Original Article

Surgical Metastasectomy in AJCC Stage IV M1c Melanoma Patients with Gastrointestinal and Liver Metastases

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Abstract

Introduction: Visceral metastases from melanoma represent the poorest prognosis based according to the revised version of the AJCC staging system that recognises both clinical and pathological features distinctive to melanoma. Given that systemic treatments in metastatic melanoma to date remains inadequate, we evaluated the efficacy of surgical metastasectomy on survival outcomes. Materials and Methods: Between year 2000 and 2009, 23 patients with visceral metastases from melanoma were evaluated for metastasectomy. Retrospective review was undertaken of the specific therapy administered following consensus meeting of a multi-disciplinary team. Results: There were 16 males and 7 females. Seventeen patients (74%) had metachronous gastrointestinal/liver metastases following previous treatment of the primary tumour. The median time to development of gastrointestinal/liver metastases, otherwise known as disease-free interval, was 49 (range, 5 to 559) months. Overall median survival period was 9 months, with a 1- and 3-year survival percentages of 39% and 30%, respectively. Survival was influenced by the number of metastases (*P* = 0.05) and the treatment received (*P* = 0.03). The disease-free and overall survival periods after metastasectomy were 14 and 21 months, respectively. The 1- and 3-year survival percentages were 60% and 40%, respectively. Patients with single site of metastasis survived longer than patients with more than one site of metastasis (*P* = 0.005). Conclusion: Patients with visceral metastases from melanoma may derive survival benefit from metastasectomy over systemic therapy. Judicious selection of patients for metastasectomy is paramount for the success of treatment in this group of patients.

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Key Words: Melanoma, Metastasectomy, Liver metastasis, Surgery, Prognosis

Introduction

The prognosis of patients with stage IV melanoma or recurrent melanoma is poor with an estimated median survival period of 6 months.[1,2] The recent revised version of the American Joint Committee on Cancer (AJCC) staging system for cutaneous melanoma has further sub-divided melanoma metastatic sites to 3 specific categories; skin, subcutaneous tissue or distant lymph node as M1a, lung metastases as M1b, and any other visceral sites as M1c.[3] In patients with M1a disease, whether or not resection is undertaken, median survival period ranges between 10 and 18 months and may reach up to 50 months if radical excision of metastases is performed.[4-6] In patients with M1b disease, results of metastasectomy from the International Registry of Lung Metastases has shown an overall median survival period of 19 months and in patients with a favourable prognosis, a 5-year survival percentage of 29% may be achieved.[7]

Unlike the aforementioned 2 subcategories of M1 melanoma, patients with M1c disease comprise a heterogeneous group. Common sites that are involved include the brain, gastrointestinal tract and liver. Brain metastases are observed clinically in up to 40% of melanoma patients and result in significant morbidity with symptomatic deposits causing headaches, focal neurological deficits and seizures. This dismal outlook leads to a mortality within 12 months even after treatment with surgery and/or radiotherapy.[8,9] Gastrointestinal and liver metastases are fairly uncommon and occur in 2% to 4% of patients with melanoma.[10] These metastatic deposits may or may not result in symptoms that include anaemia, abdominal pain, gastrointestinal bleeding, bowel obstruction and cachexia.

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Long-term survival of patients with gastrointestinal metastases has been reported following complete resection compared to those who did not undergo resection (48 vs 6 months).[11] At a time when there is a paucity of data to support the role of surgery, we reviewed our experience with patients with gastrointestinal and liver metastases, with a particular focus on patients who underwent radical curative surgery, to evaluate the outcome after treatment.

