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Guideline 5-11 Version 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Systemic Therapy in the Curative Treatment of Head and Neck Squamous Cell Cancer

The Expert Panel on Systemic Therapy in Head and Neck Squamous Cell Cancer

An assessment conducted in December 2023 deferred review of Guideline 5-11 Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 5-11 Version 2 is comprised of 6 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/31711

January 28, 2022

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For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at: Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

PEBC Report Citation (Vancouver Style): Winquist E, Agbassi C, Meyers B, Yoo J, Chan K. Systemic therapy in the curative treatment of head and neck squamous cell cancer. Winquist E, Arinze C. Toronto (ON): Cancer Care Ontario; 2016 August 10 [Endorsed 2022 January]. Program in Evidence-Based Care Guideline No.: 5-11 Version 2 ENDORSED.

PUBLICATIONS RELATED TO THIS REPORT

The evidence review has been published as a Supplement by *Journal of Otolaryngology - Head & Neck Surgery* and is available electronically at: https://journalotohns.biomedcentral.com/articles/10.1186/s40463-017-0199-x

1. Winquist E, Agbassi C, Meyers BM, Yoo J, Chan KKW. Systemic therapy in the curative treatment of head and neck squamous cell cancer: a systematic review. Journal of Otolaryngology - Head & Neck Surgery. 2017;46(1):29.

A practice guideline has been published in the peer-reviewed journal Current *Oncology Journal*: (http://www.current-oncology.com/index.php/oncology/issue/view/107)

2. Winquist E, Agbassi C, Meyers BM, Yoo J, Chan KKW, Site Group, et al. Systemic therapy in the curative treatment of head-and-neck squamous cell cancer: Cancer Care Ontario clinical practice Guideline. 2017. 2017;24(2):6.

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Guideline Document History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
Original Aug 2016	2000 to 2015	Full Report	Peer review publication. Web publication.	N.A.
Version 2 January 28, 2022	2015 to Feb 2021	New data found in Section 6: Document Assessment and Review	Updated web publication	2016 recommendations are ENDORSED

Guideline 5-11: Section 1

Systemic Therapy in the Curative Treatment of Head and Neck Squamous Cell Cancer: Recommendations Summary

The 2016 guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 6: Document Assessment and Review for a summary of updated evidence published between 2015 and 2021, and for details on how this guideline was ENDORSED.

GUIDELINE OBJECTIVES

The objective of this guideline is to make recommendations, based on data from randomized controlled trials (RCTs), regarding treatment strategies for cure and/or organ preservation in patients with locally advanced nonmetastatic (Stage III to IVB) squamous cell carcinoma of the head and neck (LASCCHN). The treatment strategies assessed are those that utilize systemically administered drugs in combination or in sequence with radiation and/or surgery.

TARGET POPULATION

Patients with LASCCHN being considered for curative intent treatment.

INTENDED USERS

Clinicians and other healthcare professionals involved in the management of LASCCHN.

IMPORTANT CAVEATS

- The importance of human papillomavirus (HPV) in the pathogenesis of LASCCHN has been recognized over the past decade. The RCTs considered in this guideline were conducted without recognition of this important biological prognostic factor. Consequently, the results of individual RCTs should be interpreted cautiously, as inadvertent imbalance in the proportion of patients with HPV-related tumours could influence trial results. The corollary is true: the pooled results of these trials should be applied to patients with HPV-related LASCCHN cautiously, as the optimal treatment approaches for these patients remain to be defined.
- Radiation treatment techniques have technically evolved and become more sophisticated since the RCTs considered in this guideline were conducted. Although it is unlikely that these changes would reduce the efficacy of concurrent drug therapy, they might influence the types and severity of adverse effects.
- The use of drug therapy, especially chemotherapy, in patients with LASCCHN significantly increases the acute and long-term adverse effects of treatment, and these may be life-threatening. Treatment plans incorporating chemotherapy in the curative treatment of patients with LASCCHN should be developed within the context of an appropriate multidisciplinary care team assessment [1] and be supervised by a medical oncologist experienced in treating head and neck cancer.

- Subset analysis of a meta-analysis of individualized patient data reported a diminishing overall survival benefit of concomitant chemotherapy with increasing age such that no benefit was observed beyond age 70 (test for trend, p = 0.003) [2]. However, diminished event-free survival with age was not observed. Furthermore, in the most recent trials (1994-2000) the proportion of deaths not due to head and neck cancer increased progressively with age from 15% in patients less than 50 to 39% in patients over age 70. In patients with potentially curable LASCCHN over age 70, the decision to add concomitant chemotherapy to curative radiation should be individualized. It may still be a reasonable option to improve overall survival if the probability of death from non-LASCCHN causes is considered low. It may also be a reasonable option if the primary goal of treatment is not overall survival (e.g. organ preservation or to enhance locoregional cancer control). The risks of severe toxicity and interference with the efficient delivery of curative radiation should be considered in every patient.

RECOMMENDATIONS

Recommendation 1
Concurrent chemoradiotherapy (CRT) is recommended to maximize the chance of cure in patients <71 years of age when radiotherapy (RT) is used as the definitive management for LASCCHN.

Qualifying Statements for Recommendation 1

- Acute and long-term adverse effects are increased with CRT versus local therapy and the relative benefits and risks for individual patients should be carefully evaluated [3].
- The optimal CRT regimens appear to consist of monoplatin or 5-fluorouracil (5-FU) plus platin chemotherapy (e.g., high-dose or weekly cisplatin, or carboplatin/5-FU: the Calais regimen) [4]. If monoplatin is used, cisplatin has the best evidence of efficacy and a dose intensity of at least 40 mg/m2 per week is considered optimal.
- Accelerated RT plus chemotherapy is not superior to conventional CRT.
- Treatment "de-escalation" for HPV-positive disease is being evaluated in several RCTs and is not currently a standard of care.
- LA SCCHN patients receiving radiation should be advised individually about the risks, benefits, and available choices for concurrent radiosensitizing chemotherapy or cetuximab by a medical oncologist with expertise in the treatment of head and neck cancer.

Recommendation 2
For patients with resected LASCCHN considered to be at high risk of locoregional recurrence, concurrent chemoradiotherapy is recommended over RT alone to maximize the chance of cure in patients <71 years of age.

Qualifying Statements for Recommendation 2

- Patients at high risk include those with microscopic evidence of positive margins and/or extra nodal extension in regional lymph nodes. Pathologic evidence of regional lymph node involvement without other high-risk features does not warrant the use of CRT.
- CRT may also improve overall survival in patients with pathologic T3/T4 tumours, perineural or lymphovascular invasion, or oral cavity or oropharynx cancers metastatic to level IV/V lymph nodes.

- Acute and long-term adverse effects are increased with CRT and the relative benefits and risks for individual patients should be carefully evaluated.
- Although fewer RCTs directly assess this question, it is reasonable to generalize from primary RT RCTs that the optimal CRT regimens appear to be monoplatinum or 5-FU and platin based chemotherapy and that overall survival benefit diminishes with age.

Recommendation 3
For patients with LASCCHN who are candidates for organ preservation strategies and would otherwise require total laryngectomy, two strategies are superior to RT alone for larynx preservation: CRT, or induction chemotherapy followed by radiation or surgery based on tumour response.

Qualifying Statements for Recommendation 3

- Strategies utilizing chemotherapy are associated with increased acute and long-term adverse effects, and the relative benefits and risks for individual patients should be carefully evaluated.
- If an induction chemotherapy strategy is used, docetaxel/cisplatin/5-fluorouracil (TPF) is associated with superior larynx preservation compared with the platin/5-fluorouracil (PF) regimen.

Recommendation 4
- The addition of cetuximab to intensified RT (concomitant boost or hyperfractionated schedule) may provide an alternative option to CRT.

Qualifying Statements for Recommendation 4

- Although the addition of cetuximab to RT in patients with locally advanced LASCCHN increased overall survival, it is unclear whether the addition of cetuximab to conventional once-daily RT would improve survival rate.
- Cetuximab did not appear to increase common adverse effects that can occur during RT but was still associated with a high rate of severe mucositis [5].
- Other epidermal growth factor receptor inhibitors have not demonstrated a better treatment effect compared with standard therapy.
- The use of radiosensitizers such as tirapazamine or nimorazole as an adjunct to radiotherapy or CRT is not recommended.

Recommendation 5
- The routine use of induction chemotherapy as neoadjuvant treatment to improve overall survival is not recommended for patients with LASCCHN.

Qualifying Statements for Recommendation 5

- In specific cases where induction chemotherapy is warranted prior to local therapy to rapidly reduce symptoms due to tumour bulk, the TPF regimen is preferred over the PF regimen.

Guideline 5-11: Section 2

Systemic Therapy in the Curative Treatment of Head and Neck Squamous Cell Cancer: Guideline

The 2016 guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 6: Document Assessment and Review for a summary of updated evidence published between 2015 and 2021, and for details on how this guideline was ENDORSED.

GUIDELINE OBJECTIVES

The objective of this guideline is to make recommendations, based on data from randomized controlled trials (RCTs), regarding treatment strategies for cure and/or organ preservation in patients with locally advanced nonmetastatic (Stage III to IVB) squamous cell carcinoma of the head and neck (LASCCHN). The treatment strategies assessed are those that utilize systemically administered drugs in combination or in sequence with radiation and/or surgery.

TARGET POPULATION

Patients with LASCCHN being considered for curative intent treatment

INTENDED USERS

Clinicians and other healthcare professionals involved in the management of LASCCHN.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1

Concurrent chemoradiotherapy (CRT) is recommended to maximize the chance of cure in patients <71 years of age when radiotherapy (RT) is used as the definitive management for LASCCHN.

Qualifying Statements for Recommendation 1

- Acute and long-term adverse effects are increased with CRT versus local therapy and the relative benefits and risks for individual patients should be carefully evaluated.
- The optimal CRT regimens appear to consist of monoplatin or 5-fluorouracil (5-FU) plus platin chemotherapy (e.g., high-dose or weekly cisplatin, or carboplatin/5-FU: the Calais regimen) [4]. If monoplatin is used, cisplatin has the best evidence of efficacy and a dose intensity of at least 40 mg/m2 per week is considered optimal.
- Accelerated RT plus chemotherapy is not superior to conventional CRT.
- Treatment "de-escalation" for human papillomavirus (HPV)-positive disease is being evaluated in several RCTs and is not currently a standard of care.

Key Evidence for Recommendation 1

- An individual patient data meta-analysis (MACH-NC) based on 50 concomitant chemotherapy trials (1965 to 2000) including 9615 patients (6560 deaths) compared locoregional RT treatment versus the same locoregional treatment plus chemotherapy. The meta-analysis detected a reduction in deaths in favour of

concomitant chemotherapy (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.78 to 0.86; p<0.0001). The absolute benefit was 6.5% at five years [2,6].
- Patients with both fully intact and fully resected tumours treated postoperatively were included in this meta-analysis.

Interpretation of Evidence for Recommendation 1

The MACH-NC meta-analysis identified concomitant chemoradiotherapy as the most effective approach to combining chemotherapy with locoregional radiotherapy, provided a precise estimate of this benefit, detected a benefit across head and neck subsites, and identified age-related interactions. However, it reports only overall survival rates, and so does not address important endpoints such as organ preservation, toxicity, and quality of life. Caveats to the interpretation and application of this evidence are necessary: these trials used older radiation techniques and did not identify or stratify for HPV-related cancers.

Recommendation 2

For patients with resected LASCCHN considered to be at high risk of locoregional recurrence, concurrent chemoradiotherapy is recommended over RT alone to maximize the chance of cure in patients <71 years of age.

Qualifying Statements for Recommendation 2

- Patients at high risk include those with microscopic evidence of positive margins and/or extra nodal extension in regional lymph nodes. Pathologic evidence of regional lymph node involvement without other high-risk features does not warrant the use of CRT.
- CRT may also improve overall survival in patients with pathologic T3/T4 tumours, perineural or lymphovascular invasion, or oral cavity or oropharynx cancers metastatic to level IV/V lymph nodes.
- Acute and long-term adverse effects are increased with CRT and the relative benefits and risks for individual patients should be carefully evaluated.
- Although fewer RCTs directly assess this question, it is reasonable to generalize from primary RT RCTs that the optimal CRT regimens appear to be monoplatin or 5-FU and platin-based chemotherapy and that overall survival benefit diminishes with age.

Key Evidence for Recommendation 2

- The risk of disease progression was reduced by 22% (p=0.04) [7] and 25% (p=0.04) [8] in two large postoperative chemotherapy trials.
- Bernier et al., in a meta-analysis of those two trials, suggested a differential benefit of CRT in subgroups of patients [9].
- Meta-analysis of RCTs studying monoplatinum CRT confirms overall survival benefit.

Interpretation of Evidence for Recommendation 2

Subanalyses of RCT data confirm the value of concurrent CRT in this setting, and support generalizability of the MACH-NC data to the subgroup of high-risk patients treated with RT after curative surgical resection. The adverse effects from chemotherapy when added to RT are manageable and the benefit in terms of survival outweighs the harms.

Recommendation 3

For patients with LASCCHN who are candidates for organ preservation strategies and would otherwise require total laryngectomy, two strategies are superior to RT alone for larynx preservation: CRT, or induction chemotherapy followed by radiation or surgery based on tumour response.

Qualifying Statements for Recommendation 3

- Strategies utilizing chemotherapy are associated with increased acute and long-term toxicities, and the relative benefits and risks for individual patients should be carefully evaluated.
- If an induction chemotherapy strategy is used, docetaxel/cisplatin/5-fluorouracil (TPF) is associated with superior larynx preservation compared with the platin/5-fluorouracil (PF) regimen.

Key Evidence for Recommendation 3

- Long-term data from a RCT comparing CRT with RT alone detected superior larynx preservation rates and laryngectomy-free survival rates with CRT.
- Data from the same trial [10,11] comparing an induction chemotherapy strategy with RT alone, also detected superior laryngectomy-free survival rates.
- A meta-analysis of three RCTs [12-14] comparing TPF with PF as part of an induction chemotherapy strategy for larynx preservation demonstrated superior results with TPF.
- Overall survival was improved with CRT compared with RT alone in patients with larynx cancer in a large meta-analysis.
- A trend to reduced overall survival was observed with CRT compared with induction PF chemotherapy in a RCT focused on larynx preservation.

Interpretation of Evidence for Recommendation 3

The optimal approach for larynx preservation is unclear. CRT followed by salvage laryngectomy has been the standard of care in Ontario based on the RTOG 9111 trial [11], which demonstrated improved larynx preservation, and on the MACH-NC meta-analysis which demonstrated improved overall survival rates for this approach compared with RT alone. However, in the long-term results of the RTOG 9111 trial, an induction chemotherapy strategy showed similar results for laryngectomy-free survival with a trend to improved overall survival compared with CRT. These findings provide support for this approach as an alternative strategy. Furthermore, RCTs have shown superior larynx preservation with TPF over PF induction chemotherapy when this strategy is used. Unfortunately it is difficult to evaluate the relative toxicity and quality-of-life effects of these strategies based on the available data.

Recommendation 4

- The addition of cetuximab to intensified RT (concomitant boost or hyperfractionated schedule) may provide an alternative option to CRT.

Qualifying Statements for Recommendation 4

- Although the addition of cetuximab to RT in patients with locally advanced LASCCHN increased overall survival (OS), it is unclear whether the addition of cetuximab to conventional once-daily RT would improve survival rates.
- Cetuximab did not appear to increase common adverse effects that can occur during RT but it was still associated with a high rate of severe mucositis [5].
- Other epidermal growth factor receptor inhibitors have not demonstrated a better treatment effect compared with standard therapy.
- The use of radiosensitizers such as tirapazamine or nimorazole as an adjunct to radiotherapy or CRT is not recommended.

Key Evidence for Recommendation 4

- With a 20-month difference in median survival time (49 versus 29 months), a large RCT that investigated the addition of cetuximab to radiotherapy detected a significant 26% reduction in the risk of death (HR, 0.74; 95% CI, 0.57 to 0.97; p=0.03) in favour of cetuximab. The risk of disease progression was also reduced by 30% (HR, 0.70; 95%

CI, 0.54 to 0.90; p=0.006) and the median duration of locoregional control was significantly longer (HR, 0.68; 95% CI, 0.52 to 0.89; p=0.005) in the cetuximab group with no difference in the incidence of Grade 3/4 toxic effects or quality-of-life scores between the groups [5,15]. These significant survival benefits were not observed in another study that compared the addition of cetuximab versus platin-based chemotherapy to concurrent hyperfractionated radiation therapy [16]. Although reported in an abstract, the two-year OS (90% versus 89%) and two-year progression free survival rate (75% versus 64%) were not significantly different between the groups.

