Small Cell Carcinoma of the Head and Neck: the University of Florida Experience

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ABSTRACT

Objective: To describe the University of Florida experience in treating small cell carcinoma of the head and neck with radiotherapy as the primary local treatment modality.

Materials and Methods: Five patients with small cell carcinoma of the head and neck were treated definitively with radiotherapy between November 1989 and September 2001. Neoadjuvant chemotherapy was used in 4 of the 5 patients. Chemotherapy was followed by definitive radiotherapy to a median dose of 65.5 Gy.

Results: Only 1 of the 5 patients survived longer than 13 months. He remains free of disease 3 years after neoadjuvant carboplatin and paclitaxel chemotherapy and radiotherapy to 74.4 Gy at 1.2 Gy per fraction twice daily. Regional or distant disease accounted for the majority of failures. One local recurrence occurred in a patient with a T4 laryngeal primary tumour.

Conclusions: Radiotherapy is a reasonable alternative to surgery for patients with early- and moderate-stage small cell carcinoma of the head and neck. Although the addition of surgery might improve local and regional control for patients with more advanced disease, the potential benefit may be offset by the high risk of distant failure. More effective systemic chemotherapy is necessary to improve the outcome for these patients.

Key Words: Carcinoma, squamous cell; Head and neck neoplasms; Radiotherapy; Surgery; Treatment outcome

INTRODUCTION

Small cell carcinoma of the head and neck is a relatively uncommon neuroendocrine tumour and has a poor prognosis. Therapeutic options include various combinations of surgery, chemotherapy, and radiation therapy (RT). Despite aggressive multimodality treatment, the majority of patients with primary small cell carcinomas arising from mucosal head and neck sites develop distant and/or regional metastases.¹

Owing to the rarity of small cell carcinoma of the head and neck, treatment guidelines have primarily been based on small-scale, single-institution experiences. The purpose of this study was to describe the experience at the University of Florida in treating small cell carcinoma of the head and neck with RT as the primary local treatment modality.

MATERIALS AND METHODS

Six patients with histopathologically documented small cell carcinoma of the head and neck received RT as a component of treatment between November 1989 and September 2001 at the University of Florida. Five patients were treated with curative intent and 1 patient who presented with a lumbar spine metastasis was treated with palliative intent. The 5 patients treated with curative intent comprise the basis of this report.

Three of the 5 patients were men and 2 were women. The age at presentation ranged from 37 to 78 years (median, 60 years). Three patients had primary lesions arising in the hypopharynx or larynx, and 2 patients had tumours of the paranasal sinuses (Table 1). Three patients had American Joint Committee on Cancer (AJCC) stage T2 tumours, whereas 1 patient each had a T3 and T4 lesion. Four of 5 patients (80%) had positive regional adenopathy at diagnosis. The patient without nodal metastases at diagnosis was a 54-year-old man...
with T2N0 small cell carcinoma of the ethmoid sinus. All patients were treated with definitive RT as the primary local treatment modality. One patient underwent a planned Caldwell-Luc procedure after achieving a clinically complete response.

Three patients were treated with 6-MV photons, and 2 were treated with cobalt 60. A hyperfractionated RT schedule (1.1 or 1.2 Gy per fraction given twice daily) was used for the 2 patients with parasal sinus cancers in an attempt to minimise the risk of visual complications, given the proximity of the tumours to the optic nerves and retina. Three patients received once-daily RT at 1.8 to 2.0 Gy per fraction. Total doses ranged from 48.4 to 74.4 Gy (median dose, 65.4 Gy) in those able to complete the planned radiation course. One patient died during her RT course at a cumulative dose of 24 Gy in 12 fractions; she had a history of alcohol dependency and oesophageal varices and died as a result of gastrointestinal bleeding. The patient who received 48.4 Gy was initially planned to receive preoperative RT followed by surgery; she completed RT as planned but did not undergo surgery because she achieved a complete response.

Chemotherapy was given to all patients with the exception of the patient who died during treatment. All 4 patients were treated with induction chemotherapy. Two patients received palliative chemotherapy for tumour recurrence. Induction chemotherapy consisted of the following regimens: 1 patient received 3 cycles of cyclophosphamide, doxorubicin, and vincristine; 1 patient received 5 cycles of cisplatin and etoposide; 1 patient received 3 cycles of cisplatin and etoposide; and 1 patient received 1 cycle of cisplatin and etoposide, and then 4 cycles of carboplatin and paclitaxel. All patients had at least 2 years of potential follow-up after RT; no patients were lost to follow-up. The time to each end-point was measured from the beginning of treatment.

