractionation arm received all 3 cycles, and approximately 24\% of patients received only two courses of bolus cisplatin.

In a review of the original GORTEC studies, Bourhis et al. showed that 71\% of patients receiving radiation with carboplatin and 5-FU developed acute grade 3 or 4 mucositis, compared to only 39\% of those receiving RT alone.\textsuperscript{34} Even weekly cisplatin in the Mumbai trial increased the risk of grade 3 or 4 mucositis (35\% vs. 21\%, p value not reported),\textsuperscript{16} and daily carboplatin also increased the risk of grade 2 toxicities (type not recorded).\textsuperscript{14} The combination of mitomycin-C and bleomycin increased the risk of grade 3 or 4 mucositis by almost one-third.

The studies of concurrent chemotherapy with AltFX also found increases in acute toxicity. The Staar et al. study showed statistically significant worse acute toxicities in the arm receiving carboplatin and 5-FU—grade 3 and 4 mucositis was 68\% versus 52\% and grade 3 and 4 vomiting was 8.2\% versus 1.6\%.\textsuperscript{19} Similarly, the use of
concurrent cisplatin-fluorouracil with split-course HFX more than doubled the risk of acute grade 3-4 mucositis (38% vs. 16%). In the GORTEC AccFX trial, the VeryAccFX-alone arm led to more acute mucosal toxicity, but a high early death rate from non-cancer cause (almost 20% at 1 year) revealed the potentially life-threatening complications of intensive chemotherapy with extreme acceleration. On the other hand, the higher radiation dose in ARO 95-06 actually showed more mucosal and skin toxicity in the RT alone cohort, and the SAKK study using daily cisplatin found fewer than 10% of chemotherapy patients developed a grade 3-4 hematologic toxicity, with no difference in acute RT effects.

Despite these acute toxicities, these trials consistently showed no significant increase in high-grade late morbidity with concurrent therapy. A careful toxicity analysis of patients treated on GORTEC 94-01 showed that only grade 3-4 dental toxicity was significantly worse with chemotherapy (44% vs. 12%). The ORO 93-01 study showed numerically more tissue, skin, and mucosal side effects with chemotherapy, but these were not statistically tested and reported to be typically transient. Neither daily carboplatin, weekly cisplatin nor mitomycin-bleomycin increased the risk of late toxicity. Moreover, none of the five trials involving AltFX with chemotherapy showed a significant increase in serious late toxicities.

Comparisons between chemotherapy regimens

While the studies mentioned above consistently showed LRC and typically OS benefits from concurrent chemotherapy, it is important to note that the choice of systemic agents varied considerably among each trial—bolus cisplatin, carboplatin/5-fluorouracil, cisplatin/5-fluorouracil, low-dose carboplatin alone, and bleomycin/mitomycin C, were each selected and administered at varying schedules and frequencies. Unfortunately, there are far fewer studies comparing different chemotherapy regimens and schedules to each other.

RTOG 9703 randomized over 241 patients to conventionally fractionated RT plus either concurrent cisplatin-fluorouracil in the last 2 weeks of radiation therapy, daily hydroxyurea-fluorouracil, or weekly cisplatin-paclitaxel; patients receiving daily chemotherapy were treated every other week. Interestingly, all of the arms compared favorably to historical controls, although the arms were not directly compared to each other. However, none of these alternative regimens have been prospectively tested against more standard agents such as bolus cisplatin.
The RTOG did not publish an additional randomized trial on competing chemotherapy agents in head and neck cancer until RTOG 0522,\(^\text{36}\) which compared bolus cisplatin with bolus cisplatin plus cetuximab, concurrent with AccFX.\(^\text{36}\) Nearly 900 patients were enrolled in this trial, which confirmed that the addition of cetuximab did not improve outcomes. LRC, disease-free survival, and OS were not significantly different between the two arms, and acute grade 3 and 4 toxicities were uniformly higher in the cetuximab arm, with a low but statistically significant increase in toxic death. Thus, cetuximab should not be combined with cytotoxic chemotherapy unless on a clinical trial.

Erlotinib is an oral biologic agent that targets EGFR by tyrosine kinase inhibition. It has been used successfully in treating certain types of non-small cell lung cancer and, like cetuximab, has demonstrated synergism when combined with chemotherapy or radiation in the pre-clinical setting. Martins et al.\(^\text{37}\) performed a phase II randomized trial of cisplatin and RT with or without concurrent erlotinib for stage III and IV locally advanced head and neck cancers, most of which were oropharynx cancer. In results that echoed RTOG 0522,\(^\text{36}\) no improvement was seen in complete response rates, LRC, progression-free survival, or OS at a median follow up of 26 months, showing that an alternative method of EGFR inhibition is also ineffective in combination with concurrent cisplatin.

The RTOG also obliquely asked a chemotherapy question in RTOG 0129\(^\text{6,33}\), whose primary hypothesis involved AccFX. This study randomized 743 patients to either 3 cycles of bolus cisplatin with conventionally fractionated RT or 2 cycles of bolus cisplatin with AccFX.\(^\text{6,33}\) The trial showed no difference in any endpoint between the arms, including distant metastasis, again confirming that the primary role of chemotherapy is radiosensitization. In a subset analysis, the authors showed that patients receiving only 1 cycle of cisplatin experienced markedly inferior survival. However, among patients treated with conventionally fractionated RT, there was no statistically significant survival decrement among the 24% of individuals who only received 2 cycles (HR 1.15, 95% CI 0.81-1.62). Although this finding casts some doubt on the benefit of the third cycle in the context of SFX, it is notable that (a) the upper end of the confidence interval was 1.62, (b) the survival curve for patients receiving 2 cycles appears to separate from the curve for the cohort receiving 3 cycles, and (c) this analysis was only based on 86 patients.

Finally, there is only one phase III trial comparing different modes of cisplatin administration. Historically, there has been interest in delivering cisplatin intra-arterially, to maximize the cisplatin dose to the tumor while infusing sodium thiosulphate systemically to minimize cisplatin toxicity.\(^\text{38}\) The RTOG performed a multi-
institutional phase II trial\textsuperscript{39} based on this approach that produced results sufficiently promising for further study, and in fact, a randomized controlled trial of this technique has been published. In this Dutch study by Rasch et al., 239 patients with stage IV head and neck SCC received once-daily RT to 70 Gy and were randomized to intravenous (three cycles of bolus infusion) versus intra-arterial (4 courses) cisplatin.\textsuperscript{40} At 3 years, there was no difference in OS (51\% vs. 47\%), distant metastasis-free survival (69\% vs. 66\%), and LRC (65\% vs 63\%). High-grade (i.e. > grade 2) renal toxicity was more common in patients receiving intravenous cisplatin (9\% vs. 1\%), although only one patient experienced permanent nephrotoxicity, and this patient was not dialysis-dependent. On the other hand, neurological toxicity (> grade 2) was significantly more common in the intra-arterial cohort (8 patients vs. 1) Given the technical and logistical challenges of administration and the absence of any oncologic benefit but an increase in neurological toxicity, intra-arterial chemotherapy should not be administered unless on a clinical protocol.

\textit{Summary of cytotoxic chemotherapy}

The data are consistent that concurrent chemotherapy in combination with radiation therapy improves LRC for patients with locally advanced oropharyngeal squamous cell carcinoma, treated with either conventional or AltFX. In most of these studies, the reduction in locoregional progression translated into a significant and meaningful OS benefit. Although chemotherapy significantly increased acute toxicities, late effects were comparable to treatment with RT alone, such that the survival benefits of concurrent therapy clearly outweigh the non-trivial but short-term risks. Since the vast majority of the patients in these trials presented with stage IV disease, concurrent systemic therapy should be delivered in this population of patients.

\textit{The role of cetuximab combined with radiotherapy}

Cetuximab is an IgG1 monoclonal antibody against epidermal EGFR, which is a growth factor receptor overexpressed in head and neck cancer and associated with poor prognosis. Pre-clinical data suggested synergy between cetuximab and RT, and a preliminary phase I trial produced encouraging tolerability and response rates. These promising outcomes generated a phase III randomized trial comparing RT alone (using standard or AltFX) with RT plus cetuximab. The results of this trial were first published in 2006 with a median follow-up of 54 months, revealing a clinically and statistically significant improvement in OS with the addition of the antibody (hazard ratio 0.74, 95\% CI 0.57-0.97), with an absolute 3 year survival difference of 10\% (p=0.05).\textsuperscript{41} Similar to cytotoxic
chemotherapy, the benefit from combined modality therapy was in LRC, with a relative 32% reduction in locoregional failure and absolute difference of 13% at 3 years (p=0.01). There was no difference in distant metastases. There was no significant difference in any acute adverse event except acneiform rash and infusion-related events, which were substantially more common with cetuximab (17% vs. 1% for grade 3 or greater rash, p<0.001; 3% vs 0% for grade 3 or greater infusion reaction, p=0.01). The risk of mucositis (any grade) was the same between the arms.

The results were updated in 2010 with a median follow-up of 60 months and additional survival data on 40% of the surviving patients. The OS advantage was maintained (HR 0.73, 95% CI 0.56-0.95) was an absolute 5-year survival difference of 9%. Patterns-of-failure information was not reported. Patients who developed a prominent rash experienced markedly superior survival in comparison to those who did not (HR 0.49, median survivals 68.8 months vs. 25.6 months, p=0.002). A series of subset analyses suggested that the following cohorts experienced significant benefit from cetuximab: oropharynx site, American Joint Committee on Cancer (AJCC) T1-T3, USA site, AltFX treatment, node-positivity, superior performance status, male gender, and younger age (< 65 years). Of the 110 patients 65 years or older, there was a non-significant trend favoring radiation therapy alone. It is critical to note, though, that even though patients were stratified by Karnofsky Performance Status (KPS) (90-100 vs lower), nodal status (N0 versus N+), tumor stage (T1-3 vs. T4), and radiation fractionation regimen, the numbers in the subgroups were quite small, and so these results should be considered hypothesis-generating.

A phase II randomized prospective trial sought to improve upon the results of Bonner et al. by comparing concurrent cetuximab-RT with the same regimen plus 12 weeks of adjuvant cetuximab. The authors of this study hypothesized that continued EGFR blockade by maintenance cetuximab would serve to eradicate any residual disease after concurrent treatment. Although there was a trend for improved response rates at 12 weeks, with adjuvant cetuximab, there was no significant improvement in LRC or OS between the two arms. Therefore, cetuximab should be delivered per the Bonner protocol when it is used in combination with RT.

Summary of systemic therapy for stage IVA-B disease

There are no randomized trials that have defined an optimal chemotherapy regimen, but individual studies have most commonly incorporated cisplatin and/or fluorouracil. Although high-dose intermittent (i.e. bolus) cisplatin can be challenging to deliver, it has the longest track record in large multi-institutional trials in the United
States, with a well-known and largely predictable side effect profile. Carboplatin-fluorouracil has also been shown to improve OS in comparison to RT alone and is thus a viable alternative to bolus cisplatin. However, there is far less practitioner experience with delivering this regimen concurrently with head and neck RT, which is significantly more resource-intensive than cisplatin monotherapy. In addition, there are few reported toxicity data on carboplatin-fluorouracil in the IMRT era, and whether the low-dose bath seen with IMRT would be particularly accentuated by a well-known mucositis agent (fluorouracil) is unknown. Thus, for patients expected to tolerate HDIC administration, the panel strongly recommends its use for patients with stage IVA-B OPSCC.

A non-trivial percentage of patients with OPSCC may not tolerate bolus cisplatin administration for a variety of reasons, including hearing loss or compromised renal function. In this circumstance, the panel strongly recommends the use of concurrent carboplatin-fluorouracil or cetuximab with definitive RT. As detailed above, the former regimen has a consistent history of improving OS in combination with RT, and concurrent cetuximab was shown in a phase III trial to improve OS in comparison to RT alone. There are several retrospective studies comparing outcomes with cetuximab-RT with CRT, but these publications are conflicting and too laden with confounding and selection bias for consideration in this guideline.

Therefore, the panel did not prioritize one drug over another for patients who do not receive high-dose cisplatin. The results from RTOG 1016 should provide important guidance in selecting the optimal concurrent systemic therapy for patients with p16-positive oropharyngeal cancer.

Although weekly cisplatin may be an acceptable alternative to high-dose administration, the evidence suggesting a survival benefit with its use is significantly weaker and based on extrapolation rather than high-level evidence. The Ghosh-Laskar randomized trial using weekly cisplatin at a dose of 30 mg/m² showed a LRC but no overall survival benefit to CRT, although the trial was underpowered to see a survival gain. The ECOG 2382 study randomized patients between RT alone with RT plus weekly cisplatin at a dose of 20 mg/m². Although OPSCC only comprised 28% of the population and the dose is now understood to be too low for adequate radiosensitization, it is notable that weekly cisplatin did not improve failure-free survival or overall survival. The prime rationale for weekly delivery is improved tolerability without compromised tumor control, but retrospective studies are mixed on the relative risks and benefits of the two schedules. It is also unclear whether total cisplatin dosing is better or worse using a weekly schedule, an issue which is difficult to adequately address in a retrospective report. Moreover, other
than the inferior survival in patients from RTOG 0129 receiving only one cycle of bolus cisplatin, there are no convincing data that total cisplatin dose meaningfully impacts outcome, especially with a weekly schedule.

The de-emphasis of weekly cisplatin relative to bolus delivery was frequently mentioned during the public comment period, and the panel again discussed the literature supporting its use and comparative effectiveness.

Relevant references were discussed but the evidence base remained unchanged because the data were generally retrospective, with small numbers of patients, and selection biases and unmeasured confounding factors significantly reduced meaningful inference from the results. That said, the panel noted that existing data do not consistently support the contentions that weekly cisplatin is better tolerated and/or allows for a similar or higher chemotherapy dose intensity. For example, although some of these studies showed increased renal toxicity and hospitalization risk from high-dose intermittent cisplatin, weekly administration was associated with more mucositis and less total cisplatin delivery. So while the panel concluded that weekly cisplatin may be given if the patient is not a candidate for bolus delivery, the lack of data guiding its use must be made clear to the patient, especially in the face of high-level data supporting OS gains with competing regimens.

The panel recognizes that there is a population of patients with stage IVA-B (and stage III) OPSCC who will not be candidates for concurrent systemic therapy. KQ4 discusses the benefits and risks of AltFX RT to provide additional recommendations on optimal treatment of this cohort.

**In the scenario of stage III disease?**

**Statement KQ1F:** Concurrent systemic therapy should be delivered to patients with T3 N0-1 oropharyngeal squamous cell carcinoma receiving definitive radiotherapy.

- **Recommendation strength:** Strong
- **Quality of evidence:** Moderate

**Statement KQ1G:** Concurrent systemic therapy may be delivered to patients with T1-T2 N1 oropharyngeal squamous cell carcinoma receiving definitive radiotherapy who are considered at particularly significant risk for locoregional recurrence, after a careful discussion of patient preferences and the limited evidence supporting its use.

- **Recommendation strength:** Conditional
- **Quality of evidence:** Low

**In the scenario of stage I-II disease?**

**Statement KQ1H:** Concurrent systemic therapy should not be delivered to patients with stage I-II oropharyngeal squamous cell carcinoma receiving definitive radiotherapy.

  - **Recommendation strength:** Strong
Quality of evidence: Low

Narrative

The addition of concurrent systemic therapy to primary RT for patients with stage III oropharyngeal squamous cell carcinoma may be appropriate in certain patient subgroups. Randomized controlled trials have generally included both stage III and IV patients, with the stage III subgroup representing a minority (4–32%) of the total study population in the studies reviewed. These trials are underpowered to address the magnitude of benefit of concurrent systemic therapy in the stage III subgroup. In addition, stage III patients are heterogeneous, and include those with T3 N0-1 and T1-2 N1 tumors.

Since concurrent systemic therapy improves outcomes primarily through radiosensitization, the key issue is the expected LRC probability with RT alone in this population. Retrospective studies have shown that local tumor control is strongly related to tumor volume and tumor stage. For example, Lok et al. reported the effect of tumor volumes on outcomes of 340 OPSCC patients managed with radiation and concurrent chemotherapy at Memorial Sloan Kettering between 1998-2009. Volumes of the primary site gross tumor (GTVp) were calculated from the original IMRT plans. When dichotomized at the median volume (32.79 cm³) GTVp was demonstrated to be an independent predictor of 2-year OS on multivariate analysis (94.3% vs 82.7%, p=0.0003). Similarly, two year probabilities of local failure (LF) at the primary site were 1.3% vs 10.4% (HR=6.01, p=0.004) based on a GTVp cut-off of 32.79 cm.³ The authors observed that GTVp was a more reliable predictor of OS and LF than T category (dichotomized as T1-2 vs T3-4).

Garden et al. have reported a retrospective analysis of 1046 OPSCC treated at MD Anderson between 2000 and 2007. Locoregional control at 5 years for 640 patients presenting with T1-2 disease was 91% for those given concurrent chemotherapy and 95% for those treated with radiation alone. In contrast, patients with T3-4 disease treated with concurrent CRT achieved a LRC probability of only 77%, which dropped to 63% with RT alone. A comparable retrospective analysis from the University of Florida described the LRC outcomes in 130 OPSCC patients treated with definitive RT, 89% and 61% of whom received AccFX and/or concurrent chemotherapy, respectively. When evaluating their local control outcomes, the authors found that T1 and T2 lesions experienced 5-year control probabilities of 93% and 91%, respectively, whereas T3 and T4 tumors recurred locally 18% and 33% of the time, respectively. These data are persuasive that patients with larger volume disease need additional local therapy beyond conventional RT alone. In fact, the MACH-NC meta-analysis showed a
significant OS improvement with chemotherapy for patients with stage III head and neck cancer, although the results were not broken down by T stage. Since concurrent chemotherapy is consistently associated with LRC and OS benefits in the aforementioned randomized trials, the panel strongly recommends that patients with T3 N0-1 OPSCC receive concurrent systemic therapy with primary RT.

The degree to which low-bulk disease, namely non-T3 stage III (T1-T2, N1) OPSCC, benefit from treatment intensification with concurrent systemic therapy is uncertain, and it remains controversial whether the added toxicity of concurrent systemic therapy is warranted in this population. Consider that the volume of a T2 tumor may range from $8 \text{ cm}^3$ to $64 \text{ cm}^3$, and thus the baseline risk of local recurrence may vary significantly in this tumor category. Other tumor features may also impact the perceived locoregional failure risk for a patient with T1-2 N1 disease, such as its human papillomavirus (HPV) status and the patient’s smoking history. For most patients with the T1-2 N1 OPSCC, the panel believes that RT alone should be sufficient to obtain LRC. The fact that the new 8th edition of the AJCC staging system re-categorizes patients with p16-positive, T1-2 N1 OPSCC as stage I speaks to their expected excellent prognosis. This downgraded stage is expected to have significant implications for their subsequent exclusions from future national chemoradiotherapy trials. However, certain patients with T1-2 N1 OPSCC who are considered at particularly significant risk for locoregional recurrence may receive concurrent systemic therapy with primary RT, since the absolute benefit of combined modality therapy may warrant its toxicities in this population. The potential benefit of concurrent systemic therapy is even less compelling in smaller tumors, unless there are other features suggesting radioresistance. Patient preferences must be engaged on the toxicity of concurrent therapy versus modestly improved tumor control, and the limited data guiding this recommendation should be made explicit.

The use of concurrent systemic therapy has not been rigorously examined in patients with stage I and II OPSCC, a population with favorable LRC outcomes with RT alone. For example, in the MACH-NC meta-analysis,$^2$ just over 500 patients with stage I-II disease were included in the study (versus over 6,000 for stage IV cancer), and the hazard ratio for chemotherapy was approximately one. Therefore, these patients should not be treated with concurrent systemic therapy.

**Key Question 2: When is it appropriate to deliver post-operative radiotherapy with and without systemic therapy following primary surgery of oropharyngeal squamous cell carcinoma (OPSCC)?**
In the scenario of positive margins and/or extracapsular nodal extension (ECE)?

