Complete metastasectomy in patients with stage IV metastatic melanoma

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Patients with stage IV melanoma have traditionally been managed with various systemic treatments; however, overall survival with this approach has been disappointing. Findings of many retrospective, single-institution, and multicentre studies suggest that participants treated with complete metastasectomy for stage IV metastases have enhanced overall 5-year survival. Complete surgical resection of metastatic disease to stage IV sites—including skin, soft tissue, distant lymph nodes, lungs, or other non-CNS visceral regions—offers the best chance for prolonged survival. This Review will present data lending support to the idea that if complete surgical metastasectomy is technically feasible, then surgery should be the first option for properly selected patients with stage IV melanoma.

Introduction

Far too often, the first treatment given to a patient diagnosed with stage IV metastatic melanoma (figure) is systemic therapy, either chemotherapy or biological drugs. However, results of trials of dacarbazine or interleukin 2 have been unsatisfactory, with complete responses uncommon and 5-year overall survival of about 5%. A partial clinical response to either drug enhances overall survival by only a few months. The reasons for this inadequate outcome of systemic therapy are many, and include poor effectiveness of peritumoral drugs against melanoma, deficient delivery of therapeutic agents to the tumour because of abnormal peritumoral neovascular blood flow, and drug resistance. The only patients with stage IV disease who have a reasonable chance of durable and increased 5-year survival are those who have a complete clinical response. New treatments are being investigated internationally in phase III clinical trials and, if successful, will offer alternative therapeutic approaches.

Until new drugs are proven to be effective by prospective randomised clinical trials, the strategy for management of distant metastases in patients with melanoma needs to be reassessed. Conventional teaching has been that resection is not indicated in people with blood-borne metastases to distant sites because the cancer is widely disseminated and its control by local surgery is impractical. Nevertheless, results of several series have shown long-term survival after resection of distant metastases in patients with stage IV melanoma. In this Review, data lending support to use of surgery as the initial treatment option for properly selected individuals with few sites of stage IV metastatic melanoma will be discussed.

Systemic treatment options

The role of chemotherapy in the treatment of melanoma remains controversial, with only a few drugs showing in-vivo activity. Dacarbazine and its active metabolite temozolomide remain the most active single agents, each of which show clinical response in about 15–20% of patients and complete response in 3–5% of patients, although the median response duration is only 4–6 months. Findings of a randomised phase III study of temozolomide versus dacarbazine in patients with metastatic melanoma showed that both drugs were equally effective, with response rates for temozolomide of 13% and dacarbazine of 12%, including a 3% complete response rate for both drugs and similar median survivals. One important thing to note about this trial, however, is that participants with brain metastases, who in theory could benefit from CNS penetration of temozolomide, were excluded. Data for small retrospective reviews suggest a benefit of temozolomide in these individuals, and multi-institutional trials are being implemented.

Interleukin 2 is the only biological drug approved by the US Food and Drug Administration (FDA) for patients with stage IV metastatic melanoma. Instead of acting on melanoma cells directly, it activates cytotoxic T lymphocytes and natural killer cells. Because of data...
indicating a dose-response relation, high-dose treatment with interleukin 2 has been standard in the USA.\textsuperscript{10} In a phase II trial\textsuperscript{10} from the National Cancer Institute that tested high doses of the substance in patients with metastatic melanoma, objective responses were recorded in 20\% of participants, with complete responses in 7\%. This initial enthusiasm has been tempered by the toxic effects associated with interleukin 2, including potentially fatal pulmonary oedema and shock. These side-effects must be balanced against the true potential for a durable complete response. Selection of patients is very important.

New effective drugs are urgently needed for treatment of stage IV melanoma. No new drug has been sanctioned by the FDA since 1996, when interferon alfa 2b was approved. Worldwide, investigators are undertaking phase III clinical studies to see whether any drugs with promising phase II data will be suitable for a prospective randomised trial. Such new treatments include inhibitors of MEK and BRAF family kinases, antibodies against cytotoxic T lymphocyte 4, and angiogenesis inhibitors.

