



The non-responding adrenal metastasis in melanoma: The case for minimally invasive adrenalectomy in the age of modern therapies

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ABSTRACT

Background: Minimally invasive adrenalectomy has facilitated resection of resistant adrenal metastases. The adrenal gland may function as a sanctuary site for metastatic growth despite systemic therapy. The objective of the study was to assess the outcomes of selective minimally invasive adrenalectomy during immunotherapy.

Methods: Candidates included patients with adrenal metastases resistant to systemic therapy who underwent minimally invasive adrenalectomy.

Results: There were 15 patients undergoing 16 minimally invasive adrenalectomies. Patients received either immunotherapy or BRAF inhibition prior to surgery. The mean operative time was 130 min with a median length of hospital stay of 2 days. At a median follow up of 24 months, 7 patients have no evidence of disease, 6 patients had progression with eventual mortality, while another patients has stable disease with maintenance therapy. One was lost to follow up.

Conclusion: Despite an increase in objective durable responses in metastatic melanoma, there is still some site-specific resistance in isolated areas like the adrenal where early minimally invasive adrenalectomy remains indicated.

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Introduction

The prognosis for patients with metastatic melanoma still remains poor.¹ The relatively recent introduction of novel strategies for advanced melanoma has, however, substantially improved the 5-year survival rates and resulted in durable responses and selective long-term control.² These treatments have broadly included immunotherapies and signal transduction targeted therapies, the former as antibodies (anti-CTLA-4 and anti-PD-1 antibodies) directed against checkpoint inhibitory (CPI) molecules which

naturally suppress T cell activation response within tumors and the latter the BRAF and MEK inhibitors which regulate the proliferation and survival of melanoma cells.^{3,4} Both of these approaches have shown efficacy in phase III trials when compared with chemotherapy alone.^{5–7}

Despite the promise of these novel treatments, one of the hallmarks of melanoma has been its ability to evade immunological attack with some evidence that there may be metastasis-specific objective tumor responses that reflect not only the site of the metastasis⁸ but also the expressed tumor antigen burden and mutational load.⁹ There are several developments in the modern era of immune therapies which potentially single out and affect adrenal practice in advanced melanoma. Firstly, autopsy studies on patients with advanced disease have shown adrenal metastases in over half the patients, although antemortem diagnosis is

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uncommon.^{10,11} Secondly, the increased availability and use of CT scanning to assess the adrenal gland has resulted in a higher detection rate of adrenal metastases which are potentially resectable.¹² Thirdly, comparative historical studies have demonstrated survival advantage for those patients undergoing selected adrenalectomy when compared with non-operative treatment.^{13–17} Finally, minimally invasive approaches (laparoscopic and robotic) have become the operative standard for adrenalectomy when compared with historical open adrenalectomy cases showing marked reductions in morbidity, postoperative complications and length of hospital stay with equivalent oncologic safety.^{18,19}

The reason why some patients do not respond to the newer treatment regimens is currently unclear.^{20,21} The prospect that the adrenal gland may represent a sanctuary site relatively protected from systemic therapies,²² highlights the importance of surgical metastasectomy in disease control and possible survival advantage. In this study, we retrospectively examine the outcome in a select group of patients with melanoma who presented with adrenal metastases non-responsive to current therapy and who were managed by minimally invasive adrenalectomy.

Patients and methods

Ethical permission for retrospective analysis of the data pertaining to this study was provided by the ethics committees of the participating hospitals. Patient information was derived from electronic medical records kept in a prospective database. Patients were identified between January 2014 until May 2019 all of whom underwent a minimally invasive adrenalectomy for Stage IV melanoma. All patients undergoing adrenalectomy provided informed consent. Patients were operated in two medical centers, the Chaim Sheba Medical Center, Tel Hashomer, and the Carmel Medical Center, Haifa, Israel. The patient demographics, tumor characteristics and treatment modalities of the cases were recorded. Potential candidates for adrenalectomy included patients being treated systemically for stage IV melanoma, with either a solitary site of metastatic disease in an adrenal gland, or patients with multiple metastatic sites, in which the adrenal gland was resistant to systemic therapy without progression of any extra-adrenal site. All patients underwent preoperative cancer staging with a PET-CT scan. Patients were referred for surgical oncology consultation after multidisciplinary (tumor board) discussion and decision. Surgical candidate patients underwent an abdominal CT using an adrenal protocol to carefully define the vascular anatomy and determine operability. Operability was assessed by two surgeons trained and experienced in advanced minimally invasive techniques (DG, DH).