Materials and Methods

The prospectively collected surgical oncology database of the Hepatobiliary and Surgical Oncology service at the St George Hospital, Sydney, Australia, was retrospectively reviewed to identify the patients who were evaluated for melanoma metastases. Between 2000 and 2009, 25 patients were evaluated, 2 patients (8%) had lung-only metastasis and 23 patients (92%) had gastrointestinal and liver metastases. The 23 patients with gastrointestinal and liver metastases formed the focus of the current study. Fifteen patients (65%) underwent surgical resection of metastases. Eight patients (35%) were deemed inappropriate for surgical resection by consensus of the multidisciplinary meeting. Patients were deemed inappropriate for surgery if their disease was considered unresectable, or if they had other metastatic sites that were untreated.

All patients underwent preoperative staging to determine eligibility for surgery, including computed tomography (CT) scans of the chest, abdomen and pelvis, magnetic resonance imaging (MRI) of the brain, and bone scans as clinically indicated. Positron emission tomography (PET) was performed in addition to confirm suspected metastatic deposits as detected on conventional imaging tests (PET was not available in the early part of this series).

Factors analysed for survival differences included patient age, sex, site of primary tumour, presence of lymphatic metastases, disease-free interval (calculated as the time from the operation for the primary melanoma to the development of gastrointestinal and liver metastases), anatomic extent and location of recurrences, treatment-related details, recurrence following resection and follow-up times.

Disease-free survival (DFS) and overall survival (OS) was calculated in months from the time of resection of gastrointestinal and liver metastases to the first recurrence of disease and death, respectively. Overall and DFS curves were calculated by the Kaplan-Meier method. Univariate survival analysis was performed using the log-rank test. Statistical significance was defined as $P \leq 0.05$.

Results

There were 16 males and 7 females. The median age at the time of diagnosis of visceral metastases was 71 years (range, 45 to 82). The primary tumour was located on the limb in 7 patients (30%), in the eye in 6 patients (26%), on the trunk in 5 patients (22%), unknown in 3 patients (13%) and on the head and neck in 2 patients (9%). Three patients (13%) had synchronous presentation of primary tumour and gastrointestinal/liver metastases. Seventeen patients (74%) had metachronous gastrointestinal/liver metastases following previous treatment of the primary tumour. The median time to development of gastrointestinal/liver metastases, otherwise known as disease-free interval, was 49 months (range, 5 to 559). Twelve patients (52%) had gastrointestinal/liver metastases as their only site of metastatic disease. Eleven patients (48%) had involvement of other sites that include the subcutaneous tissue in 2 patients (18%), distant lymph node in 4 patients (36%), lung in 4 patients (36%), kidney in 1 patient (9%), spleen in 1 patient (9%), peritoneum in 1 patient (9%), bone in 1 patient (9%) and brain in 1 patient (9%).

With a median follow-up of 9 months (range, 1 to 116), the overall median survival period was 9 months, with a 1- and 3-year survival percentages of 39% and 30%, respectively. Survival was influenced by the number of metastases (single 37 months vs multiple 7 months; $P = 0.05$) and the treatment received (metastasectomy 21 months vs clinical trial/systemic therapies 4 months; $P = 0.03$) (Table 1) (Fig. 1). Between the patients treated with metastasectomy compared to those entered into clinical trials or receiving systemic therapies, the latter group of patients was shown to have metastatic sites with multiple metastases ($P = 0.03$) (Table 2).

Amongst the 15 patients who underwent metastasectomy, 2 patients (13%) had gastrointestinal metastases and 13 patients (87%) had liver metastases. The detailed clinical history, treatment related information and pattern of failure following treatment are described in Table 3. There were no postoperative complications observed and no operative mortality. None of the patients received adjuvant local or systemic therapy. The disease-free and overall survival periods post-metastasectomy were 14 and 21 months, respectively. The 1- and 3-year survival percentages were 60% and 40%, respectively (Fig. 2). Patients with single site of metastasis survived longer than patients with more than one site of metastasis (70 vs 4 months; $P = 0.005$). Disease-free interval ($\leq$49 months vs >49 months) was not associated with any difference in survival outcome (9 vs 37 months; $P = 0.67$).

