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Surgery for Distant Melanoma Metastasis

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Abstract

Traditionally, distant metastatic melanoma has a poor prognosis due to lack of efficacious, FDA-approved systemic therapy and the limited use of surgical resection as a therapeutic option. More recently, new biologic therapies such as vemurafenib (Zelboraf) and ipilimumab (Yervoy) have showed strong promise and dramatically improved the landscape of stage IV melanoma therapy. Although there are numerous single-institution studies advocating the role for therapeutic surgical intervention, many remain skeptical of nonpalliative surgery for metastatic melanoma. Surgical resection of advanced melanoma has been proven to be effective as long as all disease is removed (R0). The combination of newer systemic therapies and surgical resection is currently under investigation. Understanding the tumor biology of melanoma and its mechanism of metastatic spread is essential to developing the most efficacious treatment strategy.

Keywords

Stage IV Melanoma; Surgery; Tumor Doubling Time

Of all malignancies, stage IV melanoma is one of the most aggressive with one of the worst prognoses. Patients diagnosed with American Joint Committee on Cancer (AJCC) stage IV melanoma (distant metastatic disease) are separated into three groups. Patients with M1a disease (distant skin, subcutaneous, or nodal metastases) have the best survival followed by patients with M1b disease (lung metastases), who in turn have a better prognosis than those with M1c disease (non-pulmonary visceral metastases or distant metastases with elevated lactate dehydrogenase [LDH] level). In general, distant metastasis confers a 5-year survival of only 5–10% and a median survival of 6–10 months, depending on the site of metastasis (Table 1).¹

This poor prognosis in part reflects metastatic melanoma's unique tumor biology, which distinguishes it from other advanced visceral solid-organ neoplasms. Most visceral, solid-organ cancers spread to the first capillary bed the venous drainage encounters; thus, colon cancer typically metastasizes to the liver through the portal venous system while sarcoma spreads first to the lung, enabling surgical resection for limited metastases. However, advanced melanoma spreads in an unpredictable fashion with widespread metastasis to any organ site but often to skin, lung, brain, liver, or small bowel. Given this complex metastatic

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profile, it is truly remarkable that one of the most effective therapies for distant metastatic melanoma is surgical resection,² rather than systemic medical therapy.

Systemic Treatment Options

Currently, there is no gold standard for treatment of stage IV melanoma. Surgical therapy for stage IV disease remains controversial. The National Comprehensive Cancer Network (NCCN) guidelines for first and second-line systemic therapy of stage IV melanoma are unclear about the role of surgery versus systemic therapy.^{3,4} Unfortunately, systemic therapies are traditionally associated with variable response rates, limited impact on survival, toxic side effects, and frequent lack of durable responses.⁵

The introduction of several new therapies in 2011 has dramatically changed the landscape of stage IV melanoma therapy. Two novel systemic treatments, a BRAF inhibitor (vemurafenib [Zelboraf]) and an anti-CTLA4 blocking monoclonal antibody (ipilimumab [Yervoy]), recently received FDA approval for advanced melanoma.

BRAF is an enzyme of the MAP-kinase pathway. BRAF inhibitors show immense promise for patients whose melanomas have the BRAF V600 mutation, with up to a 50% response rate. However, these responses are rarely durable and only 50% of melanomas have evidence of these BRAF mutations.⁶ Ipilimumab has delivered promising outcomes with response rates of 10.9% with long-term and durable response. Ipilimumab blocks CTLA-4 to potentiate an antitumor T cell response. While the outcomes are hopeful, these results are associated with significant side-effects including autoimmune toxicities such as severe colitis and drug-related mortality of 2.1%.⁷ Ipilimumab has also been used in conjunction with dacarbazine for an even more effective response (Table 2). However, serious grade 3 or 4 events were much higher in the ipilimumab plus dacarbazine group versus the dacarbazine and placebo group (56.3 versus 27.5% with $p < 0.001$).⁸

