DEFINITIVE TREATMENT OF METASTATIC NASOPHARYNGEAL CARCINOMA: REPORT OF 5 CASES WITH REVIEW OF LITERATURE

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Abstract: Background. To review the treatment outcomes of patients presenting to Memorial Sloan-Kettering Cancer Center with metastatic nasopharyngeal carcinoma.

Methods. From April 1999 to April 2008, 5 patients with histologically confirmed nasopharyngeal carcinoma initially presenting with distant metastasis underwent chemotherapy and definitive radiation therapy at our institution. Each patient received platinum-based chemotherapy concurrently with definitive radiotherapy to the primary region and subsequent consolidation radiotherapy to distant metastases. In addition, 2 patients received induction chemotherapy (cisplatin, fluorouracil), and 3 others received adjuvant chemotherapy (cisplatin or carboplatin, fluorouracil).

Results. Of 5 patients initially presenting to our institution with M1 disease, 2 have no evidence of disease as of their last follow-up (29 and 91 months). The remaining 3 patients had progression of disease within 12 months of the start of treatment.

Conclusions. Long-term disease-free survival is possible in a select group of patients with M1 disease at presentation treated with platinum-based combination chemotherapy and definitive IMRT of curative intent.

CASE REPORTS

A review of the records of 338 patients who presented to our institution with NPC between January 1996 and January 2009 revealed that 5 of these patients had initially presented with evidence of distant metastasis. Patients with recurrent or previously treated disease were excluded from analysis. All 5 patients had NPC of non-keratinizing undifferentiated subtype, which consists of the vast majority of cases in endemic areas and 60% of all cases worldwide.1–6 Consequently, carcinomas of the nasopharynx frequently present with bulky nodal disease or distant metastases (DM).7–9

Most studies of metastatic NPC have analyzed all patients with DM, including those with recurrent disease in whom DM developed after definitive treatment. The few existing reports of patients with DM at presentation have shown that their prognosis is poor, with median overall survival ranging from 3 to 9 months.1–9 Moreover, these patients are a prognostically distinct group with significantly shorter survival than those in whom DM developed subsequent to treatment.10

The optimal treatment for patients with NPC who present with distant metastasis is controversial. In light of the poor prognosis in this subset of patients, treatment has conventionally been palliative in nature.11 Platinum-based combination chemotherapy is considered to be first-line therapy.12–14 The necessity of treating the primary region with radiotherapy in patients with such limited life expectancy has been debated. With the introduction of intensity-modulated radiotherapy (IMRT), however, definitive treatment to the primary region may be of increased benefit, because IMRT has the ability to minimize the toxicities associated with radiotherapy.15 In this report, we present a case series of patients who presented to Memorial Sloan-Kettering Cancer Center with initially metastatic NPC who were treated with platinum-based combination chemotherapy and definitive IMRT of curative intent.

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histology, and all were diagnosed with distant metastases within 1 month of presentation and before definitive treatment. Disease staging was performed according to the American Joint Committee on Cancer Staging criteria. Treatment details are summarized in Table 1. Acute and late adverse effects of treatment are listed in Tables 2 and 3, respectively.

**Case 1.** The first patient was a 20-year-old man who noted a lump in the right upper neck region that had been increasing in size for several months. Fiber-optic nasopharyngoscopy revealed a large bulky mass that surrounded the right torus tubarius and extended across the midline to approach the left nasopharynx. Examination of the neck revealed multiple bilateral nodes extending to the supraclavicular fossa, with the largest measuring $9 \times 4$ cm. MRI showed extensive bilateral lateral retropharyngeal lymphadenopathy with probable extracapsular extension, as well as extensive bilateral confluent deep cervical and posterior triangle adenopathy. Histologic examination of the nasopharynx and neck lesions revealed infiltrating non-keratinizing undifferentiated carcinoma. On admission before his initial treatment, the patient was noted to have an elevated alkaline phosphatase. Bone scanning revealed increased uptake in the posterior segment of the right ninth rib and left anterior iliac crest. Subsequent radiographs of the iliac crest lesion confirmed the presence of progressive metastases. The disease stage was determined to be T2bN3bM1.

