



Pulmonary metastasectomy in the era of targeted therapy and immunotherapy

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Abstract: Metastatic melanoma is a fatal malignancy with a high mortality and morbidity. Since the early 1970s, available medical therapies were limited in improving survival. Surgery represented the best chance for a cure. However, surgery could only be offered to selected patients. The current landscape of treatment has radically evolved since the introduction of targeted and immunotherapies including BRAF and MEK inhibitors, and checkpoint blockers, like PD-1 and CTLA-4 antibodies. These new therapies have seen survival rates matching, and in some cases surpassing, that of surgery. Anti-PD1 and CTLA-4 combination treatments are associated with severe side effects and BRAF and MEK inhibitor combinations may trigger initial tumour responses but prolonged use have resulted in the development of resistant tumour clones and disease relapse. This review examines the role of pulmonary metastasectomy for lung metastasis from malignant melanoma in the current landscape of effective targeted therapy and immunotherapy.

Keywords: Melanoma; metastatic melanoma; pulmonary metastasectomy

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Introduction

In 2018, there were 287,723 cases of new cutaneous melanoma diagnosed worldwide and 60,712 deaths occurred attributable to the disease. Australia has the highest incidence of cutaneous melanoma in the world—33.6 per 100,000 person-years (1). Risk factors for melanoma include sunburns due to ultraviolet (UV) light exposure, the presence of melanocytic or dysplastic naevi, a personal and/or family history of cutaneous melanoma and fair skin-type (2). It is estimated that from data available from the United States, 4% of all melanoma diagnosed present with stage IV disease with distant metastases (3). The estimated 5-year survival of metastatic melanoma in 2015 was 6%, and the estimated

median overall survival was 7.5 months (4). The most common site of metastases is the lungs, affecting up to 30% of patients with metastatic disease (5).

Previously, metastatic melanoma heralded a grim prognosis due to the ineffectiveness of chemotherapy (6). Surgical treatment of metastases rarely occurred as distant metastases precluded a curative resection and if performed, it was typically reserved for a palliative intent (7). However, in selected patients with limited volume metastases, surgery was performed with a curative intent if a complete resection of metastases could be achieved. In selected patients with pulmonary metastases, a median survival of up to 18.3 months, and 5-year survival rates of up to 35.1% were achieved (8). The failure to identify effective chemotherapy agents coupled with the growing

