

Hepatic resection for metastatic melanoma in The Netherlands: survival and prognostic factors

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Patients with hepatic metastases of melanoma have a very poor prognosis, with a median overall survival of less than 6 months. There are several small heterogeneous studies that have shown an association with prolonged survival in those patients treated with hepatic resection, but the role of surgery remains unclear. We evaluated the safety and efficacy of hepatic resection in a population-based study in the Netherlands for patients with metastatic melanoma and assessed the factors that could affect disease-free and overall survival. Patients with hepatic melanoma metastases who underwent potentially curative resection were identified between 1994 until 2010 using the PALGA database, a nation-wide network and registry of histopathology and cytopathology in the Netherlands. They were retrospectively evaluated for clinical and pathological factors with respect to recurrence and survival using Kaplan–Meier curves to assess survival and univariate regression analysis for the assessment of potential prognostic factors. A total of 32 patients were identified in 15 hospitals, 19 men and 13 women. The median age of the patients at the time of hepatic resection was 52 years (range 27–69). Postoperative complications occurred in five patients (15%), without

postoperative mortality. The median follow-up was 21 months (range 3–65). The median disease-free survival was 11 months (range 0–57) and the median overall survival was 29 months (range 4–66). Significant prognostic factors for overall survival in univariate analysis were the distribution and number of metastases, as well as the type of hepatic resection (major or minor). Hepatic resection in patients with resectable metastatic melanoma is safe and might be associated with a prolonged survival in a highly selected group of patients. *Melanoma Res* 23:27–32 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Depending on the clinical and pathological characteristics of the primary tumor, up to one third of patients with melanoma develop distant metastases [1–3]. A common site for distant metastases is the liver. Especially patients with ocular melanoma may have hepatic metastases present at the time of diagnosis, in 40% of the cases, and the liver becomes involved in 95% of patients who develop metastatic disease [4]. Cutaneous melanoma also metastasizes to the liver in 15–20% of the patients who develop metastatic disease and, on autopsy, hepatic involvement is found in 55–75% of patients [3,5].

Patients with hepatic metastases have a very poor prognosis, with a median survival of approximately 4 months and a 5-year survival of less than 5% [6]. Response rates on traditional DTIC-based chemotherapy regimens are often low, with percentages below 10% [7]. Recent treatment with BRAF inhibitors or anti-CTLA4 has yielded response rates with a significant improvement in the 1-year survival, but the long-term survival benefits are to be awaited [8,9]. Moreover, these new agents may induce

complications, with considerable morbidity and development of other skin cancers. The optimal treatment strategy for patients with isolated hepatic melanoma metastases remains unclear, even with these new treatment options.

In patients with colorectal liver metastases, hepatic resection has widely been proven effective, with a 5-year survival of 20–50% [10–12]. With improvements in surgical techniques and anesthetic management, the perioperative mortality and morbidity have decreased, which makes partial hepatic resections relatively safe. However, patients with disseminated malignancies of noncolorectal, non-neuroendocrine origin to the liver are only referred for surgical therapy in selected cases.

The objective of this study was to evaluate all patients in the Netherlands in the past 20 years with metastatic melanoma of the liver who were treated with hepatic resection for safety, survival, and to identify potential prognostic factors to predict long-term survival after resection.

Patients and methods

Patients and data collection

Patients were identified by the results of a nation-wide research question in the PALGA-database, a nation-wide network and registry of histopathology and cytopathology in the Netherlands, which registers all pathologic reports since 1991 [13]. All patients who underwent a potentially curative liver resection for metastatic melanoma between 1994 and 2010 were included. Hospitals were visited to collect retrospective data from the patient files. The following data were collected for each patient from the file: demographics, anatomical location, and histological characteristics of the primary melanoma, details of the primary treatment of the melanoma, time interval from initial treatment of the melanoma to metastasis, surgical procedures, number, location and size of the hepatic metastases, recurrence, death date, mortality, and morbidity.

Outcome variables

Postoperative mortality and morbidity included all deaths or complications attributed to the hepatic resection and all deaths or complications within 60 days of the operative procedure. Disease-free survival was defined as the time from hepatic resection until disease recurrence. In some patients, resection had not been completed and disease-free survival was defined as 0 months. Overall survival was defined as the time between hepatic resection until the date of the last follow-up or death. Death was not specified by cause, as it was not possible to detect this because of the ethical guidelines of using de-identified data.

