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PRACTICE GUIDELINE

Systemic therapy in the curative treatment of head-and-neck squamous cell cancer: Cancer Care Ontario clinical practice guideline

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ABSTRACT

Objective The aim of the present work was to make recommendations about the use of systemically administered drugs in combination or in sequence with radiation (RT) or surgery, or both, for cure or organ preservation, or both, in patients with locally advanced nonmetastatic (stages III–IVB) squamous cell carcinoma of the head and neck (LASCCHN).

Methods The Meta-analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) reports have, *de facto*, guided practice since 2000, and so we searched the literature for systematic reviews published from January 2000 to February 2015 in reference to five research questions. A search was also conducted up to February 2015 for randomized trials (RCTS) not included in the meta-analyses. Recommendations were constructed using the Cancer Care Ontario Program in Evidence-Based Care practice guidelines development cycle.

Results In addition to updated MACH-NC reports, five additional meta-analyses and thirty RCTS were identified. Five recommendations for LASCCHN treatment were generated based on those data. Concurrent chemoradiation (CCRT) is recommended to maximize the chance of cure in patients less than 71 years of age when RT is used as definitive treatment. The same recommendation also applies to patients with resected LASCCHN considered to be at high risk for locoregional recurrence. For LASCCHN patients who are candidates for organ preservation strategies and would otherwise require total laryngectomy, either CCRT or induction chemotherapy, followed by RT or surgery based on tumour response is recommended. The addition of cetuximab to intensified RT (concomitant boost or hyperfractionated schedule) is an alternative to CCRT. Routine use of induction chemotherapy to improve overall survival is not recommended.

Conclusions We were able to use high-level evidence from patients receiving RT as definitive or postoperative treatment to generate recommendations for the use of systemic therapy in the treatment of LASCCHN. A limitation is a lack of stratification for human papillomavirus–related cancers of the oropharynx. One RCT provided evidence for the use of cetuximab as an alternative to chemotherapy in the definitive RT setting. Concurrent chemoradiation provides one strategy for larynx preservation, but the best strategy is unclear. Use of induction chemotherapy does not improve overall survival, and its use should be limited to patients requiring immediate tumour downsizing before local therapy.

Key Words Squamous cell carcinoma, head-and-neck cancer, human papillomavirus, locally advanced disease, systemic chemotherapy, induction chemotherapy, concurrent chemotherapy, systematic reviews, clinical practice guidelines, guideline recommendations

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BACKGROUND

Squamous cell carcinoma accounts for more than 90% of all head-and-neck cancers. Squamous cell carcinoma of the head and neck is ranked the 6th most common cancer worldwide, with more than 500,000 new cases and 300,000 deaths reported annually[1]. The topic of the guideline presented here is the debilitating and potentially life-threatening locally advanced squamous cell carcinoma of the head and neck (LASCCHN) arising from the mucosa 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[1].

Tobacco and alcohol use have long been identified as important risk factors for LASCCHN. Other risk factors include chewing betel quid, prior radiography of the head and neck region, ill-fitting dentures, and certain viral infections[1]. Epstein–Barr virus infection has been implicated in the pathogenesis of nasopharyngeal cancer. Since about 2005, infection with the human papillomavirus (HPV) has emerged as an important risk factor for oropharyngeal cancers. Those viral-related cancers continue to increase in incidence and often affect younger patients.

The primary management strategies for patients with squamous cell carcinoma of the head and neck (SCCHN) consist of surgery or radiation therapy (RT), or both[2]. The cure rates for early-stage cancers (stages I and II) treated with RT or surgery alone are high. A key challenge in the management of this cancer is that many patients have locally advanced disease (stages III to IVB) at presentation.

The meta-analyses of individual patient data from the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) group provided major insights into the role of chemotherapy in the curative treatment of LASCCHN and have served as *de facto* practice guidelines since their publication in 2000 and update in 2009, which included randomized controlled trials (RCTS) reported during 1965–2000[3–5]. Given that data from RCTS has continued to emerge since that time, and novel clinical treatments including epidermal growth factor receptor–targeted drugs, radiosensitizers, and taxane-based induction chemotherapy have continued to be developed, the Working Group of Cancer Care Ontario's Head and Neck Disease Site Group (DSG) updated their clinical practice guidelines to incorporate those data.