- Addition of tirapazamine (TPZ) to CRT did not result in a response-rate or survival-rate benefit [17,18]. In the study reported by Rischin et al. 2010 [18], addition of TPZ to a platin-based CRT was compared with CRT. The HRs for OS and disease free survival (DFS) were 1.07 (95 % CI, 0.86 to 1.34; p=0.53) and 0.99 (95% CI, 0.81 to 1.21; p=0.09), respectively. The locoregional control rate was also not significantly different between the groups with a HR of 0.89 (95% CI, 0.68 to 1.17; p=0.44). Similar results were reported when TPZ instead of 5FU was added to cisplatin and RT [17] and when mitomycin C was used as an adjunct to RT [19].

Recommendation 5

- The routine use of induction chemotherapy as neoadjuvant treatment to improve overall survival is not recommended for patients with LASCCHN.

Qualifying Statements for Recommendation 5

- In specific cases where induction chemotherapy is warranted prior to local therapy to rapidly reduce symptoms due to tumour bulk, the TPF regimen is preferred over the PF regimen.

Key Evidence for Recommendation 5

- The meta-analysis that investigated the impact of induction chemotherapy (IC) in the management of LASCCHN detected no difference in OS and DFS when the use of IC prior to locoregional treatment was compared with locoregional treatment alone [20]. This finding is consistent with the results of the MACH-NC meta-analysis [2,6]. Although locoregional failure was not significantly reduced in patients that received IC compared with those that received only CRT, IC reduced the incidence of distant failure by 7% (95% CI, 0 to 0.13; p 0.05) [20].
- RCTs that compared the TPF versus PF regimens [12-14,21] found that treatment with TPF demonstrated an overall survival benefit compared with PF. There was a 28% (p=0.007) and 27% (p=0.02) reduction in the risk of disease progression and death, respectively, in the TAX 323 study [14]. The median survival rates were significantly better with the use of TPF compared to PF. The TAX 324 study demonstrated similar results [12]. Although the complete remission (CR) rates were similar in both groups in the induction phase, the patients in the group treated with induction TPF showed a significant CR rate increase (33.3% versus 19.9%; p=0.004) after locoregional treatment [14]. TPF remained superior over PF even after controlling for the duration of radiation therapy [22]. Another study compared the TPF or PF regimens followed by CRT with CRT alone and found no significant survival benefit between the two groups for the intention-to-treat cohort [23].

Interpretation of Evidence for Recommendation 5

With the evidence showing both benefit and harm, the uncertainty around the use of IC in the management of LASCCHN is considered moderate. There was a considerable level of heterogeneity in the study populations, based on the fact that HPV status was not known, and different CRT regimens were used.

IMPLEMENTATION CONSIDERATIONS

- **Feasibility:** In the province of Ontario, access to systemic therapies is well established when the cost of such care is reasonable.
- **Equity**: One priority of Cancer Care Ontario is to maintain universal (including geographic) access to cancer care. At the moment, we do not anticipate that the recommendations would increase inequities in care.
- **Provider considerations**: Since this guideline is subject to an external review process, it is our assumption that the opinions expressed in this document reflect those of a broad community of clinicians.
- **Patient considerations:** The recommendations include statements that are focused on patient-centred decisions. A balance between survival rate, disease control, and long-term adverse effects was considered in making the recommendations.
- **System considerations:** The recommendations should not increase the burden on the current system of care.

RELATED GUIDELINES

- The Head and Neck Cancer Disease Site Group. Epidermal growth factor receptor (EGFR) targeted therapy in stage III and IV head and neck cancer [Internet]. Toronto (ON): Cancer Care Ontario; 2015 March 17 [Endorsed 2015 Mar. 17]. Program in Evidence-based Care Evidence-Based Series No.: 5-12 Version 3. https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/576

- Gilbert R, Devries-Aboud M, Winquist E, Waldron J, McQuestion M; Head and Neck Disease Site Group. The management of head and neck cancer in Ontario. Toronto (ON): Cancer Care Ontario; 2009 Dec 15. Program in Evidence-based Care Evidence-Based Series No.:5-3 https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/536

Systemic Therapy in the Curative Treatment of Head and Neck Squamous Cell Cancer: Guideline Methods Overview

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC and any associated programs is editorially independent from the OMHLTC.

JUSTIFICATION FOR GUIDELINE

In the past, the Head and Neck Cancer Disease Site Group (DSG), in collaboration with the PEBC, had produced evidence-based series in this topic area, but these series are outdated. At this time, the members of the DSG believe that there is enough new evidence that a change in the use of older drugs may be warranted. This guideline will replace the following PEBC guidelines, which are currently made available for educational purposes only:

- 5-1: The Role of Neoadjuvant Chemotherapy in the Treatment of Locally Advanced Squamous Cell Carcinoma of the Head and Neck (Excluding Nasopharynx)
- 5-6a: Concomitant Chemotherapy and Radiotherapy in Squamous Cell Head and Neck Cancer (Excluding Nasopharynx)
- 5-10: The Role of Post-operative Chemoradiotherapy for Squamous Cell Carcinoma of the Head and Neck

GUIDELINE DEVELOPERS

Development of this guideline was led by a Working Group of the Head and Neck Disease Site Group. The DSG members have expertise in surgical oncology, medical oncology, radiation oncology, and health research methodology (see Appendix 1 for membership). The members of the Working Group were responsible for researching the evidence base, drafting the first version of the recommendations, and leading the response to the external review. All DSG members contributed to the final interpretation of the evidence, refinement of the recommendations, and approval of the final version of the document. Each DSG member declared professional and financial competing interests in the areas of grants, publications, employment, and other relevant business entities; Appendix 2 provides further detail. In accordance with the *PEBC Conflict of Interest Policy*, Individuals with competing interests were not allowed to participate as members of the Working Group unless otherwise stated.

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GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [24,25]. This process includes a systematic review, interpretation of the evidence, and draft recommendations by the members of the Working Group, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [26] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. For this project, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- The websites of guideline developers such as the National Institute for Health and Clinical Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), New Zealand Guidelines Group (NZGG), and National Health and Medical Research Council- Australia(NHMRC) were also searched.

Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument [26]. The search for existing guidelines for adaptation or endorsement did not yield an appropriate source document; therefore a search of the primary literature was required (see Section 4).

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the Head and Neck Cancer DSG membership must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The DSG and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted to the RAP and the DSG Panel for approval.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the DSG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

ACKNOWLEDGEMENTS

The Head and Neck Cancer DSG and the Working Group would like to thank the following individuals for their assistance in developing this report:

1. Fulvia Baldassarre, Bill Evans, Glenn Fletcher, Aaron Hansen, Melissa Brouwers, Donna E. Maziak, Sheila McNair, Hans Messersmith, Jan Vermorken, Michael Vickers, for providing feedback on draft versions.
2. Elizabeth Chan for conducting a data audit.
3. Janet Rowe for copy editing.

Guideline 5-11: Section 4

Systemic Therapy in the Curative Treatment of Head and Neck Squamous Cell Cancer: Evidence Review

INTRODUCTION

Squamous cell carcinoma (SCC) is the most common malignant tumour occurring in the head and neck region, accounting for more than 90% of all head and neck cancers [27]. Superficial SCC is most common in areas that are most exposed to the sun such as the scalp, face, ears, and lips; is usually cured with local therapy; and will not be considered further. More serious, debilitating, and potentially life threatening SCC can affect the mucosal linings of the oral and nasal cavities, paranasal sinuses, nasopharynx, oropharynx, hypopharynx, and larynx with the most common sites being the larynx, oral cavity, and oropharynx [27]. These cancers will be the focus of this guideline, and it is notable that squamous cell carcinoma of the head and neck (SCCHN) is ranked the sixth most common cancer world-wide with more than 500,000 new cases and 300,000 deaths reported annually [27].

With more than 85% of patients having a history of tobacco and alcohol use, such uses have long been identified as important risk factors. Other risk factors include long-term exposure to sunlight, chewing betel quid, previous x-rays of the head and neck region, ill-fitting dentures, and certain viral infections [27]. Epstein-Barr virus infection has been implicated in the pathogenesis of nasopharyngeal cancer. Over the past decade, human papillomavirus (HPV) infection has emerged as an important risk factor, especially for oropharyngeal cancers. These viral-related cancers continue to increase in incidence, and often affect younger patients.

Depending on the disease stage at presentation, the primary management strategies for patients with SCCHN consist of surgery and/or radiation therapy (RT). The cure rates for early-stage (Stages I and II) cancers treated with radiotherapy or surgery alone are high. A key challenge in the management of SCCHN is that the majority of patients have locally advanced disease (Stages III to IVB) at first presentation. The individual patient data meta-analyses of the MACH-NC review provided major insights into the role of chemotherapy in the curative treatment of locally advanced squamous cell cancer of the head and neck (LASCCHN), and have served as de facto practice guidelines since their publication in 2000 and update in 2009, which includes randomized controlled trials (RCTs) reported 1965 to 2000 [2,6,20]**.** These analyses demonstrated a lack of overall survival benefit with the use of induction or adjuvant chemotherapy but an improved overall survival with concomitant (concurrent or alternating) chemotherapy combined with RT [2,6,20]. The absolute overall survival benefit with concomitant chemotherapy at five years was 6.5% and the hazard ratio (HR) of death was 0.81 (95% confidence interval [CI], 0.78 to 0.86; $p<0.001$) [2,6,20]. Radiotherapy has recently evolved with the adoption of techniques allowing more precise delivery (e.g., intensity-modulated radiotherapy) replacing conventional RT. There has also been interest in alternative fractionation in LASCCHN, including trials of hyperfractionated and accelerated schedules.

As RCT evidence has continued to emerge over the past decade, and novel clinical treatments (including epidermal growth factor receptor [EGFR]-targeted drugs, radiosensitizers, and taxane-based induction chemotherapy) have continued to be developed, the Working Group of the Head and Neck Cancer DSG developed this evidentiary base to inform recommendations as part of a clinical practice guideline. As the MACH-NC meta-analyses are comprehensive and have served as a de facto practice guideline, to avoid duplicating them, they were used as a reference point for the evidentiary base of this guideline (Section 2) with the objective of addressing the research questions outlined below.

RESEARCH QUESTION(S)

1. In patients with unresected squamous cell carcinoma of the head and neck, what are the chemotherapy regimens that, administered concurrently with conventional or intensified radiotherapy, are superior or equivalent to other regimens on important outcomes such as tumour response rate, survival rate, and organ preservation with fewer toxicity/adverse events?
2. In postoperative patients with squamous cell carcinoma of the head and neck, what is the optimal chemotherapy regimen that can be administered concurrently with conventional radiotherapy?
3. Compared to chemoradiotherapy, can targeted agents or radiosensitizers improve or maintain outcomes, with reduced adverse events/toxicity, when used alone or in addition to primary radiotherapy in the treatment of patients with squamous cell carcinoma of the head and neck?
4. In patients with squamous cell carcinoma of the head and neck, what are the induction chemotherapy regimens that are superior or equivalent to others on important outcomes such as tumour response rate, survival rate, and organ preservation with fewer toxicity/adverse events?
5. What are the subgroups of patients with squamous cell carcinoma of the head and neck that would benefit more than others from postoperative systemic therapy?

METHODS

This evidence review was conducted in two planned stages: a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections. The MACH-NC meta-analysis [2,6,20] was considered a complete reference for all relevant studies published prior to 2000 and served as the evidence base, for this document, for RCTs reported during that time frame.

Search for Existing Systematic Reviews

A search for existing systematic reviews on the role of systemic chemotherapy in the management of LASCCHN was conducted. Systematic reviews published as a component of practice guidelines that were not considered suitable for adaptation or endorsement were also considered eligible for inclusion in the evidence base. The Ovid interface was used to search MEDLINE and EMBASE for existing systematic reviews in this topic area. As the MACH-NC meta-analyses provided a comprehensive review of RCTs conducted 1965 to 2000 and that compared the addition of chemotherapy to local therapy with local therapy alone, the search was limited to systematic reviews published since January 2000 and up to September 2014. The Cochrane Database of Systematic Reviews was also searched using a combination of the following search terms: induction, adjuvant, concurrent or concomitant chemotherapy, and squamous cell carcinoma of the head and neck.

Identified systematic reviews were further evaluated based on their clinical content and their relevance. Relevant systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) tool [28] to determine whether they met a minimum threshold for methodological quality to be considered for inclusion in the evidence base.

Search for Primary Literature

In addition to the selection of suitable systematic reviews, the same combination of search terms was used to conduct a broad search for primary literature in MEDLINE and EMBASE (January 2000 through February 2015). The year 2000 was used as a cut-off to minimize duplication of the MACH-NC meta-analyses [2,6,29]. Details of the literature search strategy

can be found in Appendix 3. Question-specific searches were also conducted for each research question in order to capture studies that may not have been retrieved by the broad search. The Cochrane Library was also searched. The proceedings of the meetings of the American Society of Clinical Oncology (ASCO), American Society for Radiation Oncology (ASTRO), European Society for Medical Oncology (ESMO), and European Society for Therapeutic Radiation and Oncology (ESTRO) were searched for relevant abstracts. The reference lists of studies deemed eligible for inclusion were also hand searched for additional citations.

Study Selection Criteria and Process

A review of the titles and abstracts that resulted from the electronic searches was carried out by one reviewer (CA). For those items that appeared to meet the inclusion criteria, CA obtained and reviewed the full text of each item. Studies were included if they were systematic reviews, meta-analyses, or RCTs evaluating the role of induction or concurrent chemotherapy in the management of non-metastatic SCCHN, specifically in the hypopharynx, larynx, trachea, oral cavity, and oropharynx regions, or RCTs comparing one drug regimen including targeted agents and radiosensitizers with another drug regimen alone or in combination with locoregional treatment (radiotherapy and/or surgery). The studies had to report at least one of the following outcomes: overall survival rate (OS), disease free survival rate (DFS), tumour response rate, larynx preservation, Grade 3/4 toxicity or quality of life.

Exclusion Criteria

The following exclusion criteria were applied to the entire literature search:

- Studies that included nasopharyngeal carcinoma.
- Case reports, news reports, notes, commentaries, opinions, letters, editorials, qualitative studies.
- Studies on cost-effectiveness, utility, and economics.
- Studies with fewer than 30 participants.
- Studies published in a language other than English, due to the lack of funding and resources for translation.

Data Extraction and Assessment of Study Quality and Potential for Bias

Data from the included studies were extracted by the project research methodologist (CA). The characteristics of the study population, including the sample size and years of accrual, duration of follow-up, and the treatment options, were extracted. When reported, response, progression, and survival information were also extracted from the results of the included studies. In cases of duplicate publication for the same study, only the most recent version of the data was extracted in the results. All extracted data and information was audited by an independent auditor (EC). Study quality was assessed based on the risk of bias and other important quality features such as the follow-up duration and rate, power calculation, and sample size. The Cochrane Risk of Bias Assessment Tool was used for the risk-of-bias assessment.

Synthesizing the Evidence

When multiple RCTs with similar experimental and control arms were available, a meta-analysis was conducted using the Review Manager software (RevMan 5.3) provided by the Cochrane Collaboration [30]. For all outcomes, the generic inverse variance model with random effects was used. For time-to-event outcomes, hazard ratios, rather than the number of events at a certain time point, were the preferred statistic for meta-analysis. If the HR and/or its standard error were not reported, they were derived from other information reported in the study, using the methods described by Parmar et al. [31]. Statistical heterogeneity was

calculated using the x^2 test for heterogeneity and the I^2 percentage. A probability level for the x^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% was considered indicative of statistical heterogeneity.

RESULTS

Search for Existing Systematic Reviews

The search for systematic reviews yielded 214 references including 14 conference abstracts published between 2000 and 2014. Out of these 214 reports, the full text reports of 21 reviews were retrieved and reviewed. Ten reviews with pooled analysis [6,9,20,32-38] were identified as potentially relevant to the topic areas covered by this guideline. Three of the reviews were specifically on induction chemotherapy, two were on postoperative chemotherapy, two were on targeted agents, one was on concurrent and the remaining two did not specify the timing of chemotherapy. After full text review, five meta-analyses [2,6,9,20,37,38] were included. Four [32-34,36] were excluded because they reviewed RCTs of non-LASCCHN, and one meta-analysis [35] was excluded following AMSTAR assessment. No further discussions of these references will be made will be made in this guideline. Although the high quality MACH-NC meta-analysis [6] was updated in 2009 by Pignon et al. [2], the trials that formed the basis of the analysis were older studies and this applies to the meta-analysis reported by Budach et al. [37] as well. Their findings will be used as the sole reference for the studies conducted before year 2000.The findings of the meta-analyses are summarised below.