Other older systemic therapies and less efficacious FDA-approved treatments such as dacarbazine alone and interleukin-2 (IL-2) have had marginal impact on survival. Dacarbazine alone produces clinical responses in about 15–20% of patients, but the rate of complete response is only 3–5% and median duration of response is only about 4–6 months.⁹ Until recently, IL-2 was the only biological drug approved by the FDA and was considered the most aggressive therapy. Response rates can reach 20%, but responses are durable in only about 6% of patients. Moreover, IL-2 can have significant toxicity, including potentially fatal pulmonary edema and shock.¹⁰ Another immune modulator, interferon-alpha, has results which are just as abysmal with concomitant, significant toxicities.⁹

Despite the advent of new treatments this year, only marginal impact on overall survival has been observed with these systemic treatments for stage IV melanoma. Regardless, the first-line treatment offered to patients with metastatic melanoma is still often systemic therapy (chemotherapy or biological), leading us to question this algorithm.

RATIONALE FOR SURGICAL TREATMENT

Conventional teaching maintains that resection is not indicated in patients with distant metastases, except for palliation. This dogma stems from the concept that patients with multiple metastases usually also have occult micrometastases and circulating tumor cells. A study at John Wayne Cancer Institute (JWCI) by Koyanagi et al¹¹ showed that 52% of stage IV melanoma patients had detectable circulating tumor cells. Furthermore, subclinical occult metastases often lead to clinically evident disease soon after resection.¹² Therefore conventional logic would suggest their disease burden is not likely to be controlled by local surgery.

However, the development of metastases is a complex process. Tumor cells must extravasate from the primary lesion into the blood stream, avoid immune surveillance, adhere to a target organ's capillary endothelium, produce enzymes to invade the basement membrane and reach the interstitial space where they promote angiogenesis and attract growth factors to enable proliferation. Thus, despite their presence in the blood, only a small portion of circulating cancer cells can generate an organ site-specific metastatic deposit.¹³ In fact, 86% of patients with metastatic melanoma initially present with disease in only one metastatic organ site, although often there may be multiple metastases in that site. The most common metastatic site is the skin and lung, followed by lymph nodes, brain, liver and gastrointestinal (GI) tract (Table 3).¹⁴

The rationale for surgical resection of metastatic melanoma is multifactorial. Firstly, reduction of tumor burden through surgical resection limits disease progression by interrupting the metastatic cascade associated with hematogenous seeding of cells to other sites.¹⁵ Unlike chemotherapy, surgery can easily eradicate tumor masses 2 cm or larger.¹⁴ Secondly, surgery may reverse tumor-induced immunosuppression, restoring immune function and inhibiting metastatic progression.¹⁶ Thirdly, most patients tolerate surgical resection to a much greater extent than they can tolerate side-effects of systemic therapy. Improvements in surgical techniques, anesthesia, and intensive care unit treatments have reduced morbidity and mortality rates for even extensive surgical resection.¹ Patients generally recover quickly and can be discharged within a week following surgery. Recurrences after initial metastasectomy can also be treated through a secondary resection of metastases.¹⁷ Lastly, metastasectomy does not preclude systemic therapy; however, if metastasectomy is delayed, increasing tumor burden may make disease unresectable.

The advent of newer and better systemic therapies makes the role of surgical resection more relevant today than ever before. Advances in imaging with computed tomography (CT) and whole-body positron emission tomography (PET) have improved detection of early, resectable metastatic disease to the size of 5–10 mm, allowing for better preoperative planning through localization of even the smallest of metastatic sites for complete resection.¹⁸

PATIENT SELECTION

Stringent patient selection is essential. Surgery for advanced melanoma is most effective and confers the most advantage when disease is limited to a few sites and a small number of metastases (Figure 1).¹⁹ Factors to consider include site of disease, underlying co-morbidities, performance status, and duration of anticipated survival. Certainly, if a patient has limited predicted survival due to co-morbidities, then surgical resection of metastases may not be justified since it would not confer any survival or quality of life advantage.¹⁹

Tumor-volume doubling time (TDT) can assess the aggressiveness of metastatic melanoma and thereby identify candidates for metastasectomy. In 1971, Morton and associates first reported the prognostic significance of tumor doubling time in evaluating operability in pulmonary metastatic disease.²⁰ TDT is calculated by measuring changing diameters of each nodule. Median survival after pulmonary metastasectomy correlates positively with TDT; thus, patients with slow-growing tumors have better survival. Ollila and colleagues²¹ at the JWCI reported that median survival and 5-year rate of survival were 16 months and 0%, respectively, for a TDT < 60 days compared with 29.2 months and 20.7%, respectively, for a TDT ≥ 60 days. They concluded that the behavior and operability of the metastatic lesion and a patient's chances of survival are a function of tumor growth kinetics as expressed by TDT.