With the fairly poor response to chemotherapy and biological drugs, investigators have combined chemotherapeutics (cisplatin, vinblastine, dacarbazine) with biological substances (interleukin 2, interferon alfa) known to be active against melanoma. This combined approach is referred to generically as biochemotherapy.\textsuperscript{11–13} On the basis of promising phase II data,\textsuperscript{14–16} several randomised phase III trials were undertaken to investigate the addition of high-dose interleukin 2 and interferon alfa to chemotherapy. Unfortunately, none of the studies noted a significant difference in survival with interleukin 2; however, definite increases in toxic effects were recorded.\textsuperscript{17–19}

Collectively, monotherapy—either chemotherapy or biological drugs—at best has a 7\% complete response rate. This poor response to systemic treatment has led investigators to pursue locoregional approaches to haematogenous stage IV melanoma.

Rationale for surgical treatment
Understanding the anatomical sites of metastatic cancer spread began more than 100 years ago when Paget proposed the seed-and-soil hypothesis to account for non-random distribution of metastases detected in autopsy samples.\textsuperscript{20} In these samples, Paget noted site-specific spread of some cancers—eg, ocular melanoma to the liver—and postulated that particular tumour cells can only metastasise to specific organs. 40 years later, Ewing\textsuperscript{21} suggested a very different mechanism that linked metastasis to blood flow. According to his idea, circulating tumour cells lodge in the first capillary network from the primary tumour. Thus, colon cancers would spread to the liver whereas sarcomas would metastasise to the lung. Both theories are probably partly correct but neither accounts for the complexity of the metastatic process. Establishment of a visceral metastasis is a complex process, and only a small proportion of tumour cells circulating in the blood are successful at initiating a metastasis that can grow at a distant visceral site. However, once the distant site is established, and is the only area of metastatic disease, then a local treatment such as surgery should be considered.

Complete resection of distant metastases with tumour-free margins has not been a popular strategy for management of patients with American Joint Committee on Cancer (AJCC) stage IV disease because it is regarded as a local treatment. Historically, local treatments, such as surgery or radiotherapy, have been used only in patients with blood-borne metastases to palliate symptomatic disease. To be clear, complete metastasectomy is total resection of all radiographic and clinically evident sites of stage IV disease with histological tumour-free surgical margins. Most patients recover fully from the procedure—even thoracotomy\textsuperscript{22,23} or laparotomy\textsuperscript{24,25}—within 6 weeks, compared with people who have several months of toxic effects with a systemic treatment. In patients with various histological tumour types undergoing metastasectomy for distant metastases, long-term survival has been reported, suggesting that complete resection has a role in management of stage IV disease.\textsuperscript{6–10}

Staging system
The staging system for melanoma has undergone major modifications on the basis of enhanced understanding of tumour biology and outcomes data provided by several large prospective databases. The AJCC issued a revised TNM classification system that recognised clinical and pathological features distinctive to melanoma, which serve as prognostic markers.\textsuperscript{26–30} Their recommendations were based on the AJCC melanoma database that combined several prospective databases and included information for 17 600 patients at all stages of disease, with data for at least 5-year follow-up for 73\% of patients and at least 10-year follow-up for 49\%. This revised system came into effect in 2003, and included designations for primary melanoma with or without ulceration, for number of involved lymph nodes, and for microscopically positive versus macroscopically positive lymph-node involvement, and for variability in stage IV metastatic sites.\textsuperscript{31} This new classification system was then validated by another prospective melanoma database of patients' information from 13 institutions and cooperative study groups.\textsuperscript{32}

When assessing the prognostic importance of various factors, the anatomical site of stage IV tumours consistently correlates with survival.\textsuperscript{33} This relation between prognosis and anatomical site is shown in the new AJCC staging system, which divides stage IV metastatic disease into M1a for skin, soft tissue, or distant lymph-node metastases, M1b for pulmonary sites, and M1c for all other visceral lesions or any other distant site with raised concentrations of lactic
dehydrogenase. In the AJCC validation study, 1158 patients with stage IV melanoma in the database were analysed, and the most notable difference in survival was reported between non-visceral (skin, soft tissue, and distant lymph node) and visceral sites. In several other studies, the location of metastases in melanoma has been shown to be important, with non-visceral sites (M1a) faring the best, followed by pulmonary metastases (M1b), then other visceral (M1c) locations.