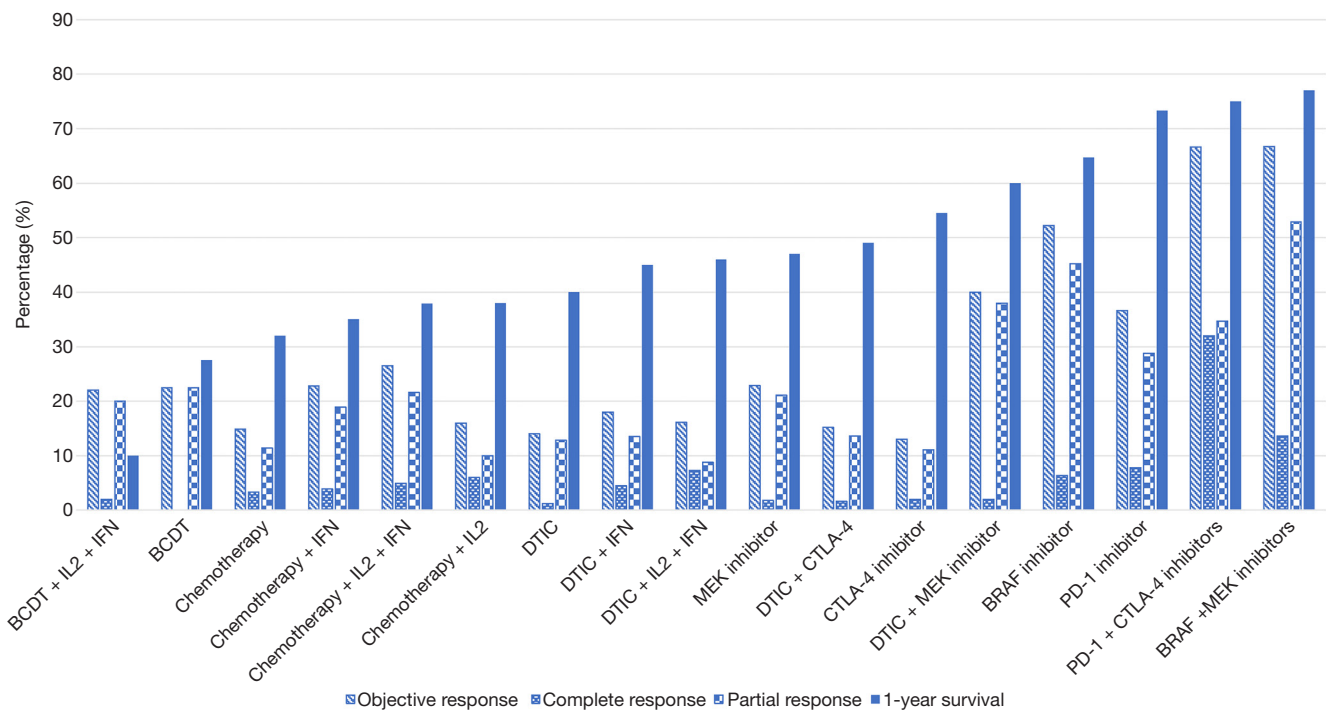


Figure 1 A comparison of different treatments for metastatic melanoma ordered according to one-year survival rates. Rates of tumour responses were also compared. “Chemotherapy” is used to summarise various treatments apart from dacarbazine and the Dartmouth regimen. BCDT, carmustine, cisplatin, dacarbazine, tamoxifen (Dartmouth regimen); DTIC, dacarbazine; IFN, interferon; IL2, interleukin-2. Summarised from: (12-30) and (31-40).

data on the immunogenicity of melanoma led to interest in immunotherapy, focused mostly around immunomodulatory cytokines such as interferon and interleukin-2. However, these agents failed to result in any significant tumour response nor improve survival (9). Recently, the introduction of new targeted and immunotherapies including BRAF- and MEK-inhibitors in association with programmed cell death (PD-1) inhibitors and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) has substantially improved outcomes of patients with metastatic disease (10).

With the significant survival gains observed, the role of surgery in patients with stage IV disease needs to be re-examined. A recent study from the Royal Marsden Hospital, in London, assessed patients undergoing surgery for stage IV melanoma before the time of effective systemic therapies (2003–2007) compared to after (2011–2015) with 69 patients in each group. The authors report the indication for surgery showed trends towards an increase in abdominal metastasectomy, decreased in-transit lesion excision and an increase in potentially curative operations for residual oligometastatic disease (11), suggesting a paradigm shift in

the role of surgery aiming for cure of metastatic melanoma. The improved tumour responses to the latest systemic therapies have achieved more effective systemic disease control that now allows surgical metastasectomy, in patients where surgery would ever have been performed. Therefore, the introduction of effective systemic therapies in metastatic melanoma requires a re-evaluation of the role of surgery. In this review, we aim to describe the progress in oncologic management of metastatic melanoma, review the role of pulmonary metastasectomy for metastatic melanoma and clarify the role of pulmonary metastasectomy in the current era of effective systemic therapy to provide best practice based on current evidence.

