Risk Factors for Distant Metastases in Head and Neck Squamous Cell Carcinoma

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Objectives: To evaluate the frequency of distant metastases (DM) and to determine the ability of certain clinical and pathologic factors to predict the development of distant metastases.

Design: Retrospective analysis.

Setting: University hospital.

Patients: A total of 1972 patients with oral, oropharyngeal, hypopharyngeal, and laryngeal squamous cell carcinomas who were treated from 1981 to 1998 and who were not diagnosed as having DM at the time of initial treatment.

Main Outcome Measures: We evaluated the frequency of DM and the influence of different variables in their appearance.

Results: A total of 181 patients (9.2%) (95% confidence interval, 7.9%-10.5%) developed DM. Younger age (<45 years), hypopharyngeal localization, an advanced T stage and/or N stage tumor according to the TNM staging system, high histologic grade, and locoregional control were found to be significantly associated with the risk of DM at both univariate and multivariate analyses.

Conclusions: The incidence of DM in subjects with head and neck squamous cell carcinoma is relatively low. The risk of DM is influenced by age, site of primary cancer, local and/or regional extension, grading, and achievement of locoregional control.


QUAMOUS CELL CARCINOMA OF the head and neck tends to remain localized at the primary site and regional lymph nodes. A significant improvement in the locoregional control of this cancer has been seen over the last decades thanks to the advent of new surgical techniques and approaches and improved understanding of head and neck squamous cell carcinoma. However, this improvement does not seem to have significantly influenced the final survival rate, partly owing to the development of distant metastases, a relatively rare but clinically relevant event. We believe that a current relevant task in this area is to precisely assess the rate and risk factors for distant metastases to define a subgroup of patients who may benefit from a different therapeutic approach. In other words, it would be of utmost interest to identify those patients for whom adjuvant chemotherapy may have a significant impact on survival.

Studies over the past 2 decades have reported rates of distant metastases varying between 4.0% and 26.0% in patients treated for squamous cell carcinoma of the head and neck. It has been noted that different prognostic factors could influence the development of distant metastases such as the locoregional control of the tumor, primary site, local and/or regional extension, and histologic features. However, the relative importance of these factors in predicting the development of distant metastases varies widely among studies.

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To shed further light on this relevant debate, results from a series of patients who were diagnosed as having head and neck cancers from 1981 to 1998 were reviewed and are presented herein. The purpose of this study was to evaluate the frequency of distant metastases and to determine the role of clinical and histologic factors in predicting the development of distant metastases.
November 1998 were evaluated. Patients were included if they had been diagnosed with head and neck squamous cell carcinoma. Patients with carcinoma in situ; multiple head and neck carcinomas; carcinoma located at the nasal cavity, paranasal sinus, or nasopharynx; or neck metastases without known primary cancer were excluded from this study. Patients were also excluded if they had metastatic disease at presentation, had received any oncologic treatment prior to referral, or had not started or completed their planned therapy, or if detailed clinical data were not available. An upper boundary to the follow-up period was set at 5 years after initial treatment. Patients were excluded if the duration of follow-up was shorter (including patients who died because of a direct consequence of therapy complications or any other reason other than their cancer); and they were thus considered lost to follow-up. Follow-up ended before 5 years only in the case of patients who were diagnosed as having a distant metastasis.

Information abstracted from this database included age, sex, primary tumor stage, site and differentiation, clinical and pathologic neck stage, time to development of distant metastases, and localization of distant metastases. Tumor site was classified as the oral cavity, oropharynx, hypopharynx, or larynx. Laryngeal tumors were subclassified as glottic or supraglottic. The tumor stage was determined according to the TNM classification recommended by the International Union Against Cancer.14 Pathologic findings in the group of patients whose treatment included neck dissection were separately reported. The treatments given were surgery, radiation therapy, chemotherapy, or any combination of these, as deemed appropriate for the stage by the treating physician. Follow-up consisted of physical examination and chest radiography; other investigations, such as liver echography, computed tomographic or magnetic resonance imaging scan, or bone scintigraphy, were performed when clinically indicated. If cancers occurred in other sites, efforts were made to obtain histologic specimens. These cancers were tabulated as distant metastases if there were nodules of the same cell type or if histologic findings were unavailable. We analyzed qualitative variables using the chi² test or Mantel-Haenszel test for linear association as appropriate with SPSS statistical software (version 12.0; SPSS Inc, Chicago, Ill). We performed multivariate analysis with a logistic regression model that included all variables that were found to be significantly associated in univariate analyses and used a binomial distribution statistical model to determine the 95% confidence interval (CI) of the probability to develop distant metastases.