Formation of the Working Group

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario. The Cancer Care Ontario Head and Neck DSG, in collaboration with the PEBC, had produced evidence-based guidelines in the topic area of the curative treatment of LASCCHN, but those guidelines required updating. A Working Group consisting of 3 surgical oncologists, 1 medical oncologist, and 1 methodologist was therefore identified from among the Head and Neck DSG members. The remaining DSG members provided feedback on the guideline as it was being developed and acted as an expert panel for the document at the internal review stage.

RESEARCH QUESTIONS

- In patients with unresected LASCCHN, which chemotherapy regimens administered concurrently with conventional or intensified RT are superior or equivalent to other regimens for important outcomes such as tumour response rate, survival rate, and organ preservation, with fewer toxicities or adverse events?
- In patients with LASCCHN who have undergone surgical resection, what is the optimal chemotherapy regimen that can be administered concurrently with conventional RT?
- Compared with chemoradiotherapy, can targeted agents or radiosensitizers improve or maintain outcomes, with reduced adverse events or toxicity, when used alone or in addition to primary RT in the treatment of patients with LASCCHN?
- In patients with LASCCHN, what are the induction chemotherapy regimens that are superior or equivalent to others for important outcomes such as tumour response rate, survival rate, and organ preservation, with fewer toxicities or adverse events?
- Which subgroups of patients with LASCCHN who have undergone surgical resection would benefit more than others from postoperative systemic therapy?

METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the practice guidelines development cycle. That 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 AGREE II framework, a 23-item validated tool designed to assess the methodologic rigour and transparency of guideline development, is used as a methodologic strategy for guideline development.

Various guideline organizations and cancer agencies were searched for existing practice guidelines and systematic reviews about the role of systemic chemotherapy in the management of LASCCHN. 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 AMSTAR tool[6] was used to determine the minimum threshold for methodologic quality. Recognizing that the MACH-NC results have, *de facto,* guided practice since 2000, the search for suitable systematic reviews was supplemented by a search of the primary literature published from January 2000 through February 2015. The year 2000 was used as the cut-off to minimize duplication of the MACH-NC meta-analyses[4,5,7]. The proceedings of meetings of the American Society of Clinical Oncology, the American Society for Radiation Oncology, the European Society for Medical Oncology, and the European Society for Therapeutic Radiation and Oncology were searched for relevant abstracts. Ongoing studies were identified by searching http://ClinicalTrials.gov/.

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

Data from the included studies were extracted by the project research methodologist. When multiple RCTs with similar experimental and control arms were available, a meta-analysis was conducted using the Review Manager software application (RevMan 5.3: The Nordic Cochrane Centre, Copenhagen, Denmark). For all outcomes, the generic inverse variance model with random effects was used. For time-to-event outcomes, a hazard ratio (HR) rather than a number of events at a certain time point was the preferred statistic for meta-analysis. If the HR or its standard error (or both) was not reported, it was derived from other information reported in the study, using the methods described by Parmar *et al.*[8]. Statistical heterogeneity was calculated using the chi-square test for heterogeneity and the I^2 percentage. A probability level for the chi-square statistic less than or equal to 10% ($p \leq 0.10$) or an I^2 greater than 50%, or both, was considered indicative of statistical heterogeneity.

The guideline was reviewed and approved by the PEBC Report Approval Panel and by the members of the Head and Neck DSG before being sent for external review. Content experts, relevant care providers, and other potential users of the guideline participated in the external review of the guideline.

RESULTS

The environmental scan found no existing guidelines or reviews that were suitable for incorporating into the present guideline. The results of five reviews and thirty primary studies were used as the evidence base for the guideline recommendations.

Recommendation 1

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

Key Evidence and Qualifying Statements

The MACH-NC studies identified CCRT as the most effective approach to combining chemotherapy with locoregional RT, provided a precise estimate of the benefit, detected a benefit across head-and neck subsites, and identified age-related interactions. However, the publications reported only OS rates, and so did not address important endpoints such as organ preservation, toxicity, and quality of life. Caveats to the interpretation and application of the associated evidence are necessary: the included trials used older RT techniques and did not identify or stratify for HPV-related cancers. In Ontario, CCRT is the usual concomitant approach used.