Another imperative surgical consideration is whether disease burden can be completely resected. Except for palliation to remove a bowel obstruction, stop bleeding or relieve symptoms, metastasectomy should not be considered unless resection of all metastases can be accomplished (Figure 2).²²

SURGERY FOR STAGE IV M1a DISEASE

Up to 40% of patients with stage IV melanoma have M1a disease (i.e., metastases of the skin, soft tissues, and distant lymph node basins).²³ Their median survival is 18–40 months, making an aggressive surgical approach defensible. Bulky nodal disease can often cause considerable symptoms. Surgical treatment for soft tissue disease should be performed before the lesions become symptomatic or bulky enough to necessitate a more extensive operation.²² Skin and soft tissue metastasis are usually associated with a better prognosis than distant lymph node disease. Positive prognostic indicators for M1a disease are fewer lesions, longer disease-free interval, and smaller size of tumors.²²

The surgical approach for M1a disease should be aggressive with 2-cm margins since the melanoma can infiltrate along tissue planes beyond the palpable tumor mass. Surgical treatment for M1a lymph node metastases is complete basin dissection. Axillary nodal disease should be removed by complete axillary lymph node dissection (levels I–III). Cervical lymph node metastases require complete neck dissection, and parotid disease requires superficial and deep parotidectomy and a modified neck dissection. Patients with inguinal nodal disease should undergo superficial groin dissection; however, if superficial nodes are palpable or contain multiple metastases, a deep groin dissection is warranted. Complete surgical resection of M1a disease can extend survival to 60 months, even after recurrence.¹⁷

SURGERY FOR STAGE IV M1b DISEASE

The lung is the most typical site of visceral metastases (12–36%) for melanoma. Pulmonary metastases are associated with a longer survival (10–11 months) than metastases to other visceral sites.^{14,24} Pulmonary lesions are typically asymptomatic and detected by routine chest x-ray. Factors predictive of improved survival include ability to achieve a complete resection, prolonged disease-free interval (>36 months), 2 or fewer pulmonary nodules (Figure 3),²⁵ no extrathoracic metastatic disease, prior response to chemotherapy/immunotherapy, and no evidence of nodal disease.

Compelling evidence for pulmonary metastasectomy exists. A report on long-term results of pulmonary metastasectomy for solid tumors, from the International Registry of Lung Metastases, was based on 5,206 patients from 18 departments. Among the subgroup of 282 patients who underwent complete resection of melanoma, 5-year survival was 21% and 10-year survival was 14%.²⁶ Multiple other studies have shown similar improvements in survival with resection of pulmonary metastases (Table 4).²⁷

Certainly, as in all cases of metastatic disease, patient selection is paramount for pulmonary resection. The morbidity of a thoracotomy mandates that a patient's baseline pulmonary condition be considered. Multiple and even bilateral pulmonary nodules are not a contraindication to surgery.²⁷ TDT is one of the major factors predictive of survival and should be used as a consideration in the decision of whether or not to operate. A longer TDT correlates with an improvement in survival and indicates that a patient is more likely to benefit from pulmonary resection (Figure 4).²⁵

The surgical approach should conserve normal lung parenchyma. Most metastases occur just below the pleura; segmental resection of a wedge of tissue ensures adequate local tumor

control. Lobectomy is occasionally indicated, but pneumonectomy is almost never required. Complete resection of pulmonary metastases can often improve 5-year overall survival from 4% to 20% and improve median survival from 10 months to 28 months (Table 4).²⁷

Tracheal and laryngeal metastases are rare, but endobronchial lesions do occur and patients are usually symptomatic with hemoptysis or cough. Diagnosis is made by endoscopy and biopsy. Treatment includes endoscopic fulguration, laser excision, external beam radiation, or, in very select cases, segmental resection or pneumonectomy.²⁹

