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BRIEF ARTICLE

Surgical resection plus biotherapy/chemotherapy improves survival of hepatic metastatic melanoma

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Abstract

AIM: To analyze the correlation of treatment method with the outcome of all the hepatic metastatic melanoma (HMM) patients from our hospital.

METHODS: There were altogether nine cases of HMM that had been treated in the PUMCH hospital during the past 25 years, from December 1984 to February 2010. All of the cases developed hepatic metastasis from primary cutaneous melanoma. A retrospective review was performed on all the cases in order to draw informative conclusion on diagnosis and treatment in correlation with the prognosis. Clinical features including symptoms, signs, blood test results, B-ultrasound and computed tomography (CT) imaging characteristics, and pathological data were analyzed in each case individually. A simple comparison was made on case by case basis instead of performing statistical analysis since the case numbers are low and patients were much diversified in each item that has been analyzed. Literatures on this subject were reviewed in order to draw a safe conclusion and found to be supportive to our finding in a much broad scope.

RESULTS: There are six males and three females whose ages ranged 39-74 years old with an average of 58.8. Patients were either with or without symptoms at the time of diagnosis. The liver function and tumor marker exam were normal in all but one patient. The incidence of HMM does not affect liver function and was not related to virus infection status in the liver. Most of these HMM patients were also accompanied by the metastases of other locations, including lung, abdominal cavity, and cervical lymph nodes. Ultrasound examinations showed lesions ranging 2-12 cm in diameter, with no- or low-echo peripheral areola. Doppler showed blood flow appeared inside some tumors as well as in the surrounding area. CT image demonstrated low density without uniformed lesions, characterized with calcification in periphery, and enhanced in the arterial phase. Contrast phase showed heterogeneous enhancement, with a density higher than normal liver tissue, which was especially apparent at the edge. Patients were treated differently with following procedures: patients #1, #6 and #8 were operated with hepatectomy with or without removal of primary lesion, and followed by comprehensive biotherapy/chemotherapy; patient #9 received hepatectomy only; patient #2 received bacille calmette-guerin treatment only; patient #7 had Mile's surgery but no hepatectomy; and patients #3, #4 and #5 had supportive treatment without specific measurement. The patients who had resections of metastatic lesions fol-

lowed by post-operative comprehensive therapy have an average survival time of 30.7 mo, which is much longer than those did not receive surgery treatment (4.6 mo). Even for the patient receiving a resection of HMM only, the post-operative survival time was 18 mo at the time we reviewed the data. This patient and the patient #6 are still alive currently and subjected to continue following up.

CONCLUSION: Surgical operation should be first choice for HMM treatment, and together with biotherapy/chemotherapy, hepatectomy is likely to bring better prognosis.

Key words: Malignant melanoma; Hepatic metastatic tumor; Hepatectomy; Hepatic metastatic melanoma; Prognosis; Biotherapy; Chemotherapy

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INTRODUCTION

Melanoma is one of the diseases with the highest mortality even though it has a low incidence rate in Chinese population. According to World Health Organization report in 2001, there are only 0.22 and 0.17 incidents per 100 000 among male and female population in China respectively[1]. Depending on the difference in the characteristics of primary tumor, up to one third of melanoma patients will eventually develop metastasis[2,3]. Nearly 40% of the ocular melanoma patients develop hepatic metastasis upon initial diagnosis, and majority of the patients with metastatic melanoma will involve liver[4,5]. The cutaneous melanoma metastasizes to liver less frequently and usually involves other organs as well; however, still 15%-20% of the disseminated diseases occur in liver[6,7]. The median survival time for melanoma patients who developed hepatic metastasis is reported to be less than 5 mo, with a one-year survival rate being 10%[8-10]. Patients with primary cutaneous melanoma may develop more systematic metastasis and resection of hepatic metastatic lesions alone may not be enough to extend patients' survival time[11]. Some studies[12,13] suggested more systematic approaches including chemotherapy and immunotherapy in combination with surgery as treatment of choice.

In this study, we reviewed 9 cases of hepatic metastatic melanoma (HMM) who had been treated in our hospital in the past 25 years, all of whom developed hepatic metastasis from primary cutaneous melanoma. We took a close look at the diagnosis and treatment in comparison with the prognosis, from which we intended to summarize out useful information for future work.

