

## Successful Thermoradiotherapy in Recurrent Mucosal Melanoma of the Nasal Cavity and Paranasal Sinus: Report of Three Cases

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We report successful thermoradiotherapy in 3 cases of recurrent mucosal melanoma of the nasal cavity and paranasal sinus. For treatment, a Thermotron RF-8 (Yamamoto Vinita, Osaka, Japan) was used for 45 to 50 minutes of hyperthermia twice a week. The first patient, who had metastases of the lymph nodes of the neck, received radiotherapy at 48 Gy given in 4-Gy fractions, and hyperthermia (41.5°C to 43°C in the tumor), and has been free from disease for 6.5 years. The second patient, who had a tumor on the left cheek and metastases of the lymph nodes of the left side of the neck, received 40 Gy to the neck and 35 Gy to the cheek in 5-Gy fractions, and hyperthermia (41.5°C to 43°C on the skin surface), and has become free of tumors. He received thermoradiotherapy again, for adrenal metastases, 1.5 years later; 40 Gy was given in 2-Gy fractions, 5 times a week. He has been in partial remission. The third patient, who had pain in the right hip caused by bone metastasis, received radiotherapy of 40 Gy given in 5-Gy fractions, and hyperthermia (41°C to 42.5°C in the bladder). Complete pain relief continued for 6 months until death. Thermoradiotherapy played an effective role in the treatment of these 3 cases.

Int J Clin Oncol 1997;2:77-80

Key words: thermoradiotherapy, mucosal melanoma, nasal cavity, paranasal sinus

### INTRODUCTION

Malignant melanoma can be classified into 3 distinct types: cutaneous, mucosal, and ocular melanoma.<sup>1,2</sup> Though more common in Japan than elsewhere,<sup>1</sup> mucosal melanoma of the nasal cavity and paranasal sinus is rare: less than 1% of all malignant melanoma and 2% to 9% of all head and neck melanomas are of this type. The role of surgery, radiotherapy, and chemotherapy in the treatment of this disease with a generally poor prognosis is therefore unclear.<sup>1-6</sup> The general recommendation is radical surgery, with postoperative irradiation for suspected residual or recurrent diseased areas.<sup>2,3,5</sup> Although it has been believed to be radioresistant,<sup>3</sup> some cases of mucosal melanoma can be controlled by radiotherapy.<sup>2,4,6</sup> There is controversy as to whether large, infrequent fractions yield better results than smaller,

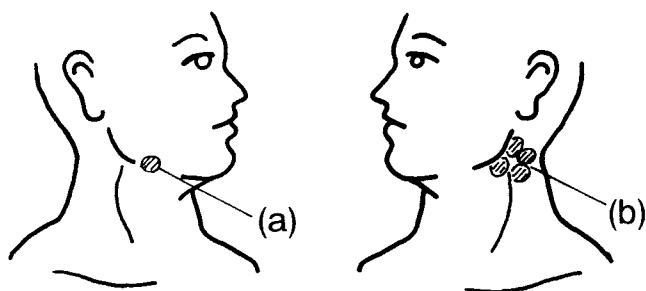
more frequent fractions.<sup>2,3,7-9</sup> A new approach, thermoradiotherapy, has been recently reported in the treatment of cutaneous melanoma,<sup>7</sup> but few reports have dealt with mucosal melanoma.<sup>4</sup> We report 3 cases of recurrent mucosal melanoma of the nasal cavity and paranasal sinus successfully treated with thermoradiotherapy.

### CASE REPORTS

#### Case 1

A man born in December 1940 had a history of radiotherapy (60 Gy) followed by partial maxillectomy through a lateral rhinotomy approach and bilateral neck dissection for mucosal melanoma of the nasal cavity from February to May 1987. The extirpated materials from the primary tumor showed poor radiation effects on pathologic evaluation. Confirmed as having bilateral neck lymph node metastasis in November 1989 (Fig. 1), the patient received thermoradiotherapy from November 1989 to January 1990. Radiotherapy (48 Gy) was given in 4-Gy fractions twice a week, using a 10 MeV electron beam (10 cm in diameter) to the lymph node of the left side of the neck and an 8 MeV electron beam (6

Received Aug. 28, 1996; revised Nov. 13, 1996; accepted for publication in revised form Feb. 10, 1997. \*Correspondence and requests reprints to: Department of Radiology, Ehime University School of Medicine, Shitsukawa 454, Shigenobu-cho, Onsen-gun 791-02, Ehime, Japan.



