Selected Patients with Metastatic Melanoma May Benefit from Liver Resection

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Abstract

Background: In the last few years there has been expanding use of hepatic resection for non-colorectal metastases. The purpose of this study is to evaluate the experience of liver resection for patients with metastatic melanoma.

Methods: Eighteen patients with metastatic melanoma were explored for possible surgical resection. All patients fitted the following criteria: absence of extra-hepatic disease after evaluation with CT/MRI and FDG-PET scans; disease-free interval longer than 24 months after the resection of the primary melanoma; presumed completely resectable lesions; absence of clinical co-morbidities.

Results: Liver resection was performed in 10 patients; 8 out of 18 presented with irresectable tumors and/or peritoneal metastases and were not operated. One patient presented with post-operative biliary fistula and was conservatively managed. No other complications or postoperative mortality were observed. After a mean follow-up of 25.4 months, 5 patients are alive and without evidence of recurrence. Overall median survival was 22 months; overall survival and disease-free survival were 70% and 50% respectively.

Conclusions: Resection of liver metastases from melanoma in a selected group of patients may increase survival. Exploratory laparoscopy should be included in the preoperative armamentarium of diagnostic tools.

Liver resection is considered the only potential curative treatment for colorectal and neuroendocrine secondaries; however, its role in other metastatic tumors is not completely defined. In the last few years, mortality rates for liver resection have dramatically declined to less than 2% in specialized centers,[1] due to advances in surgical expertise and perioperative care. This has led to increasing enthusiasm for surgical treatment for metastatic disease, with special attention directed at cases for which no other modality of treatment is effective.[2–4]

Liver metastases are diagnosed in 10%–20% of patients with melanoma, being associated with a bad prognosis and short survival time rates (mean = 4.4 months).[5] Patients with melanoma liver metastases used to be considered unsuitable for resection because this approach did not increase survival significantly. However, in the last few years, some groups have reported liver resections with long-term survival rates.[5–8]

We have faced the same problem and decided to operate on a highly selected group of patients with melanoma liver metastasis, since we believe that some patients can benefit from surgery. According to criteria based on our experience and on data from the literature, patients who were clinically well, presented no other sites

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Table 1.
Patient's characteristics, surgical findings, procedure, and follow-up

Origin/gender/age	Status (follow-up)	Surgery performed	Metastases number (size in cm)
Ocular/female/38 years	Alive; disease free (28 months)	Segmentectomy I	1 (6)
Ocular/female/39 years	Alive; disease free (12 months)	Bisegmentectomies II, III and VI,VII + wedge resection	6 (2; 1; 1; 1; 1; 1)
Ocular/male/42 years	Alive; disease free (40 months)	Left hepatectomy + right lobe nodule wedge resection	4 (5; 3; 1.5; 0.7)
Ocular/male/42 years	Alive; disease free (20 months)	Bisegmentectomy VII, VIII	1 (2.5)
Ocular/male/46 years	Alive; recurrent disease (12 months)	Bisegmentectomy II, III + wedge resection	2 (2.5; 1)
Cutaneous (lower limb)/ female/35 years	Alive; disease free (48 months)	Left hepatectomy	2 (4; 1)
Cutaneous (foot finger)/ female/69 years	Alive; recurrent disease (46 months)	Right hepatectomy + wedge resection	2 (10; 1)
Cutaneous (lower limb)/ female/42 years	Dead (15 months after liver resection)	Segmentectomy VI	1 (2.5)
Cutaneous (lower limb)/ female/57 years	Dead (24 months after liver resection)	Left hepatectomy	2 (7; 3)
Cutaneous (upper limb)/male/58 years	Dead (9 months after liver resection)	Right hepatectomy	1 (2.5)

of metastasis and had had at least 24 months free of disease since treatment of the primary tumor were subjected to hepatic resection. The aim of the present study was to describe our selection criteria and to evaluate surgical results and survival.