The MACH-NC meta-analysis of individual patient data from 50 concomitant chemotherapy trials (1965–2000) that included 9615 patients (6560 deaths) compared locoregional RT alone with the same locoregional treatment plus chemotherapy. The meta-analysis detected a reduction in deaths in favour of concomitant chemotherapy [HR: 0.81; 95% confidence interval (CI): 0.78 to 0.86; $p < 0.0001$], determining the absolute benefit to be 6.5% at 5 years[4,5]. Patients with both fully intact and fully resected tumours treated postoperatively were included in the meta-analysis.

Acute and long-term adverse effects are increased with CCRT compared with local therapy, and the relative benefits and risks for individual patients should be carefully evaluated. The optimal CCRT regimens appear to consist of platinum monotherapy (for example, high-dose cisplatin) or 5-fluorouracil (5FU) plus platinum chemotherapy [for example, carboplatin–5FU (the Calais regimen)][9]. If platinum monotherapy is used, cisplatin has the best evidence of efficacy; a dose intensity of at least 40 mg/m^2 weekly was considered optimal. Accelerated RT plus chemotherapy is not superior to conventional CCRT. Treatment "de-escalation" for HPV-positive disease is being evaluated in several RCTs and is not currently a standard of care.

Recommendation 2

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

Key Evidence and Qualifying Statements

Sub-analyses of RCT data confirm the value of CCRT 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. The adverse effects from chemotherapy, when added to RT, are manageable, and the benefit in terms of survival outweighs the harms. The risk of disease progression was reduced by 22% ($p = 0.04$)[10] and 25% ($p = 0.04$)[11] in two large postoperative chemotherapy trials.

Patients at high risk include those with microscopic evidence of positive margins or extranodal extension in regional lymph nodes, or both. Pathology evidence of regional lymph node involvement without other high-risk features does not warrant the use of CCRT. In patients with pathologic T3/4 tumours, perineural or lymphovascular invasion, or oral cavity or oropharynx cancers metastatic to level IV or V lymph nodes, CCRT might also improve OS. Acute and long-term adverse effects are increased with CCRT, and the relative benefits and risks for individual patients should be carefully evaluated. Although fewer RCTs directly assessed this question, it is reasonable to generalize from primary RT RCTs that the optimal CCRT regimens appear to be platinum monotherapy or 5FU and platinum-based chemotherapy and that the OS benefit diminishes with age. One unique RCT was included in our meta-analysis of RCTs studying postoperative platinum monotherapy CCRT, and it confirmed an OS benefit.

Recommendation 3

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

Key Evidence and Qualifying Statements

The optimal treatment approach for larynx preservation is unclear. In Ontario, CCRT followed by salvage laryngectomy has been the standard of care based on the Radiation Therapy Oncology Group 9111 trial[13], which demonstrated improved larynx preservation, and on the MACH-NC meta-analysis, which demonstrated improved OS rates for CCRT compared with RT alone. However, in the long-term results of the 9111 trial, results for laryngectomy-free survival with an induction chemotherapy strategy were similar to those with CCRT, with a trend toward improved OS. Those findings support the induction approach as an alternative strategy. Furthermore, RCTs have shown superior larynx preservation with docetaxel–cisplatin–5FU (TPF) over cisplatin–5FU (PF) induction chemotherapy when that strategy was used. Unfortunately, the available data make it difficult to evaluate the relative toxicity and quality-of-life effects of those strategies.

Long-term data from a RCT comparing CCRT with RT alone detected superior larynx preservation rates and laryngectomy-free survival rates with CCRT[13,14]. Data from the same trial comparing an induction chemotherapy strategy with RT alone also detected superior laryngectomy-free survival rates. A meta-analysis of three RCTS[15–17] comparing TPF with PF as part of an induction chemotherapy strategy for larynx preservation demonstrated superior results with TPF. In a large meta-analysis of CCRT compared with RT alone in patients with laryngeal cancer, OS was improved with the former treatment. A RCT focused on larynx preservation showed a trend toward decreased OS when CCRT was compared with induction PF chemotherapy.

Strategies using 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, the TPF regimen, compared with the PF regimen, is associated with superior larynx preservation.

Recommendation 4

The addition of cetuximab to intensified RT (concomitant boost or hyperfractionated schedule) could provide an alternative to CCRT.