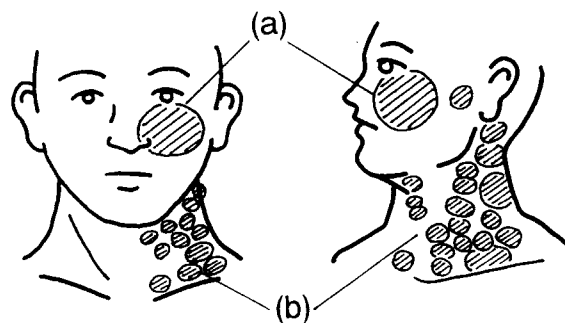
**Fig. 1.** Schematic drawing of bilateral metastases of the neck lymph nodes in the patient with mucosal melanoma of the nasal cavity described in case 1: (a) metastasis of the lymph node on the right side of the neck, 2 cm in diameter; (b) 4 metastases of the lymph node on the left side of the neck, 1.5 to 2.5 cm in diameter.

cm in diameter) to the lymph node of the right side of the neck. Immediately after irradiation, hyperthermia was induced using 8 MHz RF waves generated by a Thermotron RF-8 (Yamamoto Vinita, Osaka, Japan). Hyperthermia consisted of 12 sessions of 50-minute heating given twice a week, using opposing lateral electrodes (10 cm in diameter) with a cooling pad perfused with 15°C water. Power was 350 to 400 W, and temperature in the tumor was 41.5°C to 43°C. As of August 1996, the patient has been free of disease and complications for 6.5 years since therapy.

### Case 2

A man born in January 1926 had a history of tumor resection for mucosal melanoma of the nasal cavity and ethmoid sinus in February 1992, followed by 3 cycles of DAV chemotherapy with a cycle for 4 weeks consisting of 1 mg/m<sup>2</sup> vincristine (first day), 200 mg/m<sup>2</sup> N-[4-amino-2-methyl-5primidiny]methyl-N<sup>7</sup>-(2-chloroethyl)-N<sup>7</sup>-nitrosourea (ACNU) (second day), and 200 mg/m<sup>2</sup> dacarbazine (first 5 days). A year later, the recurrent tumor in the left submandibular region was resected, and a modified dissection of the left side of the neck was done. Three months later, the tumor in the nasal cavity invaded the left orbit and left cheek tumor, and multiple lymph node metastases in the left side of the neck were again discovered. Therefore, the patient underwent 3 cycles of CVD chemotherapy, consisting of 3 mg/m<sup>2</sup> vindesine (first day), 120 mg/m<sup>2</sup> cisplatin (second day), and 150 mg/m<sup>2</sup> dacarbazine (first 5 days). One cycle lasted 4 weeks. The tumor in the nasal cavity shrank in partial remission, but the left cheek tumor and multiple lymph node metastases in the left side of the neck continued to progress (Fig. 2).

Thermoradiotherapy to these lesions was given from November 1993 to January 1994. Radiotherapy (40 Gy) was given in 5-Gy fractions twice a week to the lymph node of the left side of the neck using opposing lateral 6 MV-X portals, followed by 35 Gy to the cheek tumor



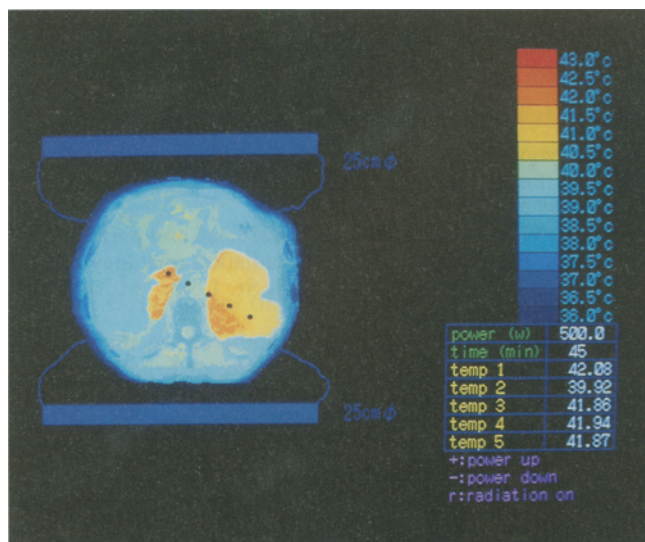
**Fig. 2.** Schematic drawing of the tumor in the left cheek and of the metastases in the lymph node of the left side of the neck of the patient with mucosal melanoma of the nasal cavity and ethmoid sinus described in case 2: (a) left cheek tumor, 4 cm in diameter; (b) multiple metastases of the lymph node of the left side of the neck. The largest lesion is 3.5 cm in diameter.