Statement KQ2A: Concurrent high-dose intermittent cisplatin should be delivered with post-operative radiotherapy to patients with positive surgical margins and/or extracapsular nodal extension; this high-risk population includes patients independent of HPV status or the extent of extranodal tumor.
- **Recommendation strength**: Strong
- **Quality of evidence**: Moderate

Statement KQ2B: Concurrent weekly cisplatin may be delivered with post-operative radiotherapy to patients who are considered inappropriate for standard high-dose intermittent cisplatin after a careful discussion of patient preferences and the limited evidence supporting this treatment schedule.
- **Recommendation strength**: Conditional
- **Quality of evidence**: Low

Statement KQ2C: For the high-risk post-operative patient unable to receive cisplatin-based concurrent chemoradiotherapy, radiotherapy alone should be routinely delivered without concurrent systemic therapy; given the limited evidence supporting alternative regimens, treatment with non-cisplatin systemic therapy should be accompanied by a careful discussion of the risks and unknown benefits of the combination.
- **Recommendation strength**: Strong
- **Quality of evidence**: Moderate

Statement KQ2D: Patients treated with post-operative radiotherapy should not receive concurrent weekly carboplatin.
- **Recommendation strength**: Strong
- **Quality of evidence**: Moderate

Statement KQ2E: Patients treated with post-operative radiotherapy should not receive cetuximab, either alone or in combination with chemotherapy, although such regimens are currently under investigation.
- **Recommendation strength**: Strong
- **Quality of evidence**: Low

Statement KQ2F: Patients treated with post-operative radiotherapy should not routinely receive concurrent weekly docetaxel given the limited evidence supporting its use, although such regimens are currently under investigation.
- **Recommendation strength**: Strong
- **Quality of evidence**: Low

Statement KQ2G: Patients treated with post-operative radiotherapy should not receive concurrent mitomycin-C, alone or with bleomycin, given the limited evidence and experience supporting its use.
- **Recommendation strength**: Strong
- **Quality of evidence**: Moderate

Statement KQ2H: Post-operative chemotherapy should not be delivered alone or sequentially with post-operative radiotherapy.
- **Recommendation strength**: Strong
- **Quality of evidence**: High
Narrative

Is there a patient population that will benefit from the addition of chemotherapy to post-operative radiotherapy?

What drug and treatment schedule should be used?

The results of two landmark trials of adjuvant CRT, EORTC 22931 \(^{50}\) and RTOG 9501 \(^{51}\), were published simultaneously in 2004 (Table 3). Both studies compared PORT with post-operative CRT, using concurrent HDIC (100 mg/m\(^2\) every three weeks for three doses) in patients deemed at high risk for disease recurrence. High-risk disease was defined as positive surgical margins, or extracapsular nodal involvement in both trials, but the RTOG study \(^{51}\) also included involvement of two or more regional nodes, and the EORTC study \(^{50}\) included perineural disease, vascular embolism, or level 4 or 5 nodal involvement in oral cavity or oropharynx primary cancers. It should be noted that in the RTOG trial, a positive surgical margin was defined as microscopic tumor at the tumor specimen edge. In the EORTC trial \(^{50}\) however, tumor within 5 mm of the specimen edge was considered a positive margin. Initial results from both studies demonstrated an improvement in LRC and disease/progression-free survival with CRT. Overall survival was statistically better in the EORTC study \(^{50}\) but only trended towards improvement in the first RTOG report. Long-term follow-up from the RTOG trial has been reported \(^{52}\), however, and it no longer demonstrated any statistical benefit from the chemotherapy in the primary comparisons.

It is of note that distant metastases were not reduced by the chemotherapy in either trial, and all three cisplatin doses could be given to only 49% and 61% of the EORTC \(^{50}\) and RTOG \(^{51}\) patients respectively. Acute toxicity, specifically mucositis, myelosuppression, nausea and vomiting, was increased in the CRT patients. However, no statistically significant increase in total late grade 3-5 toxicity could be identified after CRT in either study. This acute toxicity burden must temper any enthusiasm to use concurrent chemotherapy in an unselected population of patients receiving PORT.

The difference in survival outcomes, and the long-term results from the RTOG study merit further discussion. Bernier and colleagues \(^{53}\) performed a pooled analysis of the 750 patients from both trials, and confirmed an improvement in all endpoints, including OS, in the patients treated with chemotherapy. They suggested, however, that not all of the “high-risk” eligibility criteria conferred sufficient risk to merit the addition of concurrent chemotherapy. In their retrospective, unplanned subgroup analysis from these two trials, the addition of concurrent cisplatin proved beneficial only in those high-risk patients with either positive surgical margins or extracapsular nodal involvement. While benefit in patients with the other risk features remained a possibility, it could not be
statistically demonstrated. Similar conclusions were drawn from the long-term RTOG 9501 follow-up report.\textsuperscript{52} Again using retrospective, unplanned subgroup analysis, an improved LRC and disease-free survival (with a strong trend towards an improved OS) was identified in the CRT-treated patients with positive surgical margins or extracapsular nodal extension. These observations have led to the current strong recommendations for the addition of concurrent HDIC to adjuvant RT in these two high-risk post-operative populations. Patients with other risk features, whose surgical procedure and/or pathologic findings imply a particularly significant risk of locoregional recurrence may still benefit from concurrent cisplatin, although the evidence is limited and inconclusive.

The improved prognosis and increasing incidence of HPV-positive oropharynx cancer, however, could not be assessed in these trials and may have impacted the observed results.\textsuperscript{54} In the EORTC study 30\% of the patients had an oropharynx cancer compared to 42\% in the RTOG report (48\% on the CRT arm and 37\% of the RT alone arm). It is unknown if these good prognosis HPV-positive patients require or benefit from more intensive adjuvant therapy, even in the presence of conventional “high-risk” features.

The implications of extracapsular nodal extension in oropharynx cancer, and in particular, the HPV-positive patient have also been questioned. Retrospective reports from several groups have suggested that extracapsular nodal disease has limited prognostic importance in these patients, especially when it is only microscopically present in an HPV-positive patient.\textsuperscript{55-58} Prospective studies that replicate these provocative retrospective results are needed before PORT alone can be recommended for HPV-positive head and neck cancer with ECE. In addition, to enhance its prognostic power, ECE reporting has recently been refined with the introduction of a five-point scale (0-4), and further multi-institutional study is required for this modification to be used in clinical practice.\textsuperscript{59}

Reasonable concern clearly exists about the applicability of RTOG 9501\textsuperscript{51} and EORTC\textsuperscript{50} 22931 to the growing population of patients with HPV-positive oropharynx cancer\textsuperscript{54} and the prognostic implications of early extracapsular nodal involvement. To date, however, these two trials provide the best available evidence and continue to drive the current adjuvant recommendations. Well-designed HPV-specific trials are currently underway to better address these many unresolved questions. Similar concerns have also led to greater sophistication and nuance in the studies designed for the definitive management of oropharynx cancer. Such concerns do not render current treatment standards invalid; they only lend urgency to further investigation.
Can radiotherapy and a weekly concurrent cisplatin administration schedule be used instead of giving 100 mg/m² given every three weeks?

The high-dose, every three-week cisplatin administration schedule (100 mg/m² q3weeks for 3 doses) has proven difficult to administer. It is associated with gastrointestinal, renal, mucosal, and neurologic toxicity, and most large multi-institutional studies (including RTOG 9501 and EORTC 22931) have reported that only 50-70% of patients can receive all three drug doses. In recent years, there has been considerable interest in the lower dose weekly drug administration schedules (30-40 mg/m²/week) based on the assumption being made that such regimens will produce less toxicity, and, as such will allow equivalent or greater drug administration with equal treatment efficacy. No prospective, randomized comparisons have yet been completed comparing these two drug treatment schedules, however, and their equivalence is unknown.

In the post-operative setting, Bachaud et al. 60,61 reported the results of a very small phase III trial comparing PORT alone with RT and weekly cisplatin; 50 mg/week (approximately 25-30 mg/m²) for 7-9 doses in 83 patients (14% oropharynx cancer). Both disease-free and OS, as well as OS without locoregional treatment failure, were significantly improved in the chemotherapy treated patients. Distant metastases were not impacted by the chemotherapy, although toxicity was significantly worse.

Geiger et al. 62 conducted a retrospective analysis of 104 post-operative patients treated with RT and either concurrent high-dose intermittent (100 mg/m² q3weeks for 3 doses), or low dose weekly (25-30 mg/m²/week for 6 doses) cisplatin. Sixty-one percent of the patients had an oropharynx cancer, and 86% of these oropharynx cancers were HPV/p16 positive. Total drug administration was significantly greater in the high-dose intermittent group, but no difference was observed in either relapse-free or OS between patients treated with the two different cisplatin schedules. There was also no outcome difference identified when the analysis was limited to the HPV-positive oropharynx cancer patients.

Because of the increasing community acceptance of weekly cisplatin regimens despite this lack of demonstrated equivalence, the RTOG adopted weekly dosing as the control arm in RTOG 1216 63, a current phase II/III trial exploring the substitution of docetaxel and cetuximab for cisplatin in the postoperative adjuvant treatment of patients with high risk disease. Despite the inclusion of weekly cisplatin as the control arm in this study, the panel does not feel the evidence supporting its use is currently sufficient to strongly recommend its delivery in lieu of
HDIC when the latter would be tolerated, as the high-dose regimen was evaluated in two large prospective phase III randomized trials with positive results.

Are there alternative systemic treatment regimens that can be used concurrently with radiotherapy, particularly in the medically compromised patient?

Cisplatin remains the only systemic agent with level 1 evidence supporting its use concurrently with RT in high-risk post-operative patients. Several other systemic agents have been tested in small phase II and phase III trials with limited success (Table 4). All studies report greater toxicity when chemotherapy is added to RT without a proven survival benefit.

Radiotherapy and concurrent single agent mitomycin C (15 mg/m² for 1-2 doses) has been compared to a radiation therapy control arm in three separate randomized trials at Yale University. Poled results from the 205 post-operatively treated patients (23% oropharynx cancer) have been reported. Conventional high-risk features were not required for entry on these trials although 27% had positive surgical margins and 34% had more than one positive node. Locoregional control proved statistically superior in those patients treated with mitomycin C; however, no difference was observed in the rate of distant metastases or in overall survival.

Post-operative radiotherapy with mitomycin C (15 mg/m²) was also studied by Smid, Zakotnik et al., who combined it with bleomycin (5 mg twice weekly) and compared it to RT alone in 114 patients (30% oropharynx cancer); 59% of whom had either positive surgical margins or extracapsular nodal extension. Both LRC and disease-free survival were significantly improved in the chemotherapy treated patients, although OS only trended better (55% vs. 37%, p=0.09). Distant metastases were not improved by the use of chemotherapy.

This work, from both groups, provided modestly encouraging evidence of a potential role for mitomycin C in this setting, although patient sample sizes were small. Mitomycin C has not been further pursued in part due to the stronger data that emerged about concurrent cisplatin, and in part due to general concerns about the toxicity of this agent. Because of both the lack of an OS benefit and absence of modern experience of combining this agent with RT, the panel strongly recommends not combining mitomycin C with PORT.

Concurrent carboplatin has also been studied. Racadot et al. report the results of a randomized comparison between PORT alone, and PORT with concurrent carboplatin (50 mg/m² twice weekly) in 144 patients (49% oropharynx cancer) with node positive disease. No outcome differences were observed. Similarly, Argiris et
al. studied a post-operative patient population (32% oropharynx cancer) defined by positive margins, multiple node positivity, angiolymphatic or perineural invasion (PNI), or extracapsular nodal involvement, randomizing between RT and RT with concomitant carboplatin 100 mg/m² weekly. Only 72 patients were evaluated on the trial and no statistically meaningful outcome difference was observed, perhaps reflecting the insufficient sample size. Further studies of post-operative carboplatin and RT have not been reported, and since both randomized trials were negative, the panel strongly recommends against using concurrent carboplatin in the post-operative setting.

A large multi-institutional phase III study from the United Kingdom randomly compared PORT with RT and chemotherapy (either methotrexate alone, or methotrexate, vincristine, bleomycin and fluorouracil) in 253 post-operative patients (23% oropharynx cancer). Patients were described as “generally at high risk due to margin status or advanced stage of disease.” No outcome benefit was observed in the chemotherapy treated patients using this non-platinum containing regimen.

Cetuximab and the other EGFR inhibitors have been considered promising agents in the management of head and neck squamous cell cancer. When combined with RT in the definitive treatment of locoregionally advanced disease, a survival benefit (but no impact on distant metastases) has been demonstrated in comparison to radiation therapy alone. This result has suggested the possibility that RT and cetuximab may also be a valuable post-operative adjuvant regimen to explore. The NRG is currently comparing this combination to radiation therapy alone in “intermediate risk” patients after surgical resection in RTOG 0920. However, since there are no prospective or even retrospective studies suggesting efficacy in this scenario, the panel strongly recommends against using cetuximab with PORT if not on clinical trial.

The taxanes (paclitaxel and docetaxel) have been investigated by the RTOG in a series of post-operative trials. RTOG 0024 explored immediate post-operative paclitaxel followed by concurrent CRT with weekly paclitaxel and cisplatin in 70 high-risk post-operative patients (34% oropharynx cancer) in a single arm phase II trial. Toxicity appeared acceptable and results comparable to historical controls using high-dose cisplatin. This study was followed by RTOG 0234, a phase II randomized trial comparing post-operative cetuximab and RT with either concurrent weekly cisplatin or weekly docetaxel, in 203 high risk patients (36% oropharynx cancer). The RT, cetuximab and docetaxel arm appeared more promising and this combination is now being formally tested in a phase II/III trial in comparison to RT and cisplatin. Pending the results of this study, though, the use of docetaxel with PORT – a combination never prospectively evaluated – should not be routinely implemented with PORT.
It should again be noted that the benefit from cisplatin reflects an improvement in LRC, not a reduction in distant metastases. There is no phase III evidence demonstrating an improvement in distant metastatic recurrence from any systemic agent in this setting. In patients with a contraindication to cisplatin, radiation therapy alone provides a LRC benefit, and is the recommended treatment choice, even when the risk of disease recurrence is high.

Is there a role for post-operative adjuvant chemotherapy alone, or for the sequential administration or chemotherapy and radiotherapy, rather than concurrent treatment?

The MACH-NC Meta-analysis\textsuperscript{32,78} reported on 12 trials of more than 2500 patients, comparing adjuvant chemotherapy after locoregional treatment to locoregional treatment alone. No impact could be identified on either disease recurrence or death from the use of the adjuvant chemotherapy. Adjuvant chemotherapy is not considered a standard approach in this disease.

Laramore et al.\textsuperscript{79} reported the results of Intergroup study 0034, a phase III randomized trial conducted in 448 patients (25\% oropharynx cancer) comparing PORT alone, with sequential chemotherapy (fluorouracil and cisplatin for 3 cycles) followed by RT. No difference in LRC, disease-free survival or OS could be identified between the two treatment arms, although a statistically significant increase in distant metastases was seen in the patients not given chemotherapy. Sequential treatment with post-operative chemotherapy and RT is not recommended in this disease.

In the scenario of intermediate-risk pathologic factors such as lymphovascular invasion (LVI), perineural invasion (PNI), T3-4 disease, or positive lymph nodes?

Statement KQ2I: Patients with intermediate-risk factors should not routinely receive concurrent systemic therapy with post-operative radiotherapy.

- **Recommendation strength**: Strong
- **Quality of evidence**: Moderate

Statement KQ2J: Patients with intermediate-risk factors whose surgical procedure and/or pathologic findings imply a particularly significant risk of locoregional recurrence may receive concurrent cisplatin-based chemotherapy after a careful discussion of patient preferences and the limited evidence supporting its use in this scenario; alternative systemic treatment regimens should only be used in the context of a clinical trial.

- **Recommendation strength**: Conditional
- **Quality of evidence**: Low

Statement KQ2K: Post-operative radiotherapy should be delivered to patients with pathologic T3 or T4 disease.
• **Recommendation strength**: Strong
• **Quality of evidence**: Low

Statement KQ2L: Post-operative radiotherapy should be delivered to patients with pathologic N2 or N3 disease.

- **Recommendation strength**: Strong
- **Quality of evidence**: Low

Statement KQ2M: Post-operative radiotherapy may be delivered to patients with pathologic N1 disease after a careful discussion of patient preferences and the limited evidence of outcomes following surgery alone in this scenario.

- **Recommendation strength**: Conditional
- **Quality of evidence**: Low

Statement KQ2N: Post-operative radiotherapy may be delivered to patients with LVI and/or PNI as the only risk factor(s) after a careful discussion of patient preferences and the limited evidence of outcomes following surgery alone in this scenario.

- **Recommendation strength**: Conditional
- **Quality of evidence**: Low

Narrative

The risk of locoregional recurrence following definitive surgical resection and neck dissection is influenced by several factors. The clinical and pathologic features most clearly associated with subsequent locoregional progression are positive margins and extracapsular nodal extension, the implications of which were discussed above. On the other hand, due to the paucity of prospective randomized trials of adjuvant RT alone versus observation following surgery, the vast majority of data implicating other risk factors with locoregional recurrence are retrospective. Thus, there is almost no high-level evidence to guide adjuvant treatment recommendations in the negative margin, non-ECE setting, despite several other risk factors serving as eligibility criteria for active prospective randomized trials evaluating the role of adjuvant radiation therapy with or without chemotherapy. Nevertheless, this population comprises a significant percentage of patients for whom PORT must be considered, and so the panel used higher-quality retrospective data and expert opinion to derive treatment recommendations (Table 5).

Pathologic nodal stage is a commonly used pathologic risk factor in the adjuvant decision-making process. Resection of bulkier nodes may leave behind occult microscopic disease, and with more pathologically involved nodes, there is theoretically a higher likelihood of additional microscopic nodal deposits in dissected or undissected tissue. Indeed, the evidence supports a significant risk of regional progression in patients with N2 or N3 disease. In
one of the few prospective trials of adjuvant RT dose escalation, Peters et al. showed that among all patients, those with more than 1 positive node (i.e. N2b) experienced a higher risk of locoregional recurrence (30% vs 16%, p=0.08), despite RT delivery to all patients. Langendijk et al. performed a large retrospective analysis to define subgroups of patients with locally advanced head and neck cancer (20% oropharyngeal cancer) at higher risk for locoregional recurrence following surgery and PORT. On multivariable analysis, patients with pN2b-N2c and pN3 disease had significantly higher risks of locoregional recurrence in comparison to pN0-N2a status (RR 1.7 and 3.5, respectively), and patients with an N3 neck were placed in the “very high risk” category (5 year LRC of 58%) regardless of ECE or the primary tumor characteristics. Similarly, Ambrosch et al. reported a large series of 503 patients treated with neck dissection with or without adjuvant RT. The 48 patients with N2 disease treated without adjuvant RT experienced a 3-year neck recurrence risk of 24%, in comparison to 7% of the 188 N2-positive treated with PORT. Notably, among all patients with regional recurrence, successful salvage was feasible in only 24% of patients, and 67% of patients died specifically from the neck progression. In a smaller surgical series from Mayo Clinic, 2 out of 11 (17%) pathologic N2b oropharynx cancer patients observed after neck dissection developed a regional recurrence, as did 1 of 2 pathologic N3 patients.

The risk of regional recurrence in patients with a pathologically N1 neck is more controversial. In a paper restricted to individuals with pN1 disease without extracapsular extension (29% oropharynx), Jackel et al. reported the risks of locoregional recurrence with and without adjuvant RT. Patients observed after primary surgery (n=72) experienced a crude risk of any regional recurrence of 21%, with 10% of observed patients developing an isolated nodal failure; the estimated 3-year risk of isolated neck recurrence in this population was 11.2% (vs. 2.9% in patients who were irradiated, p=0.09); three of the 7 patients with isolated regional recurrence died from cancer. Somewhat conflicting data on the N1 neck were presented in the Ambrosch study, in which the 3-year neck recurrence risk for the 48 pN1 patients treated with surgery alone was 6.3%. This number was only slightly higher than the neck recurrence risk in pN0 patients observed after surgery (5.5% out of 213 patients). However, only 28% of these patients had oropharyngeal cancer, and the majority was either oral cavity or larynx, which have different patterns of nodal spread. In particular, oropharyngeal cancer is significantly more likely to metastasize to the retropharyngeal nodes, which are treated with RT but not accessed with conventional neck dissection; the absolute risk of retropharyngeal lymph node involvement in OPSCC has been reported between 20-30%. Smaller, modern series in oropharynx cancer also suggest high control rates following neck dissection alone for N1 disease. None of
the 10 patients observed with pN1 disease in the Mayo clinic series developed a regional recurrence, and none of the 10 patients with pN1 disease in the Penn prospective study of transoral robotic surgery (TORS) alone developed a neck progression. One significant consideration in evaluating all of these data is the reality that the quality of the neck dissections was not formally standardized, both in terms of surgical technique (e.g. levels dissected and number of nodes harvested) and pathologic evaluation processes. Thus, one must recognize this limitation in applying these results to a given neck dissection.

Two related surveillance, Epidemiology, and End Results Program (SEER) studies investigated the survival benefit of adjuvant RT following surgery for non-nasopharynx head and neck carcinoma with positive lymph nodes, and both showed a significant OS advantage for all nodal stages. For instance, Kao et al. showed that the absolute survival gains for patients with N1, N2a, N2b, and N2c-3 were 8.2%, 16.6%, 23.9%, and 12.2%, respectively (all p<0.0001). Patients with oropharyngeal cancer experienced an absolute survival improvement of 8.2% with adjuvant RT (p=0.0003). Although these survival improvements are impressive, any SEER study is limited by the nature of its retrospective, population-based data collection. For example, performance status, chemotherapy administration, ECE status, and pre-treatment imaging were all unknown. Nevertheless, these data do support a benefit of adjuvant RT for all node-positive disease.