Statistical analysis

All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA; version 16.0). Survival outcomes were calculated using Kaplan–Meier survival curves. Prognostic factors for long-term survival were identified by univariate analysis according to the Cox proportional hazard regression methodology. Because of the small number of patients, multivariate analysis was not carried out. We considered a *P*-value of less than 0.05 as significant.

Results

Patient and tumor characteristics

A total of 49 patients were identified in 15 hospitals using the PALGA database; eight patients underwent only a diagnostic liver biopsy, two patients underwent an isolated liver perfusion, and seven patients were found to have unresectable disease preoperatively. A total of 32 patients who underwent hepatic resection between 1994 and 2010 were evaluated in the present study. The median follow-up was 21 months (range 3–65).

The median age during hepatic resection was 52 years (range 27–69). There were 19 men and 13 women. The median interval between resection of the primary tumor and the hepatic resection was 62 months (range 15–188). The origin of the primary tumor was ocular melanoma in 12 patients and cutaneous melanoma in 16 patients; in four patients, the primary location of the tumor was unknown. The median Breslow thickness of the primary tumor was 2.0 mm (range 0.5–11.0 mm). Before hepatic resection, 13 patients were treated with a therapeutic lymph node dissection for regional metastatic disease (inguinal lymph node dissection, *n* = 5; axillary lymph node dissection, *n* = 10; and cervical lymph node dissection, *n* = 1). In 16 patients, the hepatic metastases were the first and only site of metastases.

Surgery characteristics

The number of metastases ranged from 1 to 10; 18 of the patients (52%) had a solitary hepatic metastasis. The distribution of the metastases was unilobar in 23 patients and bilobar in nine patients. The median size of the largest metastasis was 24 mm (range 10–160 mm). Patients were treated with a hemihepatectomy (*n* = 9), extended hemihepatectomy (*n* = 2), segmentectomy (*n* = 11), or a nonanatomical resection (*n* = 10). Resection was radical (R0) in 23 patients, microscopically irradical (R1) in six patients, macroscopically irradical (R2) in one patient, and unknown in two patients.

Postoperative mortality was not observed. Postoperative complications occurred in five patients (15%). Four patients developed either liver failure, ileus, pneumonia, or pleural effusion. All of these complications resolved with conservative treatment. One patient developed an intra-abdominal infected hematoma, which required percutaneous drainage and antibiotic treatment. The seven patients who underwent explorative laparotomy and were found to have unresectable disease did not experience postoperative morbidity.

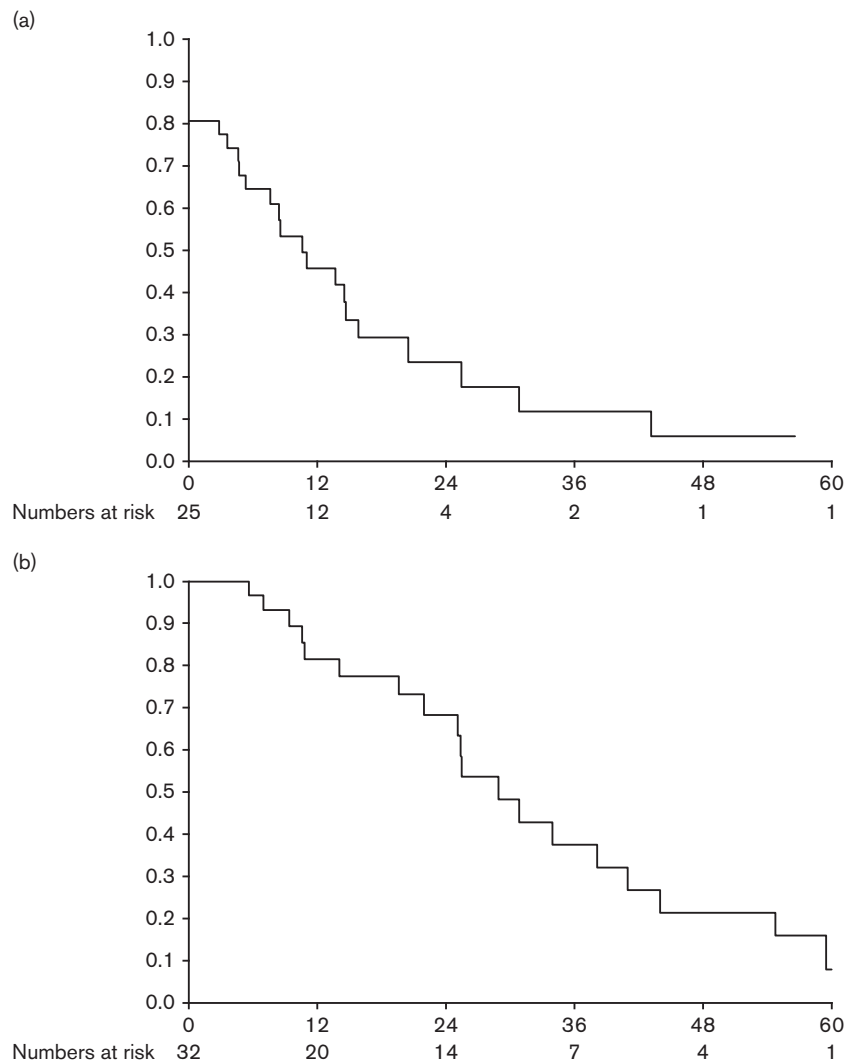
Overall survival and disease-free survival