RESULTS

A total of 153 patients were lost to follow-up, leaving 1972 cases available for data analyses. The ages of enrolled patients ranged from 33 to 82 years (mean age, 62 years). Men represented most of the cases (1855 patients [94.1%]). These epidemiological features are in line with previous reports on patients with head and neck squamous cell carcinomas.2,15

The distribution of sites was as follows: oral cavity (n=372 [18.9%]), oropharynx (n=394 [19.9%]), hypopharynx (n=233 [11.8%]), and larynx (n=973 [49.4%]). Of laryngeal cancers, 638 (32.4%) were glottic and 335 (17.0%) were supraglottic. Neck dissection was performed in 1064 cases (54.0%). Distant metastases were diagnosed in 181 cases, corresponding to a rate of 9.2% (95% CI, 7.9%-10.5%). The cumulative rate of metastases is illustrated in the Figure. The study periods and incidence rates of distant metastases were as follows: 1981-1984, 8.9%; 1985-1989, 10.0%; 1990-1994, 8.6%; and 1995-1998, 9.4%. These percentages were not significantly different. The sites of metastases were distributed as follows: lung, 101 cases (55.8%); bone, 18 cases (9.9%); liver, 7 cases (3.9%); and more than 1 site, 55 cases (30.4%).

The risk of distant metastases according to clinical characteristics of patients is shown in Table 1. Age, localization of the primary tumor, local (T stage) and regional (N stage) extension, histologic grade, and locoregional control were found to be significantly associated with this risk. Considering age at the time of diagnosis, the highest rate of subsequent distant metastases was observed among patients younger than 45 years. The odds ratio in this subgroup was 1.8 (95% CI, 1.1-3.3). When excluding patients younger than 45 years, age was not significantly associated with a risk of distant metastases (P=.76). The highest rate of subsequent distant metastases according to the site of primary cancer was observed among patients with cancer of the hypopharynx. Moreover, this risk seemed to grow with the increase of the local and regional extensions and the grade of differentiation. Finally, patients who achieved locoregional control were found to have a lower risk of distant metastases. As shown in Table 2, all associations identified at univariate analysis persisted after multivariate analysis.

Because only a subgroup of patients with head and neck cancer underwent surgical neck dissection, data on pathologic stage (pN) and extracapsular spread were available for only 1064 subjects. These data are presented separately in Table 3. Both variables were significantly associated with a risk of distant metastases.

Figure. Hazard ratio of distant metastases in patients with head and neck carcinoma.

In this study, results from a large series of 1972 patients with head and neck squamous cell carcinoma are pre-
Results from our study confirm that head and neck squamous cell carcinoma has mainly a locoregional growth. The incidence of distant metastases is relatively small compared with other malignancies such as stomach, pancreas, lung, breast, or kidney cancer. Specifically, the rate of distant metastases in our series was 9.2% (95% CI, 7.9%-10.5%). In our study, only patients who completed the follow-up period were included; it could be argued that this inclusion criteria might influence the rate of distant metastases. Indeed, we cannot eliminate the possibility that patients who were lost to follow-up may be at increased or decreased risk of distant metastases. Overall, we do not believe that this bias relevantly influenced the results. As shown in Table 4, the rate of distant metastases observed in our study is in line with rates in recent clinical series on this topic.8,9,13,16-18 Of note, the percentage observed in one of the currently largest available series was quite similar to the rate observed in our study (9.5% [179 of 1880 patients]).9 Moreover, results from our series have confirmed that most distant metastases become clinically apparent in the 2 years after diagnosis of the initial tumor.9,19,20

