Neoadjuvant Chemotherapy for Nasopharyngeal Carcinoma: Opportunities, Potential Hazards and Drawbacks

To date, there have been four randomised clinical studies conducted on the use of neoadjuvant chemotherapy for nasopharyngeal carcinoma (NPC), with two of the four showing positive results (Table 1). The VUMCA I study showed a significant reduction in tumour recurrence or progression, with a reduction in both local relapse and distant metastases after chemotherapy. Recently, Ma et al also showed significant improvement in local control after neoadjuvant chemotherapy — 5 year local recurrence rates were 18% and 26% for the chemotherapy and the radiotherapy alone arms respectively. The ‘negative’ study by Chan et al can be criticised on the grounds of its having low power. Even the Asian-Oceanian Clinical Oncology Association study, which had negative findings overall, showed a significant improvement in local control with chemotherapy among patients with very large nodes, in an unplanned subgroup analysis.

Table 1. Randomised trials evaluating neoadjuvant chemotherapy treatment for nasopharyngeal carcinoma.

<table>
<thead>
<tr>
<th>Study</th>
<th>Neoadjuvant chemotherapy</th>
<th>Benefit of chemotherapy</th>
<th>5 year overall survival rate</th>
<th>5 year relapse-free survival</th>
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<tr>
<td>VUMCA I</td>
<td>3 cycles (every 3 weeks): Cisplatin 100 mg/m² D1 Bleomycin 15 mg D1 then 12 mg/m² D1 D1-D5 Epirubicin 70 mg/m² D1</td>
<td>Significant reduction in tumour recurrence or progression in the chemotherapy arm (55/171 vs 92/168) Both local relapse and distant metastases were reduced in the chemotherapy arm</td>
<td>60% 52% NA (3 year figures read from survival curves; NS) But significant increase in toxic deaths in chemotherapy arm (8% vs 1%)</td>
<td>58% 35% NA (3 year figures read from survival curves; p &lt; 0.01)</td>
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<td>Asian-Oceanian Clinical Oncology Association (AOCOA)</td>
<td>2-3 cycles (every 3 weeks): Cisplatin 60 mg/m² D1 Epirubicin 110 mg/m² D1</td>
<td>Only 286/334 patients evaluable (134 in the CT arm; 152 in the RT arm) No difference in overall survival &amp; relapse-free survival between the two arms for all enrolled patients (n = 334) and all evaluable patients (n = 286) Significant improvement in relapse-free survival and local tumour control after chemotherapy for patients with large nodes &gt;6cm</td>
<td>78% 71% 69% (NS) (3 year figures only)</td>
<td>48% 42% 45% (NS) (3 year figures only)</td>
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<tr>
<td>Ma et al</td>
<td>2-3 cycles (every 3 weeks): Cisplatin 100 mg/m² D1 Bleomycin 10 mg/m² D1 &amp; D5 5-fluorouracil 800 mg/m² continuous IV infusion D1-D5</td>
<td>Significant enhancement of the 5 year free-from-local relapse rate after chemotherapy (82% vs 74%, p = 0.04) No significant improvement in free-from-distant metastasis rate (79% chemotherapy arm vs 75% RT alone arm, p = 0.4)</td>
<td>63% 56% NA (NS)</td>
<td>59% 49% NA (p = 0.05)</td>
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<td>Chan et al</td>
<td>2 cycles neoadjuvant (every 3 weeks) and 4 cycles adjuvant (every 3 weeks): Cisplatin 100 mg/m² D1 5-fluorouracil 1000 mg/m² continuous IV infusion D2-D4</td>
<td>No difference in locoregional relapse rate — RT 15%, CT 16%</td>
<td>NA (NS)</td>
<td>NA (NS)</td>
</tr>
</tbody>
</table>

Abbreviations: CT = chemotherapy treated group; RT = radiotherapy alone group; IV = intravenous; NA = not available; NS = not significant; CRT = chemotherapy and radiotherapy.
Of note, two retrospective studies have also shown significant enhancement of local control after the use of neoadjuvant chemotherapy. In the MD Anderson Cancer Centre’s series, 7 (20%) of the 35 patients with T4 disease treated with chemotherapy had local disease recurrence, compared with 9 (56%) of 16 T4 patients treated with radiation alone (p = 0.01). There was no significant improvement in local control seen for the early T-stages. Similarly, in the Prince of Wales Hospital series, the use of neoadjuvant chemotherapy was associated with significantly less local disease recurrence for node-positive advanced T-stages (Ho’s T3; UICC T3 and T4). Patients with early T-stage (T1 and T2) or overall stage II tumours appeared to derive no benefit from chemotherapy treatment, in contrast. Multivariate analysis undertaken showed that the use of chemotherapy was a significant factor predicting good local control for all patients with node-positive NPC, for patients with node-positive T3 tumours, and for patients with advanced disease (Stages III and IV). The rate of distant metastasis, however, was not influenced by the use of neoadjuvant chemotherapy.

