LONG-TERM SURVIVAL OF RESECTABLE SUBSET AFTER INDUCTION CHEMOTHERAPY IN PATIENTS WITH LOCALLY ADVANCED HEAD AND NECK CANCER

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Accepted 29 May 2007
Published online 30 October 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.20713

Abstract: Background. Although meta-analysis showed that survival improved with concurrent chemoradiation in locally advanced head and neck cancer, neoadjuvant chemotherapy is still unique, because it renders curative surgery feasible for marginally resectable head and neck cancer patients.

Methods. We reviewed patients with locally advanced head and neck cancer, who had been treated with neoadjuvant chemotherapy between June 1984 and February 2001 at the Seoul National University Hospital.

Results. A total of 167 patients were included. After 2 to 3 chemotherapy cycles, either surgery (38 patients) or radiation (104 patients) was conducted. Those who received surgery exhibited better survival than those who received radiation [median survival: not reached vs 33.6 months (95% CI: 22.6–44.7), p = .006]. The 5-year and 10-year survival rates of surgery group were 63.2% and 59.8%.

Conclusion. The potential benefit of neoadjuvant chemotherapy with surgery in patients with locally advanced head and neck cancers merits further evaluation in future clinical trials.

Keywords: neoadjuvant chemotherapy; locally advanced head and neck cancer; concurrent chemoradiation; survival; curative surgery

Locally advanced head and neck cancers account for over 60% of total head and neck cancer, and the outcome of treatment remains unsatisfactory.1 Surgery and/or radiotherapy (RT) are the current staples of locoregional treatment. Chemotherapy has also been added to a host of local modalities, in the form of either induction (neoadjuvant) chemotherapy or concurrent chemoradiotherapy (CRT).

The Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) collaborative group reported that a survival improvement was observed when chemotherapy was administered
concurrently with RT. This benefit of concurrent CRT was confirmed by recent update of MACH-NC database. However, concurrent CRT might exclude potential benefit of curative resection after neoadjuvant chemotherapy.

While meta-analysis comparing induction chemotherapy plus local treatment with local treatment alone indicated minimal survival advantage, induction chemotherapy appears to be unique, as it may render curative surgery a feasible option in marginally resectable patients with head and neck cancer.

In this context, we evaluated the percentage of curative resection after neoadjuvant chemotherapy and the survival outcome of those patients.

**MATERIALS AND METHODS**

**Patients.** The eligibility criteria in this study were as follows: previously untreated, histologically confirmed, squamous cell or undifferentiated head and neck carcinoma except nasopharyngeal cancer, in unresectable or marginally operable state (stage III or IV), Eastern Cooperative Oncology Group (ECOG) performance state between 0 and 2, and having received induction chemotherapy as an initial treatment at the Seoul National University Hospital, between June 1984 and February 2001.

The medical records of these patients were reviewed to assess the patients’ characteristics, including age, sex, primary site, stage, chemotherapy regimen, initial response to chemotherapy, subsequent local modalities, date of disease progression, and final status on the last follow-up examination.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>140 (83.8)</td>
</tr>
<tr>
<td>Female</td>
<td>27 (16.2)</td>
</tr>
<tr>
<td>Site</td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>50 (29.9)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>41 (24.6)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>31 (18.6)</td>
</tr>
<tr>
<td>Nasal cavity</td>
<td>24 (14.4)</td>
</tr>
<tr>
<td>Larynx</td>
<td>21 (12.6)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>164 (98.2)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>30 (18.0)</td>
</tr>
<tr>
<td>IV</td>
<td>137 (82.0)</td>
</tr>
</tbody>
</table>

Note: Total number of patients (n) is 167; age (range), y: 59 (15–79).

**TREATMENT.** All patients were scheduled to receive an initial 2 cycles of induction chemotherapy, and the responses to these treatments were evaluated by the appropriate radiological studies. Patients’ responses were categorized in accordance with the criteria provided by the World Health Organization (WHO). Responsive patients exhibiting either complete or partial remission received an additional cycle of chemotherapy and subsequent local treatment, whereas the nonresponsive patients received local treatment without additional chemotherapy. Local treatment modality (surgery vs RT) was decided by the multidisciplinary team, which consisted of head and neck surgeons, medical oncologists, radiation oncologists, and radiologists. After local treatment, the patients received regular follow-up examinations. Patients with recurrence received appropriate salvage treatments, at the physician’s discretion.