Discussion

Tremendous progress has been made in the management of melanoma over the last decade. In the management of primary melanoma, the establishment of standards of surgical care in terms of excision margins of 1 cm margins for lesions $\leq$1 mm and 2 cm margins for lesion >2 mm has been

Table 1. Characteristics of Patients with Gastrointestinal/Liver Metastases from Melanoma

M1c Melanoma with Gastrointestinal / Liver Metastases	Patients (n)	Median Survival (months)	Univariate *P* Value
Total	23	9	-
Sex			0.09
Male	16	**9**	
Female	7	**NR**	
Age			0.67
<71 years	13	**11**	
≥71 years	10	**7**	
Primary Tumour Location			0.22
Ocular	6	**66**	
Non-ocular	17	**9**	
Disease-free Interval			0.09
≤49 months	13	**5**	
>49 months	10	**37**	
Number of Metastatic Sites			**0.07**
= 1	13	**21**	
> 1	10	**5**	
Multiple Metastases			**0.05**
No	11	**37**	
Yes	12	**7**	
Treatment			**0.03**
Metastasectomy	15	**21**	
Clinical Trial/Systemic Therapies	8	**4**	

NR : not reached

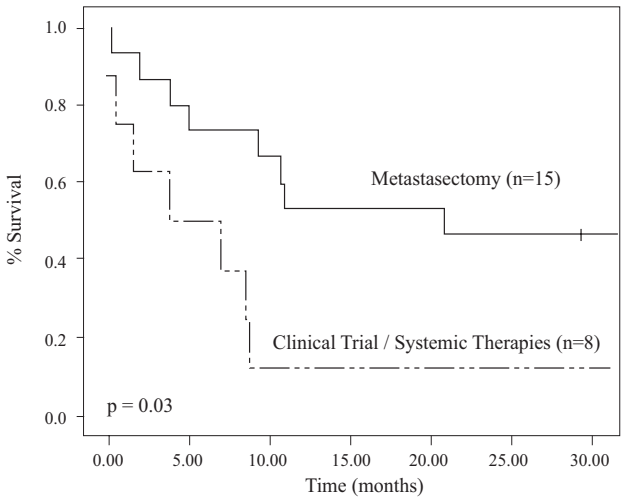

Fig. 1. Log-rank analysis of 15 patients who underwent metastasectomy vs 8 patients who were subjected to clinical trials/systemic therapies for gastrointestinal and/or liver metastases for Stage IV M1c melanoma.

Table 2. Comparison of Patients with Gastrointestinal and/or Liver Metastases Who were Subjected to Metastasectomy or Clinical Trial/Systemic Therapy

	Gastrointestinal and/or Liver Metastases from Melanoma		
	Metastasectomy	Clinical Trial/ Systemic Therapy	*P* value
Total	15	8	
Age (years)			0.11
Mean (sd)	70 (6)	63 (15)	
Sex			1.00
Male	5	2	
Female	10	6	
Site of Primary Tumour			0.62
Ocular	3	3	
Non-ocular	12	5	
Disease-free Interval			0.38
≤49 months	7	6	
>49 months	8	2	
Number of Metastatic Sites			0.69
= 1	9	4	
>1	6	4	
Multiple Metastases			0.03
No	10	1	
Yes	5	7	

shown to optimise the durability of loco-regional control with an acceptable morbidity that averts disfigurement, and complications of grafts or flaps through prospective randomised clinical trials.[12,13] Through the Multicentre Selective Lymphadenectomy Trial-I, sentinel node biopsy has been shown to improve staging, provide a more accurate depiction of prognosis, improve regional node field control, prolong disease-free survival and replaced the obsolete role of elective regional lymph node dissection that secured the oncological principles of melanoma management.[14] Nevertheless, the dismal outcome of patients with stage IV melanoma, particularly those with M1c disease, has not been rigorously investigated. This group of patients may receive surgery, radiotherapy, and are often subjected to clinical trials or receive systemic therapies.

