Case Report

Successful Treatments of Malignant Glioma in the Elderly by Radiofrequency Interstitial Hyperthermia : A Report of Two Cases

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Abstract : Two elderly patients with primary malignant gliomas underwent thermoradiotherapy without reductive surgery. Hyperthermia was effectively performed for both patients. In the first case, a 76-year-old male with a left frontal glioblastoma presented with right hemiparesis. A CT scan demonstrated an irregular enhancement lesion in the white matter under the left motor cortex. The patient was treated with 4 sessions of interstitial hyperthermia and external beam radiotherapy of 60 Gy. Stereotactic biopsy and placement of 2 radiofrequency (RF) antennae were performed under local anesthesia. A CT scan showed complete remission (CR) and diminution of local edema four months later. In the second case, an 82-year-old male with an anaplastic astrocytoma in the right putamen presented with left hemiparesis. He was also treated with 3 sessions of interstitial hyperthermia and external beam radiotherapy of 60 Gy. Interstitial hyperthermia technique was same as the first case. Follow-up CT and MRI showed CR and no evidence of brain edema. These two patients experienced no complications during and after hyperthermic treatment, and their results were encouraging. We conclude that thermoradiotherapy for unresectable malignant glioma is technically feasible, even in the elderly, and can be a reductive therapy for malignant glioma.

Key Words : glioma, RF interstitial hyperthermia, elderly, radiotherapy

Introduction

The important prognostic factors in malignant glioma are well documented and include age, histology, and performance status ¹⁻⁴. Elderly patients with malignant glioma do very poorly ⁵. The most rational surgical approach for elderly patients is a biopsy, either open or stereotactic, to obtain a tissue diagnosis and rule out a non-neoplastic lesion ; more extensive and possibly radical resection is not typically considered. Therefore, in cases reported in the literature, the length of survival in elderly patients has been very short.

Hyperthermia, a new treatment modality, has been shown to be more cytotoxic to tumor cells than

normal cells at temperatures of 41°C-42°C⁶⁾. Temperatures over 43°C cause direct coagulation necrosis of tumors. Over the past 10 years, we have developed techniques and gained clinical experience with radiofrequency (RF) interstitial hyperthermia⁷⁻⁹⁾. These techniques are particularly applicable in the treatment of unresectable tumors and in the management of elderly patients with malignant glioma.

In this report, we present two cases of malignant glioma in the elderly that were treated with RF interstitial hyperthermia without reductive surgery. Our objective was to assess the feasibility of thermotherapy for malignant glioma in the elderly.

Case Report

(Case 1)

A 76-year-old man was admitted to the Department of Neurosurgery, Niigata University Hospital. He presented with a 4-week history of right motor weakness. A CT scan and MRI of the brain revealed a mass in the left frontal white matter that was just under the motor cortex (Fig. 1a, 1b). The maximum tumor diameter on MRI was about 3.5 cm. Single photon emission CT (SPECT) revealed a low perfusion area in the tumor (Fig. 1c). Various management methods were discussed, including microsurgical removal and stereobiopsy, and finally interstitial hyperthermia was recommended because of the patient's age and tumoral location. Furthermore, RF antennae for interstitial hyperthermia were able to be placed simultaneously into the tumor, with stereotactic biopsy under local anesthesia. Histological diagnosis was a glioblastoma. Informed consent was obtained from the patient and his family. He also entered into the protocol for the development of the hyperthermic generator HEH-250c (OMRON Co. Ltd.) at Niigata University (1994-1996, Japan).

Fig. 1

(a) Pretreatment contrast enhancement CT scan. (b) Pretreatment T2WI of MRI. (c) SPECT before thermotherapy.

The interstitial hyperthermia system used in this case was constructed of a 13.56-MHz RF generator and needle-shaped electrodes (RF antennae). The RF generator, which was controlled with an automatic tuning system and temperature limitation system, was developed by our institute and OMRON Life Science Inc. (Fig. 2a). The RF antenna, which was made from 24-K gold, has a 1.3-mm thick silicone cover on all but the electrode portion (Fig. 2b).