Taken together, this evidence is persuasive that individuals with pathologic N2 and N3 disease experience an unacceptably high regional recurrence risk without RT, and therefore the panel strongly recommends that these patients receive adjuvant RT. Patients with pathologic N1 oropharynx cancer are clearly at lower risk for nodal progression following neck dissection, but there is substantial uncertainty on the true probability of regional recurrence in this population. Moreover, while it is intuitive and accepted that patients not receiving RT will have improved quality-of-life in comparison to those who do, the poor salvage ability (and potential mortality) of a neck recurrence must be considered in this decision. Since the panel favors a potential progression and/or survival benefit over modest, albeit meaningful, quality-of-life improvements, it conditionally recommends adjuvant RT in this population. That said, it is critical to discuss the uncertainty in the recurrence risk with the patient, and the physician should engage patient preferences and values on the balance between the risks of RT versus the potential for unsalvageable regional progression.

Pathologic T stage has also been frequently investigated in retrospective studies as a predictor of locoregional recurrence. Leemans et al reported on 244 head and neck cancer patients (13% oropharynx) treated
with primary surgery with or without adjuvant RT. Clinical T stage was the most significant predictor of local recurrence, with a crude recurrence risk of 5.3% for T1-2 versus 16.2% for T3-4 disease (p=0.015), and the actuarial absolute difference at 5 years was almost 20%. In a retrospective analysis of 420 oropharyngeal and hypopharyngeal patients from the Centre Henri Becquerel treated with surgery and PORT, advancing T stage was strongly associated locoregional relapse (relative risk 1.85, p<0.0001) on multivariable analysis, with T stage treated as a continuous variable; absolute risks were not stated. In the Langendijk\textsuperscript{81} analysis in which all patients received adjuvant RT, T stage did not correlate with LRC on univariable analysis. However, after identifying patients with positive or close margins (5 mm or less, which is typically seen in larger tumors of the oropharynx), patients with T3-4 disease experienced significantly worse LRC than those with T1-2 disease (absolute difference 10%). The majority of these failures were in the T3 population (5-year LRC of 51%).

A retrospective analysis of p16-positive patients by Haughey et al.\textsuperscript{90} demonstrated a significant increase in the risk of any recurrence as a function of pathology T stage: 1.5%, 5.5%, 11.5%, and 28.6% for T1, T2, T3 and T4 respectively. Indeed, on multivariable analysis of disease-free survival, both clinical T stage (T3-4 vs T1-2) and pathologic T stage (T3-4 vs T1-2) increased the hazard by over 3-fold. However, there were only 2 local recurrences in the entire series (both in T3 patients, 1 of whom did not receive adjuvant RT), so T stage was not a predictor of local-only recurrence. In the Ambrosch et al.\textsuperscript{82} study that primarily focused on regional recurrences after neck dissection, pT3/pT4 disease was significantly associated with worsened OS on multivariable analysis (risk ratio 1.6, p=0.0009), but local failure patterns were not mentioned.

Both of these latter studies highlight a major challenge in analyzing the literature to derive adjuvant treatment recommendations in patients with T3-4 disease: almost all of these individuals received PORT. While the retrospective data are convincing that these patients have a worse overall prognosis, it is hard to calculate an absolute local recurrence risk with and without RT. Nevertheless, the panel concluded that the existing literature support an increased risk of local recurrence with pathologic T3 or T4 disease even with RT, and moreover, there are insufficient LRC data to support the oncologic safety of observation following resection of T3-4 oropharyngeal cancer. Therefore, the panel does strongly recommend adjuvant RT in this population.

It is particularly difficult to estimate the risk of locoregional recurrence in patients for whom PNI or LVI is the only adverse pathologic factor. These characteristics are often found in patients with other known risk factors for recurrence and this confounding can be difficult to resolve.\textsuperscript{90} Secondly, retrospective studies don’t always comment
on these factors because they are not always properly recorded in the pathology report. Finally, historically radiation oncologists have always treated patients with LVI or PNI, and there is very little information on outcomes without adjuvant RT. For example, the large retrospective analysis from Langendijk et al.\textsuperscript{81} found that patients with PNI had a significantly higher risk of locoregional recurrence (31% vs 22% at 5 years, p<0.026), as did patients with angioinvasive (33% vs 21%, p=0.011) or lymphangioinvasive growth (38% vs. 23%, p=0.046). However, none of these factors were significant on multivariable analysis. Haughey et al. found on univariable analysis that angioinvasion was borderline associated with disease-free survival (p=0.062) and powerfully associated with disease-specific survival (HR 13.16, p=0.002). These relationships became non-significant on multivariable analysis. Moreover, only 26 patients had this pathologic factor, and of these 26, five recurred but 4 were distant metastases. There was no association between PNI and outcome in this large analysis.

There are data supporting these characteristics as independent risk factors for locoregional recurrence. In a retrospective analysis of 80 consecutive head and neck patients (28% oropharynx) treated with primary surgery at the University of Utrecht, LVI was significantly associated with local failure on both univariable analysis (50% failure with vs. 16% without, p=0.001) and multivariable analysis (p=0.005).\textsuperscript{91} Perineural invasion was qualitatively associated with local failure (27% with and 15% without), but it was non-significant on both univariable and multivariable analysis.\textsuperscript{91} In the retrospective study from the Centre Henri Becquerel,\textsuperscript{89} individuals with tumor emboli in the vessels or nerves experienced an approximately 10% increased risk of locoregional recurrence. However, in a multivariable analysis incorporating T and N stage, margin status, age, tumor emboli local relapse was marginally non-significant (relative risk 1.48, p=0.061). In another bi-institutional retrospective analysis of oral cavity and oropharyngeal cancer (33% oropharynx), McMahon et al.\textsuperscript{92} showed that PNI was a significant predictor of local recurrence in both institutions, and vascular and LVI was a significant predictor of local recurrence in only one of them. However, on multivariable analysis incorporating all patients, only PNI (over all other variables) was significantly associated with local recurrence. Neither PNI nor LVI were independently associated with disease-specific survival on multivariable analysis. Fagan et al.\textsuperscript{93} retrospectively evaluated the prognostic influence of PNI in 142 patients (66 with oral cavity or oropharynx) treated with primary surgery with or without adjuvant RT. Over half of the patients had PNI, and it was significantly associated with local recurrence (23% vs. 9%, p=0.02) and disease-specific mortality. Finally, Lanzer and colleagues analyzed locoregional and distant recurrence patterns in 291 head and neck cancer patients, 32% of whom had oropharynx cancer.\textsuperscript{94} Among all patients, the presence of PNI
was associated with a higher risk of ipsilateral and contralateral lymph node recurrence, but there were no independent associations between PNI and disease-free or overall survival.\textsuperscript{94}

Two retrospective analyses restricted to oral cavity cancer highlight the uncertainty in the adjuvant management of this population. In a large series of 460 patients with node-negative oral cavity cancer\textsuperscript{95}, Liao et al. showed that the presence of PNI was not associated with local control or OS and the addition of RT to patients with PNI did not improve any outcome; only 44 patients with PNI were observed. On the other hand, Chinn et al.\textsuperscript{96} reported on a cohort of 88 node-negative oral cavity patients from the University of Michigan, finding that PNI was associated with worse LRC (35\% vs. 12\%, \( p=0.037 \)) and a shorter disease-free interval on multivariable analysis; in addition, the addition of RT significantly improved both endpoints.\textsuperscript{96} However, only six patients with PNI were observed, limiting the interpretation of this comparison.

In summary, these entirely retrospective data are mixed on the relationship between locoregional failure and LVI and PNI, but there is certainly the suggestion that they reflect more aggressive locoregional disease. Given the morbidity and mortality risk of local recurrence, adjuvant RT may be used for patients with either pathologic factor as the only adverse characteristic. Both the lack of high-quality evidence and the conflicting retrospective data guiding this recommendation need to be described to patients, and their preferences and values on toxicity versus the risk of recurrence need to be explored.

\textbf{In the scenario of no pathologic risk factors?}

\textbf{Statement KQ20}: Post-operative radiotherapy may be delivered to patients without conventional adverse pathologic risk factors only if the clinical and surgical findings imply a particularly significant risk of locoregional recurrence, after a careful discussion of patient preferences and the potential harms and benefits of radiotherapy.

- \textbf{Recommendation strength}: Conditional
- \textbf{Quality of evidence}: Low

\textbf{Narrative}

There are limited prospective data that report outcomes following primary surgery alone for oropharyngeal cancer. In a multi-institutional prospective trial evaluating a post-surgical adjuvant therapy paradigm, Ang et al.\textsuperscript{97} demonstrated that when the surgical bed was at a low risk for relapse, defined by the absence of any adverse pathologic features (i.e. T1-2, N0, negative margin, no PNI, non-oral cavity site), observation was associated with a local-regional relapse of approximately 10\% at 5-years, despite significantly older staging and surgical techniques. Investigators from University of Pennsylvania characterized the oncologic results of 30 patients treated with TORS
alone on a prospective trial. Positive margins were defined as tumor within 2 mm of the margin, and the surgeons paid exquisite detail to the margin evaluation. All patients in this cohort had final negative margins, although one patient required an additional resection for carcinoma in situ at the inked margin. Three patients had ECE, and 15 patients were node-positive (10 N1, 5 N2a or N2b). With a minimum follow-up of 18 months, one patient (3% of total) with initial T2N0 stage developed a local recurrence, successfully salvaged with CRT. Three patients (10% of total) experienced a regional recurrence, two of whom had N2b nodal stage at original presentation and refused the recommendation to receive adjuvant RT. One patient with T2N0 cancer recurred in the ipsilateral high-neck. All patients were alive without evidence of disease at the time of the publication.

Psychogios et al. published a retrospective series of 228 patients with T2 N0-3 oropharyngeal cancer treated with primary surgery with or without adjuvant radiation treatment. Out of the 69 patients with negative margins and no pathologically involved lymph nodes, there was no difference in disease-specific survival between the 20 observed patients versus the 49 treated with radiation therapy (81.5% vs. 80.0%, p=0.361).

A joint publication from Mayo-Jacksonville and Mayo-Arizona retrospectively analyzed outcomes following transoral laser microsurgery alone in 69 patients, all of whom had negative margins. Twenty-five of these patients had an indication for RT (i.e. ECE, N2 status, LVI) but declined, and 44 individuals did not have an indication for RT. After a mean follow-up of 44 months, only 3 patients recurred at the primary site (two T1, one T2 cancer, for a 5-year local control estimate of 95%). Forty-four patients were recommended to undergo observation, and 4 of these patients recurred in the neck, leading to 5-year LRC estimates of only 90%, 73%, and 70% for stage I, II and III, respectively. However, two of those 4 patients did not have a neck dissection and were observed. The 5-year disease-specific and OS probability for stage I and II disease was 88% and 79%, respectively. Of the 25 patients with an indication for adjuvant RT, 4 developed a regional failure, with a 5-year estimate of LRC of 74%.

One of the challenges in interpreting pathologic data following transoral excision of oropharyngeal cancer is the lack of meaningful data on the appropriate surgical margin, which is not standardized. The most comprehensive study of margin status in head and neck cancer was based on 827 oral cavity cancer patients (343 stage I-II) and suggested that local control rates were significantly improved with a margin width of 7 mm or more, although even wider margin distances also seemed to predict for local failure. Of course, none of these patients had oropharyngeal cancer, and it is unclear whether these results can be translated to a separate disease site with different anatomy and even biology. For example, Wong and colleagues found no difference in local recurrence
between close (1-5 mm) and negative (> 5 mm) margins treated with surgery alone, although only 32 of 192 patients had oropharyngeal cancer. There is a general consensus among head and neck surgeons that invasive cancer within 5 mm or less is an adverse prognostic feature requiring adjuvant therapy, but whether this rule of thumb holds with modern surgical techniques in the oropharynx is unknown. Thus, while patients with pathological stage I-II disease with wide margins, a pathologically negative neck and no other adverse pathologic factors can typically be observed, patients whose surgical procedure or margin width are more concerning for local recurrence may be considered for adjuvant therapy. Careful discussion and collaboration between the members of the multidisciplinary team is necessary to optimize locoregional therapy, and patient preferences on the relative risks and benefits of RT versus observation must be understood.

The active phase II study ECOG 3311 will significantly improve our ability to estimate LRC rates following surgery alone for patients with p16-positive oropharynx cancer. Patients with T1-2, N0-N1 (without extracapsular extension) and clear (> 3 mm) margins, will be observed after transoral surgery, and the final results of this study will further refine these recommendations.

Key Question 3: When is it appropriate to use induction chemotherapy in the treatment of oropharyngeal squamous cell carcinoma (OPSCC)?

Statement KQ13A: Induction chemotherapy should not be routinely delivered to patients with OPSCC.

- **Recommendation strength**: Strong
- **Quality of evidence**: High

Narrative

The curative treatment for the majority of patients with locally advanced OPSCC requires a multidisciplinary effort, often involving various combinations of RT, chemotherapy, and surgery. Despite decades of clinical research (Table 6), however, the optimal integration of chemotherapy with RT in this setting has been controversial, and study interpretation has been complicated by changing local therapy paradigms and epidemiologic shifts. It has been recognized since the mid-1980s that patients demonstrated high response rates to neoadjuvant or Induction(IC) chemotherapy, and the clinical utility of IC was established in landmark trials of advanced larynx (VA Larynx) and pyriform sinus (EORTC) cancers, which revealed that radical surgery was avoidable without any decrement in survival. However, whether IC improves outcomes in OPSCC requires a different calculus, since OS rather than organ preservation is the key issue and outcome of concern.
One of the earliest studies of IC using modern regimens was an Italian multi-center randomized trial,\textsuperscript{102,103} which compared 4 cycles of cisplatin-fluorouracil (PF) followed by locoregional therapy with locoregional therapy alone. Operable patients were treated with resection and adjuvant RT, and inoperable patients received definitive RT alone (65-70 Gy). Slightly over half of all patients on both arms of the study had OPSCC. When the operable and inoperable patients were pooled, there was essentially no impact of IC on OS, or local control (LC), but a significant improvement in distant relapse-free survival (DRFS) was seen. A subset analysis of the inoperable group demonstrated significantly improved LC, DRFS and OS; in terms of toxicity, over a third of IC patients had at least one dose reduction, and grade 2 or greater toxicities were common, including hematologic, stomatitis, vomiting, renal and cardiac changes.

The French cooperative group Groupe d'Études des Tumeurs de la Tête et du Cou (GETTEC)\textsuperscript{104} performed the only available randomized study of IC strictly in patients with OPSCC, demonstrating a significant improvement in OS (median OS 5.1 vs. 3.3 years) with PF-based IC followed by local therapy (either surgery and PORT alone or definitive RT alone to 70 Gy) compared to an identical non-IC arm. These survival gains were seen despite the trial closing early due to concerns of the appropriateness of a chemotherapy-alone arm. The toxicity reported here focused exclusively on the induction component of the treatment and consisted of hematologic (26%), digestive (22%) and mucosal (13%) side effects.

The updated meta-analysis of chemotherapy in head and neck cancer\textsuperscript{32} provided additional information on the benefits of IC. This study found that in comparison to RT alone, concurrent CRT improved LRC (HR 0.74, \(p<0.0001\)), distant metastasis (HR 0.88, \(p=0.04\)), and overall survival (HR 0.81, 95% CI 0.78-0.86). In contrast, the analysis of 31 trials that compared IC plus local therapy with local therapy alone found that IC did not improve overall survival (OS) or LRC, but it did significantly and meaningfully improve the risk of distant failure (HR 0.73, \(p=0.0001\)). However, IC did improve OS in the subset of trials using PF (HR 0.90, 95% CI 0.82-0.99), supporting the hypothesis that a reduction in distant metastases with modern chemotherapy regimens may translate into an OS benefit, despite the high competing risk of locoregional failure in this population.

It is critical to note that RT alone – not concurrent CRT – was the standard non-surgical locoregional therapy in both of these randomized trials, as well as the non-surgical arms included in the meta-analysis. Since concurrent CRT is now understood to improve LRC and OS, the inadequate local therapy arm in these trials of IC
may entirely explain the survival gain with neoadjuvant chemotherapy. This limitation in trial design was only recently rectified in published randomized trials, as will be described below.

The insight that PF-based therapies were associated with a survival benefit produced substantial interest in improving the efficacy of IC, eventually leading to 3-drug regimens, of which TPF (docetaxel, cisplatin, and 5-FU) was the most frequently tested. This triplet was shown to be highly active in early trials and set the stage for two landmark randomized trials comparing TPF with PF. The TAX 324 study examined what has become the North American model for IC, termed “sequential therapy,” involving IC followed by concurrent CRT.105

Patients were eligible if they had squamous cell carcinoma of the oropharynx, oral cavity, larynx or hypopharynx; slightly more than 50% of the patients in each arm had OPSCC. Patients received 3 cycles of IC followed by daily radiation therapy (2 Gy per fraction to 70-74 Gy total) with weekly carboplatin. The addition of docetaxel significantly improved OS (3-year OS 62% vs. 48%), which was apparently mediated through an improvement in locoregional failure (38% vs. 30%), rather than distant metastasis. Hematologic toxicity was substantial, as grade 3-4 neutropenia (83% vs. 56%) and grade 3-4 thrombocytopenia (11% vs. 4%) were also each significantly increased in the docetaxel arm. Importantly, more than 20% of patients in both arms never completed CRT per protocol.

The TAX 323 study had different entry criteria, only allowing unresectable patients, and a slightly AltFX schema consisting of 4 cycles of IC, followed by radiation therapy alone (standard or accelerated fractionation). Oropharyngeal cancer represented slightly less than 50% of the total. Similar results were obtained as in TAX 324, though the magnitude of clinical benefit was smaller (median OS 18.8 vs. 14.5 months). Approximately 10% of patients in the TPF arm did not receive RT, and an additional 5% did not complete the full course. In a follow up quality of life (QoL) study, van Herpen et al. demonstrated trends for improved QoL with TPF both during treatment and through 6 months of follow-up, although the magnitude of improvement was not deemed “clinically meaningful.”

After these data established that TPF was superior to the previously accepted standard regimen, PF, the next logical question was whether IC adds substantially to concurrent CRT, which had been the established standard-of-care for locally advanced disease. Two small phase II studies first investigated this hypothesis. Pacagnella and colleagues compared TPF IC followed by concurrent CRT (70 Gy with 2 cycles of concurrent PF) to concurrent CRT alone in 101 patients. Just over 50% of the patients in this study had OPSCC. The primary
endpoint (rate of radiologic complete response at 6-8 weeks post-radiation) was significantly increased for the IC arm (21% vs. 50%). One limitation of this study was the non-standard concurrent regimen in this trial, consisting of two cycles of chemotherapy spaced 5 weeks apart, with conventionally fractionated RT. Another randomized phase II study, from India, assigned 105 eligible oropharyngeal cancer patients to either concurrent CRT (weekly cisplatin with 66-70 Gy) or 2-3 cycles of TPF IC followed by the same CRT. There were no significant differences in clinical outcomes or toxicities between the two arms.

Three recent phase III studies directly compared optimal induction and optimal concurrent treatment. The Dana-Farber Cancer Institute-based multi-institutional group (PARADIGM) looked at a comparison between TPF IC followed by CRT (weekly carboplatin or docetaxel with 70-72 Gy) versus a concurrent regimen consisting of concomitant boost radiation therapy and 2 cycles of concurrent bolus cisplatin. The University of Chicago-based phase III randomized Docetaxel Based Chemotherapy Plus or Minus IC to Decrease Events in Head and Neck Cancer (DeCIDE) trial used a slightly different model: the CRT consisted of docetaxel, 5-FU and hydroxyurea with twice daily (BID) RT (1.5 Gy per fraction), every other week, versus two 21-day cycles of IC followed by the same CRT regimen. The primary end point for both trials was OS. Just over half of patients in these studies had OPSCC. Both studies closed prematurely without meeting their accrual targets, and both ultimately were underpowered, due in part to the underestimation of OS in the standard arm. Neither demonstrated significant improvements in clinical outcomes between the IC and traditional CRT arms, although patients treated with IC clearly experienced higher toxicity. In PARADIGM, more induction patients developed febrile neutropenia, and there were more serious adverse events (52 versus 22) with IC. Similarly, there were substantially more serious adverse events in the induction arm of DeCIDE (47% vs. 28%), and 5 patients died due to treatment-related toxicity in the induction arm, versus none in the CRT cohort.

The Spanish Head and Neck Cancer Cooperative Group performed a 3-armed phase III study comparing the two induction combinations (TPF vs. PF) and concurrent CRT. Patients were treated with either 3 cycles of IC, followed by a concurrent regimen consisting of 70 Gy with 3 cycles of bolus cisplatin, or the same concurrent regimen alone. Inclusion criteria specified unresectable, locally advanced head and neck cancer, and 55% of the patients had OPSCC. No significant improvement in any clinical outcome was found between any of the 3 arms of the study when analyzed on an intention-to-treat basis. However, a remarkable fraction of patients treated with IC – approximately 30% – never received RT, and an additional number could not complete the planned CRT. Moreover,
of those induction patients who proceeded to CRT, there was significantly more grade 3-4 stomatitis and dysphagia in patients previously treated with IC. An unplanned “per protocol” subset analysis was able to demonstrate improved progression-free survival (HR 0.7) for the induction arms versus the concurrent arm, without an associated improvement in OS, potentially reflecting the selection bias for induction patients tolerant of and responsive to chemotherapy.

