Analysis of Risk Factors Predictive of Distant Failure After Targeted Chemoradiation for Advanced Head and Neck Cancer

Ilana Doweck, MD; K. Thomas Robbins, MD; Francisco Vieira, MD

Background: Distant metastasis (DM) is the most common mode of recurrence among patients with advanced head and neck carcinoma treated with intra-arterial cisplatin and radiotherapy (RADPLAT).

Objective: To identify which patients are at greatest risk for DM and would benefit the most from new strategies designed to treat occult metastases.

Methods: Between 1993 and 1999, 250 patients with advanced head and neck cancer were treated by RADPLAT. Excluded from the analysis were 10 patients who either did not complete the protocol or were unavailable for follow-up and 39 patients with persistent disease or local recurrence. The incidence and the risk factors for DM in these patients were evaluated in a model that included the following factors: age, T and N classification, site of tumor, histologic grade, number (0, 1, or >1) and position (high vs low) of neck levels involved, and bilateral nodal disease. Multiple stepwise logistic regression was used for the analysis.

Results: In a univariate analysis, the following variables correlated to DM: N classification (P=.02), site of tumor (P=.01), lower neck nodes (P=.002), number of neck levels involved (P=.001), and bilateral nodal disease (P=.02). In a multivariate analysis, the most significant risk factors for DM were the number of neck levels involved and the site of the primary tumor (P<.001). The highest odds ratios for DM were among patients with multiple levels of nodal involvement (3.17) and patients with hypopharyngeal carcinoma (2.8).

Conclusions: Patients with more than 1 level of clinical nodal involvement and patients with hypopharyngeal carcinoma have the highest risk of developing DM as the initial site of failure and would benefit most from treatment strategies that address occult distant disease.


Efforts to improve the outcomes of patients with advanced cancer of the head and neck have led to combined therapy protocols incorporating chemotherapy. The RADPLAT protocol involves a novel drug infusion technique for delivering cisplatin directly into the tumor bed while minimizing the effects of the drug systemically. Radiotherapy is administered simultaneously.

The RADPLAT protocol, widely used at the University of Tennessee Health Science Center, Memphis, showed high rates of complete response (90.5%) at the primary site, while the complete response rate for the regional nodes was 70.7%. The subsequent use of neck dissection (primarily the selective type) in patients with bulky nodal disease (N2 and N3) resulted in an ultimate regional control rate of 91%. The 5-year survival rates for patients dying of their disease and overall survival were 53.6% and 38.8%, respectively.

With the improvement in the locoregional control of advanced head and neck cancer, the incidence of distant metastasis (DM) as the primary site of failure has increased. Since there has been no clinical evidence of disease at other sites (local and regional) in these patients, it is surmised that they had occult DM at the time of presentation. The arising problem of death from DM among patients treated with RADPLAT requires further investigation to determine which patients are at greatest risk. The development of a risk assessment formula would be useful in identifying which patients would benefit the most from interventions designed to treat occult DM.

Among the 250 patients in the total group, 45 (18.0%) developed DM as the first site...
PATIENTS AND METHODS

Between June 1, 1993, and March 31, 1999, 250 patients with advanced head and neck cancer were treated with RADPLAT* (n = 165) and a sister protocol named Pento-RADPLAT (n = 85), in which pentoxifylline was added to reduce the chronic soft tissue toxic effects of therapy,* at the University of Tennessee Health Science Center.

Excluded from the total group of 250 patients were 6 who did not complete the protocol and 4 who were unavailable for follow-up. To determine the total number of patients who were at risk of having DM as the first site of failure, 39 patients with locoregional recurrence or persistent disease were also excluded. Therefore, any patient who ultimately developed DM was likely to have had occult distant disease at the time of diagnosis.

All patients entered into the study underwent clinical staging of disease at the primary, regional, and distant sites using history, physical examination, endoscopic findings, and radiologic studies (computed tomography and/or magnetic resonance imaging). Patients with evidence of DM at the initial diagnosis were not candidates for either protocol. The T and N classifications of the patients included in the study are shown in Table 1.

The RADPLAT protocol, which was previously described by Robbins et al.,* consists of the concurrent administration of selective supradiose intra-arterial cisplatin (150 mg/m2 weekly for 4 weeks) with parenteral sodium thiosulfate to neutralize the systemic effects of cisplatin and conventional external-beam irradiation (180-200 rad [1.8-2.0 Gy] per fraction to a total dose of 6850-7400 rad [68.5-74.0 Gy] given during 7-8 weeks). The intra-arterial cisplatin is rapidly infused through a microcatheter placed angiographically to selectively encompass only the dominant blood supply of the targeted tumor.

Patients were followed up every week during the treatment protocol. Tumor response was determined during therapy by physical examination, and restaging was performed 2 months after radiation by means of criteria based on physical examination, repeated imaging studies, and repeated endoscopy and biopsy. Neck dissection in patients with persistent nodal disease was performed 2 months after treatment.

Patients were followed up every month in the first year after completing the treatment and every 2 months thereafter. End points included site of recurrence (local, regional, or DM), site of DM, and survival. Patients included in the study had at least 12 months of follow-up after completing the treatment.