To establish locoregional control, this patient was treated with definitive IMRT to 70 Gy concurrent with 2 cycles of high-dose cisplatin. Radiotherapy was delivered with a delayed accelerated concomitant boost IMRT technique. After chemoradiotherapy, the patient went on to receive adjuvant cisplatin/5-fluorouracil (5-FU) but nevertheless had progression of osseous metastases 3 months after the start of radiotherapy. He went on to receive 5 courses of consolidation radiotherapy (35 Gy in 14 fractions) to these osseous DM and died 22 months after the start of treatment.

**Case 2.** A 52-year-old man was in his usual state of good health until experiencing severe headaches associated with increasing sensitivity of his right eye and face. MRI revealed a mass located in the upper nasopharynx, sphenoid sinus, posterior ethmoid compartment, and clivus. The patient initially underwent surgery for removal of the primary tumor, including partial ethmoidectomy and sphenoidectomy. Because of invasion of the adjacent carotid artery, only subtotal resection of the skull base malignancy was possible. Histologic examination of the surgical specimen showed undifferentiated carcinoma positive for cytokeratin. Postoperative CT of the chest, abdomen, and pelvis revealed a 2-cm lytic lesion in T11 and a 2-cm lytic lesion in the left iliac wing consistent with metastatic disease. Full-body positron emission tomography scan showed large foci of hypermetabolism corresponding to the lytic lesions in the T11 vertebral body and

**Table 1.** Treatment summary.

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>T</th>
<th>N</th>
<th>KPS at diagnosis</th>
<th>Mets at diagnosis</th>
<th>Chemotherapy</th>
<th>Definitive radiotherapy</th>
</tr>
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<tbody>
<tr>
<td>20 y</td>
<td>2b</td>
<td>3</td>
<td>80</td>
<td>Right ninth rib, left anterior iliac crest</td>
<td>Concurrent: cisplatin (100 mg/m²) × 2 cycles Adjuvant: cisplatin (100 mg/m²), and infusional 5-FU (1000 mg/m²/day) × 3 cycles</td>
<td>PTV&lt;sub&gt;70&lt;/sub&gt;: 70 Gy (1.80 Gy/fraction) + concomitant boost (1.80 Gy/fraction × 10 days)</td>
</tr>
<tr>
<td>52 y</td>
<td>3</td>
<td>2</td>
<td>100</td>
<td>T10-T12, left iliac crest</td>
<td>Induction: cisplatin (100 mg/m²), and infusional 5-FU (1000 mg/m²/day) × 3 cycles Concurrent: cisplatin (100 mg/m²)</td>
<td>PTV&lt;sub&gt;70&lt;/sub&gt;: 70 Gy (1.80 Gy/fraction) + concomitant boost (1.80 Gy/fraction × 10 days)</td>
</tr>
<tr>
<td>49 y</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td>Left axillary lymph node</td>
<td>Induction: cisplatin (100 mg/m²) and infusional 5-FU (1000 mg/m²/day) × 4 cycles Concurrent: cisplatin (100 mg/m²) × 2 cycles</td>
<td>PTV&lt;sub&gt;70&lt;/sub&gt;: 70 Gy (1.80 Gy/fraction) + concomitant boost (1.80 Gy/fraction × 10 days)</td>
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<tr>
<td>56 y</td>
<td>1</td>
<td>2</td>
<td>100</td>
<td>Right third rib, left anterior/superior iliac spine</td>
<td>Concurrent: cisplatin (100 mg/m²) × 2 cycles Adjuvant: carboplatin (AUC=5) and infusional 5-FU (1000 mg/m²/day) × 2 cycles</td>
<td>PTV&lt;sub&gt;70&lt;/sub&gt;: 70 Gy (2.12 Gy/fraction)</td>
</tr>
<tr>
<td>46 y</td>
<td>1</td>
<td>2</td>
<td>90</td>
<td>Right ilium, left acetabulum</td>
<td>Concurrent: cisplatin (100 mg/m²) × 3 cycles Adjuvant: cisplatin (80 mg/m²) and infusional 5-FU (1000 mg/m²/day)</td>
<td>PTV&lt;sub&gt;70&lt;/sub&gt;: 70 Gy (2.12 Gy/fraction)</td>
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Abbreviations: KPS, Karnofsky performance status; Mets, metastases; AUC, area under the curve; PTV<sub>70</sub>, planning treatment volume-70 (gross tumor volume plus margin).
left iliac wing with maximum standardized uptake values (SUVs) of 5.1–6.2 and 5.5–7.2, respectively. Given the findings of M1 disease, the patient underwent induction chemotherapy with cisplatin/5-FU, followed by definitive IMRT and concurrent cisplatin. The patient had a complete locoregional response and underwent consolidation radiotherapy (40 Gy in 20 fractions) to the 2 metastatic lesions. At last follow-up, he had no evidence of disease at 91 months.