**RESULTS**

One of 4 patients who completed RT as planned experienced a local recurrence. He had an extensive T4 subglottic lesion that recurred with massive local and regional disease 1 year after the commencement of RT. One patient, who presented with an 8-cm cervical lymph node and a 5-cm supraclavicular node, achieved a complete response to neoadjuvant chemotherapy and radiation and subsequently developed a regional recurrence 9 months after RT.

Distant metastases occurred in 2 patients. Distant metastases tended to be quite extensive when detected; 1 patient had metastases in the lungs, adrenal gland, and brain, while the other patient developed metastases in the lungs, liver, and bone.

The only long-term survivor was a patient with T2N0 small cell carcinoma of the ethmoid sinus who was treated with the most aggressive combined modality regimen in the study. He received induction chemotherapy that consisted of 1 cycle of fluourouracil and cisplatin followed by 4 cycles of carboplatin and paclitaxel. Chemotherapy agents were changed because his medical care was transferred during treatment. Although he had a complete clinical response after chemotherapy, a biopsy before RT showed a microscopic focus of neuroendocrine carcinoma with extensive regressive changes. He underwent definitive RT (74.4 Gy in 62 twice-daily fractions) and remains disease-free 3 years after treatment.

### Table 1. Patient characteristics and treatment outcomes.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex/age (years)</th>
<th>AJCC stage</th>
<th>Primary site</th>
<th>Dose (Gy)</th>
<th>Fractions</th>
<th>Chemotherapy</th>
<th>Local recurrence</th>
<th>Regional recurrence</th>
<th>Distant metastasis</th>
<th>Outcome at last follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/37</td>
<td>T4N1</td>
<td>Subglottic larynx</td>
<td>70.0</td>
<td>39</td>
<td>3 x cisplatin and etoposide</td>
<td>1.0 year</td>
<td>1.0 year</td>
<td>1.1 years</td>
<td>DWD, 1.1 years</td>
</tr>
<tr>
<td>2</td>
<td>M/54</td>
<td>T2N0</td>
<td>Ethmoid sinus</td>
<td>74.4</td>
<td>62</td>
<td>Cisplatin, fluorouracil, carboplatin, and paclitaxel</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>NED, 3.0 years</td>
</tr>
<tr>
<td>3</td>
<td>M/60</td>
<td>T3N3</td>
<td>Supraglottic larynx</td>
<td>65.5</td>
<td>36</td>
<td>5 x cisplatin and etoposide</td>
<td>-</td>
<td>9 months</td>
<td>-</td>
<td>DWD, 1.0 year</td>
</tr>
<tr>
<td>4</td>
<td>F/74</td>
<td>T2N1</td>
<td>Maxillary sinus</td>
<td>48.4</td>
<td>44</td>
<td>Cyclophosphamide, doxorubicin, and vincristine</td>
<td>-</td>
<td>-</td>
<td>3 months</td>
<td>DWD, 0.7 years</td>
</tr>
<tr>
<td>5</td>
<td>F/78</td>
<td>T2N2b</td>
<td>Pyriform sinus</td>
<td>24.0</td>
<td>12</td>
<td>None</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Died during treatment</td>
</tr>
</tbody>
</table>

**Abbreviations:** AJCC = American Joint Committee on Cancer; DWD = dead with disease; NED = no evidence of disease.
DISCUSSION

Neuroendocrine carcinomas of the head and neck may be stratified into a number of subsets on the basis of appearance under light microscopy, immunohistochemical staining, ultrastructural findings, and clinical course. In general, these tumours share the presence of neurosecretory granules and routinely stain positive for immunoactive peptides. However, diagnosis, prognosis, and treatment recommendations may vary substantially depending on subclassification.

Laryngeal neuroendocrine neoplasms have been divided into those of epithelial and neural origin. The neural subgroup includes only paragangliomas, which are relatively indolent tumours that have an excellent prognosis following conservative surgery alone. Epithelial neuroendocrine neoplasms include typical carcinoids, atypical carcinoids, and small cell neuroendocrine carcinomas. Although these subtypes likely represent a spectrum, it has been shown that prognosis drops precipitously from relatively benign typical carcinoids to intermediate-prognosis atypical carcinoids (with a 10-year survival of approximately 30%) and highly aggressive small cell carcinomas (with a median survival of less than a year).6,7

Cytokeratin is the most useful marker to differentiate between neural and epithelial neuroendocrine tumours. A battery of immunohistochemical markers is used to further subclassify epithelial neuroendocrine tumours. Neurone-specific enolase, chromogranin, immuno-peroxidase, synaptophysin, epithelial membrane antigen, calcitonin, and bombesin stains may be useful to establish the diagnosis. Overlap between microscopic appearance and staining patterns may lead to misdiagnosis, with atypical carcinoid tumours often being mistaken for paragangliomas or small cell neuroendocrine carcinomas. In the current series, diagnosis by light microscopy was supported with immunohistochemical evaluation for all patients.