Key Evidence and Qualifying Statements

With a 20-month difference in median survival duration (49 months vs. 29 months), a large RCT that investigated the addition of cetuximab to RT detected a significant 26% reduction in the risk of death in favour of cetuximab (HR: 0.74; 95% CI: 0.57 to 0.97; $p = 0.03$). 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 in the cetuximab group (HR: 0.68; 95% CI: 0.52 to 0.89; $p = 0.005$) with no difference between the groups in the incidence of grades 3 and 4 toxic effects or quality-of-life scores[18,19]. Those significant survival benefits were not observed in another study that compared the addition of cetuximab or of platin-based chemotherapy to concurrent hyperfractionated radiation therapy[20]. Although reported in an abstract, the 2-year OS (90% vs. 89%) and 2-year progression-free survival (75% vs. 64%) rates were not significantly different between the groups.

Although the addition of cetuximab to RT in patients with LASCCHN was associated with increased OS, it is unclear whether this proof-of-principle is generalizable to conventional once-daily RT. It is also unclear whether cetuximab is noninferior to CCRT. Cetuximab avoided chemotherapy toxicities but was associated with a high rate of severe mucositis[19]. Compared with standard therapy, other epidermal growth factor receptor inhibitors have not demonstrated a better treatment effect.

The use of radiosensitizers such as tirapazamine or nimorazole as an adjunct to RT or CCRT is not recommended. The addition of tirapazamine to CCRT did not result in a response rate or survival rate benefit[21,22]. In the study reported by Rischin *et al.*[22], the addition of tirapazamine to a platinum-based CCRT regimen was compared with CCRT alone. The HRS for OS and disease-free survival were, respectively, 1.07 (95% CI: 0.86 to 1.34; $p = 0.53$) and 0.99 (95% CI: 0.81 to 1.21; $p = 0.09$). The locoregional control rate was also not significantly different between the groups (HR: 0.89; 95% CI: 0.68 to 1.17; $p = 0.44$). Similar results were reported when tirapazamine rather than 5FU was added to cisplatin and RT[21] and when mitomycin C was used as an adjunct to RT[23].

Recommendation 5

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

Key Evidence and Qualifying Statements

With the evidence showing both benefit and harm, the uncertainty concerning the use of induction chemotherapy in the management of LASCCHN is considered moderate. The level of heterogeneity in the populations studied in the RCTS was considerable, likely because of a lack of HPV stratification and variation in the induction chemotherapy and CCRT strategies studied. The meta-analysis that investigated the effect of induction chemotherapy on the management of LASCCHN detected no difference in OS or disease-free survival when the use of induction chemotherapy before locoregional treatment was compared with locoregional treatment alone[3]. That finding is consistent with the results of the MACH-NC meta-analyses[4,5].

In specific cases in which induction chemotherapy before local therapy is warranted to rapidly reduce symptoms associated with tumour bulk, the TPF regimen is preferred over the PF regimen. The RCTS that compared the TPF and PF regimens[15–17,24] found that treatment with TPF demonstrated an OS benefit. In the TAX 323 study[17], reductions of 28% ($p = 0.007$) in the risk of disease progression and 27% ($p = 0.02$) in the risk of death were observed. Median survival rates were significantly better with the use of TPF compared with PF. The TAX 324 study demonstrated similar results[15].

Although complete remission rates were similar in both groups in the induction phase, the patients in the group treated with induction TPF showed a significant increase in their complete remission rate after locoregional treatment (33.3% vs. 19.9%, $p = 0.004$)[17]. Even after controlling for the duration of RT, TPF remained superior to PF[25]. Another study compared the TPF and PF regimens followed by CCRT with CCRT alone and found no significant survival benefit between the groups in the intent-to-treat cohort[26].

CONCLUSIONS

The recommendations presented here 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. Because 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.

The recommendations are subject to several caveats. Since the end of the 1990s, RT techniques have evolved technically and have become more sophisticated (for example, intensity-modulated RT), allowing for more precise delivery and replacing conventional RT. Although it is unlikely that such 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 those effects could be life-threatening. Treatment plans incorporating chemotherapy in the curative treatment of patients with LASCCHN should be developed within the context of assessment in an appropriate multidisciplinary care team[2] and be supervised by a medical oncologist experienced in treating head-and-neck cancer.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: EW declared being a local principal investigator for the NCIC HN.6 trial and the TAX 324 trial. JY declared having stocks, bonds, or stock options valued at $5,000 or more in a relevant business entity that might not necessarily gain or lose financially from the publication of the manuscript, either now or in the future. The other authors declare no competing interests.

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