Pignon et al. 2009

This individual patient data meta-analysis reported updated results of the MACH-NC study that included RCTs investigating the addition of chemotherapy to local therapy alone. A total of 87 RCTs (16485 patients) conducted from 1965 to 2000 were included. Overall, the HR of death was 0.88 ($p<0.0001$) for the addition of chemotherapy to local therapy with an absolute benefit of 4.5% at five years. There was a significant interaction with chemotherapy timing (adjuvant, induction, or concomitant) and treatment. Both direct (six trials) and indirect comparisons detected more benefit for the concomitant chemotherapy (i.e., administered concurrent or alternating with RT) than for induction chemotherapy. Fifty RCTs evaluated concomitant chemotherapy and demonstrated an absolute benefit of 6.5% at five years (HR, 0.81; $p<0.0001$). There was a decreasing effect of chemotherapy with age ($p=0.003$, test for trend), such that no survival benefit of concomitant chemotherapy was observed for patients over age 70.

Pignon et al. [2,6,20] attempted to dissect the benefit of concomitant chemotherapy by type of drug regimen and found that monoplatin (HR, 0.74; 95% CI, 0.67 to 0.82) or 5-fluorouracil (5-FU) plus platin (HR, 0.75; 95% CI, 0.67 to 0.84) regimens were both effective and of similar efficacy. These data established concomitant chemotherapy with RT for LASCCHN as a standard treatment option in Ontario. As alternating chemotherapy with RT has not been used in Ontario, so typically chemotherapy has been administered concurrently with RT (CRT) and this will be the focus for the remainder of this guideline. In view of this, the data provided by Pignon et al. was examined further to identify the optimal regimens for use concurrently with RT.

Ten RCTs that studied monoplatin chemotherapy concurrent with RT provided 12 comparisons. There were 10 comparisons of cisplatin concurrent with RT versus RT alone: seven used high-dose cisplatin (typically 100 mg/m^2 IV q21 days x 3 doses), two used weekly cisplatin, and one used daily cisplatin. Two comparisons examined carboplatin (one high-dose and one daily). All schedules of cisplatin (high-dose, weekly, and daily) demonstrated evidence of benefit; however, a dose threshold effect may be present. With conventionally fractionated radiotherapy administered over seven weeks (35 fractions), high-dose regimens provide 42.9

mg/m^2 of cisplatin per week. Daily cisplatin at 6 mg/m^2 provides 42 mg/m^2 per week. One RCT, reported by Quon et al. [39], using 20 mg/m^2 per week, detected no evidence of survival rate benefit whereas a small RCT using a flat dose of 50 mg cisplatin IV per week was positive. Based on these data, if cisplatin monotherapy is used, an optimal schedule cannot be recommended but a schedule providing a planned cisplatin dose intensity of at least 40 mg/m^2 per week is recommended. Both carboplatin RCTs detected a benefit for chemoradiotherapy compared with RT alone. However, although daily carboplatin 25 mg/m^2 demonstrated similar efficacy to daily cisplatin, high-dose carboplatin AUC 7 appeared less effective than high-dose cisplatin. These data suggest that carboplatin adds benefit to RT, but there is uncertainty as to whether it is as effective as cisplatin and what the optimal schedule is.

Two RCTs studied 5-FU plus platin chemotherapy concurrent with RT. Both RCTs detected evidence of a survival benefit. Adelstein et al. [40] studied a continuous infusion of both cisplatin and 5-FU administered over 96 hours during the first and fourth weeks of RT; and Denis et al. [41] administered daily bolus carboplatin and continuous infusion 5-FU for four days on the first, fourth, and seventh weeks of RT. As the latter regimen does not contain cisplatin, it may be considered a reasonable alternative to cisplatin monotherapy for patients with relative or absolute contraindications to cisplatin.

Pignon et al. included RCTs that treated patients first with surgery and then with postoperative RT, but did not report these trials separately. In Ontario, patients with fully resected primary tumours typically receive a 30-fraction course of conventionally fractionated RT. Five RCTs included patients with curatively resected tumours: three studied monoplatin chemotherapy, and two studied non-platin chemotherapy. Evidence of a survival rate benefit was present in all three cisplatin RCTs, and in one of the non-cisplatin RCTs. These data support generalizability of the overall results of the meta-analysis to the subgroup of patients treated with postoperative RT after curative surgical resection.

Bernier et al. 2005

Bernier et al. [9] combined data from two large RCTs investigating the addition of high-dose cisplatin chemotherapy to postoperative RT after curative surgical resection. In effect this was a meta-analysis of two RCTs investigating very similar study populations with virtually identical treatment. Subanalyses detected a survival rate benefit in patients with microscopically positive surgical margins and/or pathological evidence of extracapsular extension in regional lymph nodes. There was no evidence of benefit in patients with metastases in two or more regional lymph nodes as the only risk factor. There appeared to be a benefit in patients with other risk factors included in one of the RCTs, but this study was underpowered and therefore the benefit was not confirmed.

Furness et al. 2011

The oral cavity is one of the most common primary sites for SCCHN [27]. Furness et al. [38] conducted a published data systematic review and meta-analysis to determine whether the addition of chemotherapy to locoregional treatment (LRT) increases survival rate or locoregional control (LRC) and reduce disease recurrence rates in patients with oral cavity and oropharyngeal SCCHN. They also attempted to determine which chemotherapeutic agent or regimen is associated with best patient outcomes. Included studies were systematically retrieved, and data was abstracted by two or more independent reviewers. Studies that included patients with disease sites other than the oral cavity or oropharynx were excluded except if the analysis was reported separately for these patients. A total of 89 studies were included in this review. In their comparison of induction chemotherapy (IC) plus LRT versus LRT alone from 25 included RCTs, IC did not demonstrate an overall survival rate benefit (HR 0.92; 95% CI, 0.84 to 1.00). This result is consistent with the findings of the MACH-NC report by Pignon

et al. [2,6], which we considered to be more authoritative evidence base for the generation of the recommendations on induction chemotherapy. The HR of 0.78 (95% CI, 0.67 to 0.90) for DFS from eight RCTs was significantly in favour of IC irrespective of the regimen. DFS for the platinum-based regimen demonstrated a statistically significant benefit with a HR of 0.66 (95%CI, 0.48 to 0.89) for carboplatin and 0.78 (95%CI, 0.62 to 0.97) for cisplatin. It was noted that none of the included trials in this category reported blinding of participants or clinicians but the authors were confident that this was unlikely to affect the objective mortality outcome. There was little statistical heterogeneity found in the analysis of OS and DFS.

In the population with resectable tumours, surgery plus chemoradiotherapy was compared with surgery plus radiotherapy alone and the overall HR for death was 0.88 (95% CI, 0.79 to 0.99) in favour of postoperative chemotherapy. Chemotherapy administered concomitantly with RT in the postoperative setting was significantly better than RT alone with a HR of 0.84 (95% CI, 0.79 to 0.99) but when it was not administered concomitantly with RT, the HR was 0.95 (95% CI, 0.79 to 1.14). In the population with unresectable tumours, concomitant chemoradiotherapy with platin alone (HR, 0.66; 95% CI, 0.57 to 0.77) or in combination with 5FU (HR, 0.71; 95% CI, 0.62 to 0.81) demonstrated a statistically significant reduction in total mortality rate with a HR of 0.79 (95% CI, 0.74 to 0.84). Also in favour of concomitant chemoradiotherapy, there were statistically significant improvements in DFS (HR, 0.77; 95% CI, 0.70 to 0.84), progression-free survival rate (PFS) (HR, 0.77; 95% CI, 0.67 to 0.89) and LRC (HR, 0.73; 95% CI, 0.64 to 0.82) in this population.

Ma et al. 2012

To determine the definitive beneficial effect of IC in locally advanced SCCHN, Ma et al. [20] conducted a published data meta-analysis investigating the impact of IC on survival rate, diseases recurrence rate and adverse effects. A total of 40 RCTs were included in this meta-analysis. In the analysis of the studies that investigated the use of IC followed by LRT against LRT alone, the results of 28 trials were pooled and a significant reduction in distant metastasis rate was observed in favour of IC. No significant difference was found in OS (HR, 0.94; 95% CI, 0.87 to 1.01; p=0.110) in both populations (with resectable and with unresectable tumours). Event-free survival rates (HR, 0.95; 95% CI, 0.84 to 1.08; p=0.43) and locoregional recurrence rates were also not significant. However, there was a significant 13% reduction in overall mortality rate (HR, 0.87; 95% CI, 0.78 to 0.97; p=0.01) when a combination of platin and 5FU was used as the IC regimen. The three-year survival rate for the platin-5FU combination was also significant with a 7% reduction in mortality rate (95% CI, 0.88 to 0.98; p=0.01) but the five-year survival rate was not (HR, 0.96; 95% CI, 0.90 to 1.02; p=0.69). The OS and PFS in other comparisons (IC followed by concurrent chemoradiotherapy [CCRT] versus CCRT, and IC followed by RT versus CCRT or alternating chemotherapy and RT) were not significantly in favour of IC. Analyses on larynx preservation were not significant as well. The incidence of Grade 3/4 mucositis, leukopenia, and emesis was significantly reduced in patients who received IC compared with those who received only CCRT.

Search for Primary Literature

Using the search strategy outlined in Appendix 3, the broad search for primary literature in MEDLINE and EMBASE retrieved 1674 articles after duplicates were removed. These included 341 conference abstracts. The question-specific search yielded 60 and six more references for questions 3 and 4, respectively, but none for questions 1 and 2. Following title and abstract screening, 246 reports were retrieved for further review. The members of the Working Group also identified three more reports. 28 articles met the inclusion criteria and were included as the basis for the evidence used in making the recommendations in Section 1.

Study Design and Quality

The quality of included studies was assessed using the Cochrane Risk of Bias Assessment Tool and other quality features such as the follow-up rate and duration, sample size, and power calculation. Not all quality features were reported by all the studies but a majority reported using the intention-to-treat protocol as the basis of analysis. The median follow-up period ranged from six to 120 months. Although baseline characteristics for included patients were well balanced between treatment arms, it is important to note the possibility of an unintentional imbalance in patient population since none of these trials were stratified based on HPV status.

Potentially eligible RCTs identified were Phase II and III RCTs conducted between 1990 and 2013 with sample sizes ranging from 37 participants to 966 participants. The patient population was similar across studies, consisting of patients with previously untreated LASCCHN and with non-metastatic Stage III to IVB cancers of the oral cavity, oropharynx, hypopharynx, and larynx. The performance status was measured by the Karnofsky Performance Score, Eastern Cooperative Oncology Group (ECOG), or World Health Organisation (WHO) scales. Eleven trials were Phase II RCTs that addressed outcomes or comparisons not directly relevant to the research questions and were excluded: four novel induction regimens [42-45], four novel concurrent regimens [46-49], one adjuvant chemotherapy [50], one adjuvant cetuximab [51], one radiosensitizers with non-standard control arms [17]. Eleven of the RCTs identified had been included in the MACH-NC meta-analysis; including one published report of a previously unpublished RCT [52] and seven updated reports of six previously published RCTs [11,34,39,53-56]. Four RCTs [10,13,57,58] identified were also included in the review of larynx preservation reported by Denaro et al. [59] The results of the remaining unique RCTs that were not included in the MACH-NC meta-analysis were reviewed: four tested concurrent CRT [60-63], nine tested taxane-based triplet induction chemotherapy [13,14,21,23,64-68], 14 investigated anti-EGFR targeted drugs [15,16,62,69-79], two investigated radiosensitizers [18,80], and one studied organ preservation [81]. Table 1 presents a summary of the characteristics of included studies. Four comparisons from three multi-arm RCTs addressed outcomes or comparisons not directly relevant to the research questions and were excluded [23,60,65].

Table 4-1: Studies selected for inclusion.

Author (Reference), Study Name Years of Accrual	Study Design (Med F/U in Months)	Population Number of Patients	Disease Site(s)	Outcomes Measured
Concurrent Chemotherapy – Compared with RT Alone				
Racadot et al. 2008 [61] 1994 to 2002	Phase III (106)	Untreated SCCHN Curative intent surgery ECOG PS=0-2 Age <75 n=144	Oropharynx Hypopharynx Larynx	LRC,OS, toxicity
Concurrent Chemotherapy – Compared with CRT				
Greskovich et al. 2013 [82] [ABSTRACT]	Phase III (28)	n=69	Oral cavity Oropharynx Larynx Hypopharynx	LRC, OS, PFS
Bourhis et al. 2012 [60] GORTEC 99-02 2000 to 2007	Phase III (62)	Previously untreated Stage III/IV ECOG PS=0-2 n=840	Oral cavity Oropharynx Hypopharynx Larynx	PFS, OS, toxicity
Induction Chemotherapy - Triplet versus Doublet				
Lorch et al. 2011 [83] Posner et al. 2007 [68] TAX 324	Phase III (72)	Unresectable nonmetastatic Stage III/IV n=501		OS, PFS, Toxicity

Author (Reference), Study Name Years of Accrual	Study Design (Med F/U in Months)	Population Number of Patients	Disease Site(s)	Outcomes Measured
1999 to 2003				
Pointreau et al. 2009 [13]	Phase III (36)	Stage III/IV Required total Laryngectomy n=213	Hypopharynx Larynx	LP, ORR,Toxicity
Vermorken et al. 2007 [84] TAX 323 1999 to 2002	Phase III (33)	Stage III/IV Med age=53 n=358	Oral cavity Oropharynx Hypopharynx Larynx	PFS, OS, QoL, toxicity
Hitt et al. 2005 [21] 1998 to 2001	Phase III (23)	Previously untreated nonmetastatic Stage III/IV ECOGPS≤1 n=382	Oral cavity Oropharynx Hypopharynx Larynx	CR, OS, toxicity
Induction Chemotherapy - Triplet Added to CRT versus CRT				
Cohen et al. 2014 [64] DeCIDE 2004 to 2009	Phase III	Treatment-naïve Nonmetastatic Karnofsky PS>70 Mean age=56.8 n=285	nr	OS, DFS, RFS
Hitt et al. 2014 [23] 2002 to 2007	Phase III	Unresectable nonmetastatic Stage III/ IV ECOG PS=0-1 n=439	Oral cavity Oropharynx Hypopharynx larynx	PFS, TTF, OS
Haddad et al. 2013 [66] PARADIGM 2004 to 2008	Phase III	Previously untreated Nonmetastatic Stage III/IV WHO PS=0-1 n=145	Oral cavity Oropharynx Hypopharynx Larynx	OS, PFS
Paccagnella et al. 2010 [67] 2003 to 2006	Phase II (42)	Unresectable SCCHN Stage III/IV ECOG PS=0-1 Age≥18 n=101	Oral cavity Oropharynx Hypopharynx	CR, ORR, PFS, OS
Ghi et al. 2014 [65] [ABSTRACT]	Phase III (33)	Untreated Unresectable Stage III/IV ECOG PS=0-1 Med age=60 n=421	Oral cavity Oropharynx Hypopharynx	OS, CR, PFS, toxicty
Targeted – Compared with RT Alone				
Bonner et al. 2006 [15] Curran et al. 2007 [85] Bonner et al. 2010 [62]	Phase III (54)	Nonmetastatic Stage III/IV n=424 (213/211)	Oral cavity Oropharynx Hypopharynx larynx	QoL
Rodriguez et al. 2010 [84] 2002 to 2007	(nr)	Stage III/IVA n=106	Oral cavity Oropharynx Larynx Hypopharynx	CR,OS
Singh et al. 2013 [79] 2008 to 2010)		Measurable and evaluable disease Med age=55 Karnofsky PS≥70 n=60	Oral cavity	ORR
Targeted – Compared with CRT				
Ramakrishnan et al. 2009 [70]	Phase IIb	Unresectable SCCHN Stage III/IVA Karnofsky PS≥60 n=92	Oral cavity Oropharynx Larynx	ORR, PFS, DFS, OS
Bhattacharya et al. 2014 [73] 2011 to 2012		LASCCHN Stage III/IV Age=18-70	Oral cavity Oropharynx Hypopharynx	ORR, DFS

Author (Reference), Study Name Years of Accrual	Study Design (Med F/U in Months)	Population Number of Patients	Disease Site(s)	Outcomes Measured
		Karnofky PS>60 n=64	Larynx	
Al Saleh et al. 2013 [16] [ABSTRACT] 2009 to 2013	(19)	LASCCHN Nonmetastatic n=37	nr	PFS
Giralt et al. 2012 [75] [ABSTRACT] Concert 2	Phase II	Previously untreated Stage III/IVB Predominantly HPV-positive Med age=58yrs n=151	Oral cavity Oropharynx Larynx Hypopharynx	LRC, PFS, OS, safety
Bhatnagar and SIngh 2012 [72] [ABSTRACT]	(6)	Inoperable SCCHN n=56		ORR
Targeted – Added to CRT				
Ang et al. 2014 [71] RTOG 0522 2005 to 2009	Phase III (45)	Previously untreated Stage III/IV Zubrod -PS=0-1 Age≥18 n=891	Oropharynx Larynx Hypopharynx	OS, LRC, DM, PFS
Reddy et al. 2014 [77] 2004 to 2005	Phase IIb	Treatment naive Stage III/IVA Karnofsky PS≥60% n=92		ORR, PFS, OS
Harrington et al. 2013 [76]	Phase II	Unresected SSCHN Stage III/IV ECOG PS≤1 Med age=56 n=67	Oral cavity Oropharynx Larynx Hypopharynx	CR, OS, PFS, LRC, DM
Giralt et al. 2012 [74] [ABSTRACT] Concert 1	Phase II	Previously untreated Stage III/IVB Med age=57 n=150	Oral cavity Oropharynx Larynx Hypopharynx	LRC, PFS, OS, safety
Radiosensitizer - Tirapazamine				
Rischin et al. 2010 [18]	Phase III	Previously untreated Nonmetastatic Stage III/IV ECOG PS=0-2 n=861	Oral cavity Oropharynx Hypopharynx Larynx	OS, PFS, QoL, TTF

CRT – concurrent chemoradiotherapy; CR – complete response; DFS – disease-free survival; DM – distant metastasis; ECOG – Eastern Cooperative Oncology Group; F/U – follow-up; HPV – human papillomavirus; LASCCHN = locally advanced non-metastatic squamous cell carcinoma of the head and neck; LRC – locoregional control; Med – median; n – number recruited; nr – not reported; ORR – overall response rate; OS – overall survival rate; PFS – progression-free survival; PS – performance status; QoL – quality of life; RFS- recurrence-free survival; RT – radiotherapy; SCCHN – squamous cell cancer of the head and neck; TTF – time to treatment failure; WHO – World Health Organization.

