NASOPHARYNGEAL CARCINOMA
Union for International Cancer Control
2014 Review of Cancer Medicines on the WHO List of Essential Medicines

NASOPHARYNGEAL CARCINOMA

Executive Summary

Globally, nasopharyngeal carcinoma (NPC) is an uncommon cancer with approximately 80,000 new cases reported per year and accounting 0.7% of all cancers. In North America and Europe, the incidence rate is less than 1 case per 100,000 populations, but in endemic areas like Southern China (e.g. Hong Kong) and Southeast Asia, the annual age-standardized incidence rates are as high as 20 to 30 cases per 100,000 population in men and 8 to 15 cases per 100,000 populations in women. NPC has historically been classified into different histological subtypes: Type 1 (I) squamous cell carcinoma; Type 2a (II) keratinizing undifferentiated carcinoma; and Type 2b (III) non-keratinizing undifferentiated carcinoma. The World Health Organization (WHO) III subtype is the commonest form of NPC in endemic areas and differs from squamous type of NPC in its association with the Epstein Barr virus (EBV) and sensitivity to chemotherapy and radiotherapy (RT). The staging of NPC is based on the depth of invasion of the soft tissue, cranial nerves and bony structures at and near the nasopharynx by the primary tumor, the involvement of local and regional lymph nodes of the head and neck, and the presence of distant metastases. In Hong Kong, the stage distribution at presentation is: stage I, 7%, stage IIA to B, 41%, stage III, 25%, stage IVA to C, 28%. The age-adjusted mortality rate of NPC is 3.9 per 100,000 persons, the 5-year overall survival (OS) of stage I and II NPC now approaches 90%, while the 5-year OS for non-metastatic stage III and IV is around 60%.

The standard of care for the treatment of stage I NPC is radiotherapy (RT), and for non-metastatic stage II-IV NPC is concurrent chemo-radiotherapy with or without adjuvant chemotherapy. For RT, a total dose of 70 Gy is needed for eradication of gross tumor and either 50–60 Gy or 46–60 Gy for elective treatment of potential sites at risk. For RT delivery, three-dimensional RT is the minimum requirement, while intensity-modulated radiation therapy (IMRT) is the preferred approach in expert centers. Neoadjuvant chemotherapy is sometimes used to down-stage those locally advanced NPCs that cannot be encompassed readily within the radiation field without incurring significant risks to adjacent normal tissues. For metastatic NPC, the standard first-line therapy is a platinum-based ‘doublet’ that commonly consists of cisplatin or carboplatin in combination with one of the following drugs: 5-fluorouracil, gemcitabine paclitaxel and docetaxel. Other drugs such as capecitabine, irinotecan, doxorubicin, vinorelbine and oxaliplatin can also be used alone or in combination. For locally recurrent NPC, the options are individualized based on the patient’s condition, prior oncological treatment and disease stage at recurrence. These may include re-irradiation, surgery, or palliative chemotherapy.
Public Health Relevance

While nasopharyngeal carcinoma (NPC) is the most common malignant tumor of the nasopharynx, NPC itself constitutes only 0.7% of cancers worldwide (1). According to GLOBOCAN, the age-standardized incidence for both sexes in many countries is 1 per 100,000 people per year. Globally, there are 80,000 new cases per year, making NPC the 23rd most common of all new cancers worldwide. GLOBOCAN estimates that men are 2 to 3 times more likely to develop NPC than women. Geographically, Southeast Asia, Southern China, and North African countries have the highest prevalence of NPC. The stark difference in geographic distribution suggests that genetic factors play a large role in NPC susceptibility.

Requirements for diagnosis, treatment, and monitoring

Diagnostics:
The diagnosis is based on histological examination. Immunohistochemical detection for Epstein–Barr virus-encoded small RNA (EBER) expression may be useful for distinguishing inflammatory atypia from non-keratinizing NPC.

Testing:
The staging of NPC is based on the International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC) staging system. Routine staging procedures include history, physical examination including cranial nerve examination, complete blood cell count, serum biochemistry (including liver function test), chest X-ray, nasopharyngoscopy, computed tomography (CT) scan or magnetic resonance imaging (MRI) of nasopharynx and base of skull and neck. Although MRI is generally preferred if available, each center will choose the best imaging technique according to their usual clinical practice and experience. Imaging for distant metastases including isotope bone scan and CT scan of chest and upper abdomen could be considered for at-risk subsets (node positive, especially N3 stage) and for those patients with clinical or biochemical abnormalities detected. The use of positron emission tomography CT and plasma/serum load of Epstein-Barr viral DNA are optional (Reference from: ESMO guideline - Ann Oncol 2012, 23; suppl 7).