SURGERY FOR STAGE IV M1c DISEASE

Gastrointestinal Metastasis

Melanoma metastasizes to the GI tract in only 2–4% of patients. However, around 50% of people who die of metastatic melanoma have GI involvement.³⁰ The most common sites of disease are the small bowel (75%), colon (25%), and stomach (16%). In fact, melanoma is the most common metastatic tumor in the small bowel, possibly because functionally active CCR9 on melanoma cells facilitates metastasis to the small intestine.³¹ Complete resection as for other metastatic sites is necessary for prolongation of survival. GI tract metastases are often symptomatic with pain (29–55%), obstruction (27%), bleeding (27%), palpable mass (12%) or weight loss (9%). As a result, palliative intervention is often indicated to relieve obstruction or bleeding.^{30,32}

Median overall survival of patients with nonpulmonary visceral metastasis is only 5–11 months. Complete resection, however, improves 5-year survival of these patients to 38–41%,³⁰ even in patients with synchronous sites of metastases. Features predictive of improved survival include lower incidence of spread to contiguous organs or retroperitoneum and low LDH levels (Figure 5).³⁰

Hepatic Metastasis

Liver metastasis occurs in 15–20% of patients with metastatic cutaneous melanoma. Hepatic resection for colorectal metastases is a common practice and its benefits appear efficacious for melanoma as well. Patient selection is again crucial. Patients should be considered only if they can be rendered surgically free of disease. Unfortunately, this is often not the case. In a study based on data from the JWCI and the Sydney Melanoma Unit, 35 of 1750 patients (2%) were considered surgical candidates. Ultimately only 24 patients underwent surgical resection and at exploration, only 18 patients were able to have a complete resection. Overall survival was 2–4 months for patients with unresected hepatic metastasis versus 28 months for those with completely resected hepatic metastases (Figure 6).³³ Multiple reports exist for hepatic resection in noncolorectal neoplasms metastatic to the liver.^{33–45} Results in melanoma are consistent with a prolonged survival with resection (Table 5).³³ Whether radiofrequency ablation, cryosurgery, hepatic perfusion, and microwave ablation are as effective as surgical resection remains to be seen, but these treatments may prove to be effective adjuncts to reduce overall tumor burden.

Metastasis to Spleen, Adrenal Glands, or Pancreas

Patients with metastasis to other visceral sites including spleen, adrenal glands, and pancreas have a dramatic improvement in survival with resection. A JWCI study of 60 patients demonstrated that 5-year survival improved from 0% to 24% (Table 6).⁴⁶

Brain Metastasis

More than 50% of patients with stage IV melanoma will develop clinically detectable brain metastases. Sixty percent of these metastases become symptomatic. Cerebral metastases

account for 20–54% of deaths from melanoma and at time of death 65–70% of patients with metastatic melanoma have brain metastasis.⁴⁷

The development of brain metastases is associated with a very poor prognosis, with a median overall survival of approximately 4 months.⁴⁸ Surgery can improve this survival to 6–22 months.⁴⁹ The routine use of MRI for screening has dramatically improved the detection of asymptomatic CNS disease. Positive prognostic factors include younger age, good performance status, lack of neurologic symptoms, lack of extracranial disease and single focus of disease. Surgery is often preferred to whole-brain radiation as hemorrhage and edema are the major cause of symptoms. In select cases, radiosurgery and gamma knife surgery may be preferable to open surgical excision as these are often associated with less bleeding in and around the tumor.^{50–52}

Spinal Cord Metastasis

Melanoma metastases in the spinal cord are very rare and exceedingly difficult to manage.⁵³ Radiation and surgical decompression are the major treatments. A recent randomized study assessing treatment of metastatic tumors causing spinal cord compression showed that patients treated with surgery retained the ability to walk significantly longer than those treated with radiotherapy alone (median 122 versus 13 days), as well as an improvement in continence and motor function.⁵⁴