There are currently no effective systemic treatment options in melanoma. Arguably the most effective agent in melanoma, Dacarbazine, when used alone or combined with Tamoxifen, demonstrates an overall rate of response ranging between 12% and 28% with a survival period of 4 to 12 months.[15] In an analysis of 6322 patients treated with systemic therapy from 83 studies published prior to year 2000, the median survival period of patients with

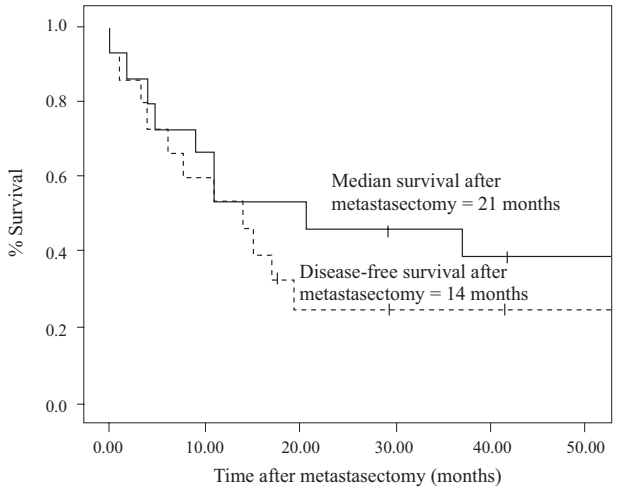

Fig. 2. Disease-free and overall survival of 15 patients who underwent metastasectomy for gastrointestinal and/or liver metastases for Stage IV M1c melanoma.

metastatic disease was 9 months.[16] However, in selected patients, complete surgical resection of metastases may be associated with 5-year survival rates of 5% to 25%.[17] Such evidence has strengthened the case for the need to reassess melanoma metastases to select patients for surgery in an era where there are still no proven effective systemic therapies.[17,18]

In the current series, metastasectomy performed in 15 patients have been shown to be able to derive survival periods of 1 to 116 months, with 6 patients (patient 4, 5, 6, 7, 10 and 11) surviving beyond 36 months. Three of these patients are still alive (patients 4, 5 and 6) having survived 116, 61 and 42 months, respectively. More importantly, there were also 7 patients (patients 1, 2, 3, 8, 9, 12 and 14) who died within 12 months of metastasectomy. Amongst these 7 patients, 4 (patients 1, 2, 3 and 8) had more than one site of metastases treated. As demonstrated in a log-rank analysis of survival in patients with single vs multiple metastatic sites who underwent metastasectomy, patients with single

Table 3. Detailed Clinical History, Treatment Information and Pattern of Failure of 15 Patients Who Underwent Metastasectomy

Patient	Site of Primary	Disease-Free Interval (months)	Sites of Metastases	Metastasectomy	Site of Recurrence	Overall Survival (months)	Status
1	Trunk	32	Gastrointestinal Lung	Right Hemicolectomy	Gastrointestinal	9	DOD
2	Trunk	37	Distant Lymph Node Liver	Left Hepatectomy Total Omentectomy	Peritoneum Gastrointestinal	5	DOD
3	Trunk	45	Distant Lymph Node Gastrointestinal	Small Bowel Resection	Abdominal Brain	4	DOD
4	Head & Neck	26	Liver	Left Hepatectomy Splenectomy	-	116	NED
5	Trunk	287	Liver	Right Hepatectomy	Liver	61	AWD
6	Unknown	-	Liver	Right Hepatectomy Right Adrenalectomy	Bone (Treated with laminectomy)	42	NED
7	Ocular	145	Liver Lung	Left Hepatectomy Segmentectomy (Seg 7/8)	Peritoneum Liver	66	DOD
8	Limb	13	Distant Lymph Node Liver	Extended Left Hepatectomy Portal Hepatis Clearance	Liver Lung	1	DOD
9	Limb	559	Liver	Wedge Resection (Seg 5/6)	Liver Lung	11	DOD
10	Limb	62	Liver	Extended Right Hepatectomy	Retroperitoneal Lymph Nodes	37	DOD
11	Ocular	373	Liver	Right Hepatectomy	Liver	71	DOD
12	Limb	77	Liver	Right Hepatectomy Ablation (Seg 3)	Liver Brain	11	DOD
13	Ocular	51	Brain Liver	Craniotomy with Radiosurgery Extended Left Hepatectomy	-	29	NED
14	Limb	229	Liver	Central Liver Resection	Brain	2	DOD
15	Unknown	-	Liver	Extended Right Hepatectomy	Retroperitoneal Lymph Nodes	21	DOD