In most studies cisplatin-containing regimens have been used prior to 2-dimensional radiotherapy, and significant improvement in local tumour control in patients with locoregionally advanced NPC has been seen, in comparison to those receiving radiotherapy treatment alone. An hypothesised mechanism for this finding is that tumours responsive to neoadjuvant chemotherapy were reduced in volume, allowing 2-dimensional radiotherapy to deliver a high dose to a more circumscribed tumour. In less privileged areas, where most endemic NPC is treated, substitution of conventional 2-dimensional methods with 3-dimensional conformal radiation treatment (3DCRT) and intensity-modulated radiotherapy (IMRT) for the delivery of radical radiotherapy is often not possible. In this situation, ‘upfront’ chemotherapy with a cisplatin-containing regimen of established efficacy can be recommended for T3/T4 lesions in an endeavour to improve local control.

In recent years, improved local control of NPC and head and neck cancer has been reported with the use of IMRT, and improved radiation fractionation. The true value of neoadjuvant chemotherapy for patients with NPC therefore should be redefined by conducting randomised studies in which IMRT with/without improved radiation fractionation replaces conventionally fractionated 2-dimensional radiotherapy in both the control and experimental arms. In addition, the neoadjuvant approach to chemotherapy is unique in its ability to test the efficacy of innovative agents and treatment combinations (such as cetuximab, gemcitabine and taxol) on the treatment-naïve tumour. Provided that we can monitor tumour response closely and identify non-responders promptly, evaluation of neoadjuvant chemotherapy of advanced stage NPC using novel agents in combination, is a worthy focus for clinical trials.

The use of neoadjuvant chemotherapy in advanced NPC also has potential hazards and shortcomings. Despite the high overall response rate to neoadjuvant chemotherapy, a residual 2-18% of NPCs are not responsive to such treatment. In cases lacking a response to chemotherapy, progression in stage and the development of cross-resistance to subsequent radiotherapy may occur. Unfortunately, the impact of neoadjuvant chemotherapy, if any, on the rate of distant metastasis is far from clear, with some studies reporting a significant reduction in the rate of metastasis while others did not. Overall survival has also not been shown to be improved by neoadjuvant chemotherapy in all four randomised studies (Table 1). In contrast to advanced stage cancers of the larynx or hypopharynx, neoadjuvant chemotherapy for NPC has no role in organ preservation. Therefore, if neoadjuvant chemotherapy is not efficacious in its primary role of enhancing local control (due to more competitive treatment approaches such as concurrent chemo-IMRT), the role for neoadjuvant chemotherapy in NPC management will be limited.

In conclusion, neoadjuvant chemotherapy for NPC should still be considered experimental. The exception is its use in conjunction with conventionally fractionated 2-dimensional radiotherapy to attempt improved local control of T3/T4 lesions. The only ‘absolute’ indication for this treatment approach, in my opinion, is in the management of a very bulky intracranial NPC, extending in close proximity to the optic chiasma and/or the brainstem. In this case, even with the use of IMRT it is not possible to achieve adequate dose-sparing of these important neural organs to within radiation tolerance. In such cases, neoadjuvant chemotherapy may help to reduce the tumour and its proximity to these critical structures, providing a wider safety margin around the gross tumour volume (GTV) for radiotherapy treatment. When chemotherapy is administered as initial therapy, close surveillance (such as by serial EBV-DNA assays)
is mandatory for early signs of tumour progression/non-response so that any undue delay in radiotherapy can be avoided. The use of neoadjuvant chemotherapy in appropriately selected patients with NPC provides opportunities for improved treatment outcomes. The cost-benefit ratio favours its utilisation, providing its potential hazards and disadvantages can be minimised.

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REFERENCES