Medical management

Medical management can be divided into three broad categories: chemotherapy, immunotherapy and targeted therapy. A comparison of those therapies (and their combinations) are summarised in *Figure 1*. Metastatic melanoma had a grim prognosis before the advent of

effective targeted immunotherapies. The first chemotherapy trials for metastatic melanoma began in the 1960s, using 1-phenylalanine mustard, also known as melphalan (41). Melphalan, however, proved to be highly toxic and ineffective. The Hunterian Lecture, of the Royal College of Surgeons of England, delivered in 1968, refers to 29 cases of metastatic melanoma that were treated with melphalan and noted several limitations, namely the dependence on anatomical arterial supply, which may not correspond with the metastatic deposit, the high general toxicity and the rapid recurrence rate after treatment (42). From 1975 onwards, dacarbazine was the chemotherapeutic agent of choice. It has been extensively investigated and remains the only FDA-approved chemotherapeutic agent for this purpose (43). Despite its ubiquity in a variety of regimens in the pre-immunotherapy era, disease response was poor and temporary in most patients. Hill *et al.* found that less than 2% of patients treated with dacarbazine alone were alive at 6 years (44). Combination treatments involving dacarbazine, including the Dartmouth regimen (consisting of cisplatin, dacarbazine, carmustine and tamoxifen) were extensively studied, but did not yield a survival benefit over dacarbazine monotherapy (12), despite having an improved overall response rates of 26% versus 5% for dacarbazine monotherapy (45). Temozolomide, an orally-administered dacarbazine analogue, garnered attention due to superior bioavailability and central nervous system (CNS) penetration compared to dacarbazine (46). The tumour response and survival rates of patients with CNS metastases treated by temozolomide however, resembled that of patients receiving dacarbazine (47). Chiarion-Sileni *et al.* showed that the rates of brain metastases were unchanged when treated with temozolomide or dacarbazine in combination with cisplatin and interleukin-2 (IL-2) (48).

Immunotherapy for metastatic melanoma initially focused on immunomodulation, via administration of cytokines. Interferon (IFN), an endogenous protein that stimulates the immune system to recognise foreign proteins, was shown to be able to recognise and destroy melanoma cells. However, it did not improve response or survival in patients with metastatic disease. A phase III randomized study of 4 weeks of intravenous interferon- α -2b versus observation conducted by the Eastern Cooperative Oncology Group showed no discernible difference between the two treatment groups in terms of relapse-free or overall survival (P values of 0.964 and 0.558, and hazard ratios for interferon versus observation of 0.98 and 1.08 respectively) (49). IL-2 is a cytokine that promotes the proliferation of

melanoma-specific T-cells. It was first approved for use in metastatic disease in 1992. It has been shown that approximately 6% of patients can achieve a complete response to treatment. Although this represented only a small subset of patients, 60% of those complete responders had durable responses lasting beyond 122 months (50). IL-2 treatment is however highly toxic, and strategies to identify patients who are more likely to respond have proven elusive (51). Attempts to combine interferon and interleukin with chemotherapy have also been unsuccessful. A trial coordinated by the Eastern Cooperative Oncology Group failed to find an improvement in overall survival or durable responses after comparing chemotherapy combined with interferon and interleukin with chemotherapy alone (median overall survival 8.7 *vs.* 9 months respectively) (13).

The current renaissance in treatments of stage IV melanoma occurred following the introduction of checkpoint blockade, particularly to CTLA-4 and PD-1; and novel targeted therapies to BRAF and MEK. Melanoma cells are highly mutagenic, and quickly evolve mechanisms to evade the immune system. The principles of checkpoint blockade therefore involve antibodies to those molecular pathways that help melanoma escape immunity. Some melanoma variants overexpress programmed cell death protein 1 ligand (PD-L1/2), which binds to PD-1 on T-cells (9). This allows such variants to masquerade as self-cells and evade the immune response. Nivolumab and pembrolizumab are the two anti-PD-1 drugs that have been approved for use in metastatic melanoma (41). CTLA-4 is expressed on activated T-cells and regulatory T-cells, acting to suppress T-cell activity when bound to B7-1/2 (52). Ipilimumab is the only anti-CTLA-4 drug approved for use in metastatic disease. Overall, PD-1 inhibitors are superior to ipilimumab in efficacy and side-effect tolerance (2). However, ipilimumab combined with nivolumab is superior to ipilimumab and nivolumab monotherapy (53). Results from the phase 3 Checkmate 067 trial showed an unprecedented 60-month median survival with combination therapy compared to monotherapy alone (14). However, combination therapy is associated with a severe side-effect profile, necessitating more stringent monitoring. The side effects can range from mild skin manifestations like pruritus and dermatitis, to life-threatening complications like colitis, neutropaenia, agranulocytosis and cardiac dysfunction. A summary of these side effects is listed in *Table 1*. While most side effects are managed safely with glucocorticoid therapy, severe manifestations require immunosuppression (56). Reassuringly, the Checkmate 067 trial found no association with early cessation of combined