MATERIALS AND METHODS

Based on the clinical documentation of 9 patients of HMM in our hospital from December 1984 to February 2010, we analyzed each case on their clinical symptoms, signs, and blood test results, B-ultrasound and computed tomography (CT) imaging characteristics, pathological data, and treatment and prognosis. A simple comparison was made on case by case basis instead of performing statistical analysis since the case numbers are low and patients were much diversified in each item that has been analyzed. Literatures on this subject were reviewed in order to draw a safe conclusion and found to be supportive to our finding in a much broad scope.

RESULTS

Of these nine patients, there are six males and three females whose ages ranged 39-74 years old with an average of 58.8. As shown in Table 1, all patients had histories of primary cutaneous melanoma at various origins. The time intervals between the diagnosis of the primary melanoma and the discovery of hepatic metastatic lesion also varied, ranging from immediate after original diagnosis to 16 years. Most of these HMM patients was also accompanied by the metastases of other locations, including lung, abdominal cavity, and cervical lymph nodes (Table 1).

Clinical symptoms

Clinical symptoms varied among the nine patients. Three were asymptomatic at initial clinic visit; hepatic lesions were discovered only when they received routine examinations or post-operative follow-up. Two had hematochezia; two presented with fever, abdominal pain accompanied by nausea, vomiting, and diarrhea; one had nausea, vomiting, and diarrhea only and one had hemorrhinia.

Laboratory exams

The incidence of HMM is not related to liver function or virus infection status in the liver. Among the nine cases, only one patient was hepatitis B surface antigen positive with elevated alanine transaminase and aspartate aminotransferase levels. One was hepatitis B core antibody (HBcAb) positive. All others have negative blood exams for hepatitis B or C. Liver functions of all the

Table 1 General information of the patients with hepatic metastatic melanoma

Case	Age (yr)	Gender	Primary melanoma lesion	Interval time before hepatic metastasis (yr)	Accompanying metastasis	Treatments	Survival time (mo)
1	39	M	Sclerotica	7	Spleen	Hepatectomy + comprehensive treatment	30
2	49	M	Left choroid	16	None	Puncture and biopsy + BCG	4
3	51	F	Rectum	0	Abdominal cavity	Biopsy + supportive therapy	1.5
4	69	M	Right lower eyelid	11	Recurrence of carcinoma *in situ*; metastasis to right hip	Biopsy + supportive therapy	2
5	68	M	Nasal cavity	0.6	Bilateral lung, pleura and cervical lymph nodes	Biopsy + supportive therapy	1.5
6	61	F	Back	8	None	Hepatectomy + comprehensive treatment	29
7	70	F	Resctum	1.5	Recurrence of carcinoma *in situ*	Mile's surgery	14
8	48	M	Right 5th dactylus	0.5	Recurrence of carcinoma *in situ*	Hepatectomy, resection of primary lesion + comprehensive treatment	33
9	74	M	Sole	9	Inguinal lymph nodes	Hepatectomy	18

Table 2 The characteristics on imaging of the hepatic metastatic melanoma

Case	Tumor location	Tumor size	B-ultrasound	Computed tomography
1	Right liver	4.3 cm × 3.3 cm × 3.1 cm	NA	NA
2	Multiple	5 mm-12 cm	Low echo	Low density
3	Multiple		NA	Low density
4	Left liver	2.4 cm × 2.5 cm	Low echo, with partially peripheral dense echo	NA
5	Right liver	6.4 cm × 5.0 cm	Low echo, with peripheral low-echo areola, and a bit of strip blood flow inside	Low density
6	Multiple	5 mm-3 cm	Low echo, with peripheral low echo areola	Low density, with higher density peripherally
7	Left liver	2.5 cm × 2.1 cm	Mid-dense echo	Low density, with nodular enhancement
8	Multiple	5 mm-2.6 cm	Low echo	NA
9	Right liver	10 cm × 8 cm	No echo, with septum, and hyperechoic lesion	Cystic mass, with mild enhancement

NA: Not available.

patients were ranked Child-Pugh grade A. Five patients had their alpha fetoprotein (AFP) tested; the patient with HBcAb positive had a level of 348.9 ng/mL while the others were all in the normal range. Five patients had their blood tested for carcinoembryonic antigen (CEA) and cancer antigen (CA)19-9, all of whom had normal levels with CEA < 3.5 ng/mL and CA19-9 < 35 U/mL. Initial routine blood tests on two patients with fever showed increased white blood cells while the other seven were normal. Lower hemoglobin was found in patients with hematochezia or hemorrhinia or symptom of nausea, vomiting, and diarrhea.