With the recent institutional acquisition of a robotic surgical device, (DaVinci Surgical System, Intuitive Surgical, Sunnyvale CA) two cases were referred for robotic adrenalectomy. Pre-operative systemic therapy was continued post operatively, either as an adjuvant, or as maintenance therapy in patients with other metastatic sites. Follow-up of patients after surgery included PET Scans at 6 monthly intervals followed by clinic visits in those cases where there was no evidence of disease (NED) and PET scans at 3 monthly intervals for cases with evidence of disease.

Results

Fifteen patients were identified from the database who underwent 16 minimally invasive adrenal metastasectomies including 6 females (total median age 66 years; range 45– years). Table 1 shows the relevant operative and follow-up data for the patient cohort, listed in order of clinical outcome. One case was re-operated for a contralateral adrenal metastasis 2 years after the first

adrenalectomy. The mean period of time between diagnosis of primary melanoma to surgery was 32.6 months (range 0–72 months) with all patients treated either with BRAF inhibition therapy (6 cases) or CPI (11 cases). There were 9 left and 7 right adrenalectomies, with 2 cases performed robotically (including one converted from a robotic to a laparoscopic approach). In this case, subhepatic exposure of the adrenal and its relationship to the inferior vena cava was limited requiring port insertion of a Nathanson liver retractor and conversion to a standard laparoscopic right adrenalectomy. The mean operative time for all cases was 130 min (range 65–283 min) with a median length of hospital stay of 2 days (range 1–4 days). In the cohort, there was no mortality with minimal morbidity including one extraction port incisional hernia (laparoscopically repaired a year later) and one abdominal wall hematoma around a trochar site where the patient was managed non-operatively with transfusion.

Surgical and Oncologic Outcome ~ At a median follow-up of 24 months (range 1–44 months) 7 patients had no evidence of disease and 7 had progressive disease, with one case of stable disease. Of those cases with progressive disease, 3 developed contralateral adrenal metastases following their initial adrenalectomy (one a right-sided isolated but inoperable metastasis, another an adrenal metastasis with widespread metastatic disease and the last case an isolated operable metastasis already mentioned). There was no patient with recurrence in the local adrenal bed. The median progression free survival (PFS) was 26 months. (Fig. 1). There were 5 patients who died during follow-up, 4 with brain metastases and one with widespread pulmonary metastases. One case with known brain metastases (presumed dead) returned to her home country and was lost to follow-up.

Discussion

Our retrospective study of a small select cohort of metastatic melanoma patients presenting with operable adrenal metastases after immunotherapy and anti-BRAF treatment shows that minimally invasive adrenalectomy is safe with minimal morbidity and is associated with medium-term survival. This data lends some support to comparative retrospective data showing survival advantage for surgery over conservative management^{13,14,17} particularly when metastasectomy is complete.^{14,16} In this regard, Branum et al.¹³ in a small number of cases showed an improved medium-term survival of resected cases when compared with unresectable patients (59 months vs. 15 months, respectively) with half of their completely resected patients living >5 years. Equally Haigh et al.¹⁴ showed a median survival advantage for complete over palliative adrenal resection (25.7 months vs. 9.2 months, respectively) as did Wood and colleagues¹⁶ where none of their incompletely resected patients (8/26) were long-term survivors.

In the age of modern anti-melanoma therapies, the benefit of incomplete metastasectomy in some series²³ might suggest either a selection bias in reporting or reflect the efficacy of the current systemic treatments in the control of residual disease. Although there was not a specific Unit policy towards a protocolized use of different systemic therapies, our data would favor selected adrenalectomy in those patients undergoing treatment who demonstrate stable disease or partial response in extra-adrenal sites during sequential imaging but who at the same time have adrenal progression. In the era of CPI, local excisional therapy for oligo-progression has been shown to be associated with a durable progression-free survival (PFS) in selected cases²⁴ with evidence that the patterns of failure, (either as progression in an established tumor or as a new metastasis), also correlates with the PFS.²⁵

In general, those patients suitable for surgery can be managed with minimally invasive techniques and without the need for open

Table 1
Operative and Follow-up data of the patient cohort.