Outcomes

Updated Trials

Seven reports published updates on six RCTs included in the MACH-NC meta-analysis. Haffty et al. [54] reported on the addition of mitomycin to RT, and Rewari et al. [34] examined a subgroup of these patients treated postoperatively. Tobias et al. [55], Quon et al. [39], Ghadjar et al. [56], and Cooper et al. [53] reported on RCTs of concomitant CRT; the latter RCT specifically investigating postoperative concurrent CRT. Forastiere et al. 2003 [10] reported on a three-arm RCT investigating both concurrent CRT and induction chemotherapy as strategies for larynx preservation. New information from these reports relevant to the guideline recommendations are addressed in the pertinent sections below.

Concurrent Chemotherapy

Concurrent addition of chemotherapy to RT was evaluated in three unique RCTs [60,61,82]. One RCT examined the addition of twice-weekly concurrent carboplatin added to postoperative RT in 144 patients treated with curative resection who had lymph node metastases (8). No benefit in locoregional control or overall survival rate was observed.

The MACH-NC meta-analysis suggested improved disease outcomes in LASCCHN with shortened RT treatment time, i.e., accelerated RT [2,6]. Two RCTs compared standard CRT regimens with accelerated RT plus modified concurrent chemotherapy [60,63]. Neither RCT detected an incremental benefit of accelerated fraction RT plus chemotherapy compared with conventionally fractionated RT.

As the MACH-NC review did not specifically address the value of concurrent postoperative CRT, and one unique RCT (8) and two MACH-NC RCT updates [34,53] were identified, a meta-analysis of six RCTs addressing the addition of concurrent chemotherapy to postoperative RT in patients with curatively resected tumours was performed [7,34,53,61,86,87]. Overall, there was a modest benefit of adding chemotherapy to RT. The hazard ratios of death and locoregional failure were 0.84 (95% CI, 0.64 to 1.03) and 0.57 (95% CI, 0.45 to 0.71), respectively. Benefit was apparent with monoplatinum chemotherapy (5, 6, 9, 85) (HR, 0.78; 95% CI, 0.61 to 0.99) but not with non-platinum-based chemotherapy [34,87] (HR, 0.97; 95% CI, 0.48 to 1.98). These data confirm the value of monoplatin-based CRT in this setting, and support the generalizability of the MACH-NC data to the subgroup of high-risk patients treated with RT after curative surgical resection.

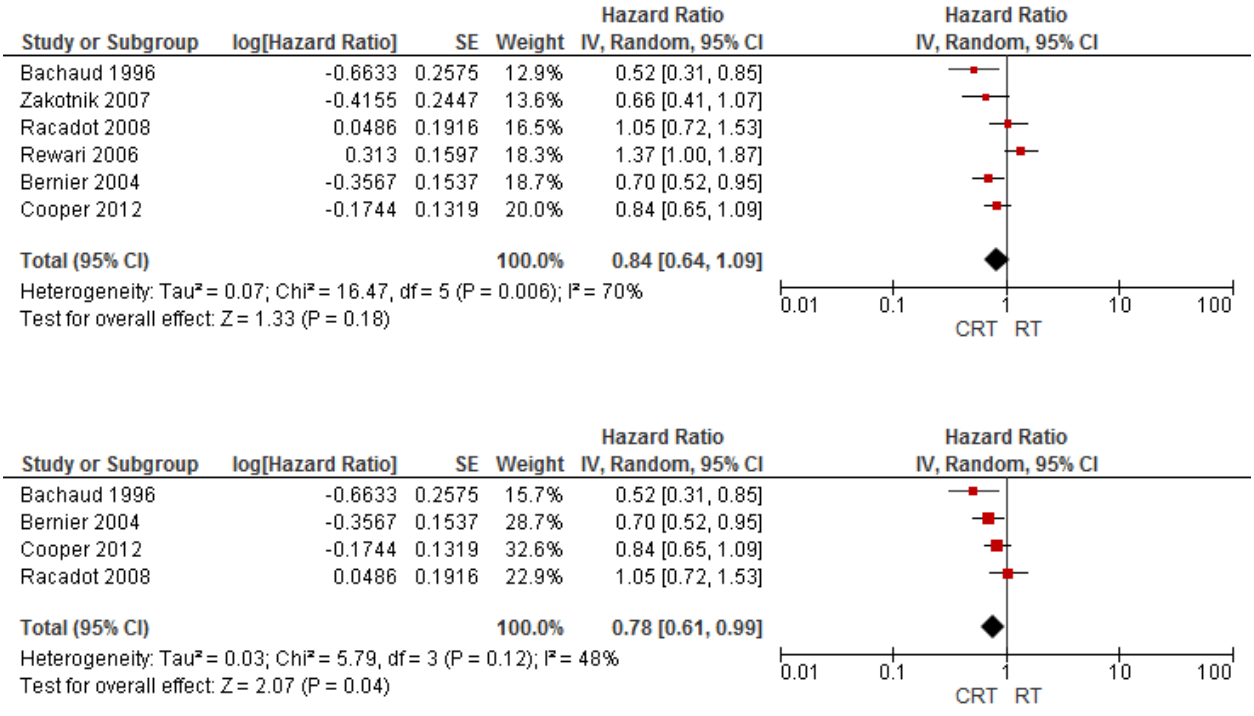


Figure 1. Overall survival rate in patients treated with A: CRT versus RT alone and B: platinum-based CRT versus RT alone.

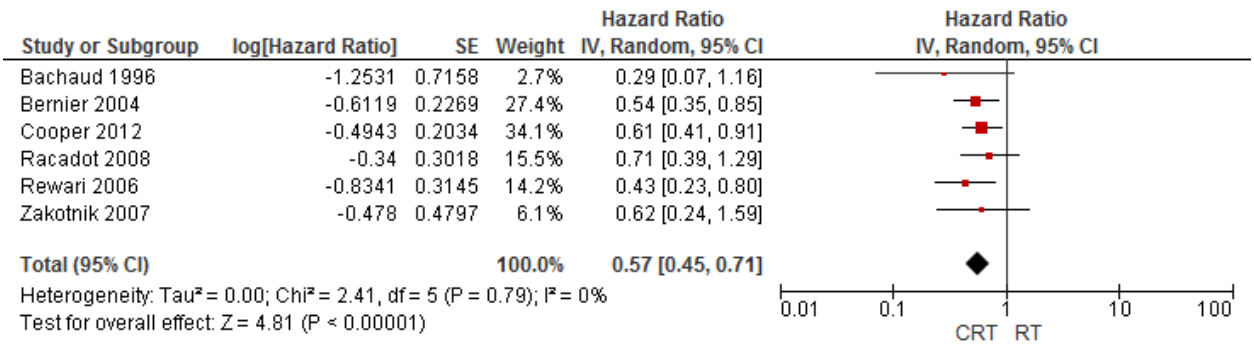


Figure 2. Locoregional control in CRT versus RT alone.

Targeted Agents and Radiosensitizers

Fourteen RCTs investigated anti-EGFR targeted monoclonal antibodies (MoAbs) added to RT in patients with LASCCHN. Six larger RCTs with more than 100 randomized patients per treatment arm were identified [62,69,71,75,88,89]. Bonner et al. compared the addition of weekly cetuximab with concomitant boost accelerated, hyperfractionated, or conventionally fractionated RT in 424 patients with LASCCHN. Cetuximab appeared to improve cancer control and survival rate in patients receiving concomitant boost or hyperfractionated radiotherapy; however, there was heterogeneity of treatment effect within subgroups. The subgroup of patients with oropharynx cancer and those treated with non-conventionally fractionated RT appeared to benefit the most. It was unclear whether these benefits were generalizable to patients who had tumours in the larynx or hypopharynx, or were being treated with conventionally fractionated RT; and no confirmatory RCT has been done. The addition of cetuximab increased treatment toxicity compared with RT alone.

Two larger RCTs investigated panitumumab combined with accelerated fraction RT [69,90] in patients with LASCCHN treated with accelerated fraction RT. Giralt et al. [90] randomized 303 patients to either concurrent panitumumab or two cycles of high-dose cisplatin. PFS demonstrated a benefit favouring cisplatin, with similar trends in locoregional control and overall survival rates. Siu et al. randomized 320 patients to either conventional CRT with high-dose cisplatin (three cycles) or concomitant boost accelerated RT plus panitumumab. No overall or progression-free survival rate benefits were observed, and non-inferiority of the experimental arm was not proven.

Three larger RCTs tested the addition of anti-EGFR MoAb to accelerated fraction CRT [71,88,89]. Ang et al. investigated the addition of cetuximab to concomitant boost accelerated RT plus high-dose cisplatin (two cycles) in 891 randomized patients. Adverse effects were increased and there was no improvement in disease outcomes, including overall survival rate. Eriksen et al. investigated the addition of zalutumumab to accelerated fraction RT plus weekly cisplatin and daily nimorazole in 619 randomized patients. No improvements in locoregional control, disease-specific or overall survival rates were observed. Mesia et al. investigated the addition of panitumumab to accelerated fraction RT plus high-dose cisplatin (two cycles) in 303 randomized patients. The cisplatin dose was reduced by 25% in the panitumumab arm. Disease outcomes were not improved by the addition of panitumumab and rates of adverse events were similar.

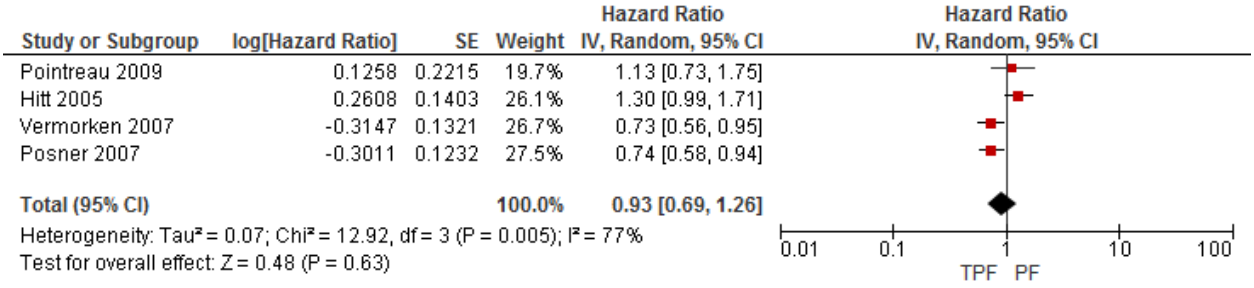
Zackrisson et al (90) were unable to identify evidence of overall survival benefit in 5 RCTs of hypoxic radiosensitizers added to RT for LASCCHN reported up to August 2001. Since the review by Zackrisson et al. [91], two unique eligible RCTs studying radiosensitizers were identified [18,80]. Rischin et al. investigated the addition of tirapazamine in 861 randomized

patients with LASCCHN receiving conventional fractionation RT plus high-dose cisplatin (three cycles). The cisplatin dose was reduced by 25% in the tirapazamine arm. No improvement in disease outcomes, including overall survival was observed. Metwally et al (80) investigated nimorazole added to accelerated RT but were only able to enroll 104 patients and were unable to demonstrate overall survival benefit.

Induction Chemotherapy

Overall, the MACH-NC meta-analysis detected no OS benefit of induction chemotherapy compared with local therapy alone (HR, 0.96; 95% CI, 0.90 to 1.02; p=0.18); and, in a more recent unique three-arm RCT, Hitt et al. [23] reported no OS benefit with the addition of cisplatin plus 5-fluorouracil (PF) induction to concurrent CRT in 284 randomized patients. However, the MACH-NC authors did report that treatment with PF-based induction chemotherapy appeared to be associated with a modest overall survival benefit (HR, 0.90; 95% CI, 0.82 to 0.99). This evidence, along with identification of the taxane drugs paclitaxel and docetaxel as active agents in SCCHN, has prompted continued interest in investigating induction chemotherapy.

As randomized Phase II trials have not demonstrated a benefit of taxane-cisplatin doublets compared with PF [32,42] we limited the scope of eligible RCTs to those adding paclitaxel or docetaxel to PF. Nine eligible RCTs were identified. Four RCTs compared taxane-based triplet induction chemotherapy (TPF) with PF induction prior to RT or CRT [13,14,21,68]. Meta-analysis of these RCTs detected an overall survival benefit favouring TPF (Figure 3) but the control arms of these RCTs do not reflect standard practice. However, these comparisons are of value in assessing the objective tumour response rates (ORRs) associated with these two approaches. Meta-analysis demonstrated that TPF is associated with a higher ORR (odds ratio, 1.46; 95% CI, 1.25 to 1.70). TPF treatment is associated with more neutropenia and risk of neutropenic sepsis than PF, but as these RCTs did not use granulocyte-colony stimulating factor prophylaxis for neutropenia, this could be abrogated with the use of primary granulocyte-colony stimulating factor prophylaxis.



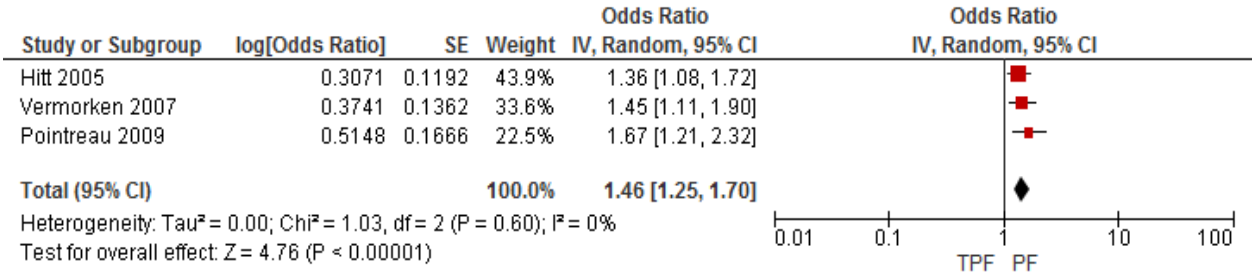


Figure 3. A: Overall survival and B: ORR for patients treated with induction TPF versus PF.