Imaging exam

Ultrasound examinations showed lesions ranging 2-12 cm in diameter, with no- or low-echo peripheral areola. Doppler showed blood flow appeared inside some tumors as well as in the surrounding area. Six patients had CT scans, the non-contrast phase showed low density solid masses, with two cases close to the water density. The lesions had heterogeneous density inside and peripheral calcification (Table 2). Contrast phase showed heterogeneous enhancement, with a density higher than normal liver tissue, which was especially apparent at the edge (Figure 1).

All cases had histology confirmation of malignant melanoma for both primary and metastatic lesions.

Treatment

One patient (#1) had a surgical resection of the hepatic metastatic lesion, followed by six courses of chemotherapy with unclear dose using dacarbazine (DTIC)/interleukin 2 (IL-2)/interferon (IFN)/cisplatin (DDP) when further hepatic metastasis arose. One (#6) had a resection of hepatic metastatic lesion and six courses of chemotherapy using DDP/IL-2/IFN every other day. One (#8) received the primary lesion surgery and four courses of biotherapy/chemotherapy using DTIC/IL-2/IFN. All these patients had a survival time more than 29 mo. Another patient (#9) had no recurrence yet for 18 mo after hepatectomy only. This patient is the one we are continuing to follow up currently. One (#7) had a resection of the primary melanoma and celiac metastatic solid mass. One patient (#2) had liver lesion biopsy, received six courses of BCG 75 g. Three patients (#3, 4 and 5) only received supportive treatment. The average survival time of the last five patients is only 4.6 mo after diagnosis. The patients who had resections of primary and metastatic lesions followed by post-operative comprehensive therapy tended to have longer survival times (Table 1).

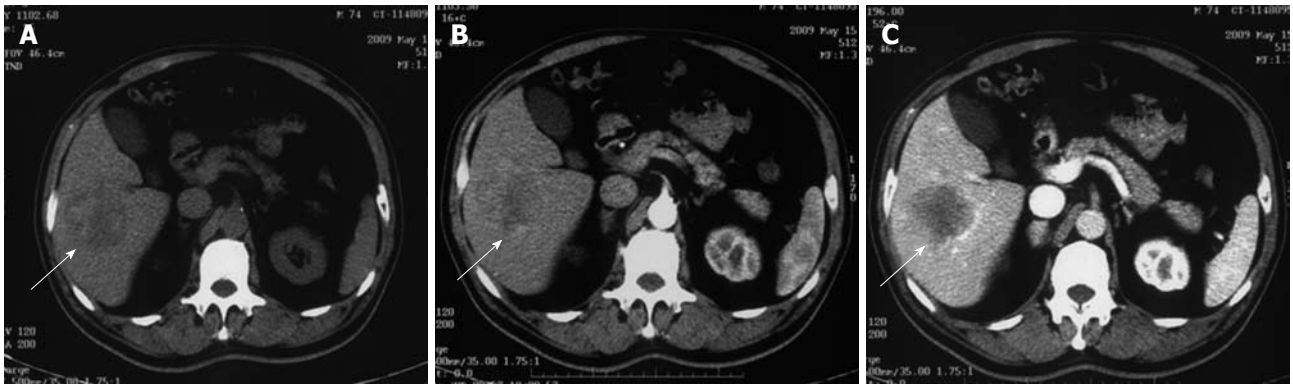

Figure 1 The hepatic metastatic melanoma was shown by computed tomography image on different phases. A: Non-contrast; B: Arterial phase; C: Portal vein phase. The lesion (arrow) showed low density without uniform, enhanced in the arterial and portal phase.

DISCUSSION

HMM is a rare disease in China. As one of the best hospitals in China, we only collected 9 cases in a span of 25 years. The symptoms of the patients were often observed in the main clinical manifestations of HMM including both the symptoms of the primary lesions and those of the hepatic metastasis. Early-stage patients can be asymptomatic; enlarged tumors can cause distention, discomfort, gastrointestinal symptoms, *etc*[14]. Since most patients have explicit histories of primary lesion, HMM should be considered as hepatic lesion being detected.

Under B-ultrasound, HMM is mainly manifested as low echo or even no echo, and frequently heterogeneous. Sometimes a solid neoplasm bulging to the cystic mass can be seen. Doppler shows peripheral surrounding blood flow, presenting as a bull's-eye configuration[15], which suggests a likely hepatic metastatic tumor.

In CT scan, HMM is shown as a solid mass of heterogeneous density: low density and even cystic degeneration in the center, and circular irregular higher density and even calcification in the periphery, presenting as the "rosette sign"[16] (Figure 1A). Enhanced CT scans show that HMM is rich in blood supply, as the arterial phase (Figure 1B) is apparently enhanced while the portal vein (Figure 1C) and delay phases have decreased density. It is similar to the signs of hepatocellular carcinoma, but mainly manifests as circular enhancement in general[17].