Administration and Care of Patients:
RT planning and delivery should be performed by a team of qualified personnel at an experienced oncology center. As a minimum, the team should comprise radiation oncologists, radiologists, oncology nurses, physicists and radiographers. During RT, the patients should be carefully monitored by clinicians and nurses for any treatment-relate toxicities at regular intervals. Supportive measures such as nutritional supplementation, skin care, anti-emetics, pain control and if applicable, chemotherapy-related marrow toxicities should be readily provided. Assessment of post-treatment response in the nasopharynx and neck should be made via clinical and endoscopic examination and/or imaging studies. MRI is often used to evaluate the response to RT or chemoradiotherapy, especially for T3 and T4 tumors, though distinction between post-irradiation changes and recurrent tumors may be difficult. Follow-up for patients includes periodic examination of the nasopharynx and neck, cranial nerve function and evaluation of
systemic complaints to identify distant metastasis. For T3 and T4 tumors, MRI might be used on a 6- to 12-month basis to evaluate the nasopharynx and the base of the skull at least for the first few years after treatment. Evaluation of thyroid function in patients with irradiation to the neck is recommended at 1, 2 and 5 years. (Reference from: ESMO guideline - Ann Oncol 2012, 23; suppl 7).

Overview of Regimens

The following tables include basic information on administration and dosing of chemotherapy during concurrent chemoradiotherapy, and palliative chemotherapy, and exclude ancillary medications pertaining to the management of side effects.

1) For concurrent chemotherapy during RT for non-metastatic stage II-IV NPC:

- **Standard Regimens**

  **Low-dose cisplatin at weekly interval starting at day 1 of RT for 6 to 8 cycles:**
  
  Cisplatin IV infusion* 40mg/m²/week

  **High-dose cisplatin at 3-weekly interval during RT**
  
  Cisplatin IV infusion* 100 mg/m² on days 1, 22, and 43

  (*Infusion time of cisplatin would depend on the volume of normal saline cisplatin has been diluted in and the hydration scheme, may vary across institutions)

  Note: the addition of adjuvant chemotherapy after concurrent treatment has not been shown to improve overall survival and is not recommended for all patients but has been included in some guidelines in the United States and Europe. Oxaliplatin, another platinum agent, has also been shown to improve outcomes in addition to radiotherapy but it is more expensive than cisplatin and has not been shown to be superior to it. Oxaliplatin is an option for patients who have contraindications or who cannot tolerate cisplatin. This alternative regimen using oxaliplatin is 70 mg/m2 weekly during radiation for 6 weeks.

  **Oxaliplatin for patients who cannot tolerate cisplatin or who have contraindications**
  
  Oxaliplatin IV infusion 70mg/m² weekly during radiation for 6 weeks
2) **For palliative chemotherapy (or neoadjuvant chemotherapy):**

- **Standard Regimens**

  5-fluorouracil (5FU) and cisplatin (or carboplatin) at 3-weekly schedule: 6 cycles if palliative intent, 2 to 3 cycles if neoadjuvant intent.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>IV infusion*</td>
<td>80 to 100mg/m² on day 1</td>
</tr>
<tr>
<td>(or Carboplatin)</td>
<td>IV infusion</td>
<td>AUC 5 or 6 on day 1</td>
</tr>
<tr>
<td>5-FU</td>
<td>IV infusion</td>
<td>1000mg/m²/24 hours on days 1 to 4, or 1 to 5</td>
</tr>
</tbody>
</table>

  Paclitaxel and carboplatin (or cisplatin) at 3-weekly schedule: 6 cycles if palliative intent, 2 to 3 cycles if neoadjuvant intent.

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>IV infusion</td>
<td>AUC 5 or 6 on day 1</td>
</tr>
<tr>
<td>(or Cisplatin)</td>
<td>IV infusion*</td>
<td>80 or 100mg/m² on day 1)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>IV infusion</td>
<td>135mg/m² on day 1</td>
</tr>
</tbody>
</table>

Several other agents have been tested in this setting and would be considered appropriate alternatives. The task force chose to list only these regimens based on their common use and widespread availability.

(*Infusion time of cisplatin would depend on the volume of normal saline within which cisplatin has been diluted and the hydration scheme, may vary across institutions. Prolonged infusion may need inpatient administration*)

**Review of Benefits and Harms**

**Benefits**

At least 8 randomized studies have confirmed the survival benefit of adding concurrent platinum-based chemotherapy to RT in patients with non-metastatic stage II to IVB NPC. Two meta-analyses have reported an 18% reduction in the risk of death and an absolute survival benefit of 4% to 6% at 5 years with the use of chemotherapy in addition to radiation. The largest effect was found for concomitant chemotherapy, with a pooled HR of 0.48 (95% CI, 0.32 to 0.72), which corresponds to an absolute survival benefit of 20% after 3 years, from approximately 65% to 85%. Metastatic or recurrent NPC is highly chemosensitive, and first-line doublet chemotherapy achieves 50–80% response rates, with a median time to progression of 5–11 months and overall survival times of about 20 months, with occasional reports of long-term survival beyond 5 years in some younger patients with disease limited to the thorax. There is a paucity of prospective randomized trials in this setting and most of the data available come from phase II studies and institutional experience. The impact of palliative chemotherapy on survival in the second and subsequent lines of treatment of metastatic or recurrent NPC is unclear.
Harms and Toxicity Considerations