Table 1 Summary of treatment-related adverse effects for nivolumab + ipilimumab therapy and nivolumab and ipilimumab monotherapy

Adverse effects	Nivolumab + ipilimumab (N=407) [CheckMate-067 (54), -069 (24)]		Nivolumab (N=787) [CheckMate-037 (55), -066 (17), -067]		Ipilimumab (N=357) [CheckMate-067, -069]	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Skin (pruritus, rash, alopecia, vitiligo)	330	30	272	4	254	7
Gastrointestinal (diarrhoea, colitis)	259	79	127	12	163	54
Pulmonary (pneumonitis, dyspnoea)	51	13	14	1	20	1
Endocrine (hypothyroidism, hypophysitis)	73	3	27	0	23	2
Hepatic (raised ALT and AST)	144	62	24	7	27	7
Musculoskeletal (arthralgia, asthenia, myalgia)	52	1	59	0	29	0
Haematological (neutropaenia, thrombocytopenia, anaemia)	NA	NA	12	2	NA	NA
Miscellaneous (fatigue, pyrexia, headache, chills, nausea and vomiting, increased lipase, constipation, anorexia, abdominal pain, Guillan-Barre syndrome, demyelination, uveitis, transfusion-related reactions, drug hypersensitivity)	557	57	510	13	305	12
Cessation of treatment due to adverse effects		158		31		54

therapy for adverse events and diminished overall and progression-free survival. Together, this suggests that the efficacy of immunotherapy may be long-lasting. Preliminary findings of the concurrent Checkmate 511 trial comparing nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (NIVO3 + IPI1) to the first-line treatment of Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (NIVO1 + IPI3) have yielded decreased side effect profiles when treated with low-dose ipilimumab. In particular, the authors describe lower rates of diarrhoea, colitis and transaminitis. The duration of treatment was also longer, consistent with a lower rate of discontinuation. Long-term surveillance to assess survival of patients on the NIVO3+IPI1 regimen are ongoing, but preliminary results have shown similar overall and progression-free survival between the two groups.

Novel targeted therapies to BRAFv600 and MEK represent the cutting edge in treatments for BRAF-mutated melanoma. Treatment with BRAF and MEK inhibitors show rapid, durable responses regardless of tumour burden and location of metastases. Pooled data from the COMBI-d and COMBI-v trials demonstrated that 19% of patients treated with Dabrafenib and Trametinib combination therapy were

still alive at 5-year follow-up. A complete response occurred in another 19% of patients, and this was associated with a survival rate of 71% at 5 years (15). However, patients who have BRAF wild-type melanoma have poor responses to targeted therapy, and treatment options for this population are scarce should immunotherapies also fail (16). Targeted therapy also induces resistance through several pathways, which include BRAF gene amplifications and MEK1 and MEK2 mutations (57). Menzies *et al.* showed that 75% of patients treated with combination BRAF and MEK inhibition progress to new metastases, even with complete responses to their initial disease burden (58), signalling an urgent need for development of new therapies for this patient population. At present, resistant clones represent a significant challenge to effective targeted therapies. Whilst theoretical inhibitory targets exist within the MAPK pathway and to its downstream targets like ERK and CDK4 (57), no current effective therapies exist for resistant clones. However, the effectiveness of combined BRAF and MEK inhibition mean that they are now first-line treatment in patients with BRAFv600 mutated melanoma. The two treatments currently available are vemurafenib and cobimetinib, and

dabrafenib and trametinib. Patients with wild-type BRAF melanomas have limited options—for such patients anti-PD1 immunotherapy is the initial agent of choice (17).