Patient	OP Type	OP Time (min)	LOHS (days)	Disease Burden at Surgery	Outcome	PFS (months)	Site of First Progression after Surgery	Last clinic follow up. (months)
1	Lap	207	3	Adrenal Solitary lesion	NED	44		44
2	Lap	156	2	Adrenal Solitary Lesion	NED	22		22
3	Lap	141	2	Adrenal, Lungs, Liver	NED	20		20
4	Lap	105	4	Adrenal Solitary Lesion	NED	36		36
5	Lap	92	2	Adrenal Solitary Lesion	NED	24		24
6	Lap	105	2	Adrenal Solitary Lesion	NED	24		24
7 ¶	Robot ¥	155	1	Adrenal Solitary Lesion	NED	4		4
8	Robot	283	2	Adrenal, CNS, Lungs,	SD, AWD	15		15
9	Lap	182	4	Adrenal, Lungs, Subcutaneous	PD, AWD	19	Contralateral adrenal	30
10 ¶	Lap	110	1	Adrenal, CNS Lungs	PD	22	Contralateral Adrenal	22
11	Lap	132	2	Adrenal, Lungs,	PD, Presumed Dead	3	CNS	LTF
12	Lap	100	4	Adrenal, Peritoneum, Bone	PD, Dead	20	Contralateral Adrenal	24
13	Lap	65	2	Adrenal Solitary Lesion	PD, Dead	13	CNS	24
14	Lap	88	1	Adrenal Solitary Lesion	PD, Dead	10	CNS	12
15	Lap	66	1	Adrenal Solitary Lesion	PD, Dead	14	Lung	14
16	Lap	94	2	Adrenal Solitary Lesion	PD, Dead	26	CNS	26

¶ same patient.

¥ conversion robot to laparoscopy.

LOHS Length of hospital stay.

SD Stable disease.

AWD Alive with disease.

NED No evidence of disease.

PD Progressive disease.

PFS Progression free survival.

CNS Central Nervous System.

LTF Lost to Follow up.

conversion. The first description of laparoscopic adrenalectomy was reported by Gagner et al., in 1992²⁶ with many studies since then showing the advantages of the laparoscopic approach as the surgical gold standard in reducing morbidity, blood loss, post-operative pain, complications and recovery period.^{18,19} In our series, one case which was commenced robotically required conversion to a laparoscopic resection. Some debate concerns the validity of the minimally invasive approach for larger masses (exceeding 6 cm in maximal diameter)^{27,28} as well as for one of the types of cases in our cohort with a less readily accessible right-sided tumor.²⁹ Novel approaches such as the posterior retroperitoneoscopic adrenalectomy (PRA) and robotic adrenalectomy^{30,31} have been further developed alongside innovative haemostatic devices³² and single-port approaches.³³ In more difficult cases it is accepted that there may be a longer operating time and more intraoperative blood loss but that the postoperative morbidity appears to be related more to the need for open conversion.^{34,35}

The pattern of tumor response in the age of the newer targeted therapies and immunotherapies is often heterogeneous with relatively little currently understood about the determinants of response. The factors implicated in acquired resistance to anti-PD-1 therapy are currently unclear as are those which govern patterns of metastases towards isolated sites and longer disease-free intervals.³⁶ The prospect remains that despite an overall greater response to combination treatment protocols, that the adrenal may act as a sanctuary site with a concomitant future increase in the need for adrenalectomy.²² It is telling that three of our patients

recurred in the contralateral *in situ* adrenal, underscoring the propensity for possible site-specific escape from systemic treatment. The fact that some initial responders also progress later on in differential sites suggests an acquired resistance to CPI, an effect which may have bearing on the need for whole exome sequencing of metastatic deposits designed to reveal biologic signatures stratifying a predicted response.³⁷