The following variables were evaluated in relation to DM: age (<40, 40-60, and >60 years), T classification (1-4), N classification (0-3), the site of origin of the tumor (oral cavity, oropharynx, larynx, hypopharynx, and other sites), histologic grade (well, moderately, and poorly differentiated), levels of nodal involvement (high levels [I and II], low levels [III-V]), total number of levels of nodal involvement in the neck (0, no clinical node; 1, only 1 level of nodal involvement; and >1, >1 level of nodal involvement), and unilateral vs bilateral nodal involvement.

The incidence and the risk factors for DM in these patients were evaluated in a model that included the previous variables (age, T and N stages, site of tumor, histologic grade, number and position [high vs low] of neck levels involved, and the presence of contralateral disease). Multiple stepwise logistic regression was used for the analysis.

The statistical analysis was done with JMP 4 for Windows (SAS Institute Inc, Cary, NC).

### Table 1. T and N Stages in 250 Patients With Advanced Head and Neck Cancer Treated With RADPLAT and Pento-RADPLAT*

<table>
<thead>
<tr>
<th>N Stage</th>
<th>T1-2</th>
<th>T3</th>
<th>T4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>43</td>
<td>27</td>
<td></td>
<td>70</td>
</tr>
<tr>
<td>N1</td>
<td>23</td>
<td>15</td>
<td></td>
<td>41</td>
</tr>
<tr>
<td>N2</td>
<td>40</td>
<td>61</td>
<td></td>
<td>107</td>
</tr>
<tr>
<td>N3</td>
<td>11</td>
<td>8</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>111</td>
<td>111</td>
<td>250</td>
</tr>
</tbody>
</table>

*See the “Patients and Methods” section for description of chemoradiation protocols.

of failure, whereas 39 patients (15.6%) had locoregional recurrence. Therefore, the most common site of failure in this patient subset was DM. The mean interval for this event to occur was 12.5±9.3 months from diagnosis of primary disease. The most common site for DM was the lung (30 patients), followed by bone (13 patients), liver (13), and brain (5). Twenty-one patients had 2 or more sites of involvement by metastases.

Univariate analyses were performed with the Pearson correlation test to determine which patient, tumor, and treatment factors correlated with the development of DM (Table 2). The following variables were corre-
of patients who presented with N0 neck disease was 52.4% compared with 28.3% for patients with a single level of nodal involvement and 18.0% for patients with more than 1 level of nodal involvement (P < .001) (Figure 3).

The mean time interval for survival among the patients who developed DM as the initial site of disease recurrence was 16.7 ± 1.6 months from the initial diagnosis.

**COMMENT**

Autopsy studies have shown that the overall incidence of DM among patients with head and neck cancer is relatively high (40%-47%). However, most patients in these analyses had uncontrolled disease at the primary site and/or the neck. The incidence of DM among patients who remain free of disease at the local and regional sites is lower, although still substantial. With the improvement of locoregional control of advanced head and neck cancer with new treatment regimens such as ours, distant failure has emerged as the most common reason for disease recurrence. The effectiveness of the RADPLAT protocol is based on the delivery of high-dose cisplatin combined with radiation therapy to the local disease. It has enabled us to achieve an excellent rate of locoregional disease control, but it does not provide systemic treatment for patients who have subclinical metastases or micrometastases at distant sites.

The recognition of risk factors for the development of DM is important to identify high-risk patients who may benefit from systemic treatment in addition to the RADPLAT protocol. Because our goal was to recognize which patients were at greatest risk for harboring micrometastases, we purposely did not include the patients with DM who also had failure in the local and/or regional sites, since their DM may have been related to the recurrent locoregional disease. In other words, they may not have had distant micrometastases at the time of initial treatment.

In the present study, the rate of DM as the first site of failure in the absence of locoregional recurrence was 18%. Similar findings were reported by Vikram et al. At autopsy, Nishijima et al reported a DM rate of 20% in patients with controlled disease above the clavicle.

Histologic criteria such as extracapsular spread and multiple positive lymph nodes were found to be related
Patients with pyriform sinus cancer were found to have an 88% “above-clavicle” disease control rate. This further strengthens our observations that patients with hypopharyngeal cancer have a high risk of distant subclinical disease at the time of presentation. One can speculate that the mechanism of tumor invasion and metastasis for cancer of the hypopharynx compared with other sites of the head and neck may be different.

The T classification and age were not related to the development of DM, as was also reported previously by Vikram et al and Alvi and Johnson. The data from our study lead us to conclude that patients who present with nodal disease involving multiple levels and/or cancer of the hypopharynx have the greatest risk of having subclinical DM and would benefit from additional systemic treatment designed to eradicate such micrometastases. However, to our knowledge, such therapies currently do not exist.

Accepted for publication July 11, 2001.


Corresponding author and reprints: Ilana Doweck, MD, Department of Otolaryngology, Head and Neck Surgery, Carmel Medical Center, 7 Michal St, Haifa 34362, Israel (e-mail: idoweck@netvision.net.il).

REFERENCES


Figure 3. Kaplan-Meier survival plot for patients without nodal disease, with single level of nodal involvement, and with multiple levels of involvement.