Five RCTs compared TPF induction chemotherapy followed by CRT with CRT alone [23,64-67]. A meta-analysis of these RCTs (Figure 4) did not show improvement in OS with induction TPF followed by CRT. However, the three-year overall survival rate in the control arms of two RCTs [66,67] was more than 75% and in three RCTs was less than 50%. When the latter three RCTs are meta-analyzed separately OS did not improve: HR 0.90 (95%CI 0.68 to 1.19)

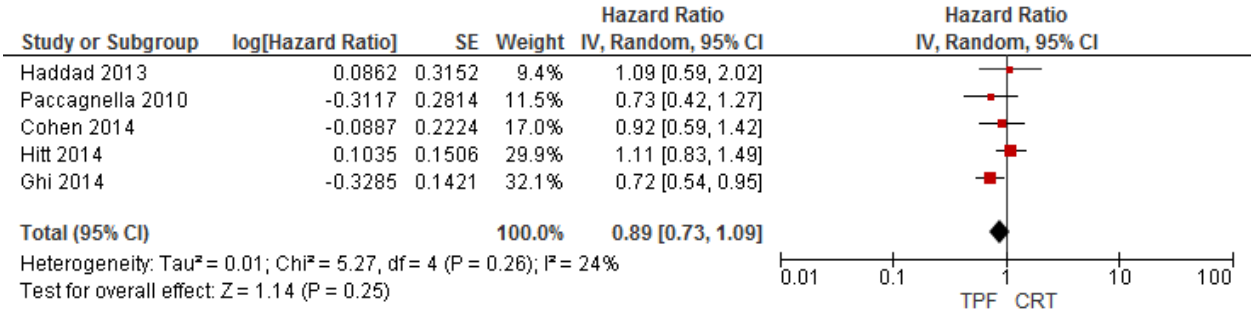


Figure 4. Overall survival rate in patients treated with induction TPF followed by CRT versus CRT alone.

Larynx Preservation

In patients with LASCCHN of the larynx or hypopharynx, potentially curable with radical surgery that requires laryngectomy, primary RT has been used to potentially provide cancer cure while also preserving the larynx and possibly the patient's natural voice. Patients suffering cancer recurrence after RT are then potentially cured with salvage surgery. Two major strategies have been investigated to improve larynx preservation and cure rates in these patients: 1. concomitant CRT in all patients with salvage surgery at relapse (the preferred approach in Ontario), and 2. Induction chemotherapy with choice of subsequent treatment based on tumour response (i.e. patients with at least partial remission are treated with primary RT and nonresponding patients are treated with laryngectomy with or without postoperative RT). The MACH-NC meta-analysis [6] identified three RCTs testing the latter strategy versus laryngectomy and reported a non-significant overall survival rate trend favouring primary surgery.

More recently Denaro et al. [59] provided a critical review of data from nine RCTs studying larynx preservation strategies. Difficulties in comparing trial results due to differing endpoint definitions were identified. Improved larynx preservation was identified, but at the cost of increased adverse effects, with concurrent, alternating, and induction chemotherapy strategies compared with RT alone. An optimal approach could not be recommended. Updated results reported by Forastiere et al. [11] showed similar laryngectomy-free survival rate with CRT and induction chemotherapy but with an overall survival trend favouring induction chemotherapy. An RCT comparing TPF with PF induction chemotherapy for organ preservation appeared to report superior outcomes with TPF; and retrospective analysis of another RCT not designed for organ preservation appeared to support these results [13]. One additional unique RCT evaluating organ preservation was identified. Soo et al. [81] compared primary surgery followed by radiotherapy with CRT in 119 patients with resectable head and neck cancers. The overall organ preservation rate was 45% with CRT, and organ preservation was higher with larynx and hypopharynx primary tumours. Three-year disease-free survival rates were similar.

Adverse Effects and Quality of Life

Concurrent Chemotherapy

Compared to RT alone, more toxic effects were reported in the CRT groups. The rates of late adverse effects were similar between the trial groups but acute adverse effects appeared to be more common in the chemotherapy groups. In the UKHAN1 trial, the incidence of acute adverse effects was doubled compared to RT alone [55]. While hematologic adverse effects were reportedly very mild, mucositis was the most common non hematologic adverse event reported in these trials. Greater number of CRT patients required enteral or parenteral feeding. In the SAAK study, the incidence of late adverse effects did not differ when cisplatin was added concurrently to hyperfractionated RT. When the addition of chemotherapy to different fractionations of RT was evaluated, patients in the very accelerated RT group had more acute adverse effects compared with patients who were administered conventional or accelerated RT (84% versus 76% or 69%) p=0.0001 [60].

Postoperatively, the addition of chemotherapy to RT increased the incidence of adverse effects in these trials but based on the study protocols, both arms were considered to have an acceptable toxicity profile. A 43% (p=0.001) difference in the rate of acute toxicity was reported in the RTOG 9501 study [8]. The tendency of developing a Grade 3 adverse effect was higher in the cisplatin arm (78%) compared to RT alone (46%); p=0.001. Similar results – 41% in the CT arm against 21% in the RT arm (p=0.001) – were reported by Bernier et al. [7]. The three studies that compared postoperative chemotherapy to no treatment also reported no significant difference in adverse effects.

Targeted Agent and Radio Sensitizers

Although most of the studies reported a trend towards a higher incidence of adverse events in the intervention groups, the differences in the rates of adverse events and quality of life (QoL) score between the groups were not significant. In the study reported by Bonner et al. [15], the incidence of Grade 3 to 5 infusion reactions and acneiform rash were was significantly higher in the cetuximab arm, and these adverse effects seemed to occur mainly in the first five to 15 days of treatment. In the trial reported by Ang et al. [71], more treatment-related Grade 5 adverse events were reported in the cetuximab arm (p=0.05). The higher rates of Grade 3 to 5 skin reactions and mucositis in the cetuximab arm did not remain significant after 90 days post-therapy, but the feeding tube dependency rate at three years was higher in the cetuximab arm (12% versus 7%; p=0.05). Rodriguez et al. [78] reported that the QoL in patients treated with epidermal growth factor receptor inhibitor (EGFRI) was significantly better in relation to their global health status, while physical, emotional, social, cognitive, and individual symptoms on a general health scale were not different between groups. However, Curran et al. reported better health on a physical function scale in patients in the group treated with an EGFRI.

Induction Chemotherapy

The most common hematologic adverse events (AEs) observed with the use of IC were myelosuppression, neutropenia, thrombocytopenia, and anemia, while mucositis, fatigue, alopecia, nausea, and dehydration were the common non-hematologic AEs. The rates of hematologic AEs were higher in patients in the IC group. Among the studies that evaluated the use of IC followed by CRT, one study reported that patients treated with IC before receiving CRT were more likely to develop an adverse event compared with those that did not receive IC: 47% versus 28%; p=0.002 [64]. In the studies that compared TPF with PF regimen, there were no significant differences in the rates of AEs between the arms. However, there were more dose delays in the PF arm than in the TPF arm (64.8% versus 10.9%; p<0.001) [14]. The need for

tracheostomy or dependence on a gastric tube was used as a surrogate measure for long-term adverse effects in one study and there was no difference between the groups [12]. There was a trend for PF regimen to have significantly more thrombocytopenic AEs in the studies, while the incidence of neutropenia and anemia were greater in TPF or other triple regimens. An earlier analysis of the TAX 324 study demonstrated a significantly higher incidence of Grade 3/4 neutropenia in the use of TPF compared with PF (83% versus 56%; p=0.001) [68].

Ongoing, Unpublished, or Incomplete Studies

The search for ongoing trials was conducted on July 15, 2015 and the included trials were first initiated between the years 2000 through 2015. Table 3 presents the list of ongoing trials identified from clinicaltrial.gov.

Table 3: Ongoing trials

Official Title	Status	Protocol ID
Concurrent Chemotherapy		
Randomized Phase IV Trial to Compare Cetuximab With Concomitant Radiation Therapy With Concomitant Mitomycin-C and 5-Fluorouracil With Radiation Therapy for Locally Advanced Squamous Cell Carcinomas of the Head and Neck Date trial summary last modified: April 29, 2015	Recruiting	NCT02015650 MITOCET
A Phase II Double-blind and Randomized Trial Comparing Concurrent Chemoradiotherapy Plus PG2 Injection Versus Concurrent Chemoradiotherapy Plus Placebo in Advanced Pharyngeal or Laryngeal Squamous Cell Carcinoma Date trial summary last modified: April 27, 2015	Recruiting	NCT01720563 PH-CP021
Randomized, Controlled, Open Label, Multicenter, Phase II Study to Evaluate the Efficacy and Safety of CetuGEX™ Plus Chemotherapy in Comparison to Cetuximab Plus Chemotherapy for the Treatment of Patients With Stage III/IV Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck Date trial summary last modified: November 13, 2014	Recruiting	NCT02052960 GEXMab52201
Concurrent Chemoradiation Versus Induction Docetaxel, Cisplatin and 5-fluorouracil (TPF) Followed by Concomitant Chemoradiotherapy in Locally Advanced Hypopharyngeal and Base of Tongue Cancer: A Randomized Phase II Study Date trial summary last modified: May 29, 2013	Recruiting	NCT01312350
A Phase I/II Study of Dasatinib, Cetuximab and Radiation With or Without Cisplatin in Locally Advanced Squamous Cell Carcinoma of Head and Neck (HNSCC)	Active, not Recruiting	NCT00882583 CA180123 J08101

Official Title	Status	Protocol ID
Date trial summary last modified: June 18, 2014		
A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas Date trial summary last modified: July 16, 2014	Active, not Recruiting	NCT00265941 RTOG 0522 NCI-2009-00729 CDR0000458049
A Phase III Randomized Trial Comparing Single Agent Cisplatin With the Combination of 5-Fluorouracil and Cisplatin, Concurrent With Radiation Therapy in Stage III and IV Squamous Cell Head and Neck Cancer Date trial summary last modified: October 6, 2014	Active, not Recruiting	NCT00608205 CASE3307 NCI-2010-01197 P30CA043703
A Phase III Trial of Concurrent Radiation and Chemotherapy for Advanced Head and Neck Carcinomas Date trial summary last modified: July 28, 2014	Active, not Recruiting	NCT00047008 RTOG 0129 CDR0000257233 RTOG-H-0129, RTOG-DEV-1069
A Randomised Phase II/III Study of Concurrent Cisplatin-Radiotherapy With or Without Induction Chemotherapy Using Gemcitabine, Carboplatin and Paclitaxel in Locally Advanced Nasopharyngeal Cancer Date trial summary last modified: April 28, 2015	Active, not Recruiting	NCT00997906 CDR0000657121 SINGAPORE-NCC0901
Postoperative Chemotherapy		
A Randomized, Double-blind, Placebo-controlled Phase III Study, to Evaluate the Efficacy of Afatinib (BIBW2992) in Maintenance Therapy After Post- Operative Radio-chemotherapy in Squamous-cell Carcinoma of the Head and Neck: GORTEC 2010-02 Date trial summary last modified: May 22, 2015	Recruiting	NCT01427478 BIBW2992 ORL 2010-023265-22
Randomized Phase II/III Trial of Surgery and Postoperative Radiation Delivered With Concurrent Cisplatin Versus Docetaxel Versus Docetaxel and Cetuximab for High-Risk Squamous Cell Cancer of the Head and Neck Date trial summary last modified: May 1, 2015	Recruiting	NCT01810913 RTOG 1216, NCI-2013-00500 U10CA021661
Phase III, Double-Blind, Placebo-Controlled Study of Post-Operative Adjuvant Concurrent Chemo-Radiotherapy With or Without Nimotuzumab for Stage III/IV Head & Neck Squamous Cell Cancer Date trial summary last modified: August 18, 2015	Recruiting	NCT00957086 IHN01
Targeted Agents and Radiosensitizers		

Official Title	Status	Protocol ID
NIMRAD (A Randomised Placebo-controlled Trial of Synchronous NIMorazole Versus RADiotherapy Alone in Patients With Locally Advanced Head and Neck Squamous Cell Carcinoma Not Suitable for Synchronous Chemotherapy or Cetuximab) Date trial summary last modified: February 9, 2015	Recruiting	NCT01950689, CFTSp032 11_DOG08_53
Phase II Trial of Mitomycin C in Patients With Incurable p16 Positive Oropharyngeal and p16 Negative Head and Neck Squamous Cell Carcinoma (HNSCC) Resistant to Platin, 5-FU, Cetuximab, and Taxane Date trial summary last modified: June 15, 2015	Recruiting	NCT02369458
A Blind Randomized Multicenter Study of Accelerated Fractionated Chemo-radiotherapy With or Without the Hypoxic Cell Radiosensitizer Nimorazole (Nimoral), Using a 15-gene Signature for Hypoxia in the Treatment of HPV/p16 Negative Squamous Cell Carcinoma of the Head and Neck Date trial summary last modified: July 16, 2015	Recruiting	NCT01880359 EORTC-1219 2013-002441-12
A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Resected Head and Neck Cancer Date trial summary last modified: March 20, 2015	Recruiting	NCT00956007 NCI-2011-00878 RTOG 0920 CDR0000651536
TROG12.01 A Randomised Trial of Weekly Cetuximab and Radiation Versus Weekly Cisplatin and Radiation in Good Prognosis Locoregionally Advanced HPV-Associated Oropharyngeal Squamous Cell Carcinoma Date trial summary last modified: August 17, 2015	Recruiting	NCT01855451 TROG 12.01 ACTRN12613000 279729
A Phase II, Randomized, Open-Label, Single Center Study In Patients With Advanced Head And Neck Cancer To Investigate Efficacy And Safety Of Standard Chemoradiation And Add-On Concurrent Cetuximab ± Consolidation Cetuximab Date trial summary last modified: December 8, 2014	Recruiting	NCT01435252
Determination of Epidermal Growth Factor Receptor-inhibitor (Cetuximab) Versus Standard Chemotherapy (Cisplatin) Early And Late Toxicity Events in Human Papillomavirus-positive Oropharyngeal Squamous Cell Carcinoma Date trial summary last modified: March 6, 2015	Recruiting	NCT01874171 ISRCTN33522080 RMRCT0034 2011-005165-21

Official Title	Status	Protocol ID
A Phase II Randomized Trial Of Surgery Followed By Chemoradiotherapy Plus Cetuximab For Advanced Squamous Cell Carcinoma Of The Head and Neck Date trial summary last modified: March 26, 2015	Active, not Recruiting	NCT00084318 RTOG-0234 CDR0000360850
DAHANCA 19: A Randomized Study of the Importance of the EGFr-Inhibitor Zalutumumab for the Outcome After Primary Curative Radiotherapy for Squamous Cell Carcinoma of the Head and Neck Date trial summary last modified: November 1, 2013	Active, not Recruiting	NCT00496652
A Phase III Study of Standard Fractionation Radiotherapy With Concurrent High-Dose Cisplatin Versus Accelerated Fractionation Radiotherapy With Panitumumab in Patients With Locally Advanced Stage III and IV Squamous Cell Carcinoma of the Head and Neck Date trial summary last modified: June 8, 2015	Active, not Recruiting	NCT00820248 HN6 CAN-NCIC-HN6 CDR0000630159
Induction Chemotherapy		
Induction Chemotherapy Followed by Cetuximab Plus Definitive Radiotherapy Versus Radiation Plus Cisplatin Date trial summary last modified: June 5, 2015	Recruiting	NCT00999700
Randomized, Placebo-Controlled, Phase 2 Study Of Induction Chemotherapy With Cisplatin/Carboplatin, And Docetaxel With Or Without Erlotinib In Patients With Head And Neck Squamous Cell Carcinomas Amenable For Surgical Resection Date trial summary last modified: September 10, 2015	Recruiting	NCT01927744, NCI-2014-01390
A Phase II Study of Carboplatin, Nab-paclitaxel and Cetuximab for Induction **Chemotherapy** for Locally Advanced Squamous Cell Carcinoma of the Head and Neck Date trial summary last modified: August 26, 2015	Active, not recruiting	NCT01412229 LCCC 1103
Multimodality Risk Adapted Therapy Including Carboplatin/Paclitaxel/Lapatinib as Induction for Squamous Cell Carcinoma of the Head and Neck Amenable to Transoral Surgical Approaches Date trial summary last modified: August 26, 2015	Recruiting	NCT01612351 LCCC 1125

Official Title	Status	Protocol ID
An Open-label, Randomized, Parallel-group, Multicenter Study of Neoadjuvant Docetaxel(Taxotere®) Plus Cisplatin Plus 5-fluorouracil Versus Neoadjuvant Cisplatin Plus 5-fluorouracil in Patients With Locally Advanced Inoperable Squamous Cell Carcinoma of the Head and Neck	Active, not Recruiting	NCT00995293 DOCET_L_02557
Date trial summary last modified: December 10, 2014		

DISCUSSION

Squamous cell carcinoma is the predominant mucosal cancer of the head and neck region. Previously untreated patients have high rates of tumour shrinkage with chemotherapy, and this has prompted studies involving multimodality treatment schedules, including induction, adjuvant, alternating, and concurrent chemotherapy treatment. More recently targeted agents and radiosensitizers have also been studied. This overview was undertaken to review and pool the existing evidence and derive a consensus around the role of systemic therapies in the management of patients with locally advanced SCCHN. Although the incidence of SCCHN has been on the rise, with overwhelming evidence in support of HPV as an important reason for the increase, this was historically unknown with the consequence of no stratification of randomization or adjustment of the results based on tumour HPV status. It is possible that an imbalance in the randomization of HPV-related cancers may have influenced the results of some RCTs.