MULTIPLE SITES AND RECURRENCE

Multiple sites of disease are not a contraindication to surgical resection. The main consideration is the extent of resection that can be performed. Recurrent stage IV disease is also not a contraindication to resection. Ollila et al¹⁷ reviewed their experience at the JWCI of 211 patients rendered clinically disease free by surgical resection of stage IV melanoma. Of these, 131 patients developed recurrent stage IV disease. Median survival following treatment for recurrent stage IV melanoma was 18.2 months after complete metastasectomy compared with 12.5 months after a palliative surgical procedure or 5.9 months after nonsurgical management. Five-year survival was 20% for patients in the complete surgical metastasectomy group compared with 7% and 2.1% for those in the palliative surgical and nonsurgical groups respectively. The two most important prognostic factors for survival after recurrence were prolonged disease-free interval prior to recurrence ($p=0.0001$) and complete surgical metastasectomy of the recurrence ($p=0.0001$). Our group has also reported specific cases of long-term survival after resection of recurrence at multiple sites (Figure 7).

NATIONAL DATABASE STUDIES

Wasif et al⁵⁵ reviewed all patients with stage IV melanoma in the Surveillance, Epidemiology and End Results (SEER) database (1988–2006). Of 4229 patients, 33.6% underwent metastasectomy and had a better median survival and 5-year overall survival rate than patients who did not: 12 months versus 5 months and 16% versus 7% ($p<0.001$). These differences were magnified in the subgroup of 1994 patients with M1a disease: median survival was 14 months versus 6 months, and 5-year overall survival was 20% versus 9% ($p<0.001$). The study further revealed that younger age and diagnosis from 2001–2006 were predictors of metastasectomy.

PROSPECTIVE TRIALS

MMAIT (Malignant Melanoma Active Immunotherapy Trial)

Recent series have shown that surgery confers a better long-term survival than systemic therapy; lending credibility to the theory that complete surgical metastasectomy can render a

patient disease free with only short-term postoperative morbidity. Perhaps the most compelling data comes from the phase III randomized Malignant Melanoma Active Immunotherapy Trial for Stage IV disease (MMAIT-IV) from the JWCI. This trial was initially conceived to test the efficacy of an allogeneic whole-cell vaccine (Canvaxin) plus Bacille Calmette-Guerin (BCG) versus placebo plus BCG after complete resection of stage IV melanoma. Although this trial did not show a difference between treatment arms, it did show a notably improved, and surprisingly high, 5-year survival rate of 42.3% for the combined arms (39.6% in the vaccine arm and 44.9% in the placebo arm).⁵⁶ Given the lack of data conferring benefit to systemic therapy, surgical resection should be strongly considered as part of the treatment paradigm. The 10-year results of this trial confirm the durable long-term survival of surgical resection and will shortly be submitted for publication.

SWOG Clinical Trial S9430 (Phase II Trial of Complete Resection of Stage IV Melanoma)

Another prospective trial was performed by the Southwest Oncology Group (SWOG) in a small series of patients with metastatic melanoma. Physical exam and imaging were used to identify patients amenable to complete resection who then underwent surgery within 28 days of enrollment. Follow-up was performed using CT or PET imaging. Seventy-seven patients were enrolled from 18 different centers. After exclusion (stage II disease, incompletely resected tumor, or no melanoma in surgical specimen), the final outcome was 64 completely resected patients with a median overall survival of 21 months, leading the authors to conclude that aggressive surgical therapy with follow-up adjuvant therapy could be the best chance for cure (Figure 8).⁵⁷

THE FUTURE OF SURGERY FOR STAGE IV MELANOMA

In study after study, the evidence has shown that systemic treatment does not provide equivalent improvement in survival as complete metastasectomy. Unfortunately, as compelling as this evidence is, most data for stage IV metastasectomy is based on single-institution retrospective reviews. The two multi-institutional studies, SWOG S9430 and MMAIT-IV, confirm that complete resection leads to a survival benefit in stage IV melanoma.^{57,58} Opponents of metastasectomy postulate that surgery for stage IV patients with multiple metastases is a local therapy and unlikely to be of value for the management of disseminated disease. They are also correct in noting that there is little evidence from randomized controlled trials. Selection bias continues to be a downside of various single-institution studies. In addition, there is no standardization of surgical procedures for stage IV metastasectomy, thus making it difficult at times to justify the aggressiveness of a surgical approach.

