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Survival outcomes following adrenalectomy for isolated metastases to the adrenal gland

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ABSTRACT

Background: Adrenal metastases can arise from different primary sites. Surgical resection of the adrenal gland in patients with isolated metastases may offer improved survival in many of these patients. However, the benefit of surgery in this heterogenous group is often disputed. The aim of this study was to identify patients undergoing adrenalectomy for isolated metastases and to describe survival outcomes based on origin of the primary malignancy.

Methods: Patients undergoing surgery for isolated adrenal metastases were retrospectively analysed from a prospectively kept database. Data collected included the age of the patient, gender, size and functional status of the tumour and the site of the primary malignancy. Overall survival and survival based on the primary tumour were calculated using Kaplan-Meier survival analyses.

Results: 42 patients were included for analysis. The median tumour size was 40 mm. 91% (n = 38) of operations were performed laparoscopically. Metastases were from the following primary organs: kidney (n = 22), lung (n = 11), breast (n = 2), gastric (n = 1), skin (n = 3), liver (n = 2) and neuroendocrine (n = 1). Overall median survival was 56 (19–93) months with 95% of patients followed up for >6 months. There was a significant difference in median survival between primary organs of origin: 83(42–123), 14(9–18), 15 and 12(3–20) months ($p < 0.05$) for kidney, lung, breast and skin respectively.

Conclusion: There is a potential survival benefit for patients undergoing surgery for isolated adrenal metastases; however this survival benefit is greater in patients undergoing resection for metastases arising from kidney primaries. A selective approach should be adopted to identify patients that will clearly benefit from surgery.

Introduction

Adrenal incidentalomas are common with a reported incidence of 4–5% in patients undergoing cross sectional imaging, with an even higher incidence in the older population [1–3]. The majority of these tumours are benign and non-functional, however, a small proportion of these can represent metastatic disease especially in patients with a history of cancer [4]. A variety of primary tumours commonly metastasize to the adrenal gland with an autopsy review identifying adrenal mets in 27% of patients with malignancies [5]. The most common primary sites for adrenal metastases are renal, breast, gastrointestinal tract, lung and skin melanoma.

The management of adrenal metastasis can be controversial and without a clear evidence base or consensus guidelines. Some authors reported good outcomes in patients treated with surgery for isolated adrenal mets arising from different primary sites [6–8], with others reporting better survival with surgery over palliative chemotherapy in selected cases [9]. However the majority of these studies were case series and single centre studies. The question of whether adrenalectomy for adrenal metastases from certain primary sites is beneficial remains unanswered. Additionally, the role of molecular targeted therapy may offer the same survival benefit as surgery without the potential risks.

The need for clear surgical margins and avoidance of tumour spillage offers patients the best chance of survival and therefore the role of laparoscopy is a contentious issue in these patients. The aim of this study was to describe the survival outcomes of patients undergoing adrenalectomy for isolated adrenal mets and to compare these outcomes according to the primary site of origin.

Methods

Patients undergoing adrenalectomy for isolated adrenal

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metastases in a tertiary referral centre in the west of Scotland were retrospectively analysed from a prospectively kept database from 2000 to 2017. Patients with extra-adrenal metastatic disease or severe co-morbidities that precluded surgical resection were excluded.

Demographic data collected included age, gender and date of the operation. Tumour characteristics were also analysed. These included size of the tumour, functionality and type of imaging used to detect evidence of malignant disease. Tumour size was based on imaging rather than histology. The time from treatment of the original primary tumour to development and treatment of the metastatic adrenal deposit was recorded.

Functionality was assessed by measuring urinary and plasma metanephrines, overnight dexamethasone suppression tests and 24hr urinary cortisol, plasma aldosterone and renin. Imaging techniques included computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET). The surgical approach was also recorded – laparoscopic, open or converted. All laparoscopic procedures were transperitoneal using a 4 port technique.

The site of the primary malignancy was recorded by obtaining medical notes. Overall survival and survival based on the site of the primary malignancy was calculated using Kaplan Meier survival analyses and comparisons between the different sites by log rank testing. All analyses were calculated using SPSS.

Results

Forty two patients were included in our analysis with 22 males and 20 females. Forty patients had isolated metachronous adrenal tumours, with 2 patients having incidental adrenal metastases without a known primary prior to diagnosis. The indication for surgery in these 2 patients was indeterminate appearances on imaging. The indication for surgery was curative intent as patients were often asymptomatic.