These three randomized trials found no progression-free or OS benefit with IC, yet all three studies confirmed higher rates of serious adverse events. Thus, induction chemotherapy should not be routinely implemented in patients with stage IV OPSCC.

Considerations in the discussion of induction chemotherapy

The panel considered the potential indications for IC at length, and as expected, there was robust discussion. Several key limitations of the available studies on the question of IC for OPSCC were noted. First, the vast majority of the referenced studies enrolled locally advanced head and neck cancer patients with diverse primary subsites, including the oral cavity and pharyngolaryngeal axis. Oropharyngeal cancer representation on most of these studies ranged from only 40-60%. Clearly, prognosis varies widely across the diseases encountered in the non-OPSCC subsites, and the resulting mixed outcomes in the pooled analyses may obscure conclusions that could be drawn specifically from the data on OPSCC patients.

Second, the epidemiology of OPSCC has shifted during the evolution of the IC literature, with the emergence of HPV-related disease, and none of the reported IC trials had the opportunity to factor these shifts into their statistical plans. Recent studies have shown better-than-anticipated disease control rates, likely reflecting the increased predominance of HPV-related OPSCC (representing over 80% of OPSCC patients on the DeCIDE study, for example). With such sizeable changes in expected-to-observed outcomes, the initial power calculations for both PARADIGM and DeCIDE were incapable of accurately predicting the number of patients required to address the primary hypothesis, and the resulting statistical power suffered from the small number of events.

Furthermore, there is significant uncertainty in the optimal patient population that would potentially benefit from IC. As seen in several individual trials and confirmed in the meta-analysis, IC reduces the risk of distant metastasis. Thus, patients with more modest risks of distant disease are unlikely to see OS gains with systemically-active chemotherapy; the toxicity of IC and the risk of compromising successful local therapy will outweigh the
improved treatment of micrometastatic disease. Only 10% and 23% of patients in PARADIGM\textsuperscript{110} presented with N3 or T4 disease, respectively, and thus one could argue that the baseline risk of metastatic disease was too low to expect to see a survival advantage with IC, irrespective of the prevalence of HPV-positive disease.

Subset analyses of DeCIDE\textsuperscript{111} provide some insight into the potential benefit of IC in these advanced cases. Among the 96 patients with N2c or N3 nodal disease, there was a non-significant trend ($p=0.19$) for improved survival with IC. Moreover, the cumulative incidence of distant metastasis in patients with LRC was significantly worse with CRT alone (absolute difference approximately 10%, $p=0.043$), supporting the hypothesis that improved systemic control may translate to an OS benefit in patients at sufficiently high risk for distant metastasis, such as in those with advanced nodal presentations.

Indeed, although historically the risk of locoregional failure has been substantially greater than that of metastasis, certain populations of patients do appear to be at particularly high risk for distant spread. For example, in a retrospective analysis of over 300 patients treated at the University of Chicago\textsuperscript{113} (slightly under half with OPSCC), patients with N2c or N3 disease experienced a greater than 2-fold risk of distant failure in comparison to lower volume nodal stage; nearly 40% of these patients treated with CRT-alone developed distant metastases. More recent data restricted to oropharyngeal cancer suggest similar patterns of failure. Investigators from Princess Margaret Cancer Centre performed a retrospective analysis of patients with oropharyngeal cancer treated with RT alone or CRT and described subgroups of both HPV-negative and HPV-positive disease that were at significantly higher risk for distant spread\textsuperscript{114}. Individuals with HPV-negative, T3-4 or N3 cancer, experienced a distant metastasis risk of 28%, and those with HPV-positive, T4 or N3 cancer experienced a metastasis risk of 22%, which may be sufficiently high to see a survival gain with IC. On the other hand, the locoregional failure risks in the high-risk HPV-positive and negative cohorts were 18% and 38%, respectively, so that the competing risks of locoregional failure may mitigate any theoretical survival gain from micrometastasis eradication. Regardless of the therapeutic paradigm, though, it is important to recognize that there are sub-populations of even HPV-positive patients whose survival outcome need significant improvement. In fact, in a separate analysis, these investigators found that younger HPV-positive patients with T4 or N3 disease achieved a 5-year survival of only 57% with CRT, implying that substantial improvements in their treatment paradigm are critically needed.\textsuperscript{115}

Unfortunately, it is unlikely that the comparative benefit of IC in a higher-risk cohort will ever be answered or even revisited through future clinical trials. Induction chemotherapy is currently incorporated into clinical trials in
order to select responsive HPV-positive patients for subsequent de-escalation,\textsuperscript{116} which is a research question to be answered in the coming years. One may conclude from the MACH meta-analysis\textsuperscript{32} that IC using modern agents appears to modestly improve survival over RT alone or surgery through its effect on distant metastasis, which supplies the proof of principle that treating micrometastatic disease may improve OS. Nevertheless, the high-level data do not support this conclusion when the standard comparator is CRT. Three phase III randomized trials comparing IC and chemoradiation therapy (CRT) with CRT alone were all clearly negative; IC was associated with more toxicity without a proven survival benefit. While each study has recognized limitations, in light of this high-level evidence, the panel chose not to specify a high-risk cohort of patients for whom IC may be considered.

Key Question 4: What are the appropriate dose, fractionation, and volume regimens with and without systemic therapy in the treatment of oropharyngeal squamous cell carcinoma (OPSCC)?

In the scenario of definitive non-surgical therapy?

Statement KQ4A: A dose of 70 Gy over 7 weeks should be delivered to gross primary and nodal disease in patients with stage III-IV oropharyngeal squamous cell carcinoma selected to receive standard, once-daily definitive radiotherapy.

- Recommendation strength: Strong
- Quality of evidence: Moderate

Statement KQ4B: The biologically equivalent dose of approximately 50 Gy in 2 Gy fractions or slightly higher should be delivered electively to clinically- and radiographically-negative regions at-risk for microscopic spread of tumor.

- Recommendation strength: Strong
- Quality of evidence: Low

Statement KQ4C: Altered fractionation should be used in patients with stage IVA-B oropharyngeal squamous cell carcinoma treated with definitive radiotherapy who are not receiving concurrent systemic therapy.

- Recommendation strength: Strong
- Quality of evidence: High

Statement KQ4D: Either accelerated radiotherapy or hyperfractionated radiotherapy may be used in patients with oropharyngeal squamous cell carcinoma treated with altered fractionation definitive radiotherapy after a careful discussion of patient preferences and the limited evidence supporting one regimen over the other.

- Recommendation strength: Conditional
- Quality of evidence: High

Statement KQ4E: Either standard, once-daily radiotherapy or accelerated fractionation may be used when treating oropharyngeal squamous cell carcinoma with concurrent systemic therapy after a careful discussion of patient preferences and the risks and benefits of both approaches.

- Recommendation strength: Conditional
- **Quality of evidence**: High

**Statement KQ4F**: Altered fractionation should be used in patients with T3 N0-1 oropharyngeal squamous cell carcinoma treated with definitive radiotherapy who do not receive concurrent systemic therapy.

- **Recommendation strength**: Strong
- **Quality of evidence**: Moderate

**Statement KQ4G**: Altered fractionation may be used in patients with T1-2 N1 or T2 N0 oropharyngeal squamous cell carcinoma treated with definitive radiotherapy alone who are considered at particularly significant risk of locoregional recurrence, after a careful discussion of patient preferences and the limited evidence supporting its use in this scenario.

- **Recommendation strength**: Conditional
- **Quality of evidence**: Low

**Narrative**

A relatively large body of literature has reported outcomes for OPSCC patients in the setting of randomized clinical trials. Important caveats in interpreting this literature, much of which directly tested dose and fractionation, must include the recognition that most of these studies included patients with advanced squamous carcinomas arising in sites other than the oropharynx, including oral cavity, larynx, and hypopharynx. Although these studies described the relative proportions of these primary sites, their conclusions were often based on a pooled analysis. Human papillomavirus-associated OPSCC has been increasing in prevalence and proven to have a much more favorable prognosis than non-HPV related OPSCC. The proportion of OPSCC patients with HPV-related cancers in most landmark studies of fractionation remains unknown and is likely to be significantly lower than in contemporary patient populations, raising the question of the generalizability of older studies to modern cohorts. The panel recognizes there is important ongoing work examining the different outcomes between and within HPV positive and negative OPSCC in order to define prognostic subgroups. This research has led to the development and implementation of prospective clinical trials examining treatment de-intensification strategies for favorable prognostic subgroups. In the future, these studies may result in significant changes in the recommended RT doses for the management of favorable-risk disease. To date, the results of RT de-intensification approaches are not yet available and there are no prospective randomized data suggesting that HPV-positive patients gain any less benefit from AltFX regimens. Thus, any recommendation made for oropharyngeal cancer patients within these guidelines apply equally to HPV-positive and negative individuals.
Primary radiation therapy has long been a standard-of-care for the management of OPSCC, and acceptable doses to gross disease and elective regions is the first consideration in the discussion of dose and fractionation regimens. Intensity modulated radiation therapy (IMRT) has become the most commonly used modality in the United States as randomized trials have shown that IMRT leads to fewer cases of moderate to severe xerostomia, commonly known as dry mouth, than other radiation techniques. Xerostomia, a potential side effect to radiation when the salivary glands are damaged, can affect basic functions like chewing, swallowing and breathing; senses such as taste and smell; and can significantly alter the patient’s appearance and voice. Although there are various IMRT treatment strategies (e.g. sequential IMRT, simultaneous integrated boost, etc.), the guideline does not endorse or recommend one approach over another.

There have been no randomized trials comparing total RT dose delivered once-daily for OPSCC, and a variety of dose-fractionation regimens have evolved over the years. In the United Kingdom, the treatment approach classically delivered 50-55 Gy in 15-20 fractions over 3-4 weeks, while in Europe and most of North America, more extended fractionation schemes were employed, delivering 66-72 Gy in 32-40 fractions over 6.5 to 8 weeks. Though retrospective in nature, comparisons between these regimens suggested that shorter courses delivering less total dose with larger fraction sizes resulted in lower rates of control for advanced disease with increased late effects. This observation, combined with the enhanced toxicity in combining concurrent chemotherapy with fraction sizes greater than 2 Gy, resulted in the emergence of a total dose of 68-70 Gy delivered in 33-35 fractions over 6.5 to 7 weeks as the most common once-daily fractionation regimen.

The delivery of 70 Gy to gross disease has been selected as the standard treatment approach for many practice-defining randomized trials of both fractionation and concurrent chemotherapy, including RTOG 9003, EORTC 22851, the US Intergroup study, and RTOG 0129. Thus, when choosing a conventionally fractionated, once-daily RT regimen for patients with stage III-IV OPSCC, the panel considers 70 Gy over 7 weeks to be the reference standard.

Standard Prophylactic Dose to Elective Volumes at Risk of Microscopic Disease

The radiotherapeutic management of all stages of OPSCC requires treatment to be delivered electively beyond areas of apparent gross disease. Elective volumes include margins around gross disease as well as nodal levels at risk of harboring microscopic nodal metastasis. The location and extent of these elective volumes will be
dictated by specific characteristics of the primary tumor (size and anatomic extent) and grossly involved nodes. The anatomic delineation of node levels at risk should be consistent with published guidelines.\textsuperscript{125} The dose and volume of elective irradiation is often the driver of dose to critical organs-at-risk, including salivary glands and dysphagia-associated structures such as the larynx and pharyngeal constrictors, emphasizing the importance of considering the dose necessary to sterilize microscopic disease.

Although the evidence is nearly entirely retrospective, prophylactic RT at 2 Gy per day to a total dose of 50 Gy has been widely regarded as the standard dose for the elective treatment of areas at risk for subclinical or microscopic involvement. This dose was first suggested by Fletcher based on observations of control rates in head and neck and breast cancer patients.\textsuperscript{126} Withers et al.\textsuperscript{122} expanded these observations to a wider range of patients, concluding a dose of 50 Gy in 2 Gy fractions was necessary to achieve a 90\% reduction in the incidence of recurrence within the electively irradiated tissues. Although this dose has been utilized in many clinical trials, many do not specifically report rates of nodal failure, or distinguish between in-field versus elective failure. Nevertheless, some insights may be gleaned from these trials.

For example, the DAHANCA 6/7 trials\textsuperscript{127} limited dose to a maximum 50 Gy in 2 Gy fractions to elective neck regions and observed isolated neck failure (elective and therapeutic regions) in only 69/1476 (4.7\%) patients. Goshal et al.\textsuperscript{128} delivered 44-45 Gy to the elective neck regions and reported isolated regional failures in 37/285 (12.9\%) patients. The ARTSCAN randomized trial\textsuperscript{129} comparing conventionally-fractionated RT with treatment over 4.5 weeks\textsuperscript{130} treated the elective nodal regions to 46 Gy and reported isolated nodal failure in 34/733 (4.6\%) patients. These three randomized studies have cumulatively reported isolated nodal failures in 140/2494 (5.6\%) of patients receiving the equivalent of 50 Gy in 2 Gy fractions or less to elective nodal regions. These recurrences would have included failures occurring in pre-existing nodes, and therefore the failure rates in the elective volumes could be assumed to be less than this.

Retrospective analyses that have specifically identified electively irradiated neck failures include Lambrecht et al.\textsuperscript{131}, observing only 2 recurrences out of 368 (<1\%) in elective neck regions receiving 44-50 Gy. More recently, investigators from MD Anderson reported a risk of elective regional failure with primary control of only 4/776 (< 1\%), and many of these controlled patients were treated with a low anterior neck field to 50 Gy.\textsuperscript{132} With the emergence of routine IMRT planning and simultaneous integrated boost/“dose-painting” approaches, RT plans are now often delivered in a single phase, rather than the conventional, serial cone-down approach using 2 Gy
per fraction. Thus, a plan delivering 70 Gy in 35 fractions to sites of gross disease must simultaneously deliver 56 Gy in 35 fractions of 1.6 Gy to areas of subclinical or microscopic involvement to achieve the radiobiologic equivalent of 50 Gy in 25 fractions. Using this approach, Duprez et al.\textsuperscript{133} have reported a regional relapse risk in 3/286 (1\%) patients within the elective neck volumes receiving 56 Gy.

The panel therefore believes there is sufficient evidence to strongly recommend the ongoing use of a radiobiologic equivalent of 50 Gy delivered in 2 Gy fractions to electively treat areas at risk of subclinical or microscopic involvement. The high rates of neck control observed with this approach raise the possibility of elective dose reduction, which would be expected to reduce dose to the salivary tissue and pharyngeal constrictors. In fact, if one considers that concurrent chemotherapy increases the biologically effective dose of any given dose of irradiation,\textsuperscript{134} treatment with concurrent CRT may afford the opportunity for dose reduction. At this time, however, there is insufficient data to recommend elective dose reduction below the equivalent of 50 Gy in 2 Gy fractions, although this is an area of active research.\textsuperscript{135}

\textit{Altered fractionation radiotherapy without concurrent chemotherapy}

Poor historical outcomes for patients with stage III-IV OPSCC treated with conventionally-fractionated RT alone\textsuperscript{13} led to efforts to improve oncologic results by intensifying treatment. This intensification utilized two distinct approaches. One approach was the addition of cytotoxic systemic therapy delivered concurrently with RT, and the other was to alter the RT fractionation schemes from standard, once-daily administration.

The concept of AltFX refers to fractionation regimens that differ from standard, once-daily treatment. AltFX regimens are based on radiobiologic principles that suggest giving a higher total dose and/or giving it over a shorter total treatment time (to counter tumor repopulation) will result in improved tumor control. Similar principles suggest delivering this dose with reduced fraction sizes (< 2 Gy) should result in reduced late tissue effects permitting delivery of a higher total dose. AltFX regimens may be classified as either AccFX, delivering a similar or reduced total dose over a shorter total time, or HFX, delivering an increased total dose over a similar time with multiple small daily fractions. Many AltFX regimens represent a hybrid of these approaches.

AltFX regimens for the treatment of head and neck squamous carcinomas, including OPSCC, have been compared to standard RT in a number of randomized phase III clinical studies (Table 7). The majority of these studies have demonstrated that AltFX regimens improve LRC by 8-20\% compared to once-daily RT alone, but the
increased control in the primary site and neck generally did not translate into an OS advantage. In addition, this disease control improvement frequently came at the cost of increased but manageable acute toxicity, with a variable impact on the risk for late toxicities.

Accelerated regimens with or without a total dose reduction have been the AltFX approach most often compared with standard RT. In the landmark RTOG 9003 trial\textsuperscript{136} reported results on 1073 patient randomized to one of three AltFX arms compared to standard RT (70 Gy in 2 Gy fractions over 7 weeks). Two of these arms represented AccFX delivered over 6 weeks. One arm delivered BID treatment throughout but had a two-week break, to achieve a total dose of 67.2 Gy, while the other arm employed a scheme without a break, delivering once daily 1.8 Gy for six weeks with a second 1.5 Gy fraction as a concomitant boost to the primary on the last 12 treatment days for a total dose of 72 Gy. The concomitant boost arm demonstrated an absolute improvement of 9.5\% and 7.6\% in two year LRC and disease free survival (DFS) (p=0.05 and 0.054 respectively) which came at a cost of an absolute increase of 24\% in grade 3 or higher acute toxicity (multiple endpoints). The split course arm demonstrated no significant improvement in LRC or DFS and neither arm improved OS. The recent final analysis of RTOG 9003\textsuperscript{123} demonstrated that the initially improved LRC with AccFX lost its statistical significance with longer follow-up, and OS was still unaffected by this regimen. Although the continuous acceleration arm did improve disease-free survival (HR 0.82, p=0.05), there were non-significant trends for worse late toxicity in this arm. Notably, patients who were disease-free at 1-year were significantly more likely to be feeding tube dependent with continuous AccFX (1-year probability 13.4\% vs. 4.6\%, p=0.02).

The DAHANCA group\textsuperscript{137} randomized 1485 patients with squamous cell carcinoma of the head and neck (larynx, pharynx, and oral cavity) to receive standard RT (66-68 Gy in 2Gy fractions) delivered 5 days per week versus the same dose delivered with AccFX with six fractions per week. They observed a statistically significant 10\% benefit in 5 year LRC (70\% vs 60\%) and a 13\% benefit in DFS (73\% vs 66\%) for the accelerated regimen. No benefit in OS was observed. Patients treated with the accelerated regimen experienced a 20\% higher risk of acute confluent mucositis, and the duration of this acute mucositis was longer, but there was no significant difference in longer-term mucosal toxicities. A similar LRC benefit (absolute 12\%) was observed with this regimen when the study was later replicated in 908 patients with more advanced disease,\textsuperscript{138} with a parallel increase in acute but not late mucosal toxicity. In an interesting subgroup analysis of the original DAHANCA study,\textsuperscript{139} the LRC benefit of RT
acceleration was maintained in p16 positive (mostly oropharynx) patients and was perhaps even greater than that observed in p16 negative (mostly non-oropharynx) patients.\textsuperscript{139}

The EORTC 22851 trial\textsuperscript{124} randomized 500 patients to receive 72 Gy delivered in twice-daily fractionation over 5 weeks versus SFX (70 Gy in 2 Gy fractions over 7 weeks). Although this study demonstrated a 13% improvement in LRC at 5 years the actuarial rates of grade 3-4 late toxicity in the accelerated arm was 37% at 3 years versus 15% for the control arm. This finding, coupled with increased rates of acute toxicity and the lack of an overall or cancer-specific survival benefit, led the authors to conclude that a less toxic scheme should be used and emphasizes that there is a limit to the degree of safe acceleration.

It should be noted not all studies have demonstrated significant benefits to AccFX. The Trans-Tasman Radiation Oncology Group (TROG) group\textsuperscript{140} reported outcomes for 343 patients (67% OPSCC) randomized to AccFX (59.4 Gy in 1.8 Gy bid over 24 days) versus standard 70 Gy in 2 Gy fractions over 7 weeks). In this modest sized study, they observed a nonsignificant trend towards improved disease free and disease specific survival at 5 years (41% and 46% vs 35% and 40% respectively, p=0.323 and 0.398) for the accelerated arm. The multicenter Swedish ARTSCAN study\textsuperscript{129} randomized 750 patients (48% OPSCC) to standard RT (68 Gy in 2 Gy fractions over 7 weeks) versus AccFX (1.1 Gy + 2 Gy/day over 4.5 weeks to 68 Gy). No significant difference was observed in OS or LRC between the two arms.

The use of pure hyperfractionation (HFX) has been demonstrated to improve outcomes. The EORTC 22791 study\textsuperscript{141} reported the results of 325 patients with T2-T3, N0-N1 OPSCC randomized to receive 70 Gy in 35 daily fractions over 7 weeks or hyperfractionated treatment delivering 1.15 Gy BID to a total dose of 80.5 Gy over 7 weeks. A significant improvement was seen in 5 year rates of local control at the primary site (59\% vs 40\% p=0.02) in the HFX arm, although improvement in OS was only borderline significant (p=0.08). There was a significant increase in acute mucositis with HFX (18\% absolute increase in grade 3 mucositis), but there was no difference in any late effect between the two arms.