Fig. 2 (a) RF generator of interstitial hyperthermia. (b) RF antennae (electrodes)

Fig. 3
(a) Craniogram before hyperthermia. (b) Bone window image of CT scan show the position of RF electrodes.
(c) Contrast enhancement CT scan 4 months after thermoradiotherapy.

The head ring of the stereotactic apparatus was secured to the patient using pin fixation under local anesthesia. A CT scan with contrast enhancement was then obtained. The positions of the implanted RF antennae and the approach direction of the catheters for the thermistor probes were determined on the CT scan. A postoperative craniogram and CT scan were obtained in order to confirm the location of the antennae and catheters and to determine the reference point (the tumor margin, Fig. 3a, 3b).

The first heating began after implantation, with a low-power output given in order to obtain a thermal profile along the thermometry catheters and confirm the actual position of the RF antenna and the reference point. Two days after the first session, the patient was treated with the objective of inducing a temperature of 43°C at the reference margin for 60 minutes.

At the same time, the patient received external beam radiotherapy of 60 Gy delivered at 2 Gy/fraction in 30 fractions during 6 weeks with 10-MV photon beam. Field size was determined via a rotational and three-field technique. The patient experienced no complications during hyperthermic treatment. The Karnofsky Performance Status (KPS) before hyperthermic treatment was 70%. Follow-up CT and MRI revealed evidence of brain edema 2 months after hyperthermia, and the patient experienced a mild right

hemiparesis. Follow-up CT and MRI 4 months after hyperthermic treatment showed complete remission (CR), and the right hemiparesis was improved (Fig. 3c). The CT scan showed a figure-8-shaped low attenuation area in the treatment area. Although the patient showed no evidence of recurrence, he died 9 months after treatment due to pneumonia.

(Case 2)

An 81-year-old man was referred to our institute with a left hemiparesis. A pretreatment CT scan (Fig. 4a) showed a low attenuation area in the right putamen with ring enhancement. MRI revealed a partially cystic mass on T1WI with gadolinium (Gd) enhancement (Fig. 4b) and perifocal edema on T2WI (Fig. 4c). The maximum tumor size at MRI was 3.5 cm in diameter. The patient received local anesthesia and underwent stereotactic biopsy and placement of 2 needle electrodes (RF antennae) and 2 catheters for thermistor probes, using a twist drill (Fig. 5a). After a histological diagnosis of anaplastic astrocytoma, hyperthermia was performed for 3 sessions for 2 weeks, with the objective of inducing a

Fig. 4

(a) Pretreatment contrast enhancement CT scan. (b) T1WI with gadolinium enhancement of MRI before treatment. (c) T2WI on MRI before treatment.

Fig. 5

(a) Craniogram before hyperthermia. (b) contrast enhancement CT scan after thermoradiotherapy

temperature of 43°C at the tumor edge for 40-60 minutes. At the same time, the patient received external beam radiotherapy of 60 Gy delivered at 2 Gy/fraction in 30 fractions during 6 weeks with 10-MV photon beam. Irradiation technique and the determination of field size were same as the first case. The patient experienced no complications during and after hyperthermic treatment. The KPS before hyperthermia was 80%, and it did not decline after treatment. Follow-up CT and MRI showed CR and revealed no evidence of brain edema (Fig. 5b). The patient received no maintenance chemotherapy because of his age. He was well after 15 months, with no neurologic deficits and no evidence of tumor recurrence. Follow-up MRI after hyperthermia revealed local recurrence, and he died 38 months after treatment.

Discussion

Some investigators have shown that old age is an adverse prognostic factor for malignant glioma¹⁻⁵⁾. One of the most unsettling decisions facing a clinician is the question of what treatment to recommend for an elderly patient whose prognosis is especially bleak. Conventional wisdom would argue that aggressive treatment should be considered for those patients who have a chance of increased survival. Some investigators have expressed the opinion that an elderly patient with a very poor prognosis should perhaps be given only supportive care, while others have suggested a very short course of palliative radiotherapy. There are some data showing a clear survival advantage associated with active treatment of elderly patients as opposed to supportive treatment only. If elderly patients could accept less invasive treatment with radiation, their survival was longer than with supportive care only or radiotherapy only.