Surgical management

Curative surgery for metastatic melanoma achieved by complete resection of metastasis, where possible, as previously stated has been associated with improved outcomes over traditional chemotherapy. A cohort analysis of 1,574 patients over 29 years at the John Wayne Cancer Institute demonstrated favourable survival rates for patients with distant skin, subcutaneous or lymph node metastases (median survival 35.1 months), gastrointestinal tract (GIT) metastases (median survival 36.7 months), and lung metastases (median survival 28.1 months). Patients with adrenal, brain and liver metastases had lower median survival rates (27.4, 21.9 and 18.2 months respectively) (59). A comparison between combination chemo- and immunotherapy versus curative surgery reported by Meyer *et al.* showed an improved median survival rate of 17 months in patients receiving curative resections regardless of metastatic sites, versus 5 months for patients receiving non-surgical treatments (60). The survival benefits conferred by curative resections are seen even in comparison to patients receiving CTLA-4 and PD-1 inhibitors. Deutsch *et al.* showed that patients who underwent metastasectomies of intestinal metastases achieved a median overall survival (OS) of 64 months, compared to 11 months when patients are treated by ipilimumab, nivolumab and pembrolizumab (61). A summary of the effectiveness of resection of pulmonary metastasis (AJCC 8th edition Stage IV M1b melanoma) are summarised in *Table 2*.

Patient selection for surgery represents a major hurdle in the provision of treatment. The number of distant metastases greatly influence survival rate. Surgery is therefore best suited for patients who have limited metastatic deposits at a single organ. The volume of the disease is important as reported by Tafra *et al.* who demonstrated that patients with solitary disease were more likely to be alive at 5-year follow-up compared to patients with multiple metastatic deposits following pulmonary metastasectomy (68). Also patients who are significantly comorbid or who have shown limited responses to chemo-immunotherapy are less likely to benefit from surgery (76). In addition, the biology as demonstrated by tumour doubling time (TDT) is an important factor regarding patient selection for pulmonary metastasectomy. The relationship between TDTs and survival is likely defined by the body's immune response to the disease and

is a measure of immunocompetence—if the TDT is rapid, it can be inferred that this implies a poor immune response and outcomes are therefore poor (70). Patients with TDTs of less than 60 days had a 5-year survival of 0 percent, whereas TDTs equal to or exceeding 60 days had a 5-year survival of 20.7% (77). The stringent selection criteria for surgery leads to a selection bias, as patients who fulfil the criteria are likely to be highly selected and with low volume metastases (78), which ultimately implies a more favourable disease profile that will most likely translate to better outcomes.

In the era of effective immunotherapies and targeted therapies further re-examination of the role of surgery is required. Effective targeted therapies have provided unprecedented survival rates. This effectiveness is seen also in patients with low volume disease, a demographic that was traditionally most effectively treated with surgery (79). A pilot study of 19 patients by He *et al.* showed durable responses in patients who were treated with metastasectomies combined with treatment by the BRAF inhibitor vemurafenib for more than 12 months (80). While the study was limited by a small sample size, it nevertheless portends an evolution in the role of surgery to complement targeted therapies, rather than being rendered obsolete by it. Recent reports have demonstrated an increasing role of surgery in the treatment of clones resistant to BRAF and MEK inhibitors (11), with one study reporting three of 69 patients (4.3%) requiring metastasectomies to remove clones resistant to immunotherapy and/or checkpoint inhibition. This mirrors the historical role of surgery as a last resort in most kinds of pathology when all other options are either exhausted or non-existent.