One arm of RTOG 9003\textsuperscript{123} utilized a hyperfractionated approach, delivering 68 BID fractions of 1.2 Gy to a total dose of 81.6 Gy. The final analysis observed not only an improved and sustained rate of LRC (relative reduction in locoregional failure of 21\%) but also an OS advantage when patients were censored at 5 years (HR 0.81, p=0.05). This benefit was lost with longer follow-up, which may relate to second primary cancers or death from other causes obscuring a disease control benefit from HFX. Treatment with HFX was associated with
significantly more acute toxicity: 54% of patients in this cohort experienced at least one grade 3 toxicity, versus 35% of patients treated once-daily. However, there was no significant increase in late toxicities with HFX. Although disease-free patients were more likely to be gastrostomy-dependent at 1 year in comparison to disease-free individuals treated with SFX (17.3% vs. 4.6%, p<0.01), by 5 years there was no significant difference between the arms, and in fact the trend favored HFX (4.8% gastrostomy-dependence following HFX vs. 8.3 % SFX, p=0.66).

These results were largely echoed by a large meta-analysis (MARCH) based on individual patient data, which examined outcomes for 6,515 patients enrolled in 15 randomized trials comparing standard to AltFX radiation therapy (accelerated or hyperfractionated) for advanced head and neck cancers. Oropharyngeal cancer comprised approximately 44% of all patients. This meta-analysis reported absolute reductions in the 5-year risk of locoregional recurrence of 9.4% and 7.3% in patients treated with HFX or AccFX (without dose-reduction) regimens, respectively. Most of this benefit was due to reduced recurrence at the primary site. The absolute probability of OS at 5 years was significantly improved by 3.4% with AltFX. There was no significant difference in this benefit for tumors arising in the oropharynx compared to hypopharynx larynx or oral cavity, but the survival advantage with AltFX was lost in patients older than 71 years. The survival benefit was significantly greater with HFX (8.2% vs. 2% at 5 years for patients receiving HFX and AccFX without a dose-reduction, respectively).

Although individual trials were unable to confirm an OS advantage with AltFX, the majority of studies have demonstrated consistent and meaningful improvements in LRC and trends towards reductions in overall mortality. The influential MARCH meta-analysis provided further evidence for the superiority of AltFX in patients with locally advanced head and neck cancer. Given the adverse clinical consequences of locoregional failure and the potential for a survival gain with its use the panel strongly recommends AltFX radiation therapy should be used for patients with stage IVA-B OPSCC managed with primary radiation therapy without concurrent systemic therapy. In comparison to treatment with concurrent chemotherapy, in which late toxicities were comparable to patients treated with RT alone, there were somewhat consistent signals that AltFX modestly worsened late toxicities. One particularly important late toxicity is swallowing dysfunction, which in the worst case can lead to the long-term requirement for enteral feeding. However, modern RT techniques may minimize these risks, as a large multi-
institution pooled analysis of 2,315 OPSCC patients managed with IMRT concluded that there was no difference in one year rates of gastrostomy tube dependence between patients managed with standard versus AccFX. Nevertheless, in patients treated with AltFX, particular attention must be paid to the dysphagia organs-at-risk and early and persistent swallowing rehabilitation.

It is unclear whether HFX or acceleration is a better treatment paradigm. The only study comparing the two concepts was RTOG 9003, which slightly favored HFX, but there are several issues that prevented the panel from declaring HFX the proverbial winner. The direct unadjusted comparisons of LRC showed no statistically significant or clinically meaningful difference between the fractionation arms, and the only improvement in HFX was seen with multivariable analysis that censored patients after 5 years (with effect estimates that are numerically nearly superimposable). Both HFX and AccFX improved disease-free survival, and while only HFX improved overall survival with censoring at 5 years, this was a post hoc analysis of uncertain legitimacy, and the difference falls away afterwards, with the curves superimposable. From a toxicity perspective, there were no statistically significant differences between HFX or AccFX (concomitant) in feeding tube rate at 6 months, 1 year, or 5 years. Either when lumping the 6 week regimens together or comparing the regimens independently, the differences in grade 3-5 toxicity were not significantly different (although the absolute differences and p values of both of these comparisons certainly favored HFX and were close to 0.05).

These results from this study are certainly provocative but not confirmatory, suggesting a favorable therapeutic ratio with HFX over AccFX. However, especially when considering the 2D treatment era in which this study was performed, such that late effect profile following AltFX with IMRT would be expected to be quite different, the guideline panel did not feel that the evidence from this trial sufficiently supports HFX over AccFX to warrant a recommendation statement to that effect.

The MARCH meta-analysis also suggested an improvement with HFX, but as detailed above, there are significant flaws with this indirect comparison. Nevertheless, HFX regimens delivered without concurrent chemotherapy are not in wide-spread use for the management of OPSCC. This pattern is in part due to the increased resources required to deliver these treatments, coupled with the emergence of concurrent chemotherapy approaches that mitigated the benefit of AltFX. AccFX, particularly using the DAHANCA approach, is significantly more convenient than BID treatments over 7 weeks, and provides a more practical platform for both clinical trials and routine practice. That said, at the present time, the panel concludes the available evidence supports the use of either
form of AltFX for the management of stage IVA-B OPSCC in patients not receiving systemic therapy, and the relative strengths and weaknesses of the strategies should be carefully discussed with patients.

*Altered fractionation radiotherapy for patients with stage III oropharyngeal cancer*

Deriving recommendations for patients with stage III OPSCC is more challenging; stage III disease may present with a wide range of primary tumor volumes (T1-T3, N1). The majority of patients in randomized studies of AltFX presented with stage IV disease, and thus the advantages of this approach are less clear with lower-bulk disease. Although most of the studies included patients with stage III disease, the proportion of patients with this stage was typically less than 30%, and the outcomes were rarely stratified by T and N or AJCC stage. One exception is EORTC 22791,\textsuperscript{141} which randomized patients with T1-3 N0-1 oropharyngeal cancer to HFX or conventional daily RT. Although the study showed an overall benefit in LRC, this gain was strictly in patients with T3 tumors. Similarly, in EORTC 22851,\textsuperscript{124} which randomized stage III and IV patients (all disease sites) to AccFX or conventional RT, the LRC advantage with acceleration was only seen in N2-3 or T4 patients. Both studies emphasize the concept that the relative benefit of AltFX is greatest with larger volume disease.

As detailed in the narrative of KQ1, single institution retrospective reports have also described significant differences in local control as a function of T-stage or tumor volume. The preponderance of data strongly suggests that patients with larger volume disease need additional local therapy beyond conventional RT alone. Since concurrent systemic therapy is most consistently associated with superior LRC and OS, patients with T3 N0-1 disease who are candidates for concomitant systemic therapy should receive it, as detailed in KQ1. For individuals who would not tolerate such treatment, the panel strongly recommends AltFX alone.

The data guiding RT fractionation recommendations for stage II and III (T1-2 N1) are far less compelling, and there is significant volume heterogeneity even in this cohort. For individuals with T2 N0 and T1-2 N1 stage III disease considered at particularly significant risk for primary and/or nodal recurrence, AltFX may be employed, but the clinician must weigh the patient’s estimated risk of locoregional failure with conventional treatment against the recognized toxicities of AltFX. The relative lack of data guiding this recommendation should be carefully discussed with patients.
The use of modestly AccFX alone was shown to result in excellent outcomes in RTOG 0022,\textsuperscript{145} which treated 67 patients with T1-2 N0-1 OPSCC with 66 Gy in 30 fractions. Most (75\%) of these patients had T2 disease. There were 7 locoregional failures, all in current or former smokers (7/36, accounting for crude 19\% risk of failure in this cohort), although two of these recurrences were in patients with major dosimetric violations. Only six patients had new or continuing grade 3 or 4 toxicity after 15 months. In total, these prospective data suggest that this accelerated regimen is a reasonable approach for selected patients.

\textit{Altered fractionation radiotherapy with concurrent chemotherapy}

The therapeutic alternative to AltFX for locally advanced head and neck cancer is concurrent CRT, the benefits of which were discussed in a prior narrative (KQ1). A large meta-analysis has reported improved survival and LRC with the addition of concurrent chemotherapy to RT,\textsuperscript{32} a benefit maintained using either standard or AltFX. The emergence of data demonstrating improved outcomes with either AltFX approach or the addition of chemotherapy to standard, once-daily RT naturally led to studies examining the addition of chemotherapy to AltFX radiation therapy. Initially the addition of chemotherapy to AltFX RT was compared to AltFX RT alone. Several randomized studies have demonstrated improved LRC and survival with such a strategy.\textsuperscript{19,146-148} For example, Brizel et al.\textsuperscript{146} achieved this with similar levels of toxicity, but this required a reduced RT dose and treatment break. Bensadoun et al. maintained the same dose of RT in both arms (75.6-80.4 Gy) while delivering full dose cisplatin (100 mg/m\textsuperscript{2}) and 5-fluorouracil infusion. Although the reported toxicity data was similar between the two arms they described a 13.6\% risk of “early death” in the combined treatment arm, emphasizing the potential risk in this treatment strategy.

The next logical question was whether AccFX was superior to conventionally-fractionated CRT, a hypothesis that was examined in two large phase III studies. RTOG 0129\textsuperscript{149} randomized 743 patients to SFX (70 Gy in 35 fractions over 7 weeks) delivered with 3 cycles of concurrent cisplatin or AccFX (70 Gy in 35 fractions over 6 weeks) delivered with 2 cycles of concurrent cisplatin.\textsuperscript{33} The mature results of this study (median follow-up 7.9 years) indicated no difference in progression free survival or OS with similar acute and late toxicities. The GORTEC) 99-02\textsuperscript{25} trial was a three arm study randomizing 840 patients to either standard CRT (70 Gy in 7 weeks plus 3 cycles carboplatin-fluorouracil) versus AccFX (70 Gy in 6 weeks plus 2 cycles carboplatin-fluorouracil)
versus VeryAccFX alone (64.8 Gy in 1.8 Gy bid over 3.5 weeks).\textsuperscript{25} No difference was observed between the CRT and AccFX arms in 3 year rates of locoregional failure, distant metastasis, progression-free survival, OS or acute or late toxicity, with both chemotherapy arms superior to the VeryAccFX approach in all aspects.

The addition of chemotherapy to aggressive AltFX approaches must be considered with caution given the potential for increased acute and late effects associated with this approach. For this reason, both RTOG 0129\textsuperscript{149} and GORTEC 99-02\textsuperscript{150} delivered less chemotherapy in the AltFX arm than the SFX arm. This strategy seems to have been successful in maintaining equivalent toxicities between the arms without compromising tumor control. In RTOG 0129, there were no statistically significant differences in acute or late toxicities, although there was a trend for increased long-term gastrostomy dependence in the accelerated arm (13.2\% vs. 5.9\% at 5 years, p=0.08). On the other hand, more patients received the correct numbers of cisplatin cycles in the accelerated arm (88\% vs. 69\%), owing to the challenge of managing the toxicities with bolus cisplatin. Similarly, in the Groupe d’Oncologie Radiothérapie Tête et Cou (GORTEC) 9902 trial, \textsuperscript{150} 92\% of patients in the accelerated CRT arm received the correct number of cycles, in comparison to only 71\% of individuals in the conventional arm.

Since two large phase III trials have shown no significant difference in oncologic outcomes or toxicities between conventional and AccFX with three and two cycles of bolus cisplatin or carboplatin/fluorouracil, respectively, the panel concludes either fractionation approach may be considered for patients with stage IVA-B oropharyngeal cancer treated with these chemotherapy regimens. The relative risks and benefits of more chemotherapy versus more intensive radiation treatment should be carefully discussed with the patient, and the decision should be made on a patient-specific basis, in concert with their preferences and values.

\textit{In the scenario of adjuvant post-operative radiotherapy?}

\textbf{Statement KQ4H}: Adjuvant post-operative radiotherapy should be delivered to regions of microscopically-positive primary site surgical margins and extracapsular nodal extension at 2 Gy/fraction once daily to a total dose between 60 and 66 Gy.

- \textbf{Recommendation strength}: Strong
- \textbf{Quality of evidence}: Moderate

\textbf{Statement KQ4I}: Adjuvant post-operative radiotherapy delivered without concurrent systemic therapy should treat regions of microscopically-positive primary site surgical margins and extracapsular nodal extension at 2 Gy/fraction once daily to a total dose of 66 Gy, although there are limited data guiding this recommendation.

- \textbf{Recommendation strength}: Conditional
- \textbf{Quality of evidence}: Weak
Statement KQ41: Adjuvant post-operative radiotherapy should be delivered to the tumor bed and involved, dissected lymph node regions at 2 Gy/fraction once daily to a total dose of 60 Gy in the absence of primary site positive margins and extracapsular nodal extension.

- **Recommendation strength**: Strong
- **Quality of evidence**: Moderate

**Narrative**

A dearth of prospective randomized data exist addressing dose-fractionation issues in the post-operative, high-risk setting. Peters et al.\(^8\) randomized patients receiving PORT alone (18% oropharynx) to one of four dose levels depending on the type and number of adverse pathologic risk factors. Patients deemed lower-risk were first randomized to 52.2-54 Gy versus 63 Gy, but an interim analysis showed this lower dose was inadequate, and the study was completed comparing 57.6 Gy in 32 fractions with 63 Gy in 35 fractions in this lower-risk population. The higher-risk patients were randomized to 63 Gy in 35 fractions versus 68.4 Gy in 38 fractions. Because the risk stratification was a function of both the type and number of adverse characteristics, patients with ECE and positive margins (less than 5 mm) were included in all dose levels. The authors found no difference in 2-year recurrence rates for all higher-risk patients. However, in a post hoc subset analysis, patients with ECE experienced superior 2-year LRC with 63 Gy and 68.4 Gy versus 57.6 Gy, but no difference between the higher dose levels (74% and 72% versus 52%, respectively, p=0.03). Consistent with this finding, in a retrospective analysis of 102 oral cavity/oropharynx patients treated with differing doses of PORT, Zelefsky et al.\(^15\) showed that non-oral tongue patients with positive or close margins receiving a minimum of 60 Gy had significantly improved LRC versus lower doses (92% vs. 44% at 7 years, p=0.0007).

Ang et al.\(^6\) performed a randomized assessment of AccFX vs SFX in high-risk post-operative patients (63 Gy/5 weeks vs 63 Gy/7 weeks). There were trends towards improved LRC (p=0.11) and OS (p=0.08) with acceleration, the latter result partially owing to a 33% incidence of distant failure. AccFX increased grade 3 mucosal toxicity (62% vs 36%). Sanguineti et al.\(^15\) also compared AccFX vs SFX (64 Gy/5 weeks vs 60 Gy/6 weeks). There were no differences with respect to local-regional control, distant failure, nor overall survival. Grade 3 mucosal toxicity was significantly increased, however (53% vs 27%). Suwinski et al.\(^15\) also compared post-operative AccFX against SFX. Approximately 40% of the patients had oral cavity/oropharynx primaries, and AccFX resulted in significantly better local-regional control (74% vs 53%) in this subset. There was no difference in OS
with accelerated treatment. Again, the cost was a significantly higher incidence of grade 3 mucosal toxicity with AccFX (60% vs 33%).

Caution should be exercised in attempting to apply these data to the clinical setting. The vast majority of patients with high-risk pathologic features now receive concurrent CRT rather than RT alone. Additionally, a minority of the patients treated on the aforementioned trials had OPSCC primary tumors (17-40%). These trials enrolled most of their subjects during the 1980s and 1990s, and OPSCC itself has evolved since then from a smoking related disease to one that is predominantly caused by HPV infection. Most investigational efforts are now focused on therapeutic de-escalation given its more favorable prognosis.

Changes in RT delivery techniques must also be kept in mind when interpreting these data. Most of the patients were treated with Co-60 or 4 MV photons using 2-D parallel opposed fields prescribed at mid-plane. It is likely that the prescribed daily dose of 1.8 Gy was 10-15% higher (2.0-2.1 Gy) in the neck as a consequence of dose inhomogeneity. In this respect, past is prologue for patients treated with contemporary IMRT dose painting techniques that commonly deliver daily doses of 2.2 Gy to high risk regions. Lukens et al. have shown a significantly increased risk of soft tissue necrosis when daily fractions of this size are used for PORT in OPSCC.154

In summary, the small volume of randomized data suggests improved LRC with treatment doses beyond 57.6 Gy for patients with positive margins and/or ECE. The three randomized trials of AccFX provided mixed results on LRC, but they were consistent in showing no OS benefit and markedly increased mucosal toxicity with intensified treatment. Therefore, the panel strongly recommends that patients receiving adjuvant PORT for positive margins and/or ECE are treated using daily fraction sizes of 2 Gy to a total dose between 60 and 66 Gy. This dose (60 Gy) is comparable to the 63 Gy in 7 weeks from Peters et al. while reducing the total package time (i.e. time from surgery to the end of RT).

There are insufficient data to properly answer whether dose-escalation beyond 60 Gy provides additional clinical benefit in patients with high-risk pathology. As detailed above, the Peters trial80 showed no further benefit to 68.4 Gy in this population. That said, the landmark RTOG 950152,155 and EORTC 2293150 trials used post-operative doses of 60-66 Gy (RTOG) and 66 Gy (EORTC) to regions of highest risk. Without concurrent cisplatin, patients in the RTOG trial with positive margins and/or ECE had a 10-year locoregional recurrence risk of 33%, and individuals in the EORTC study treated with RT alone had a 5-year locoregional recurrence risk of 31%. Given these poor LRC outcomes with RT alone, the expert panel is more concerned with the complications of locoregional
failure than mucositis. The panel conditionally recommends that patients with positive margins and/or ECE receiving PORT alone receive a total dose to these regions of 66 Gy in 2 Gy fractions, although the lack of high-quality data guiding this statement must be acknowledged.

The evidence guiding dose and fractionation regimens in the setting of negative margins and no ECE is similarly scant. The Peters study initially randomized low risk patients to 52.2-54 Gy vs 63 Gy at 1.8 Gy per fraction. Because of a higher incidence of local failure in the low dose cohort (p=0.02), the total dose subsequently was increased to 57.6 Gy. No advantages were observed with 63 Gy vs 57.6 Gy, but grade 3-4 toxicity was higher (7.7% vs 3.3%) with the higher dose. Low risk was defined as having not more than one of the following factors: oral cavity primary, mucosal margins close or positive, nerve invasion, ≥2 positive lymph nodes, largest node > 3 cm, treatment delay greater than 6 weeks, and performance status > or = 2. Ang’s trial used the same clinical and pathologic criteria with low risk defined as having none of them and intermediate risk as having only one exclusive of ECE. Low-risk patients were observed; all intermediate risk patients (n=31) received 57.6 Gy and had the same local-regional control as the low risk patients.

The panel considers that the dose of 57.6 Gy in 1.8 Gy fractions is approximately equivalent to 56 Gy in 2 Gy fractions. The daily dose is higher and total treatment time is shorter with 2 Gy fractions, arguing in favor of 56 Gy as the reference dose. However, because there are few data showing successful long-term control outcomes with 56 Gy, and as stated above, the true dose to involved stations using opposed lateral fields was presumably higher than the nominal dose, the panel chose a more conservative level and strongly recommends delivering 60 Gy to the tumor bed and involved lymph node stations in the absence of positive surgical margin (PSM) and ECE.

Currently, the most significant issue concerns the distinction between low risk and high-risk disease. It is important to recognize that most patients with high risk disease now receive adjuvant CRT (vide supra). Features including PNI and multiple positive lymph nodes in addition to PSM and ECE conferred eligibility into the RTOG and EORTC trials that developed this standard. The majority of the patients on these trials did not have oropharyngeal cancer, however, and secondary analyses have shown that chemotherapy did not clearly augment the effectiveness of RT for lower-risk pathologic features such as PNI and multiple nodes. Consequently, one could rationally infer in a contemporary setting that there is no benefit to be gained from dose escalation or acceleration without PSM or ECE.
Consensus still exists that primary site PSM is a high-risk feature. For surgically treated HPV-positive disease, however, some recent large retrospective studies suggest that minimal nodal ECE no longer constitutes high risk disease and that these patients do just as well with adjuvant RT only (60 Gy) instead of adjuvant CRT. The older studies of post-operative irradiation followed the traditional paradigm of dose intensification to improve outcome. Since HPV driven disease has a much more favorable prognosis than its HPV negative (-) counterpart, current developmental strategies are focused on therapeutic deintensification. ECOG 3311 is a randomized phase II study enrolling p16-positive oropharyngeal cancer patients who have undergone transoral resection. Patients with “intermediate-risk” pathologic factors (defined as PNI, LVI, 2-4 LN’s, <1 mm ECE, and/or margins <3 mm) will be randomized to receive 2 Gy daily either on an investigational arm of 50 Gy or a control arm of 60 Gy. The outcomes of this trial will help to redefine the standard-of-care for patients receiving adjuvant PORT in this population, but pending the mature results of this study, post-operative treatment dose and fractionation should not vary by p16 status.