The median age was 61 (range 32–77) years. All tumours were non-functioning. The median size of tumours was 40 (9–550) mm. CT alone was used in 57% (n = 24) of patients to assess the tumour, with dual imaging (PET/CT/MRI) required in 43% (n = 18) (Table 1). Ninety one per cent (n = 38) of patients had a laparoscopic adrenalectomy, with 1 patient having an open approach and the remaining 3 patients were converted from laparoscopic to an open resection. The open approach was used for a patient with a large tumour (22 cm) with evidence of local invasion. The 3 patients that were converted from laparoscopic to open had large tumours that were difficult to remove laparoscopically.

The site of the original primary tumour is shown in Fig. 1. The majority of adrenal metastases arose from renal cell cancers, followed by lung, skin melanoma, breast and other rare malignancies (neuroendocrine tumours, gastric and hepatocellular cancer). The overall median time from diagnosis of primary cancer to treatment of adrenal metastases was 3 years (range: 3 months- 14 years). Patients with metastases arising from renal cancers had median presentation time of 3.5 (1–14) years, compared to a median

Table 1
Imaging modalities used to identify adrenal metastases.

Imaging	N = 42	Primary Tumour							
		Renal	Lung	Breast	Skin	Gastric	Colon	Neuro	HCC
CT	24	17	3	1	1	0	1	0	1
CT/MRI	6	4	0	0	2	0	0	0	0
CT/PET	12	1	8	1	0	1	0	1	0
Total		22	11	2	3	1	1	1	1

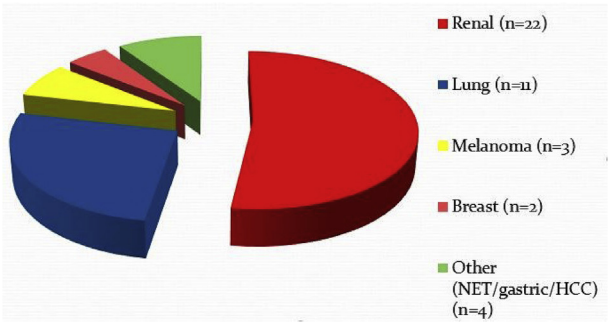

Fig. 1. Graph illustrated the frequency of primary malignancies metastasising to the adrenal gland.

presentation time of 2 years (3 months-3 years) for lung primaries and 3 years (3 months–5 years) for skin melanomas.

Of 11 patients with lung primaries, 10 had radical chemo radiotherapy for their lung cancer with the remaining patient undergoing a lobectomy. All patients with primary renal cancers, skin melanomas and breast cancers had surgical resection. None of the patients had multi-visceral resections.

All patients were followed up in the surgical clinic post-operatively at 1 and 6 months and subsequently by the oncologists thereafter. There were no intra-operative deaths and no major post-operative complication or evidence of local recurrence at subsequent follow up. Most patients experienced post-operative pain associated with retroperitoneal dissections which settled at the time of discharge. 2 patients had wound infections that required oral antibiotics. At follow up there no post-op incisional hernias.

Median overall survival for the entire cohort of patients was 56 (19–93) months. Fig. 2 illustrates the overall survival based on the origin of the primary tumour. There was a significant difference in survival based on the primary tumour with metastatic disease from a kidney primary compared to other primary sites – (kidney 83 (42–123) months vs. lung 14 (9–18) months vs. melanoma 11(3–20) vs. breast 15 months, $p < 0.05$).

Discussion

Adrenalectomy for isolated adrenal metastases remains controversial. Criteria for surgical resection, alternatives to surgery and an evidence base for identifying patients that will benefit from surgery remains elusive. This study described the survival outcomes of patients undergoing adrenalectomy for isolated adrenal metastases and to our knowledge is the first study to compare

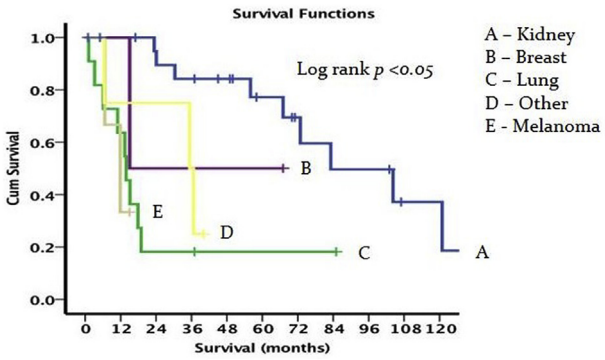

Fig. 2. Overall survival based on site of primary malignancy.

survival outcomes based on the site of the original primary tumour. It is apparent from our study that surgical resection may improve survival and interestingly, that the site of the original primary tumour has an effect on prognosis in these patients.