PATIENTS AND METHODS

Eighteen out of 367 patients with liver metastatic melanoma from 2 different institutions specialized in cancer and liver surgery, between December 1999 and January 2005, fit the proposed selection criteria (4.9%) as follows:

1. Presumed resectable lesion(s) with normal liver function
2. A 24-month disease-free interval since the resection of the primary melanoma
3. Absence of extra-hepatic disease after computed tomography or magnetic resonance evaluation
4. A negative whole body 18-fluorodeoxyglucose positron emission tomography (FDG-PET scan)
5. No significant clinical co-morbidities (*e.g.* cardiac or pulmonary disease).

During surgery, all patients were subjected to evaluation of the abdominal cavity and liver ultrasound. If diffuse hepatic disease or peritoneal and/or lymph node metastases were detected, resection was not performed. Liver resection was performed only if the complete removal of metastatic disease was possible.

RESULTS

Ten out of the 18 patients (6 women, with ages ranging between 35 and 69 years, mean 46) fulfilled the selection criteria, including the intraoperative evaluation, and were subjected to liver resection. Five patients had ocular primary melanomas and 5 had cutaneous tumors. A surgical margin of at least 1 cm was obtained in all patients. In the 8 unoperated patients, resection was not performed due to diffuse hepatic disease ($n = 6$) and peritoneal metastases ($n = 2$).

Clinical data, surgical findings, and procedures are shown in Table 1. Four patients had single liver metastases, the other presented two nodules ($n = 4$), 4 nodules ($n = 1$), and 6 nodules ($n = 1$).

One patient developed a postoperative biliary fistula, which was conservatively managed with a good outcome. No other postoperative complications were observed and there was no operative mortality. None of the patients received adjuvant local or systemic therapy.

Histological examination of the resected specimens confirmed the diagnosis of malignant melanoma and free surgical margins in all cases.

All patients with ocular melanoma metastasis are alive, 4 (80%) without recurrent disease. One patient is alive (after 12 months' follow-up) with lung recurrence 9 months after liver resection. Two of the patients (2 out of 5) with cutaneous melanoma are alive, 1 is disease free (after 48 months' follow-up) and the other developed lung and liver recurrences 16 months after surgery (46 months of follow-up). Three patients died, 1 with brain and lung recurrence, 1 with liver, peritoneal, and lung tumors and 1 with liver and peritoneal recurrence, 9, 15, and 24 months after liver resection respectively. After a mean follow-up of 25.4 months, overall survival rate was 70% and disease-free survival 50%.

Overall median survival time was 22 months. Five patients (50%) are alive and have been disease free for at least 12 months after resection (range between 12 and 48 months). Two patients are alive 12 and 46 months after liver resection and presented recurrences 9 and 16 months after surgery. Three patients died due to recurrent disease 9, 15, and 24 months after liver resection.

DISCUSSION

Melanoma recurs in approximately one-third of the patients after treatment of the primary lesion[9,10] and, with the routine use of ultrasound and the improvement of imaging diagnostic tools, metastatic disease has become more frequently identified, with liver metastases diagnosed in up to 20% of the patients.

Patients with stage IV melanoma have a 5-year survival rate of 6% and a mean survival time between 4 and 6 months.[5] The benefit of the surgical treatment for melanoma metastases remains controversial; however, there is some evidence that resection, in a selected group of patients, can increase survival time and rates ranging between 24 and 49 months have already been reported after the resection of adrenal, gastrointestinal, pulmonary, and splenic metastasis.[11–15]

Foster[16] collected a series of 13 patients from several institutions who were subjected to liver resection for metastatic melanoma. In his survey, the 5-year survival rate was 8% and mean survival time was 10 months. Other authors, with series ranging from 1 to 10 patients, report mean survival of between 10 and 20 months.[1–4]