In the scenario of early T-stage tonsillar carcinoma?

Statement KQ4K: Unilateral radiotherapy should be delivered to patients with well-lateralized (no soft palate extension or base of tongue involvement), T1-T2 tonsillar cancer and N0-N1 nodal category.
- **Recommendation strength**: Strong
- **Quality of evidence**: Moderate

Statement KQ4L: Unilateral radiotherapy may be delivered to patients with lateralized (<1 cm of soft palate extension but without base of tongue involvement) T1-T2 N0-N2a tonsillar cancer without clinical or radiographic evidence of extra-capsular extension, after careful discussion of patient preferences and the relative benefits of unilateral treatment versus the potential for contralateral nodal recurrence and subsequent salvage treatment.
- **Recommendation strength**: Conditional
- **Quality of evidence**: Low

Narrative

The hypothetical advantages of ipsilateral-only RT for tonsillar cancer include improved short- and long-term functional outcomes and quality-of-life. In addition, the smaller treatment volumes may potentially lower the small but non-zero long-term risk of radiation-associated malignancies, particularly in the younger population of patients with HPV-associated disease. The key concern of restricting RT to the ipsilateral side is the risk of contralateral nodal recurrence.
As suggested from both historical surgical literature on patterns of cervical metastases as well as more recent surgical series of tonsillar cancer patients undergoing bilateral neck dissections, contralateral nodal spread typically occurs either directly through soft palate or base of tongue involvement or via aberrant/retrograde flow from bulky unilateral nodal disease. In a review of 352 patients with oropharyngeal cancer (197 with tonsillar cancer) treated with surgical resection including bilateral neck dissection, investigators from Ludwig Maximilian University in Munich demonstrated that contralateral nodal metastasis was dramatically lower for tonsillar cancers (14.7%) as compared to cancers of the base of tongue, soft palate, or pharyngeal wall (28.8%, 25.9%, and 50.0%, respectively). Among tonsillar cancers risk for contralateral metastasis increased with higher T-category (6.3% for T1, 17.5% for T2, and 17.3% for T3-4), though local extension of tonsillar cancers to involve the base of tongue, soft palate or pharyngeal wall was not described. Additionally, risk for contralateral nodal metastases among all patients was strongly associated with N2b ipsilateral nodal category (P < 0.001).

Investigators from Hallym University in Seoul have described a series of 76 patients with tonsillar cancer treated with surgery (including 14 having elective contralateral neck dissection for contralateral N0 status). Contralateral metastases were significantly associated with T3 category, base of tongue involvement, soft palate involvement, and ipsilateral neck multilevel involvement, though only ipsilateral multilevel involvement was significant after multivariate adjustment. In another publication from this group on a subset of 53 patients, these contralateral nodal metastases were also associated with posterior pharyngeal wall involvement and extracapsular spread in the ipsilateral nodal metastases. Investigators from Yonsei University in Seoul reported on the pathologic findings in 43 patients with tonsillar cancer treated with surgery including elective contralateral neck dissection (contralateral N0 status). The authors did not comment on soft palate or base of tongue invasion, but there was a correlation of contralateral occult metastatic rate with T-category (0% for T1, 4.5% for T2, and 33.3% for T3-4) and N-category (0 for N0, 18.2% for N1-2a, and 27.3% for N2b). Consequently, these well-documented patterns of cervical metastases from tonsillar cancer treated with surgery provide support that the concept of unilateral RT for patients with early-stage, lateralized tonsillar cancer.

The evidence in the literature supporting the above consensus statement regarding ipsilateral-only RT is chiefly comprised of retrospective data with inherit selection and publication biases, variable follow-up time, limited evidence using modern RT techniques, and a lack of data on whether these findings apply specifically to
oropharyngeal cancer resulting from HPV. In developing these guideline statements, we have identified 10 studies which met our initial criteria for review (Tables 8 and 9).

One study was described as an “investigational trial” of ipsilateral-only RT, and this small study included 22 oropharyngeal cancers (13 of the tonsil) patients of whom only 15 were treated with definitive RT (7) or CRT (8). Primary endpoints of this study were prospectively recorded patient recurrence in the contralateral neck and reported xerostomia score. There were 2 (9%) patients with oropharyngeal cancer (both of the tonsil) who recurred in the contralateral neck; both were T3 N2b. No patient developed grade 2-3 xerostomia. The other prospective study of ipsilateral-only RT included only 20 patients with tonsillar cancers (none of which involved the base of tongue or soft palate) of whom only 6 received definitive CRT (using IMRT approximately half the time). No patient developed a contralateral nodal recurrence. Only one patient developed grade 2 xerostomia and there was no grade 3 or late toxicities; however, 11 patients did require a treatment break.

Of the remaining eight studies, all were retrospective with three being generally small. In a study of 32 patients with oropharyngeal cancer (12 with soft palate primaries and 20 with tonsil primaries, 7 with soft palate extension and five with base of tongue extension) treated with ipsilateral-only RT (38% received concurrent carboplatin), Kagei et al. found no patient developing a contralateral nodal recurrence. Only three patients developed grade 2 xerostomia, and with exception of one case of grade 3 osteoradionecrosis, there were no grade 3 or late toxicities. In a study of 20 patients with tonsillar cancer, of whom 70% received post-operative ipsilateral-only RT, Koo et al. found no patient developed a contralateral nodal recurrence. Only one patient developed grade 2 xerostomia, and there was no grade 3 or late toxicities. In a study of 58 patients with tonsillar cancer treated with unilateral RT, Liu et al. found no patient developed a contralateral nodal recurrence. Of note, this is the only study with p16 data: of 15 patients tested, 60% were p16 positive. Only 4 patients treated unilaterally developed late toxicities, a significantly smaller percentage than the rate of late toxicity (22%) of among patients with tonsillar cancer treated with bilateral RT.

While the remaining five studies are also retrospective, each included more than 100 patients with oropharyngeal cancer and all but one with exclusively tonsillar cancer patients as well as all but one having the vast majority of patients (>90%) treated with definitive radiation therapy. Jackson et al. reviewed 178 patients with tonsil cancer treated with ipsilateral-only definitive RT, although the local extent of disease was not stated beyond T category. The details of contralateral nodal recurrence were detailed only for the 155 with N0-N1 disease and among
these there were 4 (2.6%) contralateral recurrences (initial stage: one T2N0, one T3N0, and 2 T1-3N1). Three out of 82 patients (3.6%) of patients with stage III disease developed a contralateral recurrence, though it is possible that many patients in this older series (1975-1993) were under staged due to substandard (by today’s standards) imaging. Reported late toxicities included 2 with grade 2 soft tissue necrosis, 4 with grade 3 osteonecrosis, and 2 with grade 4 osteonecrosis.

In the largest study to date, O’Sullivan et al. reported on 228 patients with tonsillar cancer treated with definitive ipsilateral-only RT. Eight patients (3.5%) developed contralateral nodal recurrence; however, 5 were detected synchronously with a primary site recurrence and 3 also had ipsilateral nodal recurrence. There were only 3 patients (1.3%) with exclusive contralateral nodal recurrence, and of these 3, 2 had T3 primaries (all 3 with significant (>1cm) palate involvement and 2 with significant base of tongue involvement). Of the 30 patients with T3 primaries, 3 developed a contralateral recurrence. Notably, none of the 36 patients with lateral palate involvement (<1 cm) developed a contralateral recurrence, although 2 out of 39 (5%) patients with lateral base of tongue invasion did, one of which was the only site of recurrence. While all contralateral nodal recurrences occurred among the 41 N1 patients and none among the 36 patients with N2 disease (28 N2a, 8 N2b), this is an older series of patients (1970-1991) in which cross-sectional imaging was “not employed for stage allocation.” Consequently, it is likely that some proportion of the N1 patients would have been classified as N2b had contemporary imaging tools been available. The reported 5-year rate of grade 3-4 toxicity was 3.4% (chiefly osteonecrosis), although the RT was 2D-based, without CT-planning.

A recent series by Lynch et al. reported the outcomes of 136 patients with tonsillar cancer treated with primary surgical resection and post-operative ipsilateral-only RT with or without chemotherapy. None of these patients had base of tongue involvement, and only 7 patients had lateral (<1cm) soft palate extension. Eight patients (6%) recurred in the contralateral neck with 6 (4% of total) of those recurrences being the solitary site of progression. All six of these patients presented with the initial nodal category N2b, with five having extra-capsular extension and five being current smokers with >10 pack-years smoking history. Two of the seven patients with lateral soft palate involvement developed a contralateral recurrence. Late toxicity included grade 3 osteonecrosis in 9 (7%) and grade 3 fibrosis in 3 (2.2%), and only 8 patients (6%) required a feeding tube.

The final two papers were large series with a majority of patients treated with definitive IMRT and very small proportion receiving chemotherapy. Chronowski et al. found a contralateral recurrence rate of 2% in a series
of 102 patients with tonsillar cancer treated with ipsilateral-only RT, though one of these was likely a second primary of the contralateral base of tongue. Only patients with primaries confined to the tonsillar fossa or with less than 1 cm of soft palate extension (base of tongue involvement was an exclusion) were considered for ipsilateral RT. A total of 43 N2 (21 N2a, 22 N2b) patients were included in this analysis, and none of them developed a contralateral recurrence. Long term toxicity rates were not reported, though 9% of patients required feeding tubes during RT. In the study by Al-Mamgani et al.,168 185 patients (47 with soft palate primaries and 32 with N2b nodal metastases) were treated with ipsilateral-only RT, there were only 2 contralateral recurrences (1.1% of the entire cohort), and one of these was initially T1N2b (the other T2N0; both confined to the tonsillar fossa). Late grade 3 toxicity was only 2.2%, while late grade 2 toxicity was 13%.

The oncologic safety of ipsilateral-only radiation therapy for HPV-associated tonsillar cancer is suggested by high control rates and low contralateral metastases rates in these relatively modern series, in which a substantial proportion of patients presumably had disease attributable to HPV. However, the propensity of small HPV-associated oropharyngeal cancers to metastasize to lymph nodes raises some concern of whether this population has a higher risk of occult contralateral lymph nodes and subsequent contralateral nodal recurrence. In a small retrospective study restricted to T1-T2 tonsil cancers reported by Shoushtari et al.,169 25% of 28 patients with p16 positive T1-T2 tonsillar cancer presented with clinically-evident, contralateral nodal metastases, as compared to none of the 13 patients with p16 negative T1-T2 tonsillar cancer.

The key issue, though, is not the incidence of contralateral clinically-evident lymph node metastases but rather the baseline risk of occult contralateral lymph node metastases and the risk of subsequent contralateral recurrence. However, to date there are no data available to inform whether HPV-associated tonsillar cancers have a higher baseline risk of occult contralateral lymph node metastases and risk of subsequent contralateral recurrence. Also, whether these risks are modified by past smoking history is unknown. Consequently, the recommendations regarding the use of ipsilateral-only radiation therapy are made independent of HPV status and smoking history.

A substantial experience supports the use of ipsilateral only radiation therapy for tonsillar cancer with limited nodal metastases and no soft palate or tongue involvement as effective therapy with high survival rates, expected in-field control, and very rare contralateral recurrence. In addition, the majority (9 of 10) of N0-N1 patients with contralateral recurrence were observed in series dating back to the 1970s, with many such patients likely with under-staged N-category due to lack of modern cross-sectional imaging. Ipsilateral treatment should also reduce the
risk of late toxicities, including xerostomia, dysphagia, and second primary malignancies. The panel therefore strongly recommends ipsilateral treatment in this cohort. Care in the use of ipsilateral-only radiation therapy must be taken in cases of T1/T2 category OPSCC with soft palate involvement and/or N2a categories (Table 10). There is limited clinical experience that can confirm low contralateral recurrence rates in these scenarios, although the existent data reviewed above are sufficiently encouraging that ipsilateral RT may be used in this population, provided patient preferences are fully engaged on the expected quality-of-life benefits versus the uncertain risk of contralateral recurrence.

On the other hand, the vast majority of reported contralateral recurrences occurred in patients with classical contraindications to unilateral treatment (e.g. significant involvement of soft palate, base of tongue and/or T3 primary size) or tumor characteristics that suggest aberrant lymphatic flow (i.e. ECE, advanced N2b cases) (Table 9). Thus, the panel does not consider ipsilateral RT reasonable in the presence of these factors. The panel did discuss whether patients with small-volume N2b disease or those with minimal base of tongue invasion should be eligible for ipsilateral RT. Because of the paucity of data suggesting a low contralateral recurrence risk in these individuals, they are not included in the conditional recommendation for the use of ipsilateral RT.

Future research will hopefully provide additional guidance on this important treatment planning decision. For example, we eagerly await outcomes and contralateral recurrence risk to be reported on series of HPV-associated T1-T2 tonsillar cancers. At present, neither the more favorable prognosis nor the propensity for lymph node metastases of HPV-associated tonsillar cancer can inform the decision to spare the contralateral neck from radiation therapy. Similarly, prospective studies of patients with N2b nodal category are needed to better understand the contralateral recurrence risk with ipsilateral RT and further motivate treatment decisions in this relatively common clinical presentation.
References


128. Ghoshal S, Goda JS, Mallick I, Kehwar TS, Sharma SC. Concomitant boost radiotherapy compared with conventional radiotherapy in squamous cell carcinoma of the head and neck--a phase III trial from a single institution in India. *Clinical oncology (Royal College of Radiologists (Great Britain)).* Apr 2008;20(3):212-220.


Table 1. Recommendation statements, including recommendation strength, quality of evidence, and percent consensus

<table>
<thead>
<tr>
<th>Guideline statement</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
<th>Percent (%) agreement with guideline statement</th>
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<tbody>
<tr>
<td><strong>KQ1. When is it appropriate to add systemic therapy to definitive radiotherapy in the treatment of oropharyngeal squamous cell carcinoma (OPSCC)?</strong></td>
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<td><strong>In the scenario of stage IV A-B disease:</strong></td>
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<tr>
<td>A. Concurrent high-dose intermittent cisplatin should be delivered to patients with stage IVA-B oropharyngeal squamous cell carcinoma receiving definitive radiotherapy.</td>
<td>Strong</td>
<td>High</td>
<td>100%</td>
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<td>B. Concurrent cetuximab or carboplatin-fluorouracil should be delivered to patients with stage IVA-B oropharyngeal squamous cell carcinoma receiving definitive radiotherapy who are not medically fit for high-dose cisplatin.</td>
<td>Strong</td>
<td>High</td>
<td>88%</td>
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<td>C. Concurrent weekly cisplatin may be delivered to patients with stage IVA-B oropharyngeal squamous cell carcinoma receiving definitive radiotherapy who are not medically fit for high-dose cisplatin, after a careful discussion of patient preferences and the limited prospective data supporting this regimen.</td>
<td>Conditional</td>
<td>Low</td>
<td>94%</td>
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<td>D. Concurrent cetuximab should not be delivered in combination with chemotherapy to patients with stage IVA-B oropharyngeal squamous cell carcinoma receiving definitive radiotherapy.</td>
<td>Strong</td>
<td>High</td>
<td>100%</td>
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<td>E. Intra-arterial chemotherapy should not be delivered to patients with stage IVA-B oropharyngeal squamous cell carcinoma receiving definitive radiotherapy.</td>
<td>Strong</td>
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<td><strong>In the scenario of stage III disease:</strong></td>
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<td>F. Concurrent systemic therapy should be delivered to patients with T3 N0-1 oropharyngeal squamous cell carcinoma receiving definitive radiotherapy.</td>
<td>Strong</td>
<td>Moderate</td>
<td>100%</td>
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<td>G. Concurrent systemic therapy may be delivered to patients with T1-T2 N1 oropharyngeal squamous cell carcinoma receiving definitive</td>
<td>Conditional</td>
<td>Low</td>
<td>88%</td>
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radiotherapy who are considered at particularly significant risk for locoregional recurrence, after a careful discussion of patient preferences and the limited evidence supporting its use.

### In the scenario of stage I-II disease:

**H.** Concurrent systemic therapy should not be delivered to patients with stage I-II oropharyngeal squamous cell carcinoma receiving definitive radiotherapy.

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### KQ2. When is it appropriate to deliver post-operative radiotherapy with and without systemic therapy following primary surgery of oropharyngeal squamous cell carcinoma (OPSCC)?

#### In the scenario of positive margins and/or extracapsular nodal extension (ECE)?

**A.** Concurrent high-dose intermittent cisplatin should be delivered with post-operative radiotherapy to patients with positive surgical margins and/or extracapsular nodal extension; this high-risk population includes patients independent of HPV status or the extent of extranodal tumor.

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**B.** Concurrent weekly cisplatin may be delivered with post-operative radiotherapy to patients who are considered inappropriate for standard high-dose intermittent cisplatin after a careful discussion of patient preferences and the limited evidence supporting this treatment schedule.

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**C.** For the high-risk post-operative patient unable to receive cisplatin-based concurrent chemoradiotherapy, radiotherapy alone should be routinely delivered without concurrent systemic therapy; given the limited evidence supporting alternative regimens, treatment with non-cisplatin systemic therapy should be accompanied by a careful discussion of the risks and unknown benefits of the combination.

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**D.** Patients treated with post-operative radiotherapy should not receive concurrent weekly carboplatin.

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**E.** Patients treated with post-operative radiotherapy should not receive cetuximab, either alone or in combination with chemotherapy, although such regimens are currently under investigation.

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**F.** Patients treated with post-operative radiotherapy should not routinely receive concurrent weekly docetaxel given the limited evidence supporting its use, although such regimens are currently under investigation.

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G. Patients treated with post-operative radiotherapy should not receive concurrent mitomycin-C, alone or with bleomycin, given the limited evidence and experience supporting its use.  

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H. Post-operative chemotherapy should not be delivered alone or sequentially with post-operative radiotherapy.

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**In the scenario of intermediate-risk pathologic factors such as lymphovascular invasion (LVI), perineural invasion (PNI), T3-4 disease, or positive lymph nodes:**

I. Patients with intermediate-risk factors should not routinely receive concurrent systemic therapy with post-operative radiotherapy.

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J. Patients with intermediate-risk factors whose surgical procedure and/or pathologic findings imply a particularly significant risk of locoregional recurrence may receive concurrent cisplatin-based chemotherapy after a careful discussion of patient preferences and the limited evidence supporting its use in this scenario; alternative systemic treatment regimens should only be used in the context of a clinical trial.

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K. Post-operative radiotherapy should be delivered to patients with pathologic T3 or T4 disease.

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L. Post-operative radiotherapy should be delivered to patients with pathologic N2 or N3 disease.

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M. Post-operative radiotherapy may be delivered to patients with pathologic N1 disease after a careful discussion of patient preferences and the limited evidence of outcomes following surgery alone in this scenario.

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N. Post-operative radiotherapy may be delivered to patients with LVI and/or PNI as the only risk factor(s), after a careful discussion of patient preferences and the limited evidence of outcomes following surgery alone in this scenario.

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**In the scenario of no pathologic risk factors:**

O. Post-operative radiotherapy may be delivered to patients without conventional adverse pathologic risk factors only if the clinical and surgical findings imply a particularly significant risk of locoregional recurrence, after a careful discussion of patient preferences and the potential harms and benefits of radiotherapy.

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</table>
### KQ3. When is it appropriate to use induction chemotherapy in the treatment of oropharyngeal squamous cell carcinoma (OPSCC)?

| A. Induction chemotherapy should not be routinely delivered to patients with OPSCC. | Strong | High | 100% |

### KQ4. What are the appropriate dose, fractionation, and volume regimens with and without systemic therapy in the treatment of oropharyngeal squamous cell carcinoma (OPSCC)?

**In the scenario of definitive non-surgical therapy:**

| A. A dose of 70 Gy over 7 weeks should be delivered to gross primary and nodal disease in patients with stage III-IV oropharyngeal squamous cell carcinoma selected to receive standard, once-daily definitive radiotherapy. | Strong | Moderate | 100% |
| B. The biologically equivalent dose of approximately 50 Gy in 2 Gy fractions or slightly higher should be delivered electively to clinically- and radiographically-negative regions at-risk for microscopic spread of tumor. | Strong | Low | 100% |
| C. Altered fractionation should be used in patients with stage IVA-B oropharyngeal squamous cell carcinoma treated with definitive radiotherapy who are not receiving concurrent systemic therapy. | Strong | High | 94% |
| D. Either accelerated radiotherapy or hyperfractionated radiotherapy may be used in patients with oropharyngeal squamous cell carcinoma treated with altered fractionation definitive radiotherapy after a careful discussion of patient preferences and the limited evidence supporting one regimen over the other. | Conditional | High | 100% |
| E. Either standard, once-daily radiotherapy or accelerated fractionation may be used when treating oropharyngeal squamous cell carcinoma with concurrent systemic therapy, after a careful discussion of patient preferences and the risks and benefits of both approaches. | Conditional | High | 88% |
| F. Altered fractionation should be used in patients with T3 N0-1 oropharyngeal squamous cell carcinoma treated with definitive radiotherapy who do not receive concurrent systemic therapy. | Strong | Moderate | 94% |
| G. Altered fractionation may be used in patients with T1-2 N1 or T2 N0 oropharyngeal squamous cell carcinoma treated with definitive radiotherapy alone who are considered at particularly significant risk of locoregional recurrence, after a careful discussion of patient preferences | Conditional | Low | 100% |
and the limited evidence supporting its use in this scenario.