DOD : dead of disease, AWD : alive with disease, NED : no evidence of disease

site of metastasis were associated with a longer survival period (70 vs 4 months; $P = 0.005$), hence suggesting that the extent of metastatic disease (i.e. single vs multiple sites), may be a prognostic marker post-metastasectomy. Though the comparison of disease-free interval (≤49 months vs >49 months) was not statistically significant in terms of survival outcomes, the numerical difference was large between patients who underwent metastasectomy ≤49 months following the curative treatment of the primary tumour who had a median survival of 9 months compared with those who underwent metastasectomy >49 months who had a median survival period of 37 months. This led us to suggest that this factor remained an important contributor to outcome post-metastasectomy but was not significant on the statistical analysis because of the small sample size. Both of these factors are surrogate indicators of the tumour biology and are useful information that may be included in decision-making when selecting patients for metastasectomy.

The major weakness of this report was the retrospective nature of the study. We have not predetermined the selection criteria for subjecting patients to metastasectomy unless a complete resection of the tumour burden was not an expected outcome or if they had other sites of metastases that would not have been treated. Clearly this would reflect a poorer prognosis group in the non-surgical comparator group that illustrates the differential survival. However, the important message is not to compare treatment modalities, which would only have been possibly achieved in a randomised clinical trial setting, but to show that surgery in suitable patients would confer a survival advantage.

An example of an approach to selecting patients for curative metastasectomy at the Memorial Sloan-Kettering Cancer Center, where patients with single-site asymptomatic metastasis are first treated with chemotherapy for 2 to 3 months to determine whether the lesion is a "first and only" or a "first of many".[17] Such an approach be it with chemotherapy as described, or as a brief period of initial watching, may serve to sieve out a portion of patients who would ubiquitously develop metastases at multiple sites. Such was apparent in the group of patients in this study that survived less than 12 months, where treatment failure was characterised by the development of multiple disseminated gastrointestinal metastases (patient 1 and 2), peritoneal metastases (patient 2), multiple brain metastases (patient 3, 12 and 14), multiple lung metastases (patient 8 and 9), and multiple liver metastases (patient 8, 9 and 12).

In a multicentre study of 4 major hepatobiliary centres that reported the treatment outcome of hepatectomy in 40 patients with melanoma liver metastases, the authors reported a median survival period of 28 months and demonstrated the impact of the site of melanoma in determining survival outcome with a longer median survival observed in ocular melanoma than cutaneous melanoma (29 vs 24 months).[19] From a bi-institutional study of two of the world's most established melanoma units, Rose et al[20] reported 24 of 34 patients who underwent surgical resection of melanoma liver metastases amongst which complete resection was achieved in 18 patients. The median disease-free and overall survival periods in patients undergoing surgery was 12 and 28 months, respectively. For gastrointestinal metastases who underwent curative surgery such that complete resection of all visible metastases are achieved, a median survival period ranging between 15 and 48 months may be achieved.[11,21,22] The survival result reported in this study parallel the reported results in the published literature and contributes to the growing body of evidence for the role of surgery in metastatic melanoma.

At a time when the systemic therapy for melanoma remains largely inadequate for achieving long-term survival, and that there is a paucity of data supporting the role of surgery, our data demonstrate that appropriately selected patients who undergo a complete metastasectomy may achieve sustained prolongation of survival.

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