The median disease-free survival was 11 months (range 0–57 months) and the median overall survival was 29 months (range 4–64 months) (Fig. 1a and b). There was one patient with a survival of more than 5 years, and the 5-year overall survival was 3%.

Prognostic factors

Significant factors for prolonged disease-free survival in univariate analysis were the number of hepatic metastases and a cutaneous location of the primary melanoma (Table 1). Significant factors associated with prolonged overall survival in univariate analysis were the number (*P* = 0.023) and the distribution of hepatic metastases (*P* = 0.002), as well as a minor resection (*P* = 0.021) (Fig. 2a–c). There was a trend toward prolonged survival in male versus female patients (*P* = 0.054).

Fig. 1



(a) Disease-free survival of patients who underwent hepatic resection for metastatic melanoma in months. Median disease-free survival: 11 months.
 (b) Overall survival of patients who underwent hepatic resection for metastatic melanoma in months. Median overall survival: 29 months.

Discussion

This study describes the first nation-wide series of melanoma patients in the Netherlands treated surgically for hepatic metastases in the last 20 years. A histological diagnosis was available in 49 patients and only 32 (65%) patients underwent a potentially curative surgical resection. The median overall survival in this small and highly selective group of patients was 29 months. In univariate analysis, patients with solitary metastasis, unilobar disease, or a minor resection (less than three segments) had a significantly improved overall survival. Although this study had a small number of patients, it confirms results from previous studies in the literature and provides additional data.

In the literature, metastatic melanoma patients receiving systemic treatment without surgical treatment have

a median survival of less than 6 months [6]. Several surgical studies have shown an association between hepatic resection in melanoma patients and improved survival in patients with stage IV disease [14–38]. Adam *et al.* [23] reported a large series of patients with metastatic melanoma who underwent hepatic resection; they found a median disease-free and overall survival rate of 11 and 35 months, respectively. Pawlik *et al.* [25] also reported a series of 40 patients who underwent hepatic resection for metastatic melanoma. They found a median disease-free and overall survival of 8 and 28 months, respectively. Multiple other studies have reported similar overall survival rates (Table 2).

Data from the present study support the results found in previous studies, although the 5-year-overall survival was only 3% in the present study, whereas in other studies,

Table 1 Potential prognostic factors in univariate analysis for disease-free survival and overall survival after hepatic resection in patients with metastatic melanoma in the Netherlands from 1994 to 2010