There is evidence from Lee et al.⁸ that anti-PD-1 response is site-specific where in 27 patients enrolled in the KEYNOTE study complete response (CR) to pembrolizumab was more frequent with lung lesions. In this study if there was no evidence of an objective early response, the response overall was more heterogeneous in nature (i.e. newly progressing metastases with CR in other sites). Part of this differential response during anti-melanoma therapy is likely mediated by immune mechanisms specifically altering the tumor microenvironment of particular metastatic sites.^{24,38,39} One such example is the inhibitory effect on tumor infiltrating lymphocytes (TILs) and on tumor PD-1/PD-L1 expression in melanoma deposits during anti-PD-1 antibody treatment.⁴⁰ Even if the overall CR rates in metastatic melanoma patients is relatively low, however, a CR in individual metastases is a common event and may be durable. This effect is also more readily influenced by tumor size and site. Whether the immune-related adrenal insufficiency sometimes induced by CPI has any role in the heterogeneity of adrenal responsiveness is presently unclear.⁴¹

Our study has several limitations. The numbers of patients with adrenal metastases suitable for surgery are small and the

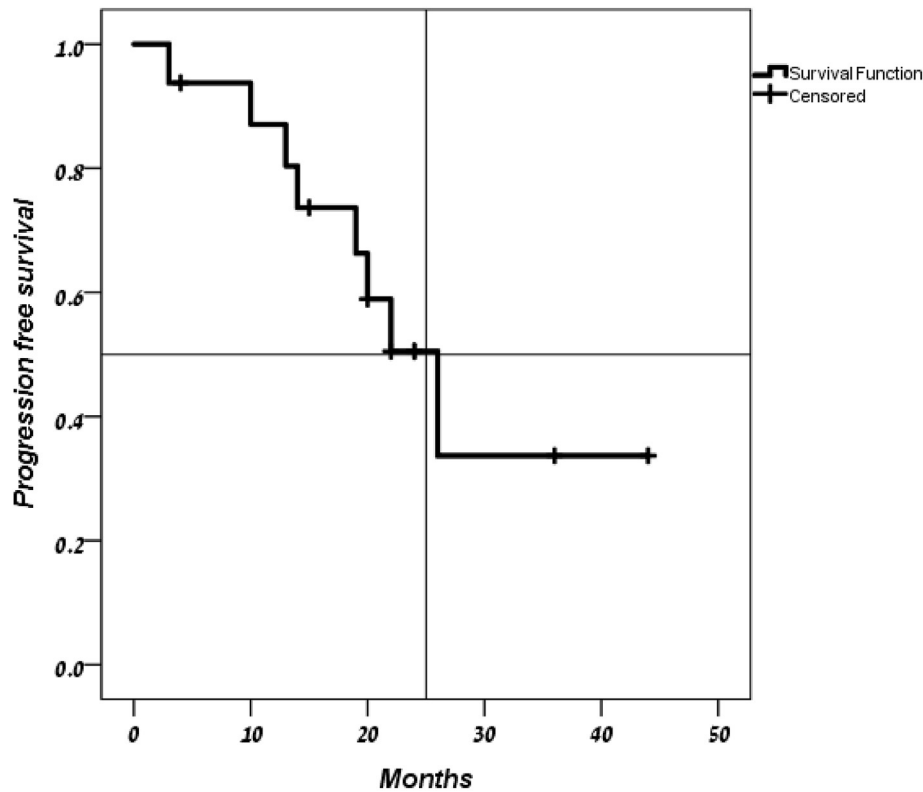


Fig. 1. Kaplan Meier plot for Progression Free Survival
Median Survival = 26 months.

retrospective design of the study will inevitably create biases towards particular therapies. Although we have shown prolonged PFS in selected cases, the study does not compare cohorts that were only managed medically. Current protocols of management towards isolated adrenal metastases where there is stable extra-adrenal disease may also change if immune response criteria are adopted in the future.⁴² In summary, our data shows encouraging medium-term PFS in a small series of selected cases of metastatic melanoma initially treated with targeted and CPI therapy who then undergo a minimally invasive adrenalectomy for adrenal progression.

Conclusion

Despite an increase in objective durable response in metastatic melanoma to immunotherapies and targeted treatments, there is still some site-specific resistance in isolated areas like the adrenal where early minimally invasive adrenalectomy remains indicated. This approach currently has merit in those patients with stable or regressing extra-adrenal disease. Data obtained from a larger series of patients undergoing checkpoint inhibition blockade for metastatic melanoma are required in order to confirm these preliminary observations and to elucidate the immunological and molecular nature of adrenal response.

Declaration of competing interest

The authors declare that there is no conflict of interest with any of the data submitted in this manuscript.

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