

LOCALLY ADVANCED SQUAMOUS CARCINOMA OF THE HEAD AND NECK

Executive Summary

The annual incidence of head and neck cancers worldwide is more than 550,000 cases with around 300,000 deaths each year [1]. Male to female ratio ranges from 2:1 to 4:1. About 90% of all head and neck cancers are squamous cell carcinomas (HNSCC). HNSCC is the sixth leading cancer by incidence worldwide. Most HNSCCs arise in the epithelial lining of the oral cavity, oropharynx, larynx and hypopharynx [2, 3]. These cancers are strongly associated with certain environmental and lifestyle risk factors like tobacco and alcohol consumption. More recently a new disease has emerged related to several strains of human papilloma virus (HPV 16,18) [4]. The prognosis of these patients is substantially better than those associated with tobacco. The five-year overall survival rate of patients with HNSCC is about 40-50%. About one third of patients present with early stage disease (T1-2, N0). Treatment for early HNSCC usually involves single-modality therapy with either surgery or radiation. Survival is comparable for the two approaches. Early stage cancers have a very favorable prognosis with high cure rates with surgery or radiation alone and chemotherapy or concurrent chemotherapy/radiation is not indicated.

For patients with pathologically staged III, IVa/b head and neck cancer, postoperative concomitant chemo-radiation with cisplatin has shown improvement in local-regional control and survival rates for those with positive microscopic surgical margins and/or extra-capsular nodal extension [5]. We recommend that concomitant cisplatin regimen be added to the essential medicines list for the postoperative treatment of advanced stage head and neck cancers.

Public Health Relevance

Head and neck cancer encompasses many site-specific cancers, including oral cavity and oropharyngeal cancers. Studies have estimated the global incidence of all head and neck cancers to be between 400,000 and 600,000 new cases per year and the mortality rate to between 223,000 and 300,000 deaths per year.[11] Alcohol and tobacco are known risk factors for most head and neck cancers, and incidence rates are found to be higher in regions with high rates of alcohol and tobacco consumption.[12] During the past few decades, several countries have witnessed a decline in oral cavity cancer incidence correlating to a decline in tobacco use. However, Canada, Denmark, the Netherlands, Norway, Sweden, the United States, and the United Kingdom, have seen an increasing rate of oropharyngeal and oral cavity cancers despite declines in smoking rates since the 1980s.[11] This has led to theories that human papillomavirus (HPV) infection might be an additional risk factor for developing certain head and neck cancers. This research is emerging and epidemiological information regarding head and neck cancers is likely to change with further discoveries.[11]

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Requirements for diagnosis, treatment, and monitoring

Diagnostics:

A detailed history and physical examination including complete head and neck examination with biopsy is necessary to establish the diagnosis. Examination with a mirror or fiberoptic scope is essential in diagnosing and staging lesions involving the larynx and pharynx.

Testing:

A panoramic radiograph of the mandible, CT scan or MRI of the neck may be done as indicated and are useful to assess the extent and stage. A chest radiograph and pretreatment dental evaluation are recommended. For patients with advanced stage disease who will receive concurrent chemotherapy and radiation, blood counts and chemistries may be done to assess critical organ function including renal and hepatic function. A multidisciplinary consultation should be sought as indicated.

Administration and Care of Patients:

Despite lack of randomized comparative trials, both surgery and definitive RT appear to offer equivalent local tumor control and survival for early stage head and neck cancers. Decision of treatment is based on different factors, including tumor accessibility, functional outcome, patient's health and preference, and the availability of treatment expertise. A multidisciplinary team evaluation is vital to optimize the outcome of these patients. Surgery is the preferred treatment modality for early stage oral cavity cancers and involves resection of the primary tumor with or without lymph nodal dissection. Patients who are medically inoperable or refuse surgery can be treated with definitive radiation therapy. Definitive radiation therapy is the preferred approach for many patients with non-oral cavity tumors, in particular to hypopharynx and supraglottic and glottic larynx, since it appears to provide a better functional outcome in comparison to larynx-sparing surgical approaches. For those with residual disease after radiation therapy, salvage surgery is recommended; for those managed by surgery, post operative radiation therapy is indicated in the presence of close or positive margins, lymphovascular or perineural invasion, or when a positive lymph node is identified, upstaging the tumor.

Administration of cisplatin requires intravenous infusion capacity. Adequate IV hydration and anti-emetics should accompany the infusion of cisplatin. Blood counts and chemistries should be serially monitored during the course of treatment.