using a right-angle pair of 6 MV-X portals without wedge filters. Hyperthermia to the lymph node of the left side of the neck consisted of 8 sessions of 50-minute heating twice a week, using opposing lateral electrodes (10 cm in diameter). The left electrode hot pad was perfused with 42.5°C water and the right electrode cooling pad was perfused with 15°C water. Power was 350 to 400 W. Temperature was 41.5°C to 43°C on the skin surface. Subsequently, hyperthermia consisting of 7 sessions of 50-minute heating was applied to the left cheek using an anterior electrode (10 cm in diameter) perfused with 42.5°C water and a posterior electrode (14 cm in diameter) perfused with 15°C water. Temperature and power were as before. The patient became free of tumors.

However, after 4 cycles of maintenance CVD chemotherapy from June 1994 to March 1995, bilateral adrenal metastasis was indicated, in November 1995, by elevated levels (921 IU/L) of lactate dehydrogenase (LDH). Thermoradiotherapy was applied to the adrenal metastases from February to March 1996. Radiotherapy (40 Gy) was given in 2-Gy fractions 5 times a week using opposing 10 MV-X portals (14 cm × 18 cm). Hyperthermia consisted of 9 sessions of 45-minute heating given twice a week using opposing anterior and posterior electrodes (25 cm in diameter) with a cooling pad (15°C water). Power was 450 to 500 W. Temperature distribution in the body, calculated using the finite element method,<sup>10</sup> during hyperthermia is shown in Fig. 3. The calculated temperature in the tumor was 41.5 to 42.5°C. On contrast enhanced computed tomography, the bilateral adrenal tumors shrank remarkably during and after therapy (Fig. 4). The elevated LDH level became normal (313 IU/L) immediately after therapy. The patient remains in partial remission.

### Case 3

A woman born in December 1931 had a history of tumor resection followed by radiotherapy (40 Gy) for mucosal

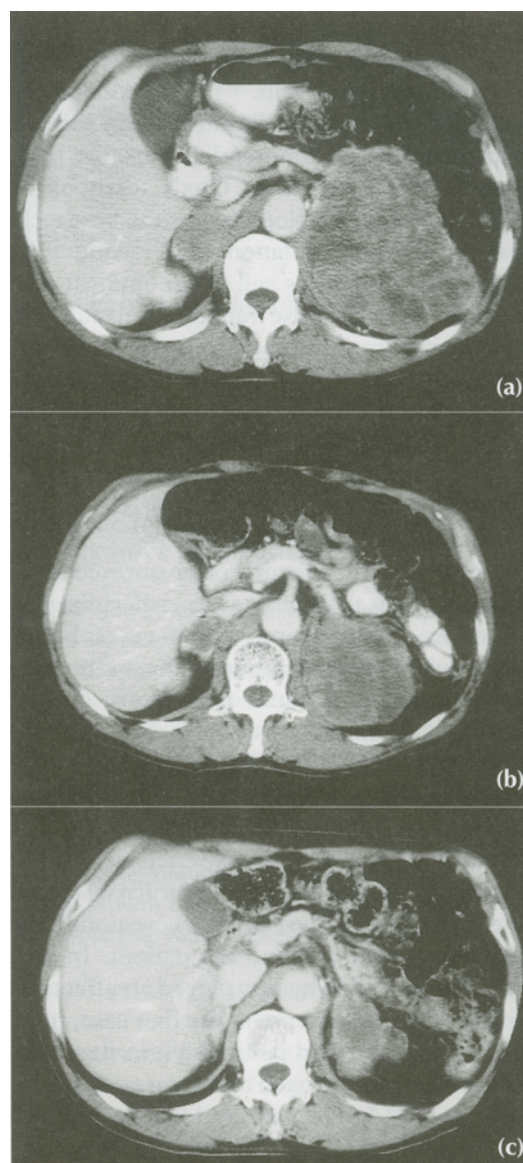


**Fig. 3.** Temperature distribution in the body of the patient described in case 2, calculated using the finite element method<sup>10</sup> during hyperthermia for adrenal metastases, with a power of 500 W. The calculated temperature in the tumor was 41.5°C to 42.5°C.