The role of chemotherapy is most clear for its concomitant use with postoperative or radical radition therapy (RT). The MACH-NC meta-analysis identified benefits in overall survival with this approach more than a decade ago, and the use of concomitant chemotherapy with RT (mainly concurrently in the Ontario setting [CRT]) is recognized as a standard of care. This benefit was more profound with platinum-based chemotherapy, and the most robust evidence is for cisplatin. High-dose cisplatin 100 mg/m^2 IV days 1, 22 and 43 of RT was most commonly studied. However, alternative cisplatin schedules may be quite reasonable, and in our review of these RCTs it seemed clear that some dose effect was present supporting optimal doses of at least 40 mg/m^2 per week. A schedule of cisplatin 40 mg/m2 IV weekly during RT is used as a standard approach for cervical cancer and has been adopted as a standard arm for clinical trials by the NRG clinical trials group. Data for carboplatin was conflicting and its routine use in CRT cannot be endorsed.There was less data supporting use of 5-FU plus platin with CRT, however, the Calais regimen (carboplatin 70 mg/m^2 bolus plus continuous infusion 5-FU 600 mg/m^2 each IV daily for 4 days weeks 1 and 4 of RT) is a reasonable alternative for patients unsuitable for cisplatin.

Of targeted agents and radiosensitizers studied in RCTs as alternatives or additions to CRT, only the anti-EGFR monoclonal antibody cetuximab has shown benefit. However, although the addition of cetuximab to RT was shown superior to RT alone, not RCTs have yet demonstrated superiority or non-inferiority of cetuximab-RT to CRT. In view of this, and the voluminous evidence supporting CRT, cetuximab-RT can only be considered a standard option for treatment in patients who are not candidates for the chemotherapy used with CRT.

Induction chemotherapy remains a controversial topic. Superior outcomes were reported in RCTs comparing induction TPF to PF prior to local therapy, including overall survival and larynx preservation. However, RCTs comparing TPF followed by CRT to CRT alone have shown mainly negative results. In part this may reflect testing of more aggressive and toxic therapy in patient populations enriched with HPV-related cancers which have an intrinsically good prognosis with CRT. Induction chemotherapy does remain useful for rapid tumour

downsizing for symptom relief prior to definitive local therapy, and in this regard TPF does appear to have a superior response rate to PF chemotherapy. TPF chemotherapy should be used by experienced medical oncologists, and its increased myelosuppressive effects may be abrogated by primary prophylaxis with G-CSF. Longterm results of the RTOG 9111 are also provocative in identifying a possible role for induction chemotherapy in larynx preservation. PF chemotherapy was associated with similar laryngectomy progression-free survival and a trend to better overall survival compared with CRT. As TPF has been shown superior to PF in such a setting, further investigation of induction approaches may be warranted.

CONCLUSIONS

Locally advanced squamous cell carcinoma of the head and neck cancer remains a lethal disease, and has particularly devastating effects on quality of life compared to other cancers. The addition of systemic chemotherapy concurrently with radical or postoperative adjuvant radiation therapy remains a standard albeit potentially toxic treatment approach for appropriate patients. The role for induction treatment beyond tumour downsizing and symptom relief prior to local therapy remains controversial. Induction chemotherapy for improving larynx preservation and survival in larynx and hypopharynx cancer may be an alternative to CRT. Triplet regimens incorporating docetaxel are of interest in this domain.There is proof of principle that concurrent cetuximab-RT is superior to RT alone, but it is unclear whether cetuximab-RT can be considered non-inferior to CRT. outcome. Evidence form RCTs studying patients with LASCCHN continues to accumulate. It is expected that clearer guidance will emerge from these in future in the realms of HPV-related cancers, the use of targeted therapy, and use of induction chemotherapy which will inform future guideline recommendations.

Systemic Therapy in the Curative Treatment of Head and Neck Squamous Cell Cancer: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the Head and Neck DSG members and the PEBC Report Approval Panel (RAP) (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in November 2015. The RAP approved the document. There were no major comments from the RAP requiring the Working Group's response.

Expert Panel Review and Approval

Of the 11 members (excluding the Working Group) of the GDG Expert Panel, nine members cast votes and two abstained, for a 81% response rate, in November 2015. Of those that cast votes, eight people (88%) approved the document. The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. The part of Recommendation 4 that says the use of the radiosensitizers is not recommended seems like an afterthought since the reasons for this statement were not really discussed in the expanded text.	We moved the recommendation about radiosensitizers to the qualifying statement section.
2. One summary statement that reads: "Although the addition of cetuximab to RT in patients with locally advanced LASCCHN increased OS, it is unclear whether the addition of cetuximab to conventional once-daily RT would improve survival" under Recommendation 4 may be a bit confusing to readers.	We modified the qualifying statement to read as follows: "Although the addition of cetuximab to RT in patients with locally advanced LASCCHN increased OS, the benefit was greatest in patients treated with non-conventional fractionation. It is unclear whether the addition of cetuximab to conventional once-daily RT would improve survival."
3. Recommendation 4. The description of "concurrent boost" in the current era of Intensity Modulated Radiation Therapy, which is the standard of care, may not be an appropriate terminology or might be best clarified by adding the following: "concurrent boost (i.e, integrated boost during once daily fractionation using IMRT-based approaches)"	We did not make this change.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Seven targeted peer reviewers from Canada, USA and Belgium who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Three agreed to be the reviewers (Appendix 1) and their responses were received. Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

The Reviewers identified a controversial topic that was discussed extensively by the Working Group. As radiation is the primary curative modality of treatment for these patients, and cisplatin is being used as a radiosensitizer, avoiding interruptions or discontinuations of radiation due to cisplatin toxicities is an important clinical consideration. It is agreed that high-dose cisplatin given q3weekly (HD cisplatin) is the concurrent chemotherapy schedule best studied in RCTs in this setting, and that HD cisplatin has not been compared directly to other cisplatin schedules. However, in generalizing these data to clinical practice, the higher frequency and severity of acute toxicities seen with HD cisplatin is also important. A significant proportion of patients receive less than 3 cycles of HD cisplatin. In the RTOG 0219 trial which included only good performance status patients of median age 56 years, 30.8% of patients received less than 3 cycles of HD cisplatin in the standard radiation arm (Nguyen-Tan et al 2014). It is likely this proportion is higher in usual clinical practice and it is unclear how this impacts treatment efficacy for these patients. See Appendix 5 for more details.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	0	0	1	2
2. Rate the guideline presentation.	0	0	0	2	1
3. Rate the guideline recommendations.	0	0	0	3	0
4. Rate the completeness of reporting.	0	0	0	2	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	0	4	1
6. Rate the overall quality of the guideline report.	0	0	0	2	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	0	0	0	2	1
8. I would recommend this guideline for use in practice.	0	0	0	2	1
9. What are the barriers or enablers to the implementation of this guideline report?	• These guidelines do not account for HPV status and for the new staging guidelines that are soon to be released for HPV-positive tumours. While currently this does not change the guidelines, with the emergence of clinical trial results in the				

	near future these recommendations will need to be updated soon. • It would be nice to have a bit of flexibility around age in Recommendation 1. • There is insufficient data to support the term "intensified RT" in Recommendation 4.

Table 5-4. Responses to comments from targeted peer reviewers.

Comments	Responses
1. In recommendation 1 – it appears that high dose cisplatin is presented as being equivalent to other cisplatin schedules. The standard chemotherapy regimen is considered to be concurrent cisplatin (100 mg/m2 every 21 days) for patients with an excellent performance status. Alternative cisplatin dosing schedules are sometimes used because of improved patient tolerance but these schedules have not been directly compared to high-dose bolus cisplatin.	See Appendix 5
2. Recommendation 1- It would be nice to have a bit of flexibility around age. Although the recommendations are suitable for the intended patients, the concern is that this guideline might support the tendency that fit older people might not receive the same standard of care treatment as younger ones. This is becoming more and more of an issue, since the HNC population will change the coming years.	The Working Group agrees with the point raised about interaction between the benefits of chemoradiation and age, and an additional caveat has been added on page 3 to address this.
3. Ensure that the statements in the Qualifying statements/key evidence sections are referenced appropriately. For example, the statement "Acute and long-term adverse effects are increased with CRT versus local therapy and the relative benefits and risks for individual patients should be carefully evaluated" has no reference.	A toxicity reference (Winquist et al 2007) has been added.
4. Recommendation 2 – it is unclear if these guidelines are recommending that patients receive adjuvant concurrent chemotherapy with RT if the following features are observed: pathologic T3/T4 tumors, perineural or lymphovascular invasion, or oral cavity or oropharynx cancers metastatic to level IV/V lymph nodes.	Clarity has been enhanced by simplifying the wording of this recommendation and the qualifying statements.
5. Recommendation 3 – the wording is somewhat confusing. Organ function-preserving chemoradiotherapy approaches are not appropriate for all patients with locoregionally advanced cancer of the	The wording around appropriate candidates for larynx preservation has been clarified.

larynx such as older patients and those with a poor performance status may not be suitable candidates;	
6. Recommendation 4 – should there be some discussion about who should be considered for cetuximab + RT as opposed to cisplatin? A challenge for clinicians is what systemic therapy to use concurrently with RT when patients are not candidates for Cisplatin (due to tinnitus, neuropathy or renal dysfunction). Should physicians use RT + Carbo/FU or cetuximab?	See Appendix 5
7. It appears that too much importance is given to subset analysis. Nevertheless, I agree completely with the position that the authors are giving to the use of cetuximab as an alternative for concurrent platinum-based chemoradiation.	Subset analyses of RCTs should be interpreted with caution. The Working Group was convinced by the combined data analysis of Bernier et al that regional lymph node involvement as there only postoperative risk factor did not warrant the addition of chemotherapy

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. Professionals in the PEBC database with an interest in head and neck cancer, and in systemic chemotherapy, were contacted by email to inform them of the survey. Seventy professionals who practice in Ontario (94%) and other provinces (6%) were contacted. Nine (12%) responses were received. Four stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from five people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	Number 5 (7%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	0	0	2	3
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0	0	0	3	2
3. I would recommend this guideline for use in practice.	0	0	0	3	2
4. What are the barriers or enablers to the implementation of this guideline report?	• The guideline generally does an excellent job of reviewing the literature from RCT's and meta-analyses. It is important for the reader to keep in mind that the guideline concerns systemic therapy in curative treatment, and does not purport to be a review of evidence for management of LASCCHN in general. How HPV status and how intensified regimens of RT will impact				

	the recommendations of the guideline will be some of the questions that readers of the guideline will be asking, and which may limit to some extent the adoption of the guideline. Of course we recognize that it is the nature of a practice guideline to lag behind current issues because the high level of evidence to deal with these emerging issues has not been published yet. • ENABLERS – This is a CCO-backed document and the Working Group has members from the major centres in Ontario. This helps to confirm most current practice. • BARRIERS- This may include limited resources, for example, recent cutbacks to hospital laboratory budgets including pathology may cause delays in biopsy and resection specimen turnaround time which may delay treatment decisions.

Table 5-6. Modifications/Actions taken/Responses regarding main written comments from professional consultants.

Comments	Responses
1. The rationale for dosing, and schedule of cisplatin not that convincing.	See Appendix 5

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1: Members of the Working Group, Expert Panel, Report Approval Panel and target reviewers and their COI declarations (see the PEBC Conflict of Interest (COI) Policy).

Name	Affiliation	COI Declared
Working Group		
Eric Winquist	London Health Sciences Centre	Yes[a]
Chika Agbassi	Department of Oncology, McMaster University	No
Brandon Meyers	Department of Oncology, McMaster University	No
John Yoo	London Health Sciences Centre	Yes[b]
Kelvin Chan	Sunnybrook Hospital	No
Expert Panel		
Margaret Anthes	Thunder Bay Regional Health Sciences Centre	No
Danny Enepekides	Sunnybrook Hospital	No
Ralph Gilbert	Princess Margaret Hospital, Toronto	No
Laval Grimard	Ottawa Hospital Regional Cancer Centre	Yes[b]
David Palma	London Regional Cancer Program	No
Kenneth Schneider	Windsor Regional Cancer Centre	No
John Waldron	Princess Margaret Hospital:	No
Michael Gupta	St. Joseph's Healthcare, Hamilton	No
Jason Franklin	Cancer Centre of Southeastern Ontario, Kingston General Hospital	Yes[c]
Justin Lee	Odette Cancer Centre, Toronto	No
Brandon Meyers	McMaster University Juravinski Cancer Centre	No
Report Approval Panel		
Melissa Brouwers	Department of Oncology, McMaster University	No
Donna Maziak	University of Ottawa	No
Bill Evans	Oncosynthesis consulting	Yes
Targeted Peer Reviewers		
Jan Vermorken	Antwerp University Hospital	Yes
Michael Vickers	Ottawa Hospital Regional Cancer Centre	No
Aaron Hansen	Princess Margaret Cancer Centre	No

[a]Local Principal Investigator for HN.6 trial. TAX 324 trial and NCIC HN.6 trial
[b]Stocks, bonds, or stock options valued at $5,000 or more in a relevant business entity
[c]Owns a relevant business entity

Appendix 2: Guideline organizations and cancer agencies searched.

Database (Acronym)	Website URL	Date of search	Search Terms or Section Browsed
National Guideline Clearinghouse	guideline.gov	July 15 2014	Squamous cell carcinoma of head and neck
National Institute for Health and Clinical Excellence (NICE)	nice.org.uk	July 15 2014	Squamous cell carcinoma of head and neck
Scottish Intercollegiate Guidelines Network (SIGN)	sign.ac.uk	July 15 2014	Squamous cell carcinoma of head and neck
National Health and Medical Research Council (NHMRC), Australia	nhmrc.gov.au	July 15 2014	Squamous cell carcinoma of head and neck
National Comprehensive Cancer Network (NCCN)	nccn.org	July 15 2014	Squamous cell carcinoma of head and neck
American Society of Clinical Oncology (ASCO) Guidelines	asco.org	July 15 2014	Squamous cell carcinoma of head and neck
Agency for Healthcare Research and Quality (AHRQ) evidence reports and technology reports	ahrq.gov	July 15 2014	Squamous cell carcinoma of head and neck
Cochrane Database of Systematic Reviews	thecochranelibrary.com	July 15 2014	Squamous cell carcinoma of head and neck
Canadian Medical Association (CMA) Infobase	cma.ca	July 15 2014	Squamous cell carcinoma of head and neck

Appendix 3: Literature Search Strategy

Complete search strategy for the primary literature systematic review
Database: EMBASE <2000 to 2015 week 8>, OVID MEDLINE(R) without revisions <2000 to February week 4 2015>, OVID MEDLINE(R) in-process and other nonindexed citations <September 14, 2014 and February 2015>

EMBASE

1. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
2. randomization/ or single blind procedure/ or double blind procedure/
3. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
4. or/1-3
5. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
6. 5 and random$.tw.
7. (clinic$ adj trial$1).tw.
8. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
9. placebo/
10. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
11. (allocated adj2 random).tw.
12. or/7-11
13. 4 or 6 or 12
14. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
15. 13 not 14
16. animal/ not human/
17. 15 not 16
18. squamous cell carcinoma/
19. squamous cell/
20. carcinoma/ or cancer/ or neoplasia/ or neoplasm/
21. 19 and 20
22. 18 or 21
23. (head and neck).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
24. hypopharynx/ or larynx/ or trachea/ or oral cavity/ or oropharynx/
25. 23 or 24
26. 22 and 25
27. 17 and 26
28. (200001$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015).ew.
29. 27 and 28

MEDLINE

1. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
2. randomization/ or single blind procedure/ or double blind procedure/
3. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
4. or/1-3
5. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
6. 5 and random$.tw.
7. (clinic$ adj trial$1).tw.
8. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
9. placebo/
10. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
11. (allocated adj2 random).tw.
12. or/7-11
13. 4 or 6 or 12
14. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
15. 13 not 14
16. animal/ not human/
17. 15 not 16
18. squamous cell carcinoma/
19. squamous cell/
20. carcinoma/ or cancer/ or neoplasia/ or neoplasm/
21. 19 and 20
22. 18 or 21
23. (head and neck).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
24. hypopharynx/ or larynx/ or trachea/ or oral cavity/ or oropharynx/
25. 23 or 24
26. 22 and 25
27. 17 and 26
28. (200001$ or 2001$ or 2002$ or 2003$ or 2004$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015).ew.
29. 27 and 28

Appendix 4: Recommendations submitted for external review.