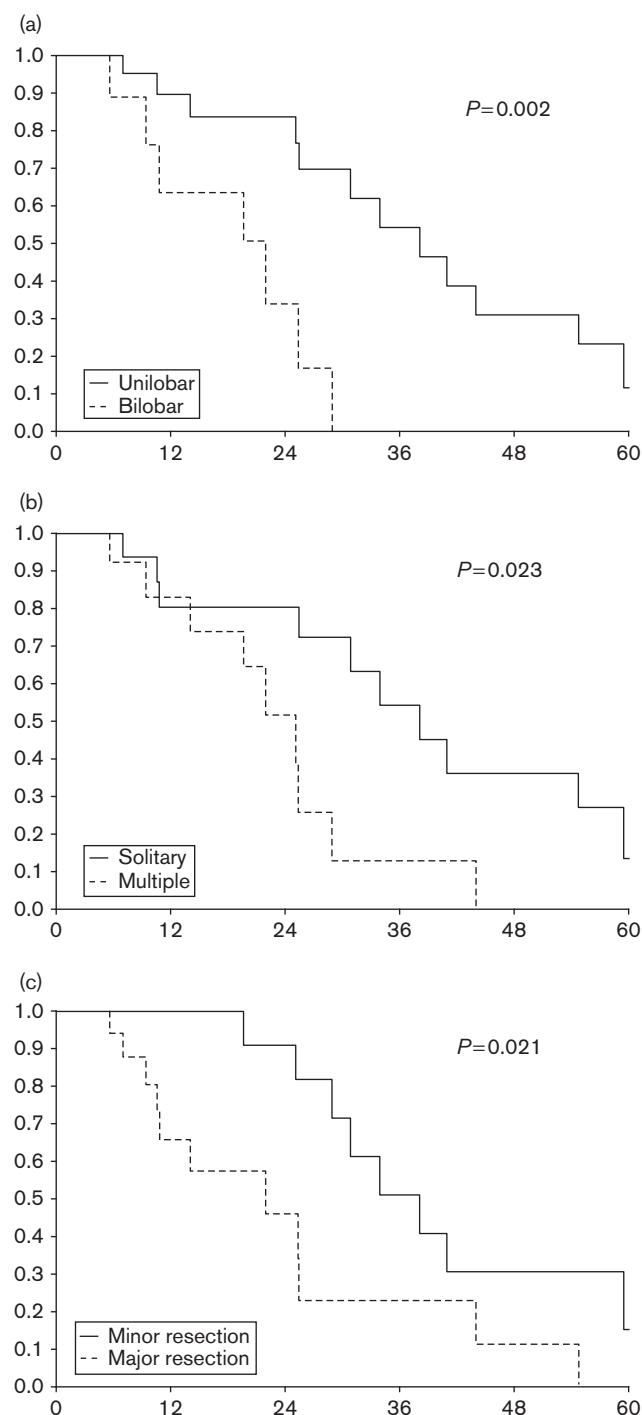
Factors	N	Median DFS (months)	P	Median OS (months)	P
Sex	-	-	0.153	-	0.054
Male	19	14	-	38	-
Female	13	8	-	25	-
Primary tumor	-	-	0.033	-	0.996
Cutaneous	16	15	-	25	-
Ocular	12	8	-	34	-
Unknown	4	9	-	29	-
Breslow's depth (mm)	-	-	0.875	-	0.623
<2	8	8	-	22	-
>2	7	15	-	25	-
Number metastases	-	-	0.030	-	0.023
Solitary	18	14	-	38	-
≥ 2	13	8	-	25	-
Distribution	-	-	0.301	-	0.002
Unilobar	23	14	-	38	-
Bilobar	9	8	-	22	-
Resection	-	-	0.687	-	0.021
<3 segments	13	13	-	38	-
>3 segments	19	7	-	22	-
Resection margins	-	-	0.000	-	0.905
R0	23	15	-	25	-
R1/R2	7	0	-	29	-
Age at the time of hepatic resection (years)	-	-	0.715	-	0.623
<60	25	10	-	31	-
>60	7	4	-	25	-
Size metastasis (mm)	-	-	0.279	-	0.453
<50	27	8	-	29	-
>50	5	2	-	11	-

DFS, disease-free survival; OS, overall survival. Bold indicates $P < 0.05$.

these percentages range between 36% [23] and 10% [25]. This may partly be explained by the short median follow-up time of 21 months. The 3-year overall survival and 4-year overall survival rates are 22%, respectively, 12.5%, which are more in agreement with data found in the literature. Several investigators have attempted to identify criteria to make the decision for hepatic resection in metastatic liver disease. For colorectal hepatic metastases, Fong *et al.* [39] have made specific recommendations on the basis of the number and size of metastases, disease-free interval from primary to metastases, presence of lymph node positivity, and preoperative carcinoembryonic antigen levels. There are fewer reports on the selection of patients for hepatic resection in noncolorectal, non-neuroendocrine metastases and even less reports specifically for metastatic melanoma.

In previous studies, a number of different prognostic factors have been shown to be important for survival [17,18,20,21,24,28–30,37]. These differences could possibly be explained by the small number and the diverse clinical characteristics, particularly the origin of the primary tumor, in the patients reported. Pawlik and colleagues reported a significantly improved long-term survival in patients with primary cutaneous melanoma, with 5-year survival rates in this group of 20.5% versus no survivors in the patients with primary ocular melanoma.