As distant metastases develop, the chance of cure is very low and the survival dramatically decreases. Detecting distant metastases even at an early stage and subjecting them to metastasectomy or radiation therapy would not be sufficient to obtain higher cure rates. Alvi and Johnson8 reported an average time to death of only 5 months. As a consequence, it was suggested that it would be useful to identify groups of patients who are at high risk for the development of distant metastases to target them for adjuvant chemotherapy. Results from studi-
ies.21-23 Investigating the role of this combined approach are currently discrepant. Findings from a study by Shin-
gaki et al23 showed improved survival rates and de-
creased distant metastases with adjuvant chemo-
therapy. Conversely, Laramore et al21 reported a sig-
nificant reduction of distant metastases in patients who received
chemotherapy, but no benefit of survival was observed.
Similar results have been recently confirmed in a ran-
domized study24 comparing radiation therapy alone with
radiation therapy plus concurrent treatment with cispla-
tin. It might be argued that the inclusion criteria used in
these studies could be, at least in part, responsible for
these conflicting results. Adequately powered trials en-
rolling only the subjects at greatest risk are warranted
to elucidate this issue. A current task in the field of head
and neck squamous carcinoma is thus to properly iden-
tify risk factors for distant metastases to determine a sub-
group of patients for whom establishing different ther-
apeutic strategies is mandatory.

Risk factors for distant metastases are a matter of
debate. This aspect has been recently exhaustively re-
viewed by Leon et al9 and is beyond the scope of the pres-
ent study. Overall, our results confirmed that the loco-
regional control and N stage are markedly associated with
an increased probability of developing distant meta-
stases. There is a general consensus on these specific risk
factors.6,8-11,13,18-20,25-28 Furthermore, our results high-
light some other factors that may play a role. Indeed, can-
cer localization, histologic grade, local extension of tu-
mor (T stage), and, to a lesser extent, younger age were
significantly associated with the risk of distant meta-
stases. Results from the present study suggest that the hy-
popharynx is the site at highest risk of subsequent dis-
tant metastases. Specifically, this localization was
associated with a relative risk of 13.7 (95% CI, 7.1-
25.4) when compared with cancer of the oral cavity, which
considerably resulted in identifying those at lowest risk.
There are reports,6,11,27 that some localizations in the head
and neck, such as in the nasopharynx and hypophary-
ynx, had a greater risk. Leon et al9 found that cancers of
the oropharynx and hypopharynx had an increased risk
in head and neck carcinoma.6-10,12,13,20,27,28 However,
results from one of the largest series on this topic univo-
cally support a significant association between the risk
of distant metastases and the local extension.3 In our study,
we documented a relationship between local extension
and risk of distant metastases. Finally, to our knowl-
edge, an increased risk in patients younger than 45 years
has not been previously reported.28,30 In this regard,
though, it should be noted that the entity of this risk is
less relevant when compared with other factors such as
localization, local extension of tumor, and N stage. Over-
all, it may be speculated that the role of younger age is
presumably of limited importance. Discrepancies among
studies are difficult to explain. It might be hypothesized
that the reduced sample size and thus the low power of
many currently available studies may in part explain these
conflicting results. Differences in the epidemiological pro-
file of patients among studies may also play a role.

In conclusion, this study confirms that the incidence
of distant metastases in subjects with head and neck squa-
mous cell carcinoma is relatively small. Moreover, our
study suggests that locoregional control of the cancer and
N stage, and also localization to the hypopharynx, his-
tologic grade, local extension of tumor, and, to a lesser
extent, younger age are factors associated with the risk
of distant metastases.

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Table 4. Studies on the Rate of Distant Metastases (DM) for Head and Neck Cancers

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>DM, No. (%)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shingaki et al,9 1996</td>
<td>103</td>
<td>21 (20.0)</td>
<td>Included patients with cancer of the maxillary sinus</td>
</tr>
<tr>
<td>Alvi and Johnson,6,8 1997</td>
<td>130</td>
<td>30 (23.0)</td>
<td>Included only patients with advanced stage and surgically treated cancer</td>
</tr>
<tr>
<td>Yücel et al,10,11 1999</td>
<td>659</td>
<td>48 (7.3)</td>
<td>Included only patients with laryngeal cancer</td>
</tr>
<tr>
<td>de Bree et al,11,12 2000</td>
<td>101</td>
<td>17 (17.0)</td>
<td>Included patients with cancer of the cervical esophagus, nose and paranasal sinus. All patients had clinically advanced or recurrent disease.</td>
</tr>
<tr>
<td>Leon et al,22 2000</td>
<td>1880</td>
<td>179 (9.5)</td>
<td>Included only patients who achieved locoregional control</td>
</tr>
<tr>
<td>Matsuo et al,10,11 2003</td>
<td>662</td>
<td>67 (10.0)</td>
<td>Included only patients with laryngeal cancer</td>
</tr>
</tbody>
</table>

REFERENCES