Recommendation 1 Concurrent chemoradiotherapy (CRT) is recommended to maximize the chance of cure in patients <71 years of age when radiotherapy (RT) is used as definitive management of LASCCHN.
Recommendation 2 For patients with resected LASCCHN considered to be at high risk of locoregional recurrence, concurrent chemoradiotherapy is recommended over RT alone to maximize the chance of cure in patients <71 years of age.
Recommendation 3 For patients with LASCCHN who would otherwise require laryngectomy, two strategies are superior to RT alone for larynx preservation: CRT or induction chemotherapy followed by radiation or surgery based on tumour response.
Recommendation 4 • The addition of cetuximab to intensified RT (concomitant boost or hyperfractionated schedule) may provide an alternative option to CRT.
Recommendation 5 • The routine use of induction chemotherapy as neoadjuvant treatment to improve overall survival is not recommended for patients with LASCCHN.

Appendix 5: Working Group Response to Reviewers comment.

Reviewer 1 The Reviewers identified a controversial topic that was discussed extensively by the Working Group. As radiation is the primary curative modality of treatment for these patients, and cisplatin is being used as a radiosensitizer, avoiding interruptions or discontinuations of radiation due to cisplatin toxicities is an important clinical consideration. It is agreed that high-dose cisplatin given q3weekly (HD cisplatin) is the concurrent chemotherapy schedule best studied in RCTs in this setting, and that HD cisplatin has not been compared directly to other cisplatin schedules. However, in generalizing these data to clinical practice, the higher frequency and severity of acute toxicities seen with HD cisplatin is also important. A significant proportion of patients receive less than 3 cycles of HD cisplatin. In the RTOG 0219 trial which included only good performance status patients of median age 56 years, 30.8% of patients received less than 3 cycles of HD cisplatin in the standard radiation arm (Nguyen-Tan et al 2014). It is likely this proportion is higher than usually seen in clinical practice and it is unclear how this impacts treatment efficacy for these patients. There are RCTs using daily (6 mg/m2 5 days per week [Jeremic et al 1997]) and weekly (50 mg weekly [Bachaud et al 1996]) schedules of cisplatin concurrently with radiation that report a similar magnitude of overall survival benefit to HD cisplatin. Furthermore, individual patient data meta-analysis of RCTs including different platin monochemotherapy schedules was not associated with heterogeneity (Pignon et al 2007). Also, by way of indirect evidence, weekly cisplatin 40 mg/m2 given concurrent with radiation improved overall survival in a RCT studying patients with locally advanced squamous cell carcinoma of the uterine cervix (hazard ratio: 0.61 [95% confidence interval, 0.44 to 0.85] [Rose et al 1999]). Data from one LA SCCHN RCT reported that cisplatin 20 mg/m2 given weekly did not improve failure-free or overall survival compared to radiation alone (Quon et al 2011). This

report plus those of Jeremic et al and Bachaud et al infer that a cisplatin dose of at least 30 mg/m2 per week concurrent with radiation is required for benefit; however, it is unclear whether higher doses or more intensive schedules of cisplatin are necessary. The Working Group agreed that the choice of cisplatin and schedule used should be individualized. If cisplatin is to be used, the dose and schedule chosen should optimize both antitumor efficacy and each patient's ability to efficiently complete radiation treatment. The patient's prognosis may also be a consideration. For a patient with a poor prognosis cancer, the incremental toxicities of HD cisplatin might be worthwhile to optimize the chance of cure. However, for patients where the risk of toxicity is unacceptable, or whose prognosis is good, the uncertain incremental benefits of HD cisplatin may not be worth the risks.
The Working Group agrees with the point raised about interaction between the benefits of chemoradiation and age, and an additional caveat has been added on page 3 to address this.

Reviewer 2

A toxicity reference has been added (Winquist et al 2007). Although the report by Bonner et al (2010) comparing radiation plus cetuximab to radiation alone raised hope that cetuximb might provide relative sparing of the normal mucosa from radiosensitization, more recent reports indicate contrary results. Specifically, Mangrini et al (2016) compared radiation plus cetuximab to radiation plus weekly cisplatin 40 mg/m2 in a phase II RCT and reported grade 3 mucositis rates of 59% and 53%, respectively. This suggests that concurrent treatment (either with chemotherapy, or with cetuximab) is associated with additional toxicity not seen in radiation alone.

LA SCCHN patients receiving radiation should be advised individually about the risks, benefits, and available choices for concurrent radiosensitizing chemotherapy or cetuximab by a medical oncologist with expertise in the treatment of head and neck cancer.

Reviewer 3

Please see previous comments to Reviewer 1 regarding cisplatin dose and schedule.
Clarity has been enhanced by simplifying the wording of this recommendation and the qualifying statements. Subset analyses of RCTs should be interpreted with caution. The Working Group was convinced by the combined data analysis of Bernier et al that regional lymph node involvement as the only postoperative risk factor did not warrant the addition of chemotherapy. However, for other potential risk factors that allowed eligibility in the EORTC RCT the data were less clear. A similar magnitude of benefit to that seen with extranodal extention and microscopic positive margins was observed but low patient numbers left this underpowered for statistical proof. This uncertainty is articulated in the first qualifying statement as "may also improve overall survival".

As postoperative RCTs were included in the MACH-NC meta-analysis, recommendations for concurrent chemotherapy choice were considered generalizable from Recommendation 1.
Agree and the wording around appropriate candidates for larynx preservation has been clarified.

Please see previous comments to Reviewer 2 regarding patients ineligible for cisplatin.

Ontario Health
Cancer Care Ontario

Evidence-Based Series 5-11 Version 2: Section 6

Systemic Therapy in the Curative Treatment of Head and Neck Squamous Cell Cancer

Document Review Summary

E. Winquist, C. Agbassi, and Members of the Expert Panel on Systemic Therapy in Head and Neck Squamous Cell Cancer

The 2016 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2016.

In December 2020, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (EW) reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Expert Panel on Systemic Therapy in Head and Neck Squamous Cell Cancer (Appendix 1) endorsed the recommendations found in Section 1 (Clinical Practice Guideline) on January 28, 2022.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1. In patients with unresected squamous cell carcinoma of the head and neck, what are the chemotherapy regimens that, administered concurrently with conventional or intensified radiotherapy, are superior or equivalent to other regimens on important outcomes such as tumour response rate, survival rate, and organ preservation with fewer toxicity/adverse events?

2. In postoperative patients with squamous cell carcinoma of the head and neck, what is the optimal chemotherapy regimen that can be administered concurrently with conventional radiotherapy?
3. Compared to chemoradiotherapy, can targeted agents or radiosensitizers improve or maintain outcomes, with reduced adverse events/toxicity, when used alone or in addition to primary radiotherapy in the treatment of patients with squamous cell carcinoma of the head and neck?
4. In patients with squamous cell carcinoma of the head and neck, what are the induction chemotherapy regimens that are superior or equivalent to others on important outcomes such as tumour response rate, survival rate, and organ preservation with fewer toxicity/adverse events?
5. What are the subgroups of patients with squamous cell carcinoma of the head and neck that would benefit more than others from postoperative systemic therapy?

Literature Search and New Evidence
The new search (2015 to February 2021) yielded 1 practice guideline and 14 RCTs. Two articles (Ghi 2016 and Siewert 2017) reported the final results of studies previously included in the original documents. An additional search for ongoing studies on clinicaltrials.gov yielded 20 potentially relevant ongoing trials. Brief results of these publications are shown in the Document Review Tool.

Impact on the Guideline and Its Recommendations
The new data support existing recommendations. However, one phase 2/3 trial reported that weekly cisplatin was at least as good (and less toxic) than cisplatin given every 3 weeks concurrently with radiation in postoperative patients (1). Although this report may have changed practice for many experts in this field, the finding does not invalidate the recommendations in this guideline. The recommendations in this guideline were not prescriptive for different cisplatin schedules in the post-operative setting. Hence, the Expert Panel ENDORSED the 2016 recommendations on Systemic Therapy in the Curative Treatment of Head and Neck Squamous Cell Cancer.

Ontario Health
Cancer Care Ontar

Document Review Tool

Number and Title of Document under Review	5-11 Systemic Therapy in the Curative Treatment of Head and Neck Squamous Cell Cancer
Original Report Date	August 10, 2016
Date Assessed (by DSG or Clinical Program Chairs)	January 2019
Health Research Methodologist	Chika Arinze
Clinical Expert	Eric Winquist
Approval Date and Review Outcome (once completed)	ENDORSE January 28, 2022

Original Question(s):

1. In patients with unresected squamous cell carcinoma of the head and neck, what are the chemotherapy regimens that, administered concurrently with conventional or intensified radiotherapy, are superior or equivalent to other regimens on important outcomes such as tumour response rate, survival rate, and organ preservation with fewer toxicity/adverse events?
2. In postoperative patients with squamous cell carcinoma of the head and neck, what is the optimal chemotherapy regimen that can be administered concurrently with conventional radiotherapy?
3. Compared to chemoradiotherapy, can targeted agents or radiosensitizers improve or maintain outcomes, with reduced adverse events/toxicity, when used alone or in addition to primary radiotherapy in the treatment of patients with squamous cell carcinoma of the head and neck?
4. In patients with squamous cell carcinoma of the head and neck, what are the induction chemotherapy regimens that are superior or equivalent to others on important outcomes such as tumour response rate, survival rate, and organ preservation with fewer toxicity/adverse events?
5. What are the subgroups of patients with squamous cell carcinoma of the head and neck that would benefit more than others from postoperative systemic therapy?

Target Population:

Patients with LASCCHN being considered for curative intent treatment.

Study Selection Criteria:

Inclusion Criteria

- Studies were included if they were systematic reviews, meta-analyses, or RCTs evaluating the role of induction or concurrent chemotherapy in the management of non-metastatic SCCHN, specifically in the hypopharynx, larynx, trachea, oral cavity, and oropharynx regions, or
- RCTs comparing one drug regimen including targeted agents and radiosensitizers with another drug regimen alone or in combination with locoregional treatment (radiotherapy and/or surgery).
- The studies had to report at least one of the following outcomes: overall survival rate (OS), disease free survival rate (DFS), tumour response rate, larynx preservation, Grade 3/4 toxicity or quality of life.

Exclusion Criteria
The following exclusion criteria were applied to the entire literature search:

- Studies that included nasopharyngeal carcinoma.
- Case reports, news reports, notes, commentaries, opinions, letters, editorials, qualitative studies.
- Studies on cost-effectiveness, utility, and economics.
- Studies with fewer than 30 participants.
- Studies published in a language other than English, due to the lack of funding and resources for translation.

Search Details:

- 2017 to July 2021 Cochrane (Database of Systematic Reviews)
- July 2015 to February 2021 (Medline and Embase)

Summary of new evidence:
Out of 1985 hits from the search of Medline, Embase, and the Cochrane Database for systematic reviews, publication of 14 primary studies and one meta-analysis were included. Two articles (Ghi 2016 and Siewert 2017) reported the final results of studies previously included in the original documents.

Clinical Expert Interest Declaration:
The Clinical expert (EW) and Health Research Methodologist (CA) delared no conflict of interest.

1. Does any of the newly identified evidence contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No
2. Does the newly identified evidence support the existing recommendations?	Yes
3. Do the current recommendations cover all relevant subjects addressed by the evidence? (i.e., no new recommendations are necessary)	One phase 2/3 trial reported that weekly cisplatin was at least as good (and less toxic) than cisplatin given every 3 weeks concurrently with radiation in postoperative patients (1). Although this report may have changed practice for many experts in this field, the finding does not invalidate the recommendations in this guideline. The recommendations in this guideline were not prescriptive for different cisplatin schedules in the post-operative setting. So I think the guideline remains accurate and I don't think it requires any modifications at this time.
Review Outcome as recommended by the Clinical Expert	ENDORSE
If outcome is UPDATE, are you aware of trials now underway (not yet published) that could affect the recommendations?	
DSG/Expert Panel Commentary	Two RCTs not retrieved in the search should be noted: Gillison et al (17) and Mehanna et al (18) show that cetuximab plus RT is LESS effective than cisplatin plus

	RT, but they don't show that cetuximab plus RT is ineffective (i.e., no better that RT alone). This evidence should be taken into account when an update of this guideline is done.

Evidence Table

Author [Ref#] Study Name	Study Design (Med F/U in Months)	Population Number of Patients	Disease Site(s)	
Concurrent Chemotherapy – Compared with RT Alone				
Gupta et al 2016 (2)	Conventionally Fractionated CCRT vs. Accelerated RT	Systematic review and Meta- Analysis	oropharynx, hypopharynx larynx	• Th CCRT arm was significantly better than RT alone in OS and LRC HR = 0.79 (95% CI 0.68 to 0.092) p = 0.002 and LRC HR = 0.71(95% CI 0.59 to 0.084) p < 0.0001 Late toxicity was significantly more in the CCRT group but there was no difference in the incidence of acute toxicity between the two groups
Gupta et al. 2020(3)	CBRT vs. CBRT + CCT vs. CFRT + CCT	Previously untreated Stage III/IV patients KPS = 70 Med Age: 58.1 Med F/U: 8.2mos n = 90	oropharynx, hypopharynx and larynx	There was no significant difference in locoregional control (LRC), disease free survival (DFS), and overall survival (OS) between the three groups
Yi et al. 2017(4)	Pre-op RT + Cis (30mg/m^2/wk) vs. Pre-op RT	Stage III/IVA-B Med F/U: 59mos n = 222	Oral cavity Oropharynx Hypopharynx/ Larynx	At 5 years, the distant metastasis-free survival (DMFS) and PFS were significantly better in the pre-op CRT compared to RT alone. Differences in LRC and OS were not significant • LRC: 0.1% v 62.4% (HR = 0.83; 95% CI, 0.50 to 1.38) P = 0.47 • DMFS: 80.4% vs. 68.1% (HR 0.53; 95% CI, 0.28 to 0.98) P = 0.04 • PFS: 53.2% vs. 38.7% (HR 0.69, 95% CI, 0.47 to 1.01) P = 0.06 • OS: 53.8% vs. 39.0% (HR 0.74; 95% CI, 0.50 to 1.10) P = 0.13
**Tao et al. 2017(5)	VA-RT (64.8Gy/3.5wk) vs. CRT. CRT was either: convt'l RT (70Gy/7wk) + 3cyc Carbo/5FU or Moderately accelerated RT: (70 Gy/6wk) + 2cyc Carbo/5FU or Strongly Intensified RT: (64 Gy/5wk) + Cis/5FU + 2cyc Cis/5FU	Previously untreated Non-metastatic N3 patients Med F/U: 5.2yrs n = 179	Oral cavity Oropharynx Hypopharynx Larynx	There was no significant difference in OS, LRF, DM, between the CRT arms and the very accelerated RT (VA-RT) arm.
Ghosh–Laska 2016(6)	Concomitant CRT vs. accelerated RT vs. RT	Previously untreated Nonmetastatic, non-nasopharynx HNSCC stage II, III, or IV KPS: > 70 Med Age: 56 Mean F/U: 54mos n = 199	Oropharynx Oral cavity Larynx Hypopharynx	CRT arm is significantly better than the RT and the accelerated RT arms. The 5yrs LRC was 49% for CRT arm and 27% for acc RT (P = 0.01) The 5yrs DFS 29% in the CRT arm and 20% in the acc. RT arm, P = 0.03) The distant metastasis (DM) and OS were not different between the arms.
Gupta 2015 et al. (7) Meta- Analysis	CCRT vs. RT	non-metastatic HNSCC KPS > 70 Med Age: 57yrs Med F/U: 12mos	oropharynx, hypopharynx larynx	Toxicity rates were similar in some grades and significantly higher in in the CCRT arm compared to RT arm in the following : • Grade 4 skin toxicity: 32.8% vs 12.1%; P = 0.02 • Grade 3 mucositis: 62.7% vs 40.9%; P = 0.015. • Grade 3 pharyngeal toxicity: 42.3% vs 28.8%; P = 0.05.