Fig. 2



(a) Overall survival (OS) in months after hepatic resection for metastatic melanoma in patients with a unilobar ($n=23$; median OS 38 months) or a bilobar ($n=9$; median OS 22 months) distribution ($P=0.002$). (b) Overall survival (OS) in months after hepatic resection for metastatic melanoma in patients with solitary ($n=18$; median OS 38 months) or multiple hepatic metastases ($n=13$; median OS 25 months) ($P=0.023$). (c) Overall survival (OS) in months in patients after minor hepatic resection, which includes less than three liver segments ($n=13$, median OS 38 months), or major hepatic resection, which includes three or more liver segments ($n=19$; median OS 22 months) for metastatic melanoma ($P=0.021$).

Table 2 Review of reports describing the factors associated with improved survival in patients with metastatic melanoma who underwent hepatic resection

References	Year	N	OS	DFS	Prognostic factors
Adam <i>et al.</i> [23]	2006	148	35	11	Age \leq 60 DFI \geq 12 months No extrahepatic disease R0/1-resection
Pawlik <i>et al.</i> [25]	2006	40	28	8.3	Minor hepatic resection ^b Unilobar distribution Neoadjuvant chemotherapy Size \leq 5 cm Metachronous metastases Solitary metastasis ^a
Frenkel <i>et al.</i> [24]	2009	35	15–55	35–37	R0-resection \leq 6 metastases ^a
Rose <i>et al.</i> [21]	2001	24	28	12	R0-resection
O'Rourke <i>et al.</i> [18]	2007	20	42	18	R0-resection DFI \geq 24 months ^b
Weitz <i>et al.</i> [20]	2005	17	42	17	Size \leq 5 cm No extrahepatic nodal disease ^b
Reddy <i>et al.</i> [37]	2007	11	44	13	DFI \geq 6 months Adjuvant chemoradiotherapy ^b
Herman <i>et al.</i> [36]	2006	10	22	NR	NR
Elias <i>et al.</i> [32]	1998	10	18	NR	NR
Present study		32	29	11	Solitary metastasis Unilobar distribution Minor hepatic resection ^a

DFI, disease-free interval between resection of the primary tumor and detection of hepatic metastases; DFS, disease-free survival in months; NR, not reported; OS, overall survival in months.

^aStatistically significant ($P < 0.05$) in univariate analysis.

^bStatistically significant ($P < 0.05$) in multivariate analysis.

They did not find other clinicopathological factors to be predictive for an improved long-term survival. Unlike the results of Adam *et al.* [23], the size of the hepatic metastases was not a prognostic factor for long-term survival in the present study. This might be explained by the fact that only five patients with a diameter of more than 5 cm were identified and 27 had a diameter of less than 5 cm. R0-resection was also not a significant predictive factor for long-term survival. According to the different levels of significance reported, the various factors are no absolute reasons to include or exclude patients for hepatic resection, but can be taken into account in providing optimal treatment for individual patients.

In the present study, there was no mortality, but five of the 32 patients (15%) experienced postoperative complications. This complication rate might be a reflection of an independent registration of the results by an external reviewer, but may also relate to the relatively low number of patients treated in each center. Mortality did not occur in this series, but centralization of liver surgery might possibly decrease the number of complications in the future. Initiatives to further centralize and register patients in a nation-wide database are now being implemented in several countries including the Netherlands.

Especially in melanoma patients, immunological treatment modalities have been studied intensively, with promising results [8,40,41]. Recent reports show an improved survival in patients treated with ipilimumab or activated, mutated BRAF inhibitors [42]. The role of surgery in patients with stage IV who become resectable after treatment with these new agents has to be established. Besides systemic treatment, other modalities

such as isolated liver perfusion have been explored in patients with melanoma metastases in the liver. Various reports show survival benefit in patients treated with melphalan or TNF, but these treatments are still experimental and survival benefit is limited, with a median survival of approximately 10 months [43–45]. The ideal therapeutic approach for melanoma patients with limited liver metastases is unclear; however, complete metastasectomy must be considered as a treatment option in highly selected patients [46].

Conclusion

Hepatic resection is safe in resectable metastatic melanoma and might be associated with a prolonged survival in highly selected patients.

Collaborators

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Conflicts of interest

There are no conflicts of interest.

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