Use of radiology to ascertain the anatomical sites of stage IV disease is controversial. PET with 18-fluorodeoxyglucose (FDG) is thought to be more sensitive by some investigators at detecting metastatic disease than conventional anatomical imaging techniques such as CT. However, the surgeon does not have corresponding anatomical scans to ascertain whether a metastasis is resectable. The technological advance of obtaining simultaneously a non-contrast enhanced CT and a PET scan allows the surgical oncologist to say whether a FDG-avid area is resectable. If available, this imaging combination is preferred by clinicians to select patients who might be candidates for complete metastasectomy.

### Skin, soft-tissue, and distant lymph-node metastases (M1a)

Outside the first draining regional nodal basin (stage III disease), skin, soft-tissue, and distant lymph-node metastases are the most usual sites of melanoma metastasis, comprising up to 40% of stage IV cancers. These sites have a more favourable prognosis than any other location—a fact recognised by the revised AJCC staging system, which classifies these sites as M1a disease. Because this group of patients with stage IV metastatic melanoma has the best outlook, an aggressive surgical approach is warranted as long as complete resection with tumour-free margins can be achieved. Median survival for all people with skin, soft-tissue, and distant lymph-node metastases, whether or not they are resected, ranges from 10 to 18 months. However, survival can rise to 24 months if complete metastasectomy is done (table).

Even within this group of patients with M1a disease, specific subsets have been identified who have better outcomes. For instance, individuals with skin and soft-tissue metastases fare better than those with distant lymph-node disease. In patients with dermal or subcutaneous metastases, the number of lesions, disease-free interval, and size of tumours have been noted as prognostic indicators. Irrespective of the site of M1a disease, these individuals have the best outlook of any patients with stage IV disease, and all efforts should be made to undertake complete resection of skin, soft-tissue, and lymph-node metastases. People with symptomatic unresectable disease might benefit from palliative excisions to alleviate symptoms.

### Pulmonary metastases (M1b)

In patients with metastatic melanoma, the lungs are the most typical site of visceral metastases, with various series reporting prevalence between 12% and 36%. Most pulmonary lesions are asymptomatic and, therefore, are detected by routine screening by chest radiography. Symptoms such as cough, chest pain, and haemoptysis are usually signs of advanced disease. Suspicious nodules noted on a screening chest radiograph should be investigated further by CT scan to better characterise the number and type of the lesions. The possibility of benign findings and other primary tumours must always be considered.

For patients with pulmonary metastases as their only site of visceral disease, complete metastasectomy with tumour-free margins enhances survival (table). Harpole and colleagues reported 5-year overall survival of 20% in people who underwent complete pulmonary metastasectomy versus 4% in those who were not completely resected. Similarly, Tafra and co-workers recorded 5-year overall survival of 27% in patients with pulmonary metastases who underwent complete resection compared with 3% in those treated nonsurgically.

However, the evidence for use of metastasectomy for pulmonary metastases is based on findings of retrospective reviews rather than on data from randomised trials, so selection of patient is still mostly left to the surgeon’s judgment. Although people with individual lesions have the best outlook, those with several metastases should still be assessed for surgical options since they might have a survival advantage after
metastasectomy if complete resection can be done.22,43,44 Multiple nodules and bilateral disease are not definite contraindications to resection if the patient can be rendered free of disease. Certainly, if complete resection can be reasonably attempted with tumour-free margins while ensuring good postoperative functional status then aggressive surgical treatment is warranted. Although some people might benefit from palliative resections, only complete resection offers a survival benefit (table).