melanoma of the left ethmoid sinus in June 1990. A year later, the recurrent tumor in the nasal septum was resected, and the patient received 3 cycles of DAV chemotherapy. However, metastatic lung nodules were detected 1.5 years after the last surgery. Suffering from right hip pain due to coxal bone metastasis with osteolytic tumor, she underwent thermoradiotherapy to the right hip lesion from April to June 1992. Radiotherapy (40 Gy) was given in 5-Gy fractions twice a week, using opposing 10 MV-X portals. Hyperthermia consisted of 5 sessions of 50-minute heating, using an opposing anterior and posterior pair of electrodes (25 cm in diameter) with a cooling pad (15°C water). Power was 350 to 400 W. Temperature was monitored at 41°C to 42.5°C in the bladder. A follow-up contrast enhanced computed tomography scan revealed the osteolytic tumor with a central low density area surrounded by the enhancement and gallium uptake areas, which appeared in the area of the lesion before treatment and disappeared afterwards (not shown). A few small burn blisterings were observed in the sacrogluteal region. The right hip pain, on an 11-point scale<sup>11</sup> for patient self-assessment of pain relief, decreased to 0 after the course of thermoradiotherapy. Complete pain relief continued for 6 months until the patient died of brain metastases.

## DISCUSSION

It has been generally recognized that the prognosis for mucosal melanoma is significantly poorer than that for cutaneous melanoma.<sup>2</sup> Because of the rarity of the disease, proper management continues to be controver-



**Fig. 4.** Contrast enhanced computed tomography scans of the patient described in case 2 before thermoradiotherapy (a), immediately after thermoradiotherapy (b), and 2 months after the therapy ended (c). During the therapy, the bilateral adrenal tumors shrank from 415 cm<sup>3</sup> to 196 cm<sup>3</sup> on the left side, and from 21.9 cm<sup>3</sup> to 8.5 cm<sup>3</sup> on the right side. Two months after the therapy ended, they decreased to 34.5 cm<sup>3</sup>, and 1.8 cm<sup>3</sup>, respectively.

sial. Surgery, radiotherapy, and chemotherapy have been recommended in various combinations.<sup>4</sup>

In mucosal melanoma, as in cutaneous melanoma, the general recommendation is radical surgery with postoperative irradiation.<sup>2</sup> Primary radiotherapy was rarely considered.<sup>2,4,6</sup> However, occasionally favorable responses to radiation have been reported.<sup>2,4,6</sup> In cutaneous melanoma, the use of high-dose fractionation, though controversial,<sup>2,3,7-9</sup> is recommended because the local control rate is better if the dose fraction is more

than 4 Gy.<sup>7</sup> This recommendation is based on a "wide shoulder" demonstrated in curves of the *in vitro* survival of malignant melanomas cells.<sup>9,12</sup> In mucosal melanoma, the influence of dose per fraction is more uncertain.<sup>3,6</sup> Some investigators recommend the use of high-dose fractionations,<sup>2</sup> but Moss in Cox's textbook recommends conventional fractionation as the best technique for treating mucosal melanoma, following the same approach as for squamous cell carcinoma.<sup>3</sup> It is important to realize that high-dose fractionations carry a higher risk of late complications than do conventional fractionations, because the therapeutic differential between slowly dividing normal tissues and acutely responding tumor is diminished when large, infrequent fractions are used.<sup>8</sup> For example, high-dose fractionation of abdominal radiation to a large volume is hazardous due to potential renal, intestinal, and liver damage.

A new approach to recurrent or unresectable cutaneous melanoma is to combine hyperthermia and high-dose fraction radiotherapy.<sup>7</sup> Few cases have been reported in which thermoradiotherapy has been used in mucosal melanoma, because it is a rare disease. We decided what size fraction to use on a case-by-case basis, depending upon the radiation tolerance of the surrounding tissues. In fact, in case 2, conventional fractionation was also effective.

We have presented our experiences on thermoradiotherapy in 3 cases of recurrent mucosal melanoma. Treatment of recurrences, both locoregional and distant, can be of great value to the patient. In the cases presented thermoradiotherapy played an effective treatment role; curing the disease in the first case, managing it in the second case, and palliating it in the third case. To develop a better approach to this rare disease, reports of many cases need to be gathered from various institutions.

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