**Statistical Analyses.** We used chi-square tests to compare the demographic data, and used Kaplan–Meyer and log-rank tests for survival analysis. Prognostic factors were analyzed via Cox-regression analysis. We conducted these analyses using SPSS (version 10.0).

**RESULTS**

**Patient Characteristics and Chemotherapy Regimen.** A total of 167 patients were included in this study. The patients’ characteristics and the neoadjuvant chemotherapy regimens are summarized in Tables 1 and 2. The median age of the patients was 59 years (range, 15–79), and males predominated in the sample (83.8%). Number of patients according to the primary site was as follows: oral cavity (n = 50, 29.9%), hypopharynx (n = 41, 24.6%), oropharynx (n = 31, 18.6%), nasal cavity (n = 24, 14.4%), and larynx (n = 21, 12.6%). Almost all (n = 164, 98.2%) patients had squamous cell carcinoma, and the majority of the patients (n = 158, 94.6%) were treated with 5-fluorouracil + cisplatin (BOMP) regimen. The median age (range) of the patients was 59 (15–79), and males predominated in the sample (83.8%).

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of patients (%)</th>
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<tbody>
<tr>
<td>5-fluorouracil + cisplatin</td>
<td>158 (94.6)</td>
</tr>
<tr>
<td>5-fluorouracil + carboplatin</td>
<td>4 (2.4)</td>
</tr>
<tr>
<td>BOMP</td>
<td>4 (2.4)</td>
</tr>
<tr>
<td>BEP</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

Abbreviations: BOMP, bleomycin + vincristine + methotrexate + cisplatin; BEP, bleomycin + etoposide + cisplatin. Note: Total number of patients (n) is 167.
Response to Chemotherapy. The overall response rate was 80.8%, including a 7.5% rate of complete remission, and a 73.3% rate of partial remission. Factor analysis revealed that cancer from the nasal cavity showed 52.2% response rate in comparison to 84.9% from other primary sites \((p = .001)\) (Table 3).

Local Treatment Modality. Local therapeutic modality was performed in 142 patients, either surgery \((n = 38)\) or RT \((n = 104)\) (Table 4). Although this study was not performed in a prospective randomized setting, there was no statistical difference in prognostic factors between the 2 groups (Table 4). After the administration of local treatment, 112 (78.9%) of treated patients or 67.1% of total patients, via intent-to-treat analysis, exhibited durable remission.

Survival and Prognostic Factor Analysis. Median overall survival and progression-free survival durations were 41.2 months (95% confidence interval [CI]: 27.0–55.3) and 19.9 months (95% CI: 14.0–25.8), respectively (Figure 1). The patients were subgrouped according to local treatment modality, and the survival characteristics of these patients were compared. Among the patients treated by local modality, those who received surgery exhibited better survival than those who received RT (median survival: not reached vs 33.6 months [95% CI: 22.6–44.7], \(p = .006\)) (Figure 2). In fact, the 10-year survival rate of the 38 patients who received surgery as a local treatment modality was 59.8%, and 23 patients remained alive at the time this article was written.

DISCUSSION

Although neoadjuvant chemotherapy has shown minimal survival advantage (2%) over local treatment alone in meta-analyses, it demonstrated a 5% survival rate increase for trials specifically using cisplatin/5-FU combination.\(^5\) In addition, a reduction in the incidence of distant metastases has been consistently demonstrated.\(^2\) The relative lack of efficacy, despite high objective response rate, seems to be due to failure in controlling locoregional disease. There have been several efforts aimed at improving the therapeutic outcome of induction chemotherapy, the first of which is the combination of induction chemotherapy and concurrent CRT. Concurrent CRT, as described above, has reduced locoregional failure rate and prolonged survival.\(^2,3\) When analyzing the pattern of failure of concurrent CRT, however, distant failure has become an increasing cause of mortality, especially in patients with advanced nodal disease.\(^6,7\) One meta-analysis indicated that neoadjuvant chemotherapy resulted in better control of distant metastases than concurrent CRT did (relative risk: 0.67 vs 0.75) in locally advanced nasopharyngeal carcinoma.\(^8\) Induction chemotherapy may offer a greater degree of systemic control of micrometastases, which may induce systemic failure at a later time. Thus, it seems that induction chemotherapy and concurrent CRT may have complementary effects on disease control. In recent years, studies have been focused on induction chemotherapy followed by concurrent CRT,\(^9–11\) and randomized phase III trials comparing concurrent CRT alone with induction chemotherapy followed by concurrent CRT are currently