Common
In patients receiving concurrent cisplatin-containing regimens during RT, the addition of chemotherapy commonly results in increased nausea and vomiting, myelosuppression, anemia, renal impairment and RT-related oropharyngeal mucositis (which may result in odynophagia and weight loss). Carboplatin has a similar adverse effect profile in the above regimens.[12] These acute toxicities can usually be successfully managed and palliated with good supportive care.[2,3,5,6]

The impact of concurrent cisplatin on the incidence of late RT-related toxicities is still being defined. Some institutional reports suggest that cisplatin may exacerbate the risk of hearing impairment following RT, but not the risk of late neurological and endocrine toxicities. Low-grade peripheral neuropathy is common in patients treated with oxaliplatin, however it is typically mild and reversible.[4]

Serious
The use of chemotherapy increases the risk of myelosuppression, and thus increases the risk of febrile neutropenia and infections, however the risk of severe infection with the above regimens in this population is low (1%).[2,3,5,6]

Systematic Reviews and meta-analyses supporting the use of concurrent chemotherapy during RT


At the time this meta-analysis was performed, it was unclear whether the addition of chemotherapy to standard radiation therapy improved clinical outcome in patients with locoregionally advanced nasopharyngeal cancer. A meta-analysis was performed to evaluate the impact of integrating chemotherapy with external beam radiation therapy in this clinical setting. Using previously described methods, a protocol was developed outlining a meta-analysis examining the influence of chemoradiation versus radiation alone (control arm) in locoregionally advanced nasopharyngeal carcinoma. The outcomes of interest were disease-free/progression-free and overall survival. Literature search techniques, study inclusion criteria, and statistical procedures were prospectively defined. Data from all available randomized controlled trials was pooled using a fixed effects model (Peto). Results were expressed as summary relative risks. Statistical tests for heterogeneity were performed. If statistical heterogeneity was demonstrated, sensitivity analyses were performed to evaluate possible sources of heterogeneity across the included studies. The literature search identified six randomized controlled trials
enrolling more than 1,500 patients. All trials compared standard radical external beam radiation therapy (control arm) with radiation plus chemotherapy delivered either adjuvantly, neoadjuvantly, or concurrently with radiation. Pooling all six studies using disease-free/progression-free survival as the endpoint demonstrated that the addition of chemotherapy to radiation therapy increased disease-free/progression-free survival by 37% at 2 years, 40% at 3 years, and 34% at 4 years after treatment. Likewise, the summary relative risk for overall survival at 2 years after treatment with the addition of chemotherapy to the treatment regimen was 0.80 (0.63-1.02), reflecting a 20% increase in 2-year survival. This finding was marginally non-statistically significant. Three- and 4-year survival was increased by 19% and 21%, respectively, with the data for 4-year survival being statistically significant. The addition of chemotherapy to standard radical radiation therapy for locoregionally advanced nasopharyngeal cancer increases both disease-free/progression-free and overall survival by 19 to 40% at 2 to 4 years after treatment, depending on the endpoint of interest.

Additional systematic reviews


Purpose The purpose of this meta-analysis was to determine the additional value of neoadjuvant, concurrent, and/or adjuvant chemotherapy to radiation in the treatment of locally advanced nasopharyngeal carcinoma (NPC) with regard to the overall survival (OS) and the incidence of local-regional recurrences (LRR) and distant metastases (DM). Patients and Methods To be eligible, full published studies had to deal with biopsy-proven NPC and have patients randomly assigned to receive conventional radiotherapy (66 to 70 Gy in 7 weeks) or radiotherapy combined with chemotherapy. Results Ten randomized clinical studies were identified, including 2,450 patients. The pooled hazard ratio (HR) of death for all studies was 0.82 (95% CI, 0.71 to 0.95; \( P = .01 \)) corresponding to an absolute survival benefit of 4% after 5 years. Three categories of trials were defined according to the sequence of chemotherapy, including neoadjuvant chemotherapy, at least concomitant chemoradiotherapy, and adjuvant chemotherapy. A significant interaction term \( (P = .02) \) was found among these three categories. The largest effect was found for concomitant chemotherapy, with a pooled HR of 0.48 (95% CI, 0.32 to 0.72), which corresponds to a survival benefit of 20% after 5 years. Comparable results were found for the incidence of LRR and DM. Conclusion The results of this study indicate that concomitant chemotherapy in addition to radiation is probably the most effective way to improve OS in NPC.

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Recommendations

The reviewers recommend the incorporation of nasopharyngeal carcinoma treatment options into the WHO Model List of Essential Medicines, and recommend specifically that cisplatin and oxaliplatin be added to the core Essential Medicines List.

Additions proposed for Section 8.2 of the EML

Cisplatin*
Oxaliplatin

*Carboplatin is currently in the WHO Essential Medicines List for Adults (2013, 18th Edition). Next to Carboplatin in the list is a symbol that indicates 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.
References


