Radiotherapy combined with hyperthermia for primary malignant melanomas of the esophagus

M. C. C. M. Hulshof,1 P. M. A. van Haaren,1 P. J. Zum Vörde Sive Vörding,1 S. Krishnadath,2 W. A. Marsman,3 M. I. van Berge Henegouwen,4 E. D. Geijsen,1 J. Crezee1

Departments of 1Radiation Oncology, 2Gastroenterology and 4Surgery, Academic Medical Center, Amsterdam, and 3Department of Gastroenterology, Kennemer Gasthuis, Haarlem, the Netherlands

SUMMARY. Primary malignant melanoma of the esophagus (PMME) forms about 0.1% of all primary esophageal cancers. Treatment options are very limited for patients unfit for surgery. This is the first report describing the results of external radiotherapy combined with regional hyperthermia for two inoperable PMME patients. Two patients with a T2-3N0M0 PMME were considered unfit for surgery based on age and general condition. External radiotherapy of a total dose of 35 Gy was given in a scheme of seven times 5 Gy, two times per week, and once weekly combined with external and intraluminal hyperthermia (aim 43°C). Toxicity was mild and both patients completed treatment according to protocol. Adequate temperatures at the intraluminal border of the tumor were achieved. In both patients, a complete remission was achieved with complete relief of obstructive symptoms and without signs of locoregional tumor progression until the end of follow-up at 11 and 15 months. External radiation combined with regional hyperthermia could be a good alternative to resection in patients unfit for surgery with a malignant melanoma of the esophagus.

KEY WORDS: esophageal melanoma, hyperthermia, radiotherapy.

INTRODUCTION

Malignant melanoma arises from melanocytes and is a typical cutaneous malignancy. However, melanocytes in the esophageal mucosa have been demonstrated in about 5% of normal esophagus at autopsy.1 Primary malignant melanoma of the esophagus (PMME) forms about 0.1% of all primary esophageal cancer.2 A PMME is characterized by aggressive biological behavior. In two large retrospective series, median survival was 10–13 months and 5-year survival less than 5%.2,3 In a more recent overview of 25 selected case reports from literature, a 5-year survival of 37% was calculated.4 All these patients underwent esophageal resection. A total esophagectomy is generally accepted as the only curative treatment option.5,6 Radiotherapy in the adjuvant setting has been suggested to be effective in the reduction of local relapses, although data are scant.2,5 The efficacy of systemic treatment, either chemotherapy or immunotherapy, has never been demonstrated in the primary or adjuvant setting. Primary resectability rates of 67% and 87% have been described.2,4 For medically or technically inoperable patients, there are no curative options. Radiotherapy alone should be considered palliative in PEMM and has resulted in a median survival of 3 months in a series of nine patients, although two patients survived more than 48 months.2

Hyperthermia (HT) has proven to enhance the radiation effect in several clinical phase III studies.7,8 The addition of HT to radiation has also proven to increase the local control in patients with superficial melanoma.9 Radiotherapy combined with HT is currently considered standard of care for superficial inoperable melanoma. Recent developments in the Academic Medical Center of Amsterdam have shown that locoregional HT for esophageal tumors is feasible, although in this study, the measured tumor temperatures were suboptimal.10,11 Combining intraluminal heating with external heating has demonstrated to improve the intraluminal temperature.12
We describe the results of the first two patients with a PMME treated with a combination of external radiation and regional HT.

PATIENTS AND METHODS

Patient 1

A 77-year-old man was referred to the gastroenterology department with progressive complaints of dysphagia. There was no passage for solid food, semisolids passed only slowly. He lost 5 kg of weight during the last 4 months. There was no history of a cutaneous malignant melanoma and examination of the skin did not reveal the presence of a primary tumor. His general condition was moderate because of his cardiovascular status. At endoscopy, a black, near obstructive, ulcerating and easily bleeding tumor of 7 cm length in the midesophagus was seen (Fig. 1a). At endosonography, the tumor was staged as a T2N0 tumor and there was no distant metastasis on the computed tomography (CT) scan. A positron emission tomography (PET) scan was not available in our institute at that time. Histological biopsies showed a malignant melanoma. Immunohistochemical analyses showed strong positivity for HMB-45 and melan-A and weak positivity for S100. Keratine-7, CAM 5.2, synaptophysine, thyroid transcription factor (TTF)-A, and Ber-EP4 were negative.