Our experience with a convenient and less invasive treatment, i. e. interstitial hyperthermia, showed a trend in which hyperthermia may be more beneficial than radiation alone. Over the past several years, we have been developing a radiofrequency heating system that is a more convenient and less invasive treatment for malignant brain tumors^{7, 8)}.

Many studies of hyperthermia for brain tumors have been reported over the last 20 years. Hyperthermic effectiveness has been observed to extend to tumor regions characterized by hypoxia, low pH, and low perfusion, all features generally associated with increased resistance to radiation and chemotherapy¹⁰⁻¹⁵⁾. Salcman¹⁶⁾ and Roberts¹⁷⁾ have reported their phase I clinical trials of interstitial hyperthermia for malignant gliomas. Their clinical trials have demonstrated technical feasibility and reasonable patient tolerance. Sneed¹⁸⁾ has reported brain hyperthermia trials at the University of California, San Francisco. Following that protocol, the median survival after thermoradiotherapy was 49 weeks for glioblastoma and 140 weeks for anaplastic astrocytoma. These trials were sufficiently encouraging to lead the investigators to conclude that hyperthermia was an effective and useful modality for treatment of malignant gliomas.

In the first presented case, CR on CT evaluation after thermoradiotherapy was obtained without reductive surgery. Furthermore in this case, a figure-8-shaped low attenuation area on the follow-up CT scan was observed corresponding to a low perfusion area on SPECT, meaning that necrosis following hyperthermia was effected in relation to blood flow. Those neuroradiologic examinations suggested a relationship between heating area and cerebral blood flow.

The second case had CR on CT evaluation with good QOL after hyperthermia. He survived 38 months after the initial diagnosis of glioma. In spite of poor prognostic factors such as higher age, deep

location, no reductive surgery, and high-grade glioma, the length of survival was beyond expectation.

Both cases had relatively small tumor volumes, two RF antennae provided adequate cover for heating. Tumor size is one of the most important factors for interstitial hyperthermia. Malignant glioma over 5 cm in diameter will be treated by excision, because of the existence of IICP and the large mass effect.

In summary, neurologic imaging of these two cases following hyperthermia was encouraging. RF interstitial hyperthermia was convenient, safe, and less invasive for treatment of these elderly glioma patients. We must now plan phase III studies or randomized trials to determine the effectiveness of this treatment for malignant glioma in the elderly.

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高齢者悪性神経膠腫に対する RF 組織内ハイパーサーミア: 2 著効例

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要 旨: 腫瘍の局在から摘出術が行えなかった悪性神経膠腫に対して温熱放射線治療が有効であった高齢者の 2 症例を報告した。症例 1 は, 76 歳男性。左前頭葉の膠芽腫で, 右片麻痺を呈していた。治療前の頭部造影 CT スキャンでは, 不整形の増強効果の認められる腫瘍が左運動領直下の白質に存在していた。局所麻酔下に定位的生検術を行うと同時に温熱治療用の 2 本の RF アンテナ (電極) を腫瘍内に挿入, 留置した。4 回の組織内加温を 10—MVX 線による通常分割の 60Gy の外照射とともに 3 回の組織内加温を行った。治療 4 ヶ月後の頭部 CT スキャンでは造影剤による増強効果部は消失しており, CR と評価された。また, 局所の脳浮腫も認められなくなっていた。症例 2 は, 82 歳男性。左片麻痺にて発症した右被殻部の退形成性星細胞腫の症例である。本症例も症例 1 と同様な手順で, 通常の 60Gy の放射線治療とともに 3 回の加温を行った。加温後の CT および MRI において CR を呈した。また, 加温による脳浮腫も認めなかった。本 2 症例とも加温前後に合併症を認めなかった。摘出術を施行し得ない悪性神経膠腫に対して温熱放射線治療は, 高齢者でさえも容易に適応し得るものであり, 腫瘍縮小効果についても有効であると考えられた。