In a cooperative study of the John Wayne Cancer Institute and the Sydney Melanoma Unit, more than 26,000 melanoma patients were evaluated and 1,750 (7%) had liver metastasis. Twenty-four of them (1.4%) underwent liver resection and the 5-year disease-free and overall survival were 12% and 29% respectively. Median overall survival time in the resected group was 28 months; on the other hand, overall median survival time in patients with non-resected liver metastasis was 6 months and the 5-year survival rate was 4%.[5]

The criteria for patient selection seem to be critical for better results. Rose et al. pointed out that patients subjected to complete resection of metastasis with histologically negative margins and the absence of extrahepatic disease had better survival rates compared with those undergoing exploration alone.[5] The available data on prognostic factors following resection of metastatic melanoma at other sites indicate that a longer disease-free interval and complete resection are associated with improved outcome.[12–14] Indeed, we agree with these authors and, in our series, there was a rigorous selection of patients who were suitable for liver resection. We treated patients with good liver function, metachronic disease, without any signs of extra-hepatic metastases and performed a complete resection independent of the number and size of the nodules, with adequate margins in all cases. With this refinement of selection, around 5% of the patients with hepatic metastases can benefit from resection. With regard to our experience, 5 patients (50%) are disease free after a median follow-up of 22.7 months and 2 are still alive, although presenting with recurrences. Patients with recurrence were treated by systemic chemotherapy with dacarbazine associated with interferon alpha according to the clinical and oncological protocol. The shortest survival time in this series was 9 months and the other deaths occurred 15 and 24 months after surgery. Given that life expectancy for patients with stage IV melanoma ranges between 4 and 6 months, the survival time of all treated patients seemed to be increased.

Studies have shown a poor prognosis for patients with metastases of primary ocular melanoma compared with those with a cutaneous primary site; however, reports of resection for stage IV melanoma include very few patients with primary intraocular tumors.[8] Therefore, the role of surgical resection for ocular metastatic melanoma is very difficult to assess from the current literature. In our series, the 5 patients with ocular melanoma metastasis treated according to our selection criteria are alive, 4 of them disease-free. On the other hand, 2 out of 5 patients with cutaneous melanoma metastasis are alive, with only one disease free.

In the last few years, the use of FDG-PET scanning has become routine for the detection of occult metastatic disease because it has been shown to be more sensitive than CT in staging patients with metastatic melanoma.[9,17] In our study, all patients were subjected to FDG-PET, and those

presenting with extra-hepatic disease were not operated on. Unfortunately, in our experience, CT, MRI and FDG-PET scanning were not able to identify metastases smaller than 10 mm on the liver, peritoneum or lymph nodes. Recently, Clark *et al.* showed no utility for PET in the detection of occult metastases of melanoma.[18] Indeed, in 8 out of 18 patients initially selected for liver resection (44%), small metastases were identified during surgery. Similar results were observed by Rose *et al.* in which 29% of the patients were operated on but not resected.[5] Thus, we are now performing staging laparoscopy as a routine preoperative procedure in all patients selected for resection in order to avoid unnecessary laparotomy.

Minimally invasive techniques as ablative procedures were developed as alternative treatments for patients with irresectable liver lesions and led to more patients treated with non-resective therapy. Radiofrequency, the most recent ablative modality, is safe and effective, especially for tumors smaller than 4 cm in diameter, but time is needed to evaluate the results properly. Perhaps, in the near future, studies may show the benefit of this less aggressive treatment modality.

Despite of the lack of long-term results there is no doubt that, in this small series, patients presented longer survival times compared with non-resected patients. We, therefore encourage the surgical treatment of liver metastasis in a highly selected group of patients, according to the described criteria. With an increase in experience and the employment of new methods of treatment, the selection criteria or even the results may be improved, perhaps in the near future. Large-scale multi-center studies should be encouraged to allow the enrolment of larger series and better assessment of the patients. However, the poor overall prognosis of the disease still indicates the need for more effective therapies.

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