Patient 2

An 83-year-old woman was referred for progressive dysphagia. Solids and semisolids passed only slowly. Her appetite had decreased without weight loss. She complained about a globus feeling without pain or cough. Her general condition was moderate because of age, chronic obstructive pulmonary disease, and cardiovascular disease. There was no history of a cutaneous malignant melanoma and skin examination did not show signs of a primary tumor. At endoscopy, a dark blue and necrotic obstructive tumor of 6 cm was seen in the distal esophagus, which could also be seen in u-turn in the cardia (Fig. 2a). Histological biopsies demonstrated a malignant melanoma, positive for S 100 and Melan A. Tumor cells were keratine AE1/AE3 negative. By endosonography, the lesion was staged as a T2N0 tumor. A PET–CT scan showed clear tumor uptake without regional or distant metastasis.

Treatment plan of both patients

The patients were initially seen by a surgeon. Because of age, general condition and dismal prognosis both cases were considered not eligible for surgery. Alternative treatment options were discussed at a multidisciplinary oncology meeting. A proposal for thermoradiotherapy was accepted because of our technical and clinical experience with HT for esophageal tumors and the fact that thermoradiation is standard of care for inoperable cutaneous melanoma in the Netherlands.

Radiotherapy

A dose of $7 \times 5$ Gy was administered, two times per week, once weekly combined with HT. A dose of 35 Gy in 5 Gy is standard in our institute for inoperable melanoma and is considered biologically equivalent to 52 Gy in fractions of 2 Gy assuming an $\alpha/\beta$ ratio of 4. The planning target volume was composed of the tumor plus 2 cm margin in craniocaudal direction and 1.5 cm laterally. The radiation fields were limited to the macroscopic tumor area in order to limit the dose to surrounding normal tissues and thus, reduce toxicity in these elderly and cardiovascularly compromised patients. A multiple-field conformal treatment plan with 10 MV photons was used.
Hyperthermia

External HT was given directly after the irradiation for four times. HT was applied using the 70 MHz AMC-4 waveguide system. The patient was lying in prone position with the arms in elevated position to provide access for two lateral antennas. The other antennas were directed toward the back and the abdomen. An additional simultaneous thermal boost was given using an intraluminal hot water balloon (HWB, Fig. 3). Water of 51–52°C was circulated through the HWB resulting in a temperature of ~43°C at the outer surface of the balloon.

Thermometry

An endoscopy was performed prior to each HT treatment under sedation with 5 mg midazolam i.v. The tumor length and location were verified under fluoroscopy and marked on the skin with lead wires for positioning of the balloon catheter. Two parallel 21-point T-type thermosensor probes (Ella CS, Hradec Kralove, Czech Republic, diameter 0.9 mm, spacing 1 cm, active length 20 cm) were mounted on opposite sides of the inflatable balloon catheter (balloon length 80 mm, diameter 10 mm), yielding c. 15 tumor measurement points in each patient.
Thermosensor points matching the tumor location were identified and the tumor temperature distribution was evaluated using T10, T50, and T90, i.e., the temperature achieved in at least 10%, 50%, and 90% of the measurement points at tumor level, respectively. Inflation of the balloon ensured adequate tumor tissue contact and intraluminal fixation. Furthermore, an e-field probe (diameter 1 mm) was mounted on the balloon adjacent to the tumor to assist in determining the system settings resulting in focusing the energy of the waveguide array onto the tumor target. For spinal cord temperature monitoring, an intramuscular thermometry catheter was placed in the m. erector spinae under local anesthetics at the level of the tumor before each treatment. The insertion depth ranged between 3 and 5 cm. For body temperature monitoring, a rectal 14-point T-type thermocouple probe was used.

After a warming up period (maximum 30 minutes), the effective heating period of 1 hour started when a steady state tumor temperature was reached, aiming at a temperature of 41°C measured in at least one point in the tumor.

RESULTS

Acute toxicity

Both patients completed the treatment as scheduled. Acute toxicity was limited to grade 1 esophagitis in patient 1. His general condition remained stable and there were no complaints of nausea, cough, or dyspnea. Patient 2, however, developed grade 3 toxicity, composed of general fatigue, nausea, vomiting, and dysphagia and was admitted to the hospital. She recovered spontaneously in 3 months.

Temperature

Average T10, T50, and T90 over four sessions at the intraluminal border of the tumor were 40.5°C, 42.3°C, and 43.3°C for patient 1 and 39.5°C 41.8°C, and 43.0°C for patient 2, respectively.