Adrenal metastases represent a heterogeneous group with a variety of primary malignancies often spreading to the adrenal gland with a reported prevalence of 3% among autopsies. Lam et al. quoted in his review over a 30 year period that primary lung cancers metastasized most commonly to the adrenal gland followed by the stomach, oesophagus, liver/bile ducts, pancreas, large intestine and kidney [10]. Our data has shown that the most common primary site was from the kidney. This may reflect our referral system where patients with only oligometastatic disease are referred and this will exclude a large percentage of patients (e.g. those with lung cancer) that often have multivisceral involvement and therefore not suitable for surgery with curative intent. It may also be accounted for by patients with metastatic disease are offered adjuvant/palliative chemotherapy as an alternative to surgery. Furthermore, patients with primary malignancies may be unsuitable for surgery due to severe co-morbidities such as chronic obstructive pulmonary disease precluding them from surgical intervention.

From the current study, it is possible that survival after resection is dependent on the biology of the primary tumour. Renal cell cancers usually have a good prognosis and 5 year survival rates over 70% [11]. Additionally, early detection of metastatic disease can improve outcomes, prevent progression to disseminated disease and can be curative [12]. Surgical resection in metastatic melanoma has also been reported to improve overall survival with reported median survival of 26 months; however the included cohort was highly selective with adherence to strict inclusion criteria [8,13]. Additionally, the role of checkpoint inhibitors and BRAF/MEK inhibitors has changed the approach for managing patients with metastatic melanoma with patients often benefiting with adjuvant therapy prior to surgical resection. Several studies have also reported favourable outcomes for patients undergoing surgery for isolated metastases from non-small cell lung cancers with median survival of 11–30 months among a very select cohort of patients [14,15].

Our study has reported that patients undergoing adrenalectomy for renal cell primaries may have a significant survival benefit compared to other primaries. This has also been reported by Moreno et al., in his large retrospective review of 30 European centres [16]. He reported that the median survival for renal cell cancers that metastasized to the adrenal gland was 84 months compared to lung cancers with a median survival of 27 months. However, the survival benefits for lung cancer and skin melanomas reported in the literature were not replicated in our study and there are several reasons that may account for this. Firstly, our historical cohort consisted of patients who underwent surgery 20 years ago when imaging modalities were not as sensitive for the detection of occult disease and it is possible that some of our patients may have had occult extra-adrenal disease which may account for their poor survival. Secondly, the above mentioned studies included a very select group of highly motivated patients which may not be reflective of those seen in clinical practice. Additionally, patients in other studies may have benefited from newer adjuvant therapies which would have an impact on survival. This was observed in one study where it was reported surgery and adjuvant systemic therapy were independent prognostic factors for survival [16].

The time from initial treatment of the primary tumour to the development of adrenal metastases may also be used as a prognostic indicator of patients that will benefit from an adrenalectomy. From the current study, the median time from treatment of primary to metastatic disease was 3 years with some metastases developing within 3 months. Patients with primary lung and skin cancers often metastasized early in our cohort and these patients had poor survival compared to renal cancer metastases which often developed many years after (maximum 14 years in the current study) their initial primary. It is therefore possible to identify patients that will significantly benefit from surgery based on the time interval between primary and development of metastases.

Historically, and in the largest studies evaluating adrenal metastases, the majority were removed via an open approach mainly due to concerns about resection margins and tumour spillage but also the unavailability of laparoscopy [10,17]. However, various authors have reported that laparoscopic resection, regardless of the primary site, is safe with no impact on survival and recurrence rates [16,18–20]. In one of the largest retrospective cohort studies, 46% of adrenalectomies for metastatic disease were performed laparoscopically with no significant difference in survival compared to the open approach [16]. The majority of patients (>90%) in the current study had a laparoscopic resection with minimal complications (post-operative pain and wound infections), and no local recurrences, suggesting that for isolated disease with no evidence of local invasion, the laparoscopic approach is feasible and safe.

There are a few limitations with our study. All operations were performed by a single surgeon in a single tertiary referral centre and therefore the generalizability of the study to other settings is limited. However, adrenal surgery is complex and requires an advanced level of laparoscopic skill and should only be performed in high volume centres. This was a descriptive case series without a control group and therefore comparisons between surgery and non-surgical options are not possible. However, given the rarity of adrenal metastases, large multicentre studies will be required to allow meaningful comparisons.

Our study has demonstrated a potential survival benefit in patients undergoing surgery for isolated adrenal metastases. We believe that careful patient selection, a strict inclusion criteria and discussion at a multidisciplinary team meeting is necessary to ensure that patients benefit from surgical intervention.

Conflict of Interest

Survival outcomes following adrenalectomy for isolated metastases to the adrenal gland.

We the authors, Jason Ramsingh, Patrick O'Dwyer and Carol Watson, have no conflicts of interests to declare.