**In the scenario of adjuvant postoperative radiotherapy:**

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<tr>
<td>H.</td>
<td>Adjuvant post-operative radiotherapy should be delivered to regions of microscopically-positive primary site surgical margins and extracapsular nodal extension at 2 Gy/fraction once daily to a total dose between 60 and 66 Gy.</td>
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<tr>
<td>I.</td>
<td>Adjuvant post-operative radiotherapy delivered without concurrent systemic therapy should treat regions of microscopically-positive primary site surgical margins and extracapsular nodal extension at 2 Gy/fraction once daily to a total dose of 66 Gy, although there are limited data guiding this recommendation.</td>
<td>Conditional</td>
<td>Weak</td>
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<tr>
<td>J.</td>
<td>Adjuvant post-operative radiotherapy should be delivered to the tumor bed and involved, dissected lymph node regions at 2 Gy/fraction once daily to a total dose of 60 Gy in the absence of primary site positive margins and extracapsular nodal extension.</td>
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**In the scenario of early T-stage tonsillar carcinoma:**

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<tr>
<td>K.</td>
<td>Unilateral radiotherapy should be delivered to patients with well-lateralized (no soft palate extension or base of tongue involvement), T1-T2 tonsillar cancer and N0-N1 nodal category.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L.</td>
<td>Unilateral radiotherapy may be delivered to patients with lateralized (&lt; 1cm of soft palate extension but without base of tongue involvement) T1-T2 N0-N2a tonsillar cancer without clinical or radiographic evidence of extra-capsular extension, after careful discussion of patient preferences and the relative benefits of unilateral treatment versus the potential for contralateral nodal recurrence and subsequent salvage treatment.</td>
<td>Low</td>
<td>Conditional</td>
</tr>
</tbody>
</table>
Table 2. Summary of phase III randomized trials comparing definitive radiotherapy with definitive radiotherapy plus concurrent systemic therapy (KQ 1)

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Number of patients</th>
<th>% oropharynx</th>
<th>% stage III</th>
<th>Radiotherapy regimen</th>
<th>Chemotherapy regimen/schedule</th>
<th>LRC benefit</th>
<th>OS benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adelstein, 2003&lt;sup&gt;12&lt;/sup&gt;</td>
<td>295 total (271 analyzed)</td>
<td>59%</td>
<td>4%</td>
<td>70 Gy in 35 fx over 7 weeks</td>
<td>Bolus cisplatin q3 weeks vs. cisplatin + 5-FU with split-course</td>
<td>--</td>
<td>YES</td>
</tr>
<tr>
<td>Ruo Redda, 2010&lt;sup&gt;14&lt;/sup&gt;</td>
<td>164 (157 analyzed)</td>
<td>56%</td>
<td>23%</td>
<td>70 Gy in 35 daily fx over 7 weeks</td>
<td>Carboplatin q2 weeks</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>Zakotnik, 1998&lt;sup&gt;15&lt;/sup&gt;</td>
<td>64</td>
<td>64%</td>
<td>6%</td>
<td>66-70 Gy in 33 to 35 daily fx over 7 weeks</td>
<td>Mitomycin C after 10 Gy and on last day of RT + bleomycin twice weekly</td>
<td>--</td>
<td>NO</td>
</tr>
<tr>
<td>Denis, 2004&lt;sup&gt;18&lt;/sup&gt;</td>
<td>226</td>
<td>100%</td>
<td>32%</td>
<td>70 Gy in 35 daily fx over 7 weeks</td>
<td>Carboplatin and 5-FU q3 weeks</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Semrau, 2006&lt;sup&gt;19&lt;/sup&gt;</td>
<td>240</td>
<td>74%</td>
<td>4%</td>
<td>50.4 Gy in 28 daily fx over 38 days + 19.5 Gy boost in 13 daily fx (total 69.9 Gy)</td>
<td>Continuous infusion 5-FU and carboplatin for 5d, weeks 1 and 6</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Ghadjar, 2012&lt;sup&gt;20&lt;/sup&gt;</td>
<td>224</td>
<td>100%</td>
<td>29% (plus 5% stage II)</td>
<td>74.4 Gy in 62 fx BID</td>
<td>Daily cisplatin 20 mg/m2 for 5d, weeks 1 and 5</td>
<td>YES</td>
<td>No</td>
</tr>
<tr>
<td>Author and year</td>
<td>Number of patients</td>
<td>% oropharynx</td>
<td>% stage III</td>
<td>Radiotherapy regimen</td>
<td>Chemotherapy regimen/ schedule</td>
<td>LRC benefit</td>
<td>OS benefit</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------</td>
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<td>-------------</td>
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<td>------------------------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Wendt, 1998&lt;sup&gt;21&lt;/sup&gt;</td>
<td>298 (270 analyzed)</td>
<td>42%</td>
<td>Not reported; 5% T1-2, 35% N0-1</td>
<td>70.2 Gy in 39 fx BID over 51 days in 3 cycles of 23.4 Gy with 11 days in between</td>
<td>Cisplatin, 5-FU, and leucovorin q3 weeks</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Bourhis, 2011&lt;sup&gt;22&lt;/sup&gt;</td>
<td>109</td>
<td>62%</td>
<td>0%</td>
<td>64 Gy in 32 fx BID (VeryAccFX alone) vs. 62-64 Gy in 31-32 fx BID with RT every other wk (CRT)</td>
<td>Cisplatin and 5-FU q2 weeks</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Budach, 2005&lt;sup&gt;24&lt;/sup&gt;</td>
<td>384</td>
<td>60%</td>
<td>6%</td>
<td>16 Gy in 8 daily fx + 61.6 Gy in 44 fx BID (total 77.6 Gy) (RT) vs. 30 Gy in 15 daily fx + 40.6 Gy in 29 fx BID (total 70.6 Gy) (CRT)</td>
<td>Continuous infusion fluorouracil on days 1-5 + bolus mitomycin on days 5 and 36</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Bourhis, 2012&lt;sup&gt;25&lt;/sup&gt;</td>
<td>840</td>
<td>66%</td>
<td>N/R</td>
<td>70 Gy in 35 daily fx over 7 weeks (CRT) vs. 40 Gy in 20 daily fx over 4 weeks plus 30 Gy in 20 fx BID over 2 weeks (AccFX) vs. 64.8 Gy in 36 fx BID over 3.5 weeks (AccFX)</td>
<td>Carboplatin (3 cycles of 4 days for CRT, 2 cycles of 5 days for AccFX) + fluorouracil (q3 wks for CRT, q4 wks for AccFX)</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Ghosh-Laskar, 2014&lt;sup&gt;16&lt;/sup&gt;</td>
<td>186</td>
<td>89%</td>
<td>46% (stage II and III)</td>
<td>66-70 Gy in 5 fx per week (SFX +/- chemo) vs. 66-70 Gy in 6 fx per week (AccFX)</td>
<td>Weekly cisplatin 30 mg/m²</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

**Notes:**
- **LRC benefit:** Yes or no indicates whether there was a statistically significant improvement in locoregional control.
- **OS benefit:** Yes or no indicates whether there was a statistically significant improvement in overall survival.
- **CRT:** Chemotherapy and radiation therapy.
- **AccFX:** Accelerated fractionation.
- **VeryAccFX:** Very accelerated fractionation.
- **SFX:** Standard fractionation.
- **p-values:** Indicate the level of statistical significance for the observed differences.
<table>
<thead>
<tr>
<th>Author and year</th>
<th>Number of patients</th>
<th>% oropharynx</th>
<th>% stage III</th>
<th>Radiotherapy regimen</th>
<th>Chemotherapy regimen/schedule</th>
<th>LRC benefit</th>
<th>OS benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fallai, 2006&lt;sup&gt;28&lt;/sup&gt; Olmi, 2003&lt;sup&gt;17&lt;/sup&gt;</td>
<td>192</td>
<td>100%</td>
<td>27% (all T3 N0-1)</td>
<td>66-70 Gy in 33-35 daily fx (RT arm 1, CRT) vs. 64-67.2 Gy in 40-42 fx BID, with 2-week break (RT arm 2)</td>
<td>Carboplatin and 5-FU q4 weeks</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Ang, 2014&lt;sup&gt;16&lt;/sup&gt;</td>
<td>891</td>
<td>70%</td>
<td>14%</td>
<td>72 Gy in 42 fx (3d-CRT) or 70 Gy in 35 fx (IMRT) over 6 weeks</td>
<td>Bolus cisplatin q3 weeks vs. bolus cisplatin + cetuximab</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Nguyen-Tan, 2014&lt;sup&gt;33&lt;/sup&gt; Ang, 2010&lt;sup&gt;6&lt;/sup&gt;</td>
<td>743 (721 analyzed)</td>
<td>60%</td>
<td>22%</td>
<td>70 Gy in 35 fx over 7 weeks (SFX) vs. 72 Gy in 42 fx over 6 weeks (AccFX)</td>
<td>Bolus cisplatin q3 weeks (3 cycles for SFX, 2 cycles for AccFX)</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Rasch, 2010&lt;sup&gt;40&lt;/sup&gt;</td>
<td>239</td>
<td>63%</td>
<td>5%</td>
<td>46 Gy in 23 daily fx + 24 Gy boost in 12 daily fx (total 70 Gy)</td>
<td>Weekly intra-arterial cisplatin vs. intravenous cisplatin q3 weeks</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Bonner, 2006&lt;sup&gt;41,42&lt;/sup&gt;</td>
<td>424</td>
<td>60%</td>
<td>25%</td>
<td>70 Gy in 35 daily fx over 7 weeks or 72-76.8 Gy in 60-64 fx BID over 10 weeks or 32.4 Gy in 18 daily fx + 39.6 Gy boost in 24 fx BID</td>
<td>Weekly cetuximab (+ loading dose one week before RT)</td>
<td>YES</td>
<td>YES</td>
</tr>
</tbody>
</table>

**Abbreviations:** CRT = Chemoradiotherapy; N/R = Not Reported, NS= Not significant; SFX = Standard fractionation; AccFX = Accelerated fractionation; fx= Fractions; BID = Twice daily; LRC = locoregional control; OS = Overall survival.
Table 3. Summary of phase III randomized trials comparing postoperative radiotherapy with postoperative radiotherapy plus concurrent high-dose intermittent cisplatin (KQ 2)

<table>
<thead>
<tr>
<th>Trial number</th>
<th>Number of patients</th>
<th>Median follow-up</th>
<th>% oropharynx</th>
<th>LRC Benefit</th>
<th>DM Benefit</th>
<th>DFS/PFS Benefit</th>
<th>OS Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernier, 2004&lt;sup&gt;50&lt;/sup&gt;</td>
<td>334</td>
<td>5 years</td>
<td>30%</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>(EORTC 22931)</td>
<td></td>
<td></td>
<td></td>
<td>5-year cumulative incidence of recurrence: 18% CRT vs. 31% RT (p=0.007)</td>
<td>NO</td>
<td>YES</td>
<td>5-year: 53% (CRT) vs. 40% (RT) (p=0.02)</td>
</tr>
<tr>
<td>Cooper, 2004&lt;sup&gt;155&lt;/sup&gt;</td>
<td>416</td>
<td>3.8 years</td>
<td>42%</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>(RTOG 9501)</td>
<td></td>
<td></td>
<td></td>
<td>At median follow-up 45.9 months, cumulative incidence of recurrence: 19% CRT vs. 30% CRT (p=0.01)</td>
<td>NO</td>
<td>YES</td>
<td>Hazard ratio 0.78 (p=0.04) favoring CRT</td>
</tr>
<tr>
<td>Cooper, 2012&lt;sup&gt;52&lt;/sup&gt;</td>
<td>410</td>
<td>9.4 years</td>
<td>42%</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>(RTOG 9501)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** EORTC = European Organisation for Research and Treatment of Cancer; RTOG = Radiation Therapy Oncology Group LRC = Locoregional control; DM = Distant metastasis; DFS = Disease-free survival; OS = Overall survival; CRT = Chemoradiotherapy; RT = Radiotherapy
Table 4. Summary of phase III randomized trials comparing postoperative radiotherapy with postoperative radiotherapy plus concurrent systemic therapy not using high-dose intermittent cisplatin (KQ 2)

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Number of patients</th>
<th>Patient risk factors</th>
<th>% oropharynx</th>
<th>Chemotherapy schedule</th>
<th>RT dose/schedule</th>
<th>LRC Benefit</th>
<th>DM Benefit</th>
<th>DFS Benefit</th>
<th>OS Benefit</th>
</tr>
</thead>
</table>
| Bachaud, 1996<sup>60</sup> Bachaud, 1991<sup>61</sup> | 83                 | ECE: 100% PSM: 35%  
≥3 positive nodes or bulky mass: 33% | 15%          | Cisplatin weekly 50 mg x 7-9 | 54 Gy in 32 fx over 6.5 weeks  
Close/positive margins: boost to 65-70 Gy in 1.8-2.0 Gy fx  
Metastatic nodes: boost to 65-74 Gy in 3 Gy fx | YES | NO | YES | 5-year: 23% (RT) vs. 45% (CRT), p<0.02 | YES | 2-year: 13% (RT) vs. 36% (CRT), p<0.01 |
| Rewari, 2006<sup>64</sup> | 205                | PSM 27%  
≥2 positive nodes: 34% | 23%          | Mitomycin C 15 mg/m² x 1-2 | At least 54 Gy in 27-30 fx over 5.5-6 weeks, median 60 Gy | YES | NO | N/R | NO |
| Zakotnik, 2007<sup>70</sup> Smid, 2003<sup>69</sup> | 114               | ECE: 53% PSM: 12%  
LVI: 18%  
PNI: 4% | 30%          | Mitomycin C 15 mg/m²  
Bleomycin 5 mg twice weekly | 56–70 Gy in 28-35 fx over 5.5-7 weeks | YES | NO | YES | 5-year: 65% (RT) vs. 88% (CRT), p=0.026 | NO | 5-year: 33% (RT) vs. 53% (CRT), p=0.035 | NO |
| Racadot, 2008<sup>71</sup> | 144               | ECE: 31% PSM: 22% | 49%          | Carboplatin 50 mg/m² twice weekly x 6-8 weeks | 54 Gy in 30 fx over 6 weeks for negative margins  
72 Gy in 40 fx | NO | N/R | N/R | NO |
<table>
<thead>
<tr>
<th>Author and year</th>
<th>Number of patients</th>
<th>Patient risk factors</th>
<th>% oropharynx</th>
<th>Chemotherapy schedule</th>
<th>RT dose/schedule</th>
<th>LRC Benefit</th>
<th>DM Benefit</th>
<th>DFS Benefit</th>
<th>OS Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argiris, 2008\textsuperscript{12}</td>
<td>72</td>
<td>≥2 positive nodes: 36%</td>
<td>32%</td>
<td>Carboplatin 100 mg/m\textsuperscript{2} weekly x 6 weeks</td>
<td>At least 59.4 Gy in 33 fx over 6.5 weeks (boost allowed)</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Tobias, 2010\textsuperscript{13}</td>
<td>253 (pts who received surgery)</td>
<td>PSM: 53%</td>
<td>23%</td>
<td>Methotrexate or vincristine, bleomycin, fluorouracil + methotrexate on days 1 + 14 of RT</td>
<td>Varied by center</td>
<td>N/R</td>
<td>N/R</td>
<td>NO</td>
<td>NO</td>
</tr>
</tbody>
</table>

Abbreviations: RT = Radiation Therapy; CRT = Chemoradiotherapy; Pts = Patients; Fx = Fractions; Yrs = Years; N/R = Not reported; DM = Distant metastases; OS = Overall survival; LRC = Locoregional control; LRF = Locoregional failure; w/o = Without; NS = Not significant; Min = Minimum; DFS = Disease-free survival; ECE = Extracapsular extension; PSM = Positive surgical margins; PNI = Perineural invasion; LVI = Lymphovascular invasion
Table 5. Summary of key studies investigating intermediate-risk pathologic factors for recurrence following primary surgical resection with and without adjuvant radiotherapy (KQ 2)

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Number of patients</th>
<th>% oropharynx</th>
<th>N stage: N0/N1/N2/N3</th>
<th>T stage: T1/T2/T3/T4</th>
<th>Prevalence of LVI and/or PNI</th>
<th>LRF Impact</th>
<th>DFS Impact</th>
<th>OS Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Langendijk, 2005(^{81})</td>
<td>801</td>
<td>20%</td>
<td>N0: 29%</td>
<td>T1: 12%</td>
<td>LVI: 4%</td>
<td>YES (LVI, PNI)</td>
<td>YES (class I) vs. class II vs. class III, p&lt;0.0001*</td>
<td>YES (class I) vs. class II vs. class III, p&lt;0.0001*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N1: 15%</td>
<td>T2: 24%</td>
<td>PNI: 16%</td>
<td>YES</td>
<td>5-year: 65% (class I) vs. 47% (class II) vs. 32% (class III), p&lt;0.0001*</td>
<td>YES (class I) vs. class II vs. class III, p&lt;0.0001*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N2a: 3%</td>
<td>T3: 32%</td>
<td></td>
<td></td>
<td>5-year: 33% (LVI present) vs. 21% (LVI absent), p=0.011 31% (PNI present) vs. 22% (PNI absent), p=0.026</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N2b: 37%</td>
<td>T4: 32%</td>
<td></td>
<td>YES</td>
<td>5-year: 67% (class I) vs. 50% (class II) vs. 36% (class III), p&lt;0.0001*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N2c: 13%</td>
<td></td>
<td></td>
<td></td>
<td>3-year risk of isolated regional recurrence: 11.2% (no RT) vs. 2.9% RT (p=0.09)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N3: 3%</td>
<td></td>
<td></td>
<td></td>
<td>ANY +/- RT: 9% vs. 21% (10% isolated, no p-value)</td>
<td></td>
</tr>
<tr>
<td>Ambrosch, 2001(^{82})</td>
<td>503</td>
<td>28%</td>
<td>N0: 50%</td>
<td>T2: 38%</td>
<td>P values not reported</td>
<td>N/R</td>
<td>N/R</td>
<td>YES (pT category: risk ratio 1.6, pT3/4 vs. pT1/2 (p=0.0009))</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N1: 18%</td>
<td>T3: 30%</td>
<td>3-year: 8.5% (surgery) vs. 4.7% (surgery + RT)</td>
<td></td>
<td>3-year: 8.5% (surgery) vs. 4.7% (surgery + RT)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N2a: 2%</td>
<td>T4: 18%</td>
<td>Failure in neck without RT: pN0: 5.5% vs. 0% pN1: 6.3% vs. 3% pN2: 24% vs. 7%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N2b: 26%</td>
<td>(oropharynx only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N2c: 5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jackel, 2008(^{83})</td>
<td>118</td>
<td>29%</td>
<td>N1: 100%</td>
<td>T1: 24%</td>
<td>NO (+/- RT)</td>
<td>N/R</td>
<td>N/R</td>
<td>NO (+/- RT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T2: 38%</td>
<td>Any regional failure without RT: 9% vs. 21% (10% isolated, no p-value)</td>
<td></td>
<td>3-year risk of isolated regional recurrence: 11.2% (no RT) vs. 2.9% RT (p=0.09)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T3: 27%</td>
<td></td>
<td></td>
<td>ANY +/- RT: 9% vs. 21% (10% isolated, no p-value)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T4: 12%</td>
<td></td>
<td></td>
<td>3-year risk of isolated regional recurrence: 11.2% (no RT) vs. 2.9% RT (p=0.09)</td>
<td></td>
</tr>
</tbody>
</table>