<table>
<thead>
<tr>
<th>Primary site</th>
<th>No. of patients (%) by response</th>
<th>Response rate, %</th>
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<tbody>
<tr>
<td>Oral cavity</td>
<td>49/50 3 (6.1) 38 (77.6) 83.7</td>
<td></td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>40/41 4 (10.0) 29 (72.5) 82.5</td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>31/31 3 (9.7) 24 (77.4) 87.1</td>
<td></td>
</tr>
<tr>
<td>Nasal cavity</td>
<td>23/24 0 (0.0) 12 (5.2) 52.2</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>19/21 2 (10.5) 15 (78.9) 89.4</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>162/167 12 (7.4) 118 (72.8) 80.2</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary site</td>
<td>Surgery  RT</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>23 19</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>3 33</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>3 25</td>
</tr>
<tr>
<td>Nasal cavity</td>
<td>6 14</td>
</tr>
<tr>
<td>Larynx</td>
<td>3 13</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>5 22</td>
</tr>
<tr>
<td>IV</td>
<td>33 82</td>
</tr>
<tr>
<td>Chemo-response</td>
<td></td>
</tr>
<tr>
<td>CR/PR</td>
<td>1/28 10/74</td>
</tr>
<tr>
<td>SD/PD</td>
<td>7/2 11/9</td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>38 104</td>
</tr>
</tbody>
</table>

Abbreviations: RT, radiotherapy; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
in progress.\textsuperscript{12} As another method to improve the therapeutic efficacy of induction chemotherapy, the chemotherapeutic agent taxane has been added to cisplatin/5-FU combination and its efficacy has been demonstrated in phase II clinical trials.\textsuperscript{13,14} A recent randomized phase III clinical trial reported that neoadjuvant docetaxel combined with cisplatin/5-FU was superior to neoadjuvant cisplatin/5-FU combination alone in terms of progression-free survival and overall survival.\textsuperscript{15} Molecular targeted agents also offer promise for this particular patient group.\textsuperscript{16}

In our study, among 38 patients who underwent surgery as a local treatment modality, significant proportion survived. Likewise, surgery as a local modality was an independent good prognostic factor. Although no significant difference was observed in the proportion of stage IV disease (87\% vs 79\%) and response to chemotherapy between surgery group and RT group (Table 4), however, it cannot be excluded that more unresectable patients were included in RT group because this study is not a randomized trial.

Induction chemotherapy may induce a “downstaging” of the primary tumor in “unresectable or marginally operable” patients with head and neck cancer, allowing for curative surgery. However, treatment of such patients with concurrent CRT from the beginning may exclude possibility of curative surgery in a subset of patients described in this study. Indeed, analysis of the 10-year follow-up data of a randomized phase III trial of neoadjuvant chemotherapy showed that operable patients had a better survival rate than did inoperable patients.\textsuperscript{17}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Survival times of overall patients. Median overall survival (A) and progression-free survival (B) were 41.2 months (95\% confidence interval: 27.0–55.3) and 19.9 months (95\% confidence interval: 14.0–25.8), respectively. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{Survival times according to local treatments. Those who received surgery showed better survival than those who received radiation (median survival: not reached vs 33.6 months [95\% confidence interval: 22.6–44.7], \( p = .006 \)). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
\end{figure}
If the benefits of induction chemotherapy and surgery in these patients are observed in future trials, a so-called “hybrid” approach, in which, after induction chemotherapy, operable patients would undergo curative surgery and inoperable patients would receive CRT as a definitive local treatment, may indeed become a reasonable option.

If, in a future trial, “limited surgery” in chemoresponsive patients is associated with a survival rate equivalent to that of radical surgery, induction chemotherapy combined with surgery may also provide the chance of organ preservation.18

In conclusion, the possible benefit of induction chemotherapy followed by surgery in patients with locally advanced head and neck cancer merits further evaluation in future clinical trials.

REFERENCES