**Case 3.** The third patient was a 49-year-old man who presented with left-sided cervical and axillary lymphadenopathy. Nasopharyngoscopy revealed slight asymmetry around the left fossa of Rosenmüller in comparison to the right. Staging CT scans and physical examination revealed shotty left-sided cervical lymphadenopathy, as well as multiple 2-cm left axillary lymph nodes. Histologic examination of the nasopharynx biopsy specimen showed undifferentiated carcinoma positive for cytokeratin. The axillary metastases were confirmed to be consistent with the nasopharyngeal primary on biopsy, and the patient was evaluated as having T1N1M1 disease.

The treatment strategy for this patient involved induction cisplatin/5-FU followed by concurrent cisplatin and definitive IMRT to 70 Gy, including 59 Gy to the left axilla and 50 Gy to the mediastinum. There was persistent disease in the left axilla after definitive treatment but the patient declined surgical salvage treatment. He therefore was treated with palliative docetaxel but had further progression of disease and died 31 months after the initiation of treatment.

**Case 4.** The fourth patient was a 56-year-old woman who had initially noted a sense of fullness in her left ear and a swelling in the left side of her neck. Nasopharyngoscopy revealed a 2-cm area of swelling in the nasopharynx, whereas CT of the neck showed multiple bilateral lymphadenopathy. Positron emission tomography scanning revealed focal radiotracer accumulation in the right third rib, as well as the left anterior superior iliac spine associated with a lytic component on CT.

Determined to have T1N2M1 disease, the patient was treated with a concurrent chemoradiotherapy approach, including definitive IMRT to 70 Gy, concurrent high-dose cisplatin, and adjuvant carboplatin/5-FU. The patient had a complete locoregional response, underwent consolidation RT (40 Gy in 20 fractions) to the 2 metastatic lesions, and at last follow-up had no evidence of disease at 29 months.

**Case 5.** The fifth patient was a 46-year-old man who had initially presented to his primary care physician with serous otitis and bilateral cervical adenopathy. Nasopharyngoscopy revealed a 2- to 3-cm lesion in the left nasopharynx with surrounding associated hemorrhage. CT scanning showed a 2-cm left-sided jugulodigastric lymph node, as well as multiple bilateral posterior triangle lymph nodes, the largest of which was 2 cm. Unfortunately positron emission tomography/CT revealed a punctate hypermetabolic focus in the right ileum. An MRI confirmed the right ileum lesion measuring 1.4 cm and revealed another lesion in the left acetabulum. Histologic examination of the nasopharyngeal lesion revealed non-keratinizing undifferentiated carcinoma. The disease stage was determined to be T1N2M1.

This patient was treated with definitive IMRT, concurrent high-dose cisplatin, and adjuvant cisplatin/5-FU. He also received consolidation radiotherapy (30 Gy in 10 fractions) to the 2 osseous metastases. He had a complete initial response to treatment but had progression of osseous metastases at 8 months. At last follow-up, at 18 months, he was alive with oligo-osseous metastases.

### DISCUSSION

Because of the short median survival times in patients with NPC and DM at diagnosis, there has historically been debate with regard to whether the benefit of establishing locoregional control in these patients is outweighed by the treatment toxicities associated with radiotherapy. Reports on the median overall survival of patients with this diagnosis range from 3 to 9 months. Efforts toward treatment have therefore been mostly palliative. Understandably, most physicians have sought to avoid causing significant toxicities in patients with such limited expectation for long-term survival.