A multicenter stage IV surgery study currently open at worldwide sites should provide data to define the role of surgery in stage IV melanoma. This study is a phase III, randomized trial of surgical resection, with or without BCG, versus best medical therapy as initial treatment for patients with resectable stage IV melanoma (NIH Clinical Trials Identifier NCT010013623).

Currently no therapy other than surgery can render a patient disease-free with only a short period of treatment-associated morbidity. In appropriately chosen patients with stage IV melanoma, surgery should be considered as an initial therapy rather than a salvage therapy. A multidisciplinary approach is essential given that after complete metastasectomy, melanoma is likely to recur so adjuvant systemic therapy may be necessary. In the end, a better understanding of the tumor biology of the melanoma is likely to be the key to determining what combination and sequence of therapies are most effective in the management of stage IV melanoma.

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Figure 1. Cumulative survival of stage IV patients according to single or multiple sites (n = 444). Adapted with permission from Meyer et al.¹⁹

Figure 2.

Survival curves of 144 patients with nonregional metastatic melanoma who underwent complete versus incomplete resection of metastatic melanoma. Actuarial 5-year survival rate of patients undergoing complete resection was 28%. No patients who underwent incomplete resection survived longer than 5 years. Reprinted with permission from Wong et al.²²

Figure 3.
Survival of patients with one to four versus at least five melanoma metastases in the lung.
Reprinted with permission from Tafra et al.²⁵

Figure 4.

Survival after surgical resection of melanoma metastatic to the lung. Survival curves are based on the growth rates of the pulmonary metastases as determined by a tumor volume doubling time less than or equal to 60 days versus greater than 60 days. Reprinted with permission from Taft et al.²⁵

Figure 5. Survival of patients with melanoma and gastrointestinal tract metastasis undergoing surgical vs no surgical intervention ($P < .001$). Reprinted with permission from Ollila et al.³⁰

Figure 6.

Overall survival of patients undergoing resection of hepatic metastases. Patients with surgically resectable disease had a statistically better survival than patients who underwent exploration alone. Reprinted with permission from Rose et al.³³

Figure 7.

CT scans for a 39-year-old man show a pulmonary metastasis (top left), a perinephric metastasis (top right), and subsequent a small bowel metastasis (bottom). Despite multiple visceral sites of metastasis, this patient remains disease free more than 6 years after surgery and postoperative adjuvant immunotherapy with Canvaxin vaccine. Reprinted with permission from Faries et al.⁵⁹

Figure 8.

Kaplan-Meier estimates of overall survival (OS) for SWOG S9430 patients who underwent complete resection of all disease. OS was defined as the interval between complete resection and death due to any cause. Patients last known to be alive were censored at the date of last contact and are marked on the curve with a tic representing the last follow-up time. OS rates at specified time points with 95% confidence intervals are presented at the bottom of the figure. Reprinted with permission from Sosman et al.⁵⁷

TABLE 1

Survival in patients with metastatic disease in skin, soft-tissue, and lymph nodes; lungs; and gastrointestinal tract after complete metastasectomy

Author	Institution (Year)	Number of Patients	Median survival (mo.)	5-year Overall Survival (%)
Skin, soft-tissue and lymph node				
Eton et al ⁶⁰	MDACC (1988)	57	10	5%
Barth et al ¹⁴	JWCI (1995)	281	15	14%
Pulmonary				
Petersen et al ⁶¹	Duke (2007)	249	19	21%
Andrews et al ⁶²	Moffitt (2006)	86	35	33%
Leo et al ⁶³	International Registry of Lung Metastases (2000)	282	19	22%
Tafra et al ²⁵	JWCI (1995)	106	18	27%
Gastrointestinal, liver and adrenal				
Mittendorf et al ⁶⁴	MDACC (2008)	20	20.7	Not Listed
Collinson et al ⁶⁵	SMU (2008)	13	15	Not Listed
Rose et al ³³	JWCI, SMU (2001)	18	18.2	23
Ollila et al ³⁰	JWCI (1996)	46	48.9	41

Table 2

New systemic agents for stage IV melanoma, as compared with dacarbazine

	Prior Therapy	Response Rate	Median OS (mo)	12-month survival
Dacarbazine⁸	No	10.3%	9.1	36.3%
Ipilimumab (Yervoy) + Dacarbazine⁸	No	15.2%	11.2	47.3%
Ipilimumab(Yervoy)⁷ Secondary Therapy	Yes	10.9%	10.1	45.6%
Vemurafenib (Zelboraf)⁶	No	48%	9.5	45% (9 mo.)

