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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

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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.

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.