Nevertheless, establishing locoregional control may reduce the incidence of symptoms because of mass effect and tumor necrosis, including hemorrhage, cranial nerve palsy, severe headache/neck pain, infection, and airway compression. With the advent of IMRT and the associated reduction in the incidence and severity of

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<tr>
<th>Table 2. Acute adverse effects.</th>
<th>No. of patients by toxicity grade</th>
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<tr>
<td>Adverse effect</td>
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<tr>
<td>Mucositis</td>
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<tr>
<td>Dysphagia</td>
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<td>Xerostomia</td>
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<td>Dermatitis</td>
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<td>Nausea/Vomiting</td>
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<th>Table 3. Late adverse effects.</th>
<th>No. of patients by toxicity grade</th>
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<tr>
<td>Adverse effect</td>
<td>1</td>
</tr>
<tr>
<td>Xerostomia</td>
<td></td>
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<tr>
<td>Dysphagia</td>
<td></td>
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<tr>
<td>Fatigue</td>
<td></td>
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<tr>
<td>Peripheral neuropathy</td>
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</table>

**Adverse effect**

Nausea/Vomiting: 3, 2, 0, 0

Dermatitis: 2, 2, 1, 0

Xerostomia: 2, 2, 1, 0

Dysphagia: 2, 1, 0, 0

Mucositis: 0, 1, 3, 0

Peripheral neuropathy: 3, 0, 0, 0
toxicities related to treatment, radiotherapy to the primary region is less likely to result in severe adverse effects and could improve quality of life and contribute to adequate palliation. In this case series of 5 patients, no patient had an acute toxicity of grade 4 or greater and no patient was noted to have any late adverse effects of grade 3 or greater.

In addition to reducing adverse normal tissue effects, IMRT allows for improved target coverage in those with parapharyngeal extension, intracranial extension, or significant nodal disease, features commonly found in patients with metastatic disease. Many series, both retrospective and prospective, have confirmed that the improved target coverage afforded by IMRT can result in higher rates of local control.

The establishment of local control with radiotherapy appears to increase the disease-free interval in patients with DM at presentation. Yeh et al. in a study of 125 patients with NPC and with initially metastatic disease, found improved 1-year OS in patients receiving RT alone versus chemotherapy alone or versus no treatment (48% vs 36% vs 25%, respectively), despite using conventional radiotherapy. The improved survival rate of those treated with RT was seen despite the fact that these patients did not receive systemic therapy for their disseminated disease. Presumably, a significant subset of patients not undergoing radiotherapy died as a result of locoregional failure. Of note, 38 of 58 patients (66%) receiving conventional radiotherapy in this study went on to have development of significant xerostomia.

Although locoregional radiotherapy appears to extend the disease-free interval, reports of long-term survival in patients with DM at presentation are rare. The Institute Gustav-Roussy series identified 7 patients with initially metastatic undifferentiated NPC, treated with systemic chemotherapy, who had disease-free survival of at least 36 months. A recent analysis of the Surveillance Epidemiology and End Results database identified 177 patients with NPC with DM at presentation and found a 5-year OS rate of 20% and median OS of 9 months. These results suggest that long-term survival in this population is possible in selected patients with few metastases.

As evidenced by the existence of long-term survivors despite relatively poor median survival, patients with initially metastatic disease appear to be part of a heterogeneous population in terms of prognosis. One possibility is that improved therapies, including wider use of combined modality therapy and the development of modern radiotherapy techniques, are allowing selected patients to survive long-term. This assertion is supported by the experience at our institution in treating 2 long-term survivors who are now without evidence of disease at 29 and 91 months.

In light of this heterogeneity in outcome, one future avenue for research may be in identifying clinical factors associated with long-term survival. Prognostic stratification of patients with initially metastatic disease may allow for identification of those who are better candidates for aggressive multimodal treatment. Prognostic indexes that predict outcome and help stratify patients with metastatic NPC have been designed, but these have been based on data from mostly recurrent disease. It remains to be seen whether those with initial M1 disease can be stratified according to prognosis.

CONCLUSION

To our knowledge, there are no previously existing reports regarding the treatment of patients with initially metastatic disease treated with IMRT and concurrent chemotherapy. Of the 5 patients who presented to our institution with initially metastatic NPC, we report 2 long-term survivors with no evidence of disease at their last follow-up at 29 and 91 months, respectively.

REFERENCES