TABLE 3

Characteristics of distant metastasis in 1521 patients with stage IV melanoma at initial presentation *

	Number of patients
Site of first metastasis	
Lung	473 (31%)
Skin, lymph nodes	278 (18%)
Brain	212 (14%)
Liver	177(12%)
Gastrointestinal tract	91 (6%)
Bone	81 (5%)
Multiple sites	209 (4%)
Number of metastatic sites	
1	1312 (86%)
2	126 (8%)
3	83 (6%)

* John Wayne Cancer Institute melanoma database

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TABLE 4

Survival after resection of pulmonary metastases

Author	Institution	Number of Patients	Median Survival	5-Year Overall Survival Rate
Leo et al ⁶³	International Registry of Lung Metastases	282	19 months	22%
Petersen et al ⁶¹	Duke (2007)	249	19 months	21%
Harpole et al ²⁸	Duke (1992)	98	20 months	20%
Andrews et al ⁶²	Moffitt	86	35 months	33%
Neuman et al ⁶⁶	Memorial Sloan Kettering	26	40 months	29%
Ollila et al ²¹	John Wayne Cancer Institute	45	23.1 months	15.6%
Tafra et al ²⁵	John Wayne Cancer Institute	106	23 months	27%

Adapted with permission from Caudle and Ross.²⁷

TABLE 5

Reported outcomes after hepatic resection for metastatic melanoma

Source, year	No. of Non-colorectal Metastases	No. of Melanoma Metastases	Melanoma Metastases		
			Median Overall Survival	Range of Overall Survival	5-Year Survival Rate
Foster, ³⁴ 1978	72	13	10 months	2–72 months	8%
Iwatsuki et al., ³⁵ 1983	19	1	-	-	-
Papachristou et al., ³⁶ 1983	-	3	16 months	-	-
Ekberg et al., ³⁷ 1986	8	3	19 months	5–72 months	-
Olak et al., ³⁸ 1986	30	1	-	-	-
Stehlin et al., ³⁹ 1988	30	4	13 months	3–52 months	-
Wolf et al., ⁴⁰ 1991	10	1	-	-	-
Karakousis et al., ⁴¹ 1994	2	2	-	-	-
Harrison et al., ⁴² 1997	96	7	-	-	-
Lindell et al., ⁴³ 1998	32	3	51 months	5–184 months	33%
Elias et al., ⁴⁴ 1998	147	10	20	-	<20%
Lang et al., ⁴⁵ 1999	140	10	-	-	22%
Rose et al JWCJ, ³³ 2001	-	24	28 months	2–147 months	29%

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Median overall survival and 5-year survival rate after surgical resection of intra-abdominal metastases at the John Wayne Cancer Institute.

TABLE 6

All Operative Patients				Complete Resection			Incomplete Resection		
No. of Patients	Median Survival (mo)	5-Year Survival Rate	No. of Patients	Median Survival (mo)	5-Year Survival Rate	No. of Patients	Median Survival (Mo)	5-Year Survival Rate	
Metastatic site									
Adrenal	26	20.0	9%	18	28.2	13%	8	7.7	0
Liver	15	14.1	20%	9	27.7	33%	6	10.4	0
Pancreas	8	23.8	37.5%	6	24.4	50%	2	8.2	0
Spleen	11	27.6	0	11	27.9	0	0	NA	NA
All Sites	60	20.9	17%	44	27.6	24%	16	8.4	0
Number of organ sites									
Single	30	27.6	23%	NA	NA	NA	NA	NA	NA
Multiple	14	27.5	25%	NA	NA	NA	NA	NA	NA

NA, not available

Adapted with permission from Wood et al⁴⁶