		n = 133		• Grade 2 and Grade 3 laryngeal toxicities: 55.2% vs 31.8%; P = 0.028.
Budach 2015(8)	Concomitant CRT (5FU/Mitomycin/RT) vs. HART alone	Previously untreated Inoperable Stage III and IV Med F/U: 8.7yrs n = 384	Oropharynx Oral cavity Hypopharynx	• LRC: The 10 years LRC rate was significantly better in the CCRT arm compared to the HART arm: 38.0% vs. 26.0%; P =.002. The median time to LRF was 4yr vs. 1.2yrs • PFS rates at 10yrs were significantly better in the CCRT arm: 25% vs. 18%; P = 0.033. The median PFS was 1.4yrs vs. 0.9yrs OS was better in CCRT compared to HART: 10% vs. 9%; P =.049. The Cancer specific survival rate was 39% vs. 30% P = 0.042.
Concurrent Chemotherapy – Compared with another CRT				
Seiwert et al 2016(9)	IC (Cet/Pac/CarP) + CCRT(CET/ 5FU/RT) vs. IC (Cet/Pac/CarP) CCRT (CET + CIS + RT)	Stage: III - IV ECOG: 0-1 HPV +ve: 42.7% Med Age: 57 vs. 56 Med F/: 72mos n = 110	Hypopharynx Larynx Nasal cavity Nasopharynx Oral cavity Oropharynx	There were no significant differences in PFS and OS in both arms.
Induction Chemotherapy				
Janoray et al 2016(10)	IC (Doc/Cis/5FU) + RT vs. IC (Cis/5FU) + RT	Operable patients with untreated Stage III or IV Med Age: nr Med F/U: 105mos n = 213	Larynx Hypopharynx	• Larynx preservation at 10yrs was better in the TPF arm compared to the PF arm 70.3% (95% CI = 0.58 to 0.8) vs 46.5% (95% CI = 0.31 to 0.63) P = .01 • At 10yrs, larynx dysfunction-free survival was also better in the TPF arm compared to the TF arm: 63.7% (95% CI = 0.52 to 0.74) vs 37.2% (95% CI = 0.24 to 0.52, P = .001) • There were no differences between the two arms in ○ LRC: 27.9 (19.7 to 37.9) vs. 20.8 (12.8 to 32.0) HR = 1.16 (0.81 to 1.67) ○ DFS: 25.0 (17.1 to 35.0) vs. 18.7 (11.1 to 29.6); HR = 1.30 (0.91 to 1.86) ○ OS: 30.2 (21.5 to 40.6) vs. 23.5 (14.9 to 34.9); HR = 1.07 (0.74 to 1.57) Late grade 3-4 toxicity was significantly fewer in the TPF arm compared to the TF arm: 9.3% vs 17.1%, G-test) P = .038
Ghi et al 2017(11)	CCRT OR CET-RT vs. ICT (TPF) + CCRT or CET-RT	Stage III - VI ECOG: 0-1 Med Age: 60 vs. 61 Med F/U: 44.8mos n = 421	Oropharynx Oral cavity Hypopharynx	• The difference in overall response rate and distant failure different between the two arms were not significant • Complete response was significantly better with Induction CT compared to no induction CT: 42.5% vs. 28%, P = 0.0028 • LRF was significantly lower in the ICT arm compared to no ICT: HR 0.74; 95% CI 0.55 to 0.98; P = 0.036 • Median PFS (30.5mos vs 18.5mos) and OS (54.7 vs. 31.7) were better with ICT compared to no ICT. At three years, the ICT arm showed significantly better PFS and OS than the arms without IC. The significance was maintained after adjustment for prognostic factors. - PSF: HR = 0.72; 95% CI = 0.56 to 0.93; P = 0.013 - OS: HR = 0.74; 95% CI = 0.56 to 0.97; P = 0.031) at 3yrs Toxicity: There were no difference in Grade 3-4 mucositis and dermatitis but neutropenia was significantly higher in the IC arm compared to no IC arm (4% vs.1%, P = 0.038).
Lakshmaiah et al. 2015(12)	Cis + 5FU vs. cis + taxane	Previously untreated non-metastatic Stage: III - IV ECOG >2 Med Age: 46 Med F/U: nr n = 100	Oral cavity Oropharynx Hypopharynx Larynx	Toxicity: neutropenia, mucositis significantly more in the cisplatin arm compared to the taxane arm

EGFRI				
Bonner et al. 2016(13)	Cetuximab + RT vs. RT alone	Subgroup analysis of p16-positive or negative patients n = 181	Oropharynx	QoL: there was no significant difference in toxicity based on the p16 status of the patients in both arms
*Magrini et al. 2016(14)	RT + Cetuximab vs. RT + Cis	Patients for first line treatment of LASCC ECOG 1-2 Age 36 to 80 Med F/U:19.3 n = 70	Oral cavity Supraglottic larynx Hypopharynx Oropharynx	• LRC and survival rates were similar between the arms • Treatment related toxicity was significantly higher in the cetuximab arm compared to the cisplatin arm (19% vs. 3%, P = 0.044)
*Gebre-Medhin et al. 2021(15) ARTSCAN III	RT + Cetuximab (400mg/m2/wk) vs. RT + Cisplatin (40 mg/m2/wk)	Locoregionally advanced Stage III-IV P16-positive: 89% ECOG: 0-2 n = 291	Oral cavity Larynx Hypopharynx Oropharynx	At three years, compared to the cisplatin group, the: • LRF incidence was significantly higher in the cetuximab group 23% (95% CI = 16% to 31%) vs. 9% (95% C = 4 to 14) P = 0.0036 HR = 2.49 (95% CI = 1.33 to 4.66) P = 0.0045 • Distance failure was not different between the two groups HR, 1.45; 95%CI, 0.63 to 3.32) p= 0.39 • Event free survival (EFS) was significantly lower in the cetuximab group 67% (95%CI, 59% to 76%) vs. 85%(95%CI, 79% to 91%) HR= 1.99 (95% CI, 1.23 to 3.22) P = 0.0053 • OS was not significantly different between the two groups: HR = 63; (95% CI, 0.93 to 2.86) P=0. 086
Harrington et al. 2015(16)	RT + Cis + Lapatinib vs. RT + Cis + placebo	Resected high-risk SCCHN Stage II to IVA Surgical margin ≤ 5mm Med Age: 54 vs. 55 Med F/U: 35.3mos n = 688	Oral cavity Larynx Hypopharynx Oropharynx	DFS: The median DFS was 53.6 mos in the lapatinib arm but was not reached in the placebo arm arm. OS: were not reached in the lapatinib arm.

*Study was closed early
**pooled analysis of a subset of patients with N3 HNSCC from two randomized GORTEC

CBRT: concomitant boost radiotherapy; LASCC: locally advanced squamous cell carcinoma; LA: locally advanced; CCRT: concomitant chemoradiotherapy; CCT: concomitant chemotherapy; CET: Cetuximab; CFRT: conventionally fractionated radiotherapy; CT: chemotherapy; DF: distance failure; DFS: disease-free survival; DM: distant metastasis; DMFS: distant metastasis-free survival; ECOG: Eastern Cooperative Oncology Group; EFS: event free survival; GORTEC: French Head and Neck Oncology and Radiotherapy Group; HART: Hyperfractionated accelerated RT; HPV: human papillomavirus; HNSCC: head and neck squamous cell carcinomas; HR: hazard ratio; IC: Induction chemotherapy; IQR: interquartile range; KPC: Karnofsky performance score; LRF: locoregional failure; MA-RT: Moderately

accelerated RT; mos: months; OS: overall survival; PFS: progression-free survival; QoL: quality of Life; RT: radiotherapy; RTOG: Radiation Therapy Oncology Group; SI-RT: Strongly Intensified RT; VA-RT: Very accelerated RT; wk: week;

Table of Ongoing Trials

Official Title	Status	Protocol ID	Last Updated
Albumin-bound Paclitaxel Combined With Cisplatin Versus Docetaxel Combined With Cisplatin Induced Chemotherapy in Advanced Head and Neck Squamous Tumor	Recruiting	NCT04766827	February 23, 2021
Study of Safety and Tolerability of Nivolumab Treatment Alone or in Combination With Relatlimab or Ipilimumab in Head and Neck Cancer	Recruiting	NCT04080804	April 5, 2021
Induction Chemotherapy for Locally Advanced Head and Neck Squamous Cell Carcinoma (INDUCTION)	Recruiting	NCT03815903	July 18, 2019
A Prospective Randomized Trial of Capecitabine Treatment in Patients With HNSCC	Recruiting	NCT03678649	September 19, 2018
A Trial Evaluating the Addition of Nivolumab to Cisplatin-RT for Treatment of Cancers of the Head and Neck (NIVOPOSTOP)	Recruiting	NCT03576417	February 15, 2021
Multicentric Comparative Study Between a Conventional and an Intensive Follow up Strategy After Treatment of a Head and Neck Squamous Cell Carcinoma (SURVEILL'ORL	Recruiting	NCT03519048	February 17, 2020
Adjuvant Nivolumab After Salvage Resection in Head and Neck Cancer Patients Previously Treated With Definitive Therapy	Active, not Recruiting	NCT03355560	July 1, 2021
Neodjuvant Nivolumab and Lirilumab, Followed by Surgery, Followed by Adjuvant Nivolumab and Lirilumab, in SCCHN	Active, not Recruiting	NCT03341936	July 23, 2021
Trial of Laryngeal Preservation Comparing Induced CT Followed by RT vs CT Concomitant to RT (SALTORL)	Recruiting	NCT03340896	April 10, 2020
Comparison of Two Concomitant Administration of RT With Cisplatin in Standard Infusion or Fractional Infusion (CisFRad)	Recruiting	NCT03330249	February 15, 2021
Docetaxel and Loplatin Induction Chemotherapy Followed by Concurrent Chemoradiotherapy for Locally Advanced SCCHN	Recruiting	NCT03117257	April 17, 2017
Postoperative CCRT With Docetaxel vs Cisplatin in High Risk HNSCC	Recruiting	NCT02923258	September 26, 2018
Radiation Therapy With or Without Cisplatin in Treating Patients With Stage III-IVA Squamous Cell Carcinoma of the Head and Neck Who Have Undergone Surgery	Recruiting	NCT02734537	May 21, 2020
Tolerance and Efficacy of Pembrolizumab or Cetuximab Combined With RT in Patients With Locally Advanced HNSCC (PembroRad)	Active, not Recruiting	NCT02707588	April 9, 2021
Pembrolizumab + Radiation for Locally Adv SCC of the Head and Neck (SCCHN) Not Eligible Cisplatin	Active, not Recruiting	NCT02609503	March 19, 2021
IRX-2 Regimen in Patients With Newly Diagnosed Stage II, III, or IVA Squamous Cell Carcinoma of the Oral Cavity (INSPIRE)	Active, not Recruiting	NCT02609386	August 12, 2020
Nab-Paclitaxel and Cisplatin or Nab-paclitaxel as Induction Therapy for Locally Advanced Squamous Cell Carcinoma of the Head and Neck (HNSCC) (APA)	Active, not Recruiting	NCT02573493	March 2, 2021

Official Title	Status	Protocol ID	Last Updated
Safety And Efficacy Study Of Palbociclib Plus Cetuximab Versus Cetuximab To Treat Head And Neck Cancer	Active, not Recruiting	NCT02499120	September 20, 2019
Study of Chemotherapy With Cisplatin/Carboplatin, and Docetaxel With or Without Erlotinib in Patients With Head and Neck Squamous Cell Carcinomas Amenable for Surgical Resection	Active, not Recruiting	NCT01927744	August 10, 2020
Testing Docetaxel-Cetuximab or the Addition of an Immunotherapy Drug, Atezolizumab, to the Usual Chemotherapy and Radiation Therapy in High-Risk Head and Neck Cancer	Recruiting	NCT01810913	July 27, 2021
Radiation Therapy With Cisplatin or Cetuximab in Treating Patients With Oropharyngeal Cancer	Active, not Recruiting	NCT01302834	February 23, 2021
Paclitaxel, Carboplatin and Cetuximab (PCC) With Cetuximab, Docetaxel, Cisplatin and Fluorouracil (C-TPF) in Previously Untreated Patients With Locally Advanced Head and Neck Squamous Cell Carcinoma	Active, not Recruiting	NCT01154920	July 16, 2021
Induction Chemotherapy Followed by Cetuximab Plus Definitive Radiotherapy Versus Radiation Plus Cisplatin (INTERCEPTOR)	Active, not Recruiting	NCT00999700	September 5, 2017
Cisplatin and RT With or Without Gemcitabine, Carboplatin, and Paclitaxel in Treating Patients With Locally Advanced NPC	Active, not Recruiting	NCT00997906	August 28, 2019
Radiation Therapy With or Without Cetuximab in Treating Patients Who Have Undergone Surgery for Locally Advanced Head and Neck Cancer	Active, not Recruiting	NCT00956007	March 30, 2018

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Appendix 1. Members of the Expert Panel

Name	Affiliation	Conflict of Interest Declaration
Marc Gaudet	Radiation Oncologist The Ottawa Hospital Ottawa	None declared.
Ralph Gilbert	Head & Neck Surgeon Toronto General Toronto	None declared.
Michael Gupta	Head & Neck Surgeon St. Joseph's Hospital Hamilton	None declared.
Aaron Hansen	Medical Oncologist Princess Margaret Cancer Centre, Toronto	Consulted for GSK, Eisai, Novartis, Merck, AstraZeneca, Pfizer, and BMS. Received grants or research support to the institution from GSK, Merck, Pfizer, MedImmune/Genetech, Roche, Janssen, BMS, AstraZeneca, Astellas, Boeringher-Ingelheim, and Bayer.
Brandon Meyers	Medical Oncologist Juravinski Cancer Centre Hamilton	Consulted for Merck.

Appendix 2. Search Strategy

Complete search strategy for the primary literature systematic review
Database: EMBASE <2015 to 2021 February 12>, Ovid MEDLINE(R) 1996 to February 12, 2021, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 2017 to February 12, 2021

EMBASE

1. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
2. randomization/ or single blind procedure/ or double blind procedure/
3. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
4. or/1-3
5. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
6. 5 and random$.tw.
7. (clinic$ adj trial$1).tw.
8. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
9. placebo/
10. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
11. (allocated adj2 random).tw.
12. or/7-11
13. 4 or 6 or 12
14. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
15. 13 not 14
16. animal/ not human/
17. 15 not 16
18. squamous cell carcinoma/
19. squamous cell/
20. carcinoma/ or cancer/ or neoplasia/ or neoplasm/
21. 19 and 20
22. 18 or 21
23. (head and neck).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
24. hypopharynx/ or larynx/ or trachea/ or oral cavity/ or oropharynx/
25. 23 or 24
26. 22 and 25
27. 17 and 26
28. (2015$ or 2016$ or 2017$ or 2018$ or 2019$ or 2020$ or 2021$).ew.
29. 27 and 28

MEDLINE

1. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
2. randomization/ or single blind procedure/ or double blind procedure/
3. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
4. or/1-3
5. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
6. 5 and random$.tw.
7. (clinic$ adj trial$1).tw.
8. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
9. placebo/
10. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
11. (allocated adj2 random).tw.
12. or/7-11
13. 4 or 6 or 12
14. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
15. 13 not 14
16. animal/ not human/
17. 15 not 16
18. squamous cell carcinoma/
19. squamous cell/
20. carcinoma/ or cancer/ or neoplasia/ or neoplasm/
21. 19 and 20
22. 18 or 21
23. (head and neck).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
24. hypopharynx/ or larynx/ or trachea/ or oral cavity/ or oropharynx/
25. 23 or 24
26. 22 and 25
27. 17 and 26
28. (2015$ or 2016$ or 2017$ or 2018$ or 2019$ or 2020$ or 2021$).ed
29. 27 and 28

DEFINITIONS OF REVIEW OUTCOMES

1. **ARCHIVE** – ARCHIVE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is out of date or has become less relevant. The document, however, may still be useful for education or other information purposes. The document is designated archived on the CCO website and each page is watermarked with the words "ARCHIVED."

2. **ENDORSE** – ENDORSE means that a Clinical Expert and/or Expert Panel has reviewed new evidence pertaining to the guideline topic and determined that the guideline is still useful as guidance for clinical decision making. A document may be endorsed because the Expert Panel feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **UPDATE** – UPDATE means the Clinical Expert and/or Expert Panel recognizes that the new evidence pertaining to the guideline topic makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The Expert Panel advises that an update of the document be initiated. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making, unless the recommendations are considered harmful.