Small cell neuroendocrine carcinomas are frequently treated with chemotherapy and RT, either definitively or after surgery. These tumours are often disseminated at diagnosis; thus, it is important to perform thorough metastatic investigations to detect regional and/or distant metastases before initiating treatment.

Regional lymph nodes are present at diagnosis in at least half of patients who present with small cell neuroendocrine carcinoma. Aguilar et al reported a 54% incidence of cervical adenopathy at diagnosis in 54 patients, with supraglottic cancers having the highest rate. Moisa observed cervical adenopathy in 43 (59%) of 73 patients with small cell neuroendocrine carcinoma of the larynx. Even higher rates of regional metastases have been reported by Mills et al (14 of 15; 93%), if subsequent neck failures are included. The current study is consistent with the reported literature with 4 of 5 patients having cervical adenopathy at diagnosis.

Small cell carcinoma of the head and neck is also notable for frequent haematogenous dissemination. Aguilar et al reported a 17% rate of distant metastases at diagnosis, with an additional 21% subsequently developing brain metastases. Moisa reported subsequent distant metastases in 40 of 73 patients (55%), including 11% with brain metastases. Ten of 14 patients (71%) with laryngeal small cell undifferentiated carcinoma developed distant metastases in an early report from the University of Virginia. Small cell carcinoma of the major salivary glands appears to be the exception to this pattern. In the largest report of salivary gland small cell tumours, although all patients presented with local or regional disease only, death was usually due to distant metastases. In the current series, 2 patients developed distant metastases despite induction chemotherapy. Additional concurrent or maintenance chemotherapy may be warranted to reduce the risk of distant failure.

Local recurrence is typically less common than either distant or regional recurrence. This finding may be as much a function of early death from metastases as from successful local treatment. Alternatively, the low rates of local failure may represent inherent radiosensitivity that could translate into prolonged survival with better systemic control. Radiation doses of 36 to 40 Gy in combination with laryngectomy have controlled local disease until death from metastases in a number of cases. Higher postoperative doses have resulted in excellent local control with minimal toxicity. When RT is used as the primary local treatment, doses have ranged from approximately 60 to 70 Gy, with most patients dying of metastatic disease with the primary site controlled. The University of Florida favours an organ-preservation treatment approach when possible, given the lack of demonstrable benefit from surgery and the high rate of eventual metastatic disease.

Hyperfractionated RT has been reported in the literature for small cell carcinoma of the head and neck.
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and is routinely used at this institution. Hyperfractionation affords better local control with comparable or reduced late toxicity in squamous cell carcinoma of the head and neck.\textsuperscript{17-19} The gain in treatment outcome is frequently at the expense of increased acute toxicity. Experience with hyperfractionation for small cell lung cancer has mirrored these findings. The Intergroup trial by Turrisi et al\textsuperscript{20} demonstrated a 10% survival advantage with a significant increase in acute oesophagitis for the hyperfractionation arm.

Chemotherapy regimens for small cell carcinoma of the head and neck have typically been based on current recommendations for small cell carcinoma of the lung. Cisplatin, etoposide, cyclophosphamide, and doxorubicin are commonly used agents. Of these, cisplatin and etoposide are most frequently combined with RT. At least 1 retrospective report has shown a survival advantage for patients who received chemotherapy, with 52% surviving 2 years if chemotherapy was used, compared with 10% for those who did not receive chemotherapy.\textsuperscript{9} The high likelihood of dissemination and resulting low survival rates indicate that further advances in systemic therapy are desperately needed.

Despite aggressive combined modality treatment, outcomes for small cell carcinoma of the head and neck remain poor. Most series and reviews of the literature have reported median survivals of less than 1 year,\textsuperscript{9,10,21,22} with a recent large review showing a 5-year survival of 5%.\textsuperscript{7} Data from this study are in agreement, with all but 1 patient dying within 13 months from the start of RT. The current report is notable for demonstrating prolonged disease free survival in a patient treated with high dose hyperfractionated RT and multiagent induction chemotherapy. Novel molecular-based systemic therapies and radiosensitising chemotherapy such as gemcitabine or paclitaxel may be useful avenues to pursue in this disease.

REFERENCES