Systemic therapy now affords survival rates rivalling and even exceeding that of surgery in those selected cases in the past and even for patients with widespread metastases. The treatment strategies for lung metastases today has become complex. Without any available consensus guidelines, pulmonary metastasectomy must be discussed within the setting of a multi-disciplinary team comprising of surgeons, medical oncologists, radiologists, pathologists and other clinicians. If the melanoma lung metastasis is localised, the possible treatment options would include resection and adjuvant therapy or neoadjuvant therapy and pulmonary metastasectomy if the disease persists but without progression. In selected patients with widespread disease with partial tumour response to systemic therapy, consideration for surgery may be made if the disease is low volume, is amendable to complete metastasectomy and the surgery carries acceptable morbidity profile.

In conclusion, surgery remains relevant in the era

Table 2 A summary of survival data for resection of melanoma metastatic to lung

Author	Institution	Country	Publication year	N	Median survival (months)	3-year survival	5-year survival (%)	Prognostic factors
Feun <i>et al.</i> (62)	MD Anderson Cancer Center, Texas	USA	1982	26	16	NA	NA	NA
Overett and Shiu (63)	Memorial Sloan-Kettering Hospital, New York	USA	1985	17	19	NA	NA	NA
Wong <i>et al.</i> (64)	John Wayne Cancer Institute, California	USA	1988	38	24	NA	31	NA
Karp <i>et al.</i> (65)	New York University Medical Center, New York	USA	1990	22	11	NA	4.5	NA
Gorenstein <i>et al.</i> (66)	MD Anderson Cancer Center, Texas	USA	1991	54	18	NA	18	Site of first recurrence, DFI
Harpole <i>et al.</i> (67)	Duke University Medical Center, North Carolina	USA	1992	84	20	NA	20	Number of pulmonary metastases, DFI
Tafra <i>et al.</i> (68)	John Wayne Cancer Institute, California	USA	1995	106	23	37	27	Number of pulmonary metastases, TDT
Pastorino <i>et al.</i> (69)	18 departments of thoracic surgery in Europe, the USA and Canada	Multinational	1997	282	NA	NA	21	NA
Leo <i>et al.</i> (70)	European Institute of Oncology	Italy	2000	282	19	30	18	Time elapsed from primary tumour to pulmonary metastases, number of pulmonary metastases
Meyer <i>et al.</i> (60)	University Hospital of Erlangen	Germany	2000	10	28	NA	NA	NA
Dalrymple-Hay <i>et al.</i> (71)	Royal Prince Alfred Hospital, Sydney	Australia	2002	121	16	36.6	22	Number of pulmonary metastases, DFI, PET usage
Andrews <i>et al.</i> (72)	H.Lee Moffitt Cancer Center and Research Institute, Florida	USA	2006	86	35	50	33	NA
Petersen <i>et al.</i> (73)	Duke University Medical Center, North Carolina	USA	2007	318	17	28	21	NA
Neuman <i>et al.</i> (74)	Memorial Sloan-Kettering Hospital, New York	USA	2007	26	40	51	NA	Number of pulmonary metastases
Schuhan <i>et al.</i> (8)	Thoraxklinik am Universitätsklinikum, Heidelberg	Germany	2011	30	18.3	48	35.1	Gender
Chua <i>et al.</i> (75)	Melanoma Institute Australia, Royal Prince Alfred Hospital, Sydney	Australia	2012	292	23	42	34	Number of pulmonary metastases, size of metastatic deposits
Hanna <i>et al.</i> (6)	Cancer Research Institute, Queen's University, Ontario	Canada	2018	99	22.9	25	21	Size of metastatic deposits

DFI, disease-free interval; NA, not available; PET, positron emission tomography; TDT, tumour doubling time.

of effective immunotherapies and targeted therapies for metastatic melanoma, despite their unprecedented effectiveness. Modern medical therapies are associated with a side effect profile that may limit wider application. Surgical resection of pulmonary metastases will remain relevant specifically to achieve complete resection of metastases in patients with low volume metastatic disease and to address resistant clones after targeted therapy and immunotherapy. Together, the combined adoption of multimodality therapy with surgery, targeted therapies and immunotherapy has the potential to maximise melanoma survival outcomes.

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