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References

[1] Bovio S, Cataldi A, Reimondo G, Speron P, Novello S, Berruti A, et al. Prevalence of adrenal incidentaloma in a contemporary computerised tomography series. J Endocrinol Invest 2006;29(4):298.
[2] Terzolo M, Stilgliano A, Chiodini I, Loli P, Furlani L, Analdi G, et al. AME position paper on adrenal incidentaloma. Eur J Endocrinol 2001;164(6):851.
[3] Song JH, Chaudhry FS, Mayo-Smith WW. The incidental adrenal mass on CT: prevalence of adrenal disease in 1049 consecutive adrenal masses in patient with no known malignancy. AJR Am J Roentgenol 2008 May;190(5):1163–8. 10.2214.
[4] Cawood TJ, Hunt PJ, O'Shea D, Col D, Soul S. Recommended evaluation of adrenal incidentalomas is costly, has high false-positive rats and confers a risk of fatal cancer that is similar to the risk of the adrenal lesion becoming malignant; time for a rethink. Eur J Endocrinol 2009;161(4):513. pub 009 May 13.
[5] Abrams HL, Spiro R, Goldstein N. Metastases in carcinoma: analysis of 1000 autopsied cases. Cancer 1950;3:74–85.
[6] Twomy P, Montegomery C, Clark O. Successful treatment of adrenal metastases from large cell carcinoma of the lung. J Am Med Assoc 1982;248:581–3.

[7] Branum GD, Epstein R, Light GS, Seigler HF. The role of resection in the management of melanoma metastatic to the adrenal gland. Surgery 1991;109:127–31.
[8] Haigh PI, Essner R, Wardlaw JC, Stern SL, Morton DL. Long term survival after complete resection of melanoma metastatic to the adrenal galnd. Ann Surg Oncol 1999;6(7):633.
[9] Higashiyama M, Doi O, Kodama K, Yokouchi H, Imaoka S, Koyama H. Surgical treatment of adrenal metastasis following pulmonary resection for lung cancer: comparison of adrenalectomy with palliative therapy. J Clin Oncol 2008 Mar 1;26(7):1142–7. https://doi.org/10.1200/JCO.2007.14.2091.
[10] Lam Ky, Lo CY. Metastatic tumours of the adrenal gland – 30yr experience in a teaching hospital. Clin Endocrinol 2002 Jan;56(1):95–101.
[11] Panuck AJ, Zisman A, Blldegrun AS. The changing natural history of renal cell carcinoma. J Urol 2001;166(5):1611.
[12] Thomas Az, Adibi M, Borgals LD, Hoang LN, Tamboli P, Jonasch E, et al. Surgical management of local retroperitoneal recurrence of renal cell carcinoma after radical nephrectomy. J Urol 2015 Aug;194(2):316–22. Epub 2015 Mar 7.
[13] Flaherty DC. Adrenalectomy for metastatic melanoma: current role in age of nonsurgical management. Am Surg 2015 Oct;81(10):1005–9.
[14] Porte H, Siat J, Guibert B, Lepimpec-Barthes F, Jancovici R, Bernard A, et al. Resection of adrenal metastases from non-small cell lung cancer: a multicentre study. Ann Thorac Surg 2001 Mar;71(3):981–5.
[15] Pfannschmidt J, Scholaut B, Muley T, Hoffman H, Dienmann H. Adrenalectomy for solitary adrenal metastases from non-small cell lung cancer. Lung Canc 2005 Aug;49(2):203–7. Epub 2005 Apr 9.
[16] Moreno P, De La Quintana B, Musholt TJ, Paunovic I, Puccini M, Vidal O, et al. Adrenalectomy for solid tumour metastases:results of a multicentre European study. Surgery 2013 Dec;154(6):1215–22. https://doi.org/10.1016/j.surg.2013.06.021. discussion 1222-3.
[17] Lo CY, van Herden JA, Soreide JA, Grant CS, Thompson GB, Lloyd RV, et al. Adrenalectomy for metastatic disease to the adrenal glands. Br J Surg 1996;83:528–31.
[18] Strong VE, D'angelica M, Tang L, Prete F, Gonen M, Coit D, et al. Laparoscopic adrenalectomy for isolated adrenal metastasis. Ann Surg Oncol 2007 Dec;14(12):3392–400. Epub 2007 Jul 31.
[19] Lucchi M, Dini P, Ambrogi MC, Berti P, Matrazzi G, Miccoli P, et al. Metachronous adrenal masses in resected non-small cell lung cancer patients: therapeutic implications of laparoscopic adrenalectomy. Eur J Cardiothoracic Surg 2005 May;27(5):753–6.
[20] Puccini M, Panicucci E, Candalise V, Ceccarelli C, Neri CM, Buccianti P, et al. The role of laparoscopic resection of metastases to adrenal glands. Gland Surg 2017 Aug;6(4):350–4. https://doi.org/10.21037/gs.2017.03.20.