Similar to the former studies, this study also showed that routinely tested tumor markers, such as AFP and CA series, are not helpful in the clinical diagnosis of HMM[14]. New biomarkers have been evaluated but not yet in clinical application[18]. As HMM can be of various tissue origin, different cell morphologies, arrangement structures, or amounts of melanin pigment are observed. The final diagnosis of malignant melanoma mainly relies on pathological examination and immunohistochemistry staining.

Therapeutic options for HMM were few with limited effectiveness. It includes surgical resection, systemic or local catheterized chemotherapy, radiotherapy, immunotherapy, and biotherapy. Response rate to chemotherapy is only 10%-30%, and it differs significantly between ocular and cutaneous melanoma[19,20]. For patients with primary ocular melanoma, the response rate to chemotherapy is extremely low. However, percutaneous hepatic perfusion, as a novel approach to chemotherapy delivery, has been applied in clinic[21]. With ocular melanoma, a 50% overall response rate was observed, including two complete responses[22]. Also other methods such as hepatic artery chemoembolization resulted in radiologic response (38.9%) or disease stabilization (47.2%) in most patients[23]. Nevertheless, the median overall survival and time to progression of liver disease were 7.7 mo and 6 mo, respectively.

Some researchers have proposed that chemotherapy combined with biotherapy using IL-2, IFN, *etc*., could increase the response rate and prolong survival time[13]. When data were pooled, biochemotherapy was superior to chemotherapy in response and delayed progression at 6 mo, but not in decreased mortality at 12 mo. However, this regimen may need further exploration because of the toxicity of biochemotherapy, which may induce serious complications and significantly affect patient's quality of life[24].

Surgical resection has been shown to prolong the survival time, since metastatic lesions for primary ocular melanoma are usually confined in liver[5]. Although the recurrence rate is high, ocular melanoma patients tend to remain disease free longer than cutaneous patients[11]. Recently, investigators have indicated that for patients without metastasis to extrahepatic organs, resection of hepatic metastatic lesions may prolong the survival times, with apparently a higher 2-year survival rate than that of chemotherapy, biotherapy, or supportive therapy alone[25-28]. Meyer *et al*[29] also imply surgical resection could apparently prolong the survival time even if the metastatic lesion is resected palliatively. Aoyama *et al*[30] has reported at an earlier time that after resection, recurrence-free and overall 5-year survival rates of those patients were 15.6% and 53.3%, respectively. Other reports also demonstrated advantages of resection over non-surgical measurement[31,32]. It has reported that combination therapy of resection with TIL treatment dramatically improved survival[33]. In our case, three patients received resection plus comprehensive therapy, and all had survival times longer than 2 years. Even for the patient receiving a resection of primary lesion only, the post-operative

survival time was longer than 1.5 year. Two patients with hepatectomy (#6, 9) are still living currently under following up. These results suggested that resection of the primary and HMM lesions and/or in combination with chemotherapy and immunotherapy may enhance the effectiveness of the treatment and prolong survival time, even with other extrahepatic lesions. Further study with larger number of the patients is needed to accumulating the evidence.

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COMMENTS

Background

Melanoma is a disease with the highest mortality but low incidence rate in Chinese population. Liver metastasizes is very common in melanoma. The median survival time for melanoma patients who developed hepatic metastasis is reported to be less than 5 mo, with a one-year survival rate being 10%. Therapeutic options for hepatic metastatic melanoma (HMM) were few with limited effectiveness. Surgical resection has been shown to prolong the survival time. This study provides useful information on making right decision on treatment method on HMM patient for better prognosis.

Research frontiers

The hotspots or important area for HMM is how to choose the best treatment method in order to obtain maximum survival time.

Innovations and breakthroughs

The finding provides further evidence on the conclusion that resection of the primary and HMM lesions and in combination with chemotherapy and immunotherapy may enhance the effectiveness of the treatment and prolong survival time.

Applications

This paper, together with other related publications, can be collectively instructive to oncologists in their practice in treat HMM patients.

Terminology

HMM: Hepatic metastatic melanoma, is a metastatic tumor originated from melanoma.

Peer review

In this study, authors describe their experience on 9 patients with HMM and surgical resection in some of them. They concluded that surgical operation in this pts should be firstly considered, which in association with biochemotherapy, has better prognosis. The manuscript is well prepared.

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