Concurrent chemotherapy increases the risk for radiation related adverse effects including mucositis, dysphagia, dermatitis etc. Patients should be carefully monitored for these and supportive care provided as indicated. Care should be taken to maintain adequate hydration, nutrition and analgesia before, during and after completion of treatment. Optimal monitoring and supportive care requires trained clinicians experienced in the management of these cancers with access to inpatient care and laboratory services. Late treatment related toxicities such as xerostomia, dysphagia, speech dysfunction, gastric tube dependence, tracheostomy dependence, neuropathies, depression, and cosmetic disfigurement can significantly impact quality of life and psychosocial wellbeing and therefore need to be identified and addressed.

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Overview of Regimens

Concurrent radiation and 3 doses of cisplatin are recommended. The following excludes ancillary medications pertaining to the management of cisplatin administration and side effects.

Standard Regimen

Concomitant Chemotherapy-Radiation

Cisplatin 100 mg/m² IV, q 3 weeks x 3 cycles (days 1, 22, 43)

Note: Despite a lack of large, randomized studies and based on phase II trials and center experience, many report administering weekly cisplatin in an attempt to decrease toxicity and increase tolerability of concomitant chemotherapy and radiation

Review of Benefits and Harms

Benefits

Early stage head and neck cancers are highly curable with either surgery or radiation therapy. Certain high risk features have been shown to significantly increase the risk of recurrence. Two randomized trials have demonstrated improved outcomes with the addition of concomitant cisplatin to postoperative radiation in patients with locally advanced disease or certain adverse risk features. Both studies compared the addition of concomitant cisplatin (100 mg/m² on days 1, 22, and 43) to radiotherapy versus radiotherapy alone given after surgery in patients with advanced stage cancers of the oral cavity, oropharynx, larynx, or hypopharynx. The RTOG 9501/Intergroup trial randomized 459 patients and showed significant improvement in local-regional control rates and disease free survival but not overall survival in the chemo-radiation arm [6]. Two-year rate of local and regional control was 82% in the combined-therapy group versus 72% in the radiotherapy group. Disease-free survival was significantly longer in the combined-therapy group (HR for disease or death, 0.78; 95% CI, 0.61 to 0.99; P=0.04). The EORTC 22931 trial randomized 334 patients and showed improved 5-year progression-free survival of 47% vs 36% and overall survival of 53% vs 40% respectively, in favor of the concomitant cisplatin group [7]. The estimated 5-year cumulative incidence of local or regional relapses was 31% with radiation versus 18% after combined therapy. A comparative analysis of data pooled from the two trials showed that extracapsular extension and/or microscopically involved surgical margins were the only risk factors for which the impact of concomitant chemo-radiation was significant in both trials [5]. There was also a trend in favor of the combined modality arm in the group of patients who had stage III-IV disease, perineural infiltration, vascular embolisms, and/or clinically enlarged level IV-V lymph nodes secondary to tumors arising in the oral cavity or oropharynx. A ten-year follow up of the RTOG 9501/Intergroup trial confirmed the superiority of the combined arm for local-regional control and disease-free survival in the subgroup of patients with microscopically involved margins and/or extracapsular nodal spread [8].

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Primary combined chemotherapy with cisplatin and radiation is also the standard for patients with locally advanced, unresectable tumors. In this setting, the addition of cisplatin to radiation improves disease control and overall survival. A meta-analysis including 50 studies showed an absolute benefit of 6.5% in overall survival with a HR of 0.81, $p < 0.0001$, for patients who received combined chemoradiation [13].

Cetuximab, a monoclonal antibody that targets the epidermal growth factor receptor, EGFR, has been shown to improve outcomes when compared to radiation alone in the primary treatment setting of patients with locally advanced disease but has not been shown to be superior to cisplatin and it is much more costly and is therefore not recommended for inclusion to the essential medicines list.

Neoadjuvant chemotherapy approaches have been studied in several trials with controversial and inconclusive findings to date. While this approach cannot be recommended as a standard for all patients, it is a reasonable alternative for patients with very large burden of disease who would not be candidates for surgery or primary chemotherapy + radiation.

Harms and Toxicity Considerations

Common

Nausea and vomiting occur in almost all patients treated with cisplatin and is often severe, necessitating the use of anti-emetic medications. Major dose limiting toxicities of cisplatin include renal impairment (28-36%), ototoxicity (40-60% children; 10-31% adults) and myelosuppression.[9] Ototoxicity usually manifests as tinnitus and high frequency hearing loss. Myelosuppression can lead to anemia, leucopenia and thrombocytopenia with associated complications.

In the RTOG 9501 trial, the incidence of acute toxicity of grade 3 or greater was 34% in the radiotherapy group versus 77% in the concomitant cisplatin arm. Similarly, in the EORTC trial, severe adverse effects were more frequent after combined therapy (41%) than after radiotherapy (21%, $P=0.001$).[6,8]

Serious

Renal toxicity caused by cisplatin can be significant and may result in electrolyte abnormalities. Intravenous hydration both before and after administering cisplatin is necessary to reduce the incidence of renal toxicity.[10] This should be particularly considered in elderly patients and patients with compromised renal function. Combining cisplatin chemotherapy with radiation significantly increases the rates of grade 3 and 4 radiation related toxicity including dysphagia, dermatitis and mucositis.[6,8]

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Systematic Reviews

Pignon JP, et al. Group OBOTM-NC. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. *Radiotherapy and Oncology*. 2009;92(1):4–14. doi:10.1016/j.radonc.2009.04.014.