**Gastrointestinal metastases (M1c)**

Findings of autopsy studies show that melanoma metastasises to the gastrointestinal tract in 2–4% of patients.6 However, around 50% of people who die of disseminated melanoma have gastrointestinal involvement.56,57 The small bowel is the most usual site (75–90%), followed by colon (20–25%), and stomach (3–16%).51,52 Patients with gastrointestinal metastases are usually (but not always) symptomatic, with anaemia (60%), abdominal pain (29–59%), bleeding (26–40%), obstruction (27%), palpable mass (12%), or weight loss (9%).22,43

As with other sites of stage IV melanoma metastases, the technical ability to undertake complete metastasectomy is the best prognostic indicator.44 Data for several single-institution studies show augmented overall survival after total resection, with median survival increasing from 5–8 months to 15–49 months after complete metastasectomy (table).24,51,55 Even patients with many gastrointestinal metastases should be referred for surgical assessment because median survival does not differ between individuals with one versus many synchronous sites, as long as complete resection can be achieved.46 In symptomatic patients in whom complete metastasectomy is not possible, a palliative procedure should be undertaken since it is successful at alleviating symptoms more than 90% of the time.24,51,55

**Stage IV metastasectomy trial**

Unfortunately, most published data for metastasectomy for patients with stage IV melanoma are for single-institutional series. Opponents of this procedure cite the scarcity of evidence from randomised controlled trials that lend support to this aggressive surgical approach. Furthermore, critics emphasise the inherent selection bias in any single-institution series, with only the best candidates chosen for surgery. Finally, even advocates for metastasectomy admit that neither standardisation of surgical procedures nor quality control have been done.

One of the staunchest advocates of metastasectomy in patients with stage IV melanoma, Donald Morton, recognised these shortcomings and launched an international trial.57 To be eligible for the study, all participants had to have undergone complete metastasectomy of their stage IV metastases with tumour-free surgical margins. After surgery, patients were randomly allocated to either adjuvant immunotherapy with onamelatucel-L or placebo. Although the main aim of the trial—to assess onamelatucel-L as an adjuvant treatment after surgery—did not show a survival benefit, two important conclusions were made.

First, correct selection of patients is vital. Only people with three or fewer visceral sites of stage IV disease who could be rendered clinically and radiographically free of disease were eligible for this trial. To ascertain the extent of disease and resectability, some institutions relied heavily on CT, others on PET scans, whereas others depended on fusion PET and CT. More data from this trial are needed before commenting on which imaging modality is more effective or whether they were, in fact, equivalent.

Second, uniformity of resection can be accomplished in an international, randomised controlled trial. Surgeons from around the world undertook similar complete metastasectomy procedures for various anatomical sites and achieved tumour-free surgical margins. This similarity in resections led to an unprecedented 40% 5-year survival for the entire study cohort.58 Such results for 5-year survival have not yet been achieved in a randomised controlled trial of stage IV melanoma. More importantly, a 40% 5-year survival rate has, so far, not been seen in any study of chemotherapy or biological treatment for patients with stage IV melanoma.

Data for this randomised controlled trial diffuse several arguments against an aggressive surgical approach for patients with stage IV disease.57 The findings lend strong support to the idea that the best initial option for patients with stage IV disease is not systemic chemotherapy or biological treatment but, rather, complete metastasectomy, if technically feasible. Thus, the first step for people with newly diagnosed stage IV disease should be assessment of resectability by a skilled surgical oncologist.

**Conclusion**

Systemic treatments for people with stage IV melanoma, to date, do not confer the survival advantage of complete metastasectomy.59 The time has come to reposition surgery as the first option for properly selected patients with stage IV disease, as long as complete metastasectomy can be undertaken. This procedure, irrespective of the anatomical site, confers survival advantages not seen with other treatment modalities.25,54,55 Use of this aggressive surgical approach should be tempered with the knowledge that incomplete resections put patients at increased risk without any proven survival benefit and should be reserved only for palliation of symptoms.

The ideal therapeutic approach for stage IV melanoma patients would be complete metastasectomy followed by a new adjuvant treatment that is effective and can prolong 5-year survival beyond that of mere resection. Medical and surgical oncologists need to work together to develop the best strategy for this group of people.
Conflicts of interest
I declare no conflicts of interest.

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