\(^{81}\) Langendijk, 2005

\(^{82}\) Ambrosch, 2001

\(^{83}\) Jackel, 2008
<table>
<thead>
<tr>
<th>Author and year</th>
<th>Number of patients</th>
<th>% oropharynx</th>
<th>N stage: N0/N1/N2/N3</th>
<th>T stage: T1/T2/T3/T4</th>
<th>Prevalence of LVI and/or PNI</th>
<th>LRF Impact</th>
<th>DFS Impact</th>
<th>OS Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leemans, 1994&lt;sup&gt;8&lt;/sup&gt;</td>
<td>244</td>
<td>13%</td>
<td>N/R</td>
<td>T1: 2% T2: 7% T3: 27% T4: 43% T1-T2/T3/T4: N/R</td>
<td>N/R</td>
<td>YES (T stage) 94.7% (T1-2) vs. 83.8% (T3-T4), p=0.015 (primary site failure)</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Haughey, 2012&lt;sup&gt;9&lt;/sup&gt;</td>
<td>171</td>
<td>100%</td>
<td>N0: 9% N1: 14% N2a: 18% N2b: 42% N2c: 10% N3: 7%</td>
<td>T1: 41% T2: 34% T3: 16% T4: 9% LVI: 15% PNI: 12%</td>
<td>N/R</td>
<td>NO (T-stage)</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Ravasz, 1993&lt;sup&gt;19&lt;/sup&gt;</td>
<td>80</td>
<td>28%</td>
<td>N/R</td>
<td>T1-T2: 15% T3-T4: 85% LVI: 41% PNI: 13%</td>
<td>N/R</td>
<td>YES (LVI) 50% (LVI present) vs. 16% (LVI absent), p=0.005 (local only failure) (PNI not significant)</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Bastit, 2001&lt;sup&gt;99&lt;/sup&gt;</td>
<td>420</td>
<td>45%</td>
<td>N0: 32% N1: 29% N2: 34% N3: 5%</td>
<td>T1: 5% T2: 30% T3: 55% T4: 11% Either LVI or PNI: 18%</td>
<td>N/R</td>
<td>YES (LVI) Tumor emboli RR 1.48, p=0.061</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>McMahon, 2003&lt;sup&gt;22&lt;/sup&gt;</td>
<td>237 Sydney, 95 Lanarkshire</td>
<td>42% Sydney, 23% Lanarkshire</td>
<td>Sydney N0: 43% N1: 15% N2a: 3% N2b: 29% N2c: 7% N3: 3% Lanarkshire N0: 69% N1: 10%</td>
<td>Sydney T1: 18% T2: 41% T3: 30% T4: 11% Lanarkshire T1: 17% T2: 63% T3: 17% T4: 4%</td>
<td>N/R</td>
<td>YES (PNI) (on multivariable analysis)</td>
<td>N/R</td>
<td>NO (PNI, LVI)</td>
</tr>
<tr>
<td>Author and year</td>
<td>Number of patients</td>
<td>% oropharynx</td>
<td>N stage: N0/N1/N2/N3</td>
<td>T stage: T1/T2/T3/T4</td>
<td>Prevalence of LVI and/or PNI</td>
<td>LRF Impact</td>
<td>DFS Impact</td>
<td>OS Impact</td>
</tr>
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<tr>
<td>Fagan, 1998&lt;sup&gt;93&lt;/sup&gt;</td>
<td>142</td>
<td>47% (oral cavity and oropharynx)</td>
<td>N/R</td>
<td>T1: 8% T2: 42% T3: 26% T4: 24%</td>
<td>PNI: 52%</td>
<td>YES (PNI)</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Lanzer, 2013&lt;sup&gt;94&lt;/sup&gt;</td>
<td>291</td>
<td>32%</td>
<td>N0: 37% N1: 13% N2a: 10% N2b: 31% N2c: 5% N3: 4%</td>
<td>T1-2: 52% T3-4: 30% Tx: 8%</td>
<td>LVI: 7% PNI: 8%</td>
<td>YES (PNI)</td>
<td>NO (PNI, LVI)</td>
<td>NO (PNI, LVI)</td>
</tr>
</tbody>
</table>

- Ipsilateral regional recurrence:
  - 26% (PNI present) vs. 6% (PNI absent), p=0.001
  - 19% (LVI present) vs. 7% (LVI absent), p=0.048
- Contralateral regional recurrence:
  - 9% (PNI present) vs. 1% (PNI absent), p=0.002
  - LVI: negative
<table>
<thead>
<tr>
<th>Author and year</th>
<th>Number of patients</th>
<th>% oropharynx</th>
<th>N stage: N0/N1/N2/N3</th>
<th>T stage: T1/T2/T3/T4</th>
<th>Prevalence of LVI and/or PNI</th>
<th>LRF Impact</th>
<th>DFS Impact</th>
<th>OS Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peters, 1993³⁰</td>
<td>240</td>
<td>18%</td>
<td>Nx: 8%</td>
<td>N0: 38%</td>
<td>N1: 18%</td>
<td>N2: 22%</td>
<td>N3: 15%</td>
<td>Tx: 11%</td>
</tr>
</tbody>
</table>

**Abbreviations:** LVI = Lymphovascular invasion; PNI = Perineural invasion; N/R = Not reported; LRF = Locoregional failure; DFS = Disease-free survival; OS = Overall survival

* Class I (intermediate risk): free surgical margins and no extranodal spread; class II (high risk): T1, T2, and T4 tumors with close or positive surgical margins or one lymph node metastasis with extranodal spread; class III (very high risk): T3 tumors with close or positive surgical margins or multiple lymph node metastases with extranodal spread or N3 neck.
Table 6. Summary of phase III randomized trials comparing radiotherapy (or chemoradiotherapy) with induction chemotherapy followed by the same (KQ 3)

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Number of patients</th>
<th>% oropharynx</th>
<th>Induction regimen</th>
<th>Concurrent regimen</th>
<th>Radiotherapy regimen</th>
<th>LRC Benefit</th>
<th>DM Benefit</th>
<th>OS Benefit</th>
</tr>
</thead>
</table>
| **Induction chemotherapy followed by local therapy (surgery or radiotherapy alone)**
Zorat 2004³⁰³ Pacagnella 1994³⁰² | 237 | 59.3% (group A), 54.6% (group B) | Cisplatin-5FU x 4 cycles | None | Resection and adjuvant RT (45-50 Gy) for operable pts and definitive RT for inoperable (65-70 Gy) (group B) | YES | YES | YES |
Domenge, 2000³⁰⁴ | 318 (161pts - no IC grp) | 100% | Cisplatin-5FU x 3 cycles | None | 70 Gy/35 fx over 7 weeks, plus 5 Gy boost to residual tumor; or resection | NO | NO | YES |
Lewin,1997³⁰⁷ | 461 | 55% | Cisplatin-5FU x 3 cycles | None | 64-70 Gy in 2 Gy daily fx | N/R | NO | NO |
| **Sequential (Induction chemotherapy followed by chemotherapy)**
Hitt,2014³¹² | 439 pts: 155 (TPF-CRT), 156 (PF-CRT) and 128 (CRT alone) | 43% | Cisplatin-5FU vs. Cisplatin-5FU-Docetaxel x 3 cycles | Bolus cisplatin q3 weeks | 70 Gy/35 daily fx | NO | NO | NO |
Haddad, 2013³¹⁰ | 145 | 55% | Cisplatin-5FU-Docetaxel x 3 cycles | Bolus cisplatin q3 weeks (no IC); weekly carboplatin (AUC 1.5) after TPF for good responders, weekly docetaxel (20 mg/m²) for poor responders | CRT: 72 Gy in 6 weeks (accelerate boost) | NO | NO | NO |
Cohen, 2014³¹¹ | 285 | 58% | Cisplatin-5FU-Docetaxel x 2 cycles | Docetaxel, hydroxyurea, 5-74-75 Gy in 4 courses of BID | NO | NO | NO |
<table>
<thead>
<tr>
<th>Author and year</th>
<th>Number of patients</th>
<th>% oropharynx</th>
<th>Induction regimen</th>
<th>Concurrent regimen</th>
<th>Radiotherapy regimen</th>
<th>LRC Benefit</th>
<th>DM Benefit</th>
<th>OS Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>FU</td>
<td>RT, 1 week apart</td>
<td></td>
<td></td>
<td>Except ~10% (IC) vs. 20% (CRT) DM without prior LRR (p=0.043)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CRT = Chemoradiotherapy; RT = Radiotherapy; N/R = Not Reported; IC = Induction chemotherapy; NS= Not significant; fx = Fractions; BID = Twice daily; DM = Distant metastasis; Gy = Gray; LRR = Locoregional recurrence. FU = fluorouracil; TPF = docetaxel, cisplatin, fluorouracil; AUC = Area under curve; N/R = Not reported
### Table 7. Summary of phase III randomized trials comparing radiotherapy with altered fractionation radiotherapy (Key Question 4)

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Number of patients</th>
<th>% oropharynx</th>
<th>% stage III</th>
<th>Altered fractionation RT regimen</th>
<th>Reference RT regimen</th>
<th>Chemotherapy regimen/schedule</th>
<th>LRC Benefit</th>
<th>OS Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bourhis, 2012(^{25})</td>
<td>840</td>
<td>66%</td>
<td>--</td>
<td>40 Gy in 20 daily fx over 4 weeks plus 30 Gy in 20 fx BID over 2 weeks (AccFX), 64.8 Gy in 36 fx BID over 3.5 weeks (VeryAccFX)</td>
<td>70 Gy 35 fractions over 7 weeks</td>
<td>Carboplatin (3 cycles of 4 days for CRT, 2 cycles of 5 days for AccFX) + fluorouracil (q3 wks for CRT, q4 wks for AccFX)</td>
<td>YES (to CRT)</td>
<td>YES (to CRT)</td>
</tr>
<tr>
<td>Nguyen-Tan, 2014(^{33})</td>
<td>743 (721 analyzed)</td>
<td>60%</td>
<td>21%</td>
<td>AccFX with boost plus cisplatin (72 Gy in 42 fx over 6 weeks)</td>
<td>70 Gy in 35 fractions over 7 weeks plus cisplatin</td>
<td>Bolus cisplatin q3 weeks (3 cycles for SFX, 2 cycles for AccFX)</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Beitler, 2014(^{123})</td>
<td>1076</td>
<td>60%</td>
<td>Not reported</td>
<td>HFX (81.6 Gy BID); AccFX - continuous (72 Gy in 6 weeks); AccFX - split (67.2 Gy with 2-wk rest after 38.4 Gy)</td>
<td>70 Gy/35 fx, once-daily</td>
<td>None</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Horiot, 1997(^{124})</td>
<td>500</td>
<td>100%</td>
<td>--</td>
<td>Hyperfractionated and AccFX (72 Gy in 45 fx over 5 weeks)</td>
<td>70 Gy in 35 fx</td>
<td>None</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Zackrisson, 2011(^{130})</td>
<td>750</td>
<td>49%</td>
<td>28%</td>
<td>AltFX (68 Gy in 23 fx of 2 Gy and 20 daily boost fx of 1.1 Gy, over 4.5 weeks)</td>
<td>68 Gy/34 fx, once-daily</td>
<td>None</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Overgaard(^{137})</td>
<td>1476</td>
<td>29% (pharynx)</td>
<td>21%</td>
<td>AccFX, 66-68 Gy/33-34 fx, 6 fx per week</td>
<td>66-68 Gy in 33-34 fx, 5 fx per week</td>
<td>None</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

**References:**
- Bourhis, 2012\(^{25}\)
- Nguyen-Tan, 2014\(^{33}\)
- Beitler, 2014\(^{123}\)
- Horiot, 1997\(^{124}\)
- Zackrisson, 2011\(^{130}\)
- Overgaard\(^{137}\)
<table>
<thead>
<tr>
<th>Author and year</th>
<th>Number of patients</th>
<th>% oropharynx</th>
<th>% stage III</th>
<th>Altered fractionation RT regimen</th>
<th>Reference RT regimen</th>
<th>Chemotherapy regimen/ schedule</th>
<th>LRC Benefit</th>
<th>OS Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overgaard138</td>
<td>900</td>
<td>53% (pharynx)</td>
<td>37%</td>
<td>AccFX, 66-70 Gy/33-35 fx, 6 fx per week</td>
<td>66-68 Gy in 33-34 fx, 5 fx per week</td>
<td>None</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Poulsen, 2001140</td>
<td>343</td>
<td>67%</td>
<td></td>
<td>Favorable-12 % Unfavorable - 19%</td>
<td>AccFX (59.4 Gy in 33 fx over 24 days)</td>
<td>70 Gy in 35 fx over 49 days</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Horiot, 1992141</td>
<td>325</td>
<td>100%</td>
<td>56%</td>
<td>80.5 Gy in 70 BID fractions in 7 weeks</td>
<td>70 Gy 35 fractions over 7 weeks</td>
<td>None</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

Abbreviations: OS = Overall survival; DFS = Disease free survival; AccFX= Accelerated fractionation; SFX = Standard fractionation; fx = Fractions; CRT = Chemoradiotherapy; BID = Twice per day; HFX = Hyperfractionation
Table 8. Studies exploring the role of ipsilateral-only radiation therapy in patients with oropharyngeal cancer squamous cell carcinoma, including years, primary site distribution, treatment, and TNM staging (KQ 4)

<table>
<thead>
<tr>
<th>Author and year</th>
<th>Years of Treatment</th>
<th>Number of Patients (#OP)</th>
<th>% OP Cancers in the Tonsil</th>
<th>% Definitive XRT</th>
<th>% IMRT</th>
<th>% Chemo</th>
<th>% T-Category</th>
<th>% N-Category</th>
<th>% Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Sullivan, 2001</td>
<td>1970-1991</td>
<td>228 (228)</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>Tx: 0</td>
<td>Nx: 0</td>
<td>I: 19</td>
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<tr>
<td></td>
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<td></td>
<td>T1: 32</td>
<td>N0:58</td>
<td>II: 33</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>T2: 52</td>
<td>N1:25</td>
<td>III: 28</td>
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<td>T3: 13</td>
<td>N2a:12</td>
<td>IV: 20</td>
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<td></td>
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<td>T4: 3</td>
<td>N2b:4</td>
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<td>N3:1</td>
<td></td>
</tr>
<tr>
<td>Corvo, 2004</td>
<td>2001-2002</td>
<td>30 (22)</td>
<td>59</td>
<td>68</td>
<td>0</td>
<td>53</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Rusthoven, 2009</td>
<td>2003-2007</td>
<td>20 (20)</td>
<td>100</td>
<td>30</td>
<td>45</td>
<td>95</td>
<td>Tx: 0</td>
<td>Nx: 0</td>
<td>I: 0</td>
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<td>T1: 55</td>
<td>N0: 0</td>
<td>II: 0</td>
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<td>T2: 35</td>
<td>N1: 20</td>
<td>III: 20</td>
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<td>T3: 10</td>
<td>N2a: 15</td>
<td>IV: 80</td>
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<td>T4: 0</td>
<td>N2b: 65</td>
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<td>N3: 0</td>
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<tr>
<td>Kagei, 2000</td>
<td>1989-1996</td>
<td>32 (32)</td>
<td>63</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>Tx: 0</td>
<td>Nx: 0</td>
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<td>N0:69</td>
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<td>N1:16</td>
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<td>T3: 37</td>
<td>N2a:13</td>
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<td></td>
<td></td>
<td>T4: 6</td>
<td>N2b:13</td>
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<td>N3: 3</td>
<td></td>
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<tr>
<td>Koo, 2013</td>
<td>2003-2011</td>
<td>20 (20)</td>
<td>100</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>Tx: 0</td>
<td>Nx: 0</td>
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<td>T1: 35</td>
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<td>III: 50</td>
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<td>N2a: 10</td>
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<td>T4: 0</td>
<td>N2b: 40</td>
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<td></td>
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<td>N3: 0</td>
<td></td>
</tr>
<tr>
<td>Liu, 2014</td>
<td>1990-2002</td>
<td>58 (58)</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>-37</td>
<td>Tx: 2</td>
<td>Nx: 0</td>
<td>I: 10</td>
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<td>T1: 15</td>
<td>N0:43</td>
<td>II: 17</td>
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<td>T2: 52</td>
<td>N1: 24</td>
<td>III: 40</td>
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<td>T3: 29</td>
<td>N2a: 18</td>
<td>IV: 33</td>
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<td>N2b: 7</td>
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<td></td>
</tr>
<tr>
<td>Study, Year</td>
<td>Time Period</td>
<td>Number (Cases)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
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</tr>
<tr>
<td>Jackson, 1999&lt;sup&gt;165&lt;/sup&gt;</td>
<td>1975-1993</td>
<td>178 (178)</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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</tr>
<tr>
<td>Lynch, 2014&lt;sup&gt;**166&lt;/sup&gt;</td>
<td>1995-2011</td>
<td>136 (136)</td>
<td>100</td>
<td>43</td>
<td>0</td>
<td>-63</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Chronowski, 2012&lt;sup&gt;167&lt;/sup&gt;</td>
<td>1970-2007</td>
<td>102 (102)</td>
<td>100</td>
<td>92</td>
<td>67</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Al-Mangani, 2013&lt;sup&gt;168&lt;/sup&gt;</td>
<td>2000-2011</td>
<td>185 (185)</td>
<td>70</td>
<td>100</td>
<td>100</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Smoking status available for 53 patients with 38% current smokers and 17% never smokers; P16 available for 15 patients with 60% P16 positive

**Smoking status available for 113 patients with 54% having >10 pack/years and 37% never smokers
Table 9. Studies exploring the role of ipsilateral-only radiation therapy in patients with oropharyngeal cancer with details of survival and contralateral nodal metastases (KQ 4)

<table>
<thead>
<tr>
<th>Author and year</th>
<th>% Grade 3+ Late Toxicity</th>
<th>5yr % Overall Survival</th>
<th>5yr % Disease Specific Survival</th>
<th>5yr % Local Recurrence</th>
<th>5yr % Regional Recurrence</th>
<th>Crude Contralateral Nodal Recurrence Risk (%)</th>
<th>Isolated (no other site of recurrence) Contralateral Recurrence Risk (%)</th>
<th>TNM of Those with Isolated Contralateral Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Sullivan, 2001</td>
<td>3.4</td>
<td>N/R</td>
<td>76 (3yr)</td>
<td>23 (3 yr)</td>
<td>19 (3yr)</td>
<td>3.5</td>
<td>3</td>
<td>T2N1 (SP-BOT ext.)</td>
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<tr>
<td>Corvo, 2004</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>6.7</td>
<td>6.7</td>
<td>T3N2b</td>
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<tr>
<td>Rusthoven, 2009</td>
<td>0</td>
<td>80 (2yr)</td>
<td>80 (2yr DFS)</td>
<td>21 (2yr)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Kagei, 2000</td>
<td>3.1</td>
<td>64 (3yr)</td>
<td>79 (3yr)</td>
<td>26</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
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<tr>
<td>Koo, 2013</td>
<td>0</td>
<td>95</td>
<td>95 (PFS)</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Liu, 2014</td>
<td>7</td>
<td>N/R</td>
<td>83 (crude DFS)</td>
<td>9</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>Jackson, 1999</td>
<td>3.4</td>
<td>56</td>
<td>69</td>
<td>25</td>
<td>14</td>
<td>2.6</td>
<td>N/R</td>
<td>T2N0 T3N0 T1-3N1 T1-3N1</td>
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<tr>
<td>Author and year</td>
<td>% Grade 3+ Late Toxicity</td>
<td>5yr % Overall Survival</td>
<td>5yr % Disease Specific Survival</td>
<td>5yr % Local Recurrence</td>
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<td>Isolated (no other site of recurrence) Contralateral Recurrence Risk (%)</td>
<td>TNM of Those with Isolated Contralateral Recurrence</td>
</tr>
<tr>
<td>----------------</td>
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<td>------------------------</td>
<td>--------------------------</td>
<td>-----------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Lynch, 2014&lt;sup&gt;166&lt;/sup&gt;</td>
<td>9</td>
<td>89</td>
<td>86</td>
<td>2 (crude)</td>
<td>7 (crude)</td>
<td>5.9</td>
<td>4.4</td>
<td>T2N2b (ECE) T2N2b (ECE) T2N2b (ECE) T2N2b (ECE) T2N2b (ECE)</td>
</tr>
<tr>
<td>Chronowski, 2012&lt;sup&gt;167&lt;/sup&gt;</td>
<td>N/R</td>
<td>95</td>
<td>96 (DFS)</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>T2N0 (spm)</td>
</tr>
<tr>
<td>Al-Mamgani, 2013&lt;sup&gt;168&lt;/sup&gt;</td>
<td>2.2</td>
<td>70</td>
<td>84 (DFS)</td>
<td>9</td>
<td>4</td>
<td>1.1</td>
<td>1.1</td>
<td>T1N2b T2N0</td>
</tr>
</tbody>
</table>

**Abbreviations:** YR = year; N/R = Not Reported; DFS: Disease-free survival; PFS: Progression-free survival; N/A = Not applicable; SP-BOT ext. = Soft palate and/or base of tongue extension; spm: most likely a second primary malignancy of contralateral base of tongue with nodal metastasis; ECE = Extra-capsular nodal extension
Table 10. Consensus statement for use of ipsilateral-only radiation therapy in patients with oropharyngeal squamous cell carcinoma (KQ 4)

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Strongly recommended (if all of the following)</th>
<th>Conditionally recommended (based on extension or N category)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft Palate involvement</td>
<td>None</td>
<td>&lt;1cm</td>
</tr>
<tr>
<td>T Category</td>
<td>T1 or T2</td>
<td>T1 or T2</td>
</tr>
<tr>
<td>N Category</td>
<td>N0 or N1</td>
<td>N2a</td>
</tr>
<tr>
<td>Extra-Capsular Nodal Extension</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Human Papillomavirus Status</td>
<td>Unknown impact</td>
<td>Unknown impact</td>
</tr>
</tbody>
</table>