Background: Our previous individual patient data (IPD) meta-analysis showed that chemotherapy improved survival in patients curatively treated for non-metastatic head and neck squamous cell carcinoma (HNSCC), with a higher benefit with concomitant chemotherapy. However the heterogeneity of the results limited the conclusions and prompted us to confirm the results on a more complete database by adding the randomised trials conducted between 1994 and 2000. **Methods:** The updated IPD meta-analysis included trials comparing loco-regional treatment to loco-regional treatment+chemotherapy in HNSCC patients and conducted between 1965 and 2000. The log-rank-test, stratified by trial, was used to compare treatments. The hazard ratios of death were calculated. **Results:** Twenty-four new trials, most of them of concomitant chemotherapy, were included with a total of 87 trials and 16,485 patients. The hazard ratio of death was 0.88 ($p<0.0001$) with an absolute benefit for chemotherapy of 4.5% at 5 years, and a significant interaction ($p<0.0001$) between chemotherapy timing (adjuvant, induction or concomitant) and treatment. Both direct (6 trials) and indirect comparisons showed a more pronounced benefit of the concomitant chemotherapy as compared to induction chemotherapy. For the 50 concomitant trials, the hazard ratio was 0.81 ($p<0.0001$) and the absolute benefit 6.5% at 5 years. There was a decreasing effect of chemotherapy with age ($p=0.003$, test for trend). **Conclusion:** The benefit of concomitant chemotherapy was confirmed and was greater than the benefit of induction chemotherapy.

Baujat B, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. *Radiation Oncology Biology*. 2006;64(1):47–56. doi:10.1016/j.ijrobp.2005.06.037.

Introduction: The recently updated meta-analysis of chemotherapy in head and neck cancer (MACH-NC) demonstrated the benefit of the addition of chemotherapy in terms of overall survival in head and neck squamous cell carcinoma (HNSCC). The magnitude of the benefit according to tumour site is unknown as well as their potential interactions with patient or trial characteristics. **Methods:** Eighty seven randomized trials performed between 1965 and 2000 were included in the present analysis. Patients were divided into four categories according to tumour location: oral cavity, oropharynx, hypopharynx and larynx. Patients with other tumour location were excluded (999, 5.7%). For each tumour location and chemotherapy timing, the logrank-test, stratified by trial, was used to compare treatments. The hazard ratios of death or relapse were calculated. Interactions between patient or trial characteristics and chemotherapy effect were studied. **Results:** Individual patient data of 16,192 patients were analysed, with a median follow-up of

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5.6years. The benefit of the addition is consistent in all tumour locations, with hazard ratios between 0.87 and 0.88 (p-value of interaction=0.99). Chemotherapy benefit was higher for concomitant administration for all tumour locations, but the interaction test between chemotherapy timing and treatment effect was only significant for oropharyngeal (p<0.0001) and laryngeal tumours (p=0.05), and not for oral cavity (p=0.15) and hypopharyngeal tumours (p=0.30). The 5-year absolute benefits associated with the concomitant chemotherapy are 8.9%, 8.1%, 5.4% and 4% for oral cavity, oropharynx, larynx and hypopharynx tumours, respectively. **Conclusion:** The benefit of the addition of chemotherapy to locoregional treatment is consistent in all tumour locations of HNSCC. The higher benefit of concomitant schedule was demonstrated only for oropharyngeal and laryngeal tumours but this may be only a consequence of a lack of power.

Recommendations

The reviewers recommend the incorporation of head and neck cancer treatment options into the WHO Model List of Essential Medicines, and recommend specifically that cisplatin be added to the core Essential Medicines List. It is important to note that for this indication, carboplatin is not an acceptable alternative to cisplatin.

Additions proposed for Section 8.2 of the EML

Cisplatin*

*Carboplatin is currently in the WHO Essential Medicines List for Adults (2013, 18th Edition). Next to Carboplatin in the WHO List is a symbol that states that the listing of the drug indicates “similar clinical performance within a pharmacological class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources. Not all square boxes are applicable to medicine selection for children — see the second EMLc for details. Therapeutic equivalence is only indicated on the basis of reviews of efficacy and safety and when consistent with WHO clinical guidelines. National lists should not use a similar symbol and should be specific in their final selection, which would depend on local availability and price.” The present proposal calls for the explicit addition of Cisplatin to the EML given its distinct use in the treatment of a number of cancers.

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