Response patient 1

The dysphagia disappeared completely within 1–2 months after treatment. He was able to eat all types of solids until the end of follow-up. A CT scan at 3 months showed a complete remission without signs of metastasis. On endoscopy at 3 and 7 months, a clinically complete regression was observed. There was only a flat pigmented, nonobstructing remnant in the mucosa. The surrounding noninvolved esophageal mucosa showed no macroscopic side effects of the treatment (Fig. 1b). Biopsies were not taken. At 10 months, after the treatment, he developed progressive abdominal symptoms caused by peritoneal and liver metastasis with malignant ascites. At this point, he still had no signs of esophageal or mediastinal recurrence. He died at 11 months after start of treatment.

Response patient 2

The obstruction symptoms remained for 3 months, during which she was fed via a gastric enteral tube. Thereafter, the tube was removed and she was able to eat all types of solid food up to the last follow-up at 15 months. Endoscopy at 3 months after start of treatment showed partial remission with improved passage of the esophagus, which was in contrast with her dysphagia complaints (Fig. 2b). Endoscopy at 7, 10, and 14 months (Fig. 2c) after start of treatment showed further tumor regression, with a small black shining flat remnant of the tumor with some ulceration and mucosal atrophy. A biopsy at 7 and 14 months did not show malignant cells. After 15 months, she is still alive with no evidence of disease and in good general shape without dysphagia complaints.
No routine follow up CT or PET scans were made in both patients because of absence of any clinical consequences in these elderly patients.

DISCUSSION AND SUMMARY

Two patients with a large obstructive primary malignant melanoma of the esophagus were treated with a combination of external radiotherapy and HT. Both patients developed a complete local tumor regression, both clinically and endoscopically, without signs of local progression or late toxicity until the end of follow up. Despite the good local response, one patient died of fast-growing distant metastasis at 11 months. The other patient is alive at 15 months and in good general condition with no signs of local recurrence or distant metastasis. These results demonstrate that radiotherapy combined with HT can achieve persistent local control and can be considered a serious alternative treatment option for inoperable PMME patients. However, follow-up period is still short and only two patients are reported.

The applied hypofractionated dose schedule is unusual for esophageal tumors. This fractionation was chosen because it is our standard scheme for inoperable melanoma in the skin and lymph nodes. Furthermore, in our schedule, half of the radiation dose could be combined and thus sensitized by HT. This would have been only 20% of the dose with weekly HT in a conventional fractionated scheme. Finally, a hypofractioned scheme does reduce the treatment impact and traveling time for these elderly patients. Acute toxicity was expected to be acceptable because of the limited irradiation volumes, the twice weekly schedule and the midesophageal tumor location. However, there was some concern about late stenosis or ulceration caused by the large dose per fraction. The addition of heat was not expected to increase late toxicity. Although no severe late toxicity was encountered, the small number of patients and lack of long follow-up makes this finding inconclusive and the concern remains. The grade 3 acute toxicity encountered in patient 2 could not be explained medically, although a small ulceration at the tumor site was present for months. Both radiation oncologist, gastroenterologist, and finally, also the patient herself concluded the complaints were mainly of psychosomatic origin triggered by the feeding tube and a small ulceration. This suggestion was confirmed by the disappearance of all complaints directly after removing the tube.

This is the first report on the combination of radiotherapy and HT for PMME. Surgery is considered the mainstay of treatment in PMME and is described as the only curative treatment option. However, even after curative surgery, prognosis is still dismal. Radiotherapy is considered as an adjuvant to surgery or as palliative, although some patients with long-term survival after radiotherapy only have been described. PMME occurs prevalently in the sixth and seventh decades. Considering the older age category and the poor prognosis, a significant part of the patients will be unfit for surgery or will refuse surgery. Therefore, there is a need for alternative treatment options that can result in long-term local control and palliation of obstruction symptoms. At present, no adequate systemic treatment for malignant melanoma is available. The presented study demonstrates that combined external radiation plus HT could be offered as an alternative for patients. More patients and longer follow-up are needed to confirm this statement. Unfortunately, only few institutes are equipped with HT systems and experience with locoregional HT for esophageal tumors is even scarcer. However, HT is probably the most potent radiosensitizer, is generally nontoxic, and is cost-effective compared with pharmaceutical radiosensitizers. The reluctance to invest in HT equipment and education is hard to understand for oncologists active in the field of HT. Unfamiliarity among physicians and the absence of financial support from industries seem to be the main reasons for the lagging behind of this combined treatment modality.

In conclusion, combined radiotherapy and HT might be a good alternative to surgery in medically inoperable patients with an esophageal melanoma.

References

10 Albregts M, Hulslof M C et al. A feasibility study in oesophageal carcinoma using deep


