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Adrenalectomy Improves Outcomes of Selected Patients with Metastatic Carcinoma

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Abstract

Background Indications and survival benefit for adrenalectomy (ADX) in the setting of metastasis are not clearly defined. We aimed to determine which patients with primary malignancies may benefit from ADX performed for metastasis. Mayo Clinic institutional outcomes in patients with metastatic disease to the adrenal(s) treated by adrenalectomy were compared to stage-matched historical controls from the Surveillance Epidemiology and End Results (SEER) database.

Methods A retrospective review (1992–2010) was conducted to identify patients treated with ADX for metastatic cancer at Mayo Clinic, Rochester. Associations of clinical, surgical, and pathologic features with overall survival (OS) were evaluated using Cox proportional regression models. OS for those treated with ADX was compared with that for SEER database stage-matched patients who underwent primary resection without resection of distant disease using log-rank tests.

Results A total of 166 patients underwent ADX for metastatic primaries involving the kidney 60, lung 24, sarcoma 19, colon 15, pancreas 13, and other-35. Patients with sarcoma and kidney, lung, and pancreatic tumors who underwent ADX had better OS at 1, 2, and 3 years than did the SEER-matched controls. Respectively, the rates were for sarcoma (100, 93, 86% vs. 57, 36, 30%), kidney (86, 80, 72% vs. 55, 37, 27%), lung (91, 69, 52% vs. 52, 34, 25%), and pancreas (79, 56, 45% vs. 33, 20, 12%). Univariate analysis identified primary diagnosis <2 years before ADX, other distant site, pancreatic primary, palliative operation, and persistent disease as risk factors for death.

Conclusions An aggressive surgical approach results in improved OS in patients with metastatic disease arising from soft tissues, kidney, lung, and pancreas. Other tumors may benefit, but larger study cohorts are needed for a meaningful comparison.

Introduction

The adrenal glands are commonly a site for metastatic disease, with postmortem series reporting the incidence as high as 38% for patients diagnosed with extraadrenal cancers [1–4]. Metastatic disease to the adrenal glands is rarely found in patients without a history of cancer [5]. The prevalence of metastatic lesions among incidentally discovered adrenal masses has been reported to be 2.5% [5–7]. Patients with adrenal metastasis are frequently deemed inoperable, and supportive-palliative therapy is often adopted.

Despite small series reporting improved survival [8–12] among those with metastatic melanoma, renal cell carcinoma, and lung cancer, among others, the indications for adrenalectomy (ADX) in the setting of metastatic cancer have not been clearly defined. The lack of randomized controlled trials represents the biggest challenge to developing treatment guidelines for this specific subset of patients. The current American Association of Clinical Endocrinologists/American Association of Endocrine Surgeons (AACE/AAES) practice guidelines for the management of incidental adrenal masses suggests that an adrenal metastatic lesion can be resected for symptomatic palliation [5]. Furthermore, their guidelines

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state that surgical resection can improve disease-free survival in a very select group of patients with good control of their extraadrenal disease and a good performance status [5]. This study aimed to review our experience retrospectively to identify prognostic factors for overall survival (OS) and determine which malignancies may benefit from ADX in the setting of metastatic disease.

Materials and methods

Protocol

A retrospective chart review, from August 1992 through October 2010, was conducted with the purpose of identifying patients treated with ADX in the setting of metastatic cancer. Patient medical records were reviewed for demographics, timing of diagnosis of primary disease and metastasis, type of primary tumor, operative interventions (i.e., open, laparoscopic, en bloc). surgical intent and findings, presence of persistent disease, recurrence, and length of follow-up. Recurrence-free survival (RFS) and OS were determined using the Kaplan-Meier method. Associations of clinical, surgical, and pathologic features with OS were evaluated using Cox proportional hazards regression models. The duration of follow-up was calculated from the time of ADX to the time of recurrence, death, or date of last follow-up. Statistical analyses were performed using the SAS software package (SAS Institute, Cary, NC, USA). All tests were two-sided, and $p < 0.05$ were considered statistically significant.

SEER data

The OS for those treated with ADX was compared to the OS of the National Institutes of Health Surveillance Epidemiology and End Results (NIH-SEER) [13] database of stage IV patients who underwent primary resection without removal of distant disease. Overall survival data for patients with stage IV kidney, lung, or pancreatic cancer diagnosed between 2004 and 2007 were retrieved from the SEER database. Patients whose primary tumors were not treated surgically and those whose distant metastases were treated surgically were excluded. The OS for the SEER patients was compared to the OS for the patients treated with ADX for distant metastases arising from the kidney, lung, and pancreas described above using log-rank tests. For these analyses, the duration of follow-up was calculated from the primary tumor diagnosis date to the death or last follow-up date. There were 60, 24, and 13 patients treated with ADX for distant metastases arising from the kidney, lung, and pancreas, respectively, of which 59, 21, and 11 had primary diagnosis dates available.

To ensure that this project met federal and state regulations and institutional policies for the protection of the rights, privacy, and welfare of all participants, it was reviewed and committee-approved by the Mayo Clinic's institutional review board.

Results

Diagnosis

A total of 166 patients (61 women, 105 men) underwent ADX to resect metastatic disease. The mean age at ADX was 60.4 years. The ADX was performed a mean of 2.3 years from diagnosis of the primary malignancy, with 40% of patients undergoing ADX within 6 months of diagnosis. The primary malignancies were kidney ($n = 60$), lung ($n = 24$), sarcoma ($n = 19$), colon ($n = 15$), pancreas ($n = 13$), and other sites ($n = 35$) (Table 1). Intent of surgery was cure in 45% and palliation in 55% ($n = 161$). Mean size for the metastatic mass was 4.5 cm with adrenal metastatic disease unilateral in 36%, bilateral in 2%, and to the adrenal and another organ in 62%. In all, 45 patients (30%) were diagnosed as having persistent disease after surgery for adrenal disease; and 58 of 81 patients with recurrence data recurred at a mean of 1.3 years. Estimated RFS rates at 1, 5, and 10 years were 51, 19, and 14%, respectively (median RFS 1.1 years). At last follow-up, 101 (61%) patients had died at a mean of 1.9 years after ADX. The mean follow-up for the 65 patients alive was 3.1 years. Estimated OS rates at 1, 5, and 10 years following ADX were 68, 31, and 17%, respectively, with a median OS of 2.2 years (Fig. 1).

Univariate analysis identified primary diagnosis <2 years before ADX, metastasis size, other distant site, pancreatic primary, palliative operation, and persistent disease as risk factors for death ($p < 0.05$). There were no statistically significant relations between age, sex, open versus laparoscopic resection, or tumors of the lung and kidney or colon and kidney with death (Table 2).

### Comparisons with SEER data

Sarcoma

Estimated OS [95% confidence interval (CI), number still at risk] at 1, 2, and 3 years following diagnosis of the primary tumor were 100% (100–100; 15), 93% (82–100; 13), and 86% (70–100; 12), respectively, for the 19 patients treated with ADX for metastasis arising from a sarcoma compared with 57% (52–61; 245), 36% (31–41; 110), and 30% (26–35; 110), respectively, for the 564 patients with stage IV sarcoma from the SEER database ($p < 0.001$).

Table 1 Clinical, surgical, and pathologic features of 166 patients

Feature	Mean ± SD (median; range)
Age at adrenalectomy (years)	60.4 ± 12.5 (61; 21–85)
Interval: primary Dx to adrenalectomy (years; $n = 153$)	2.3 ± 3.1 (1.1; 0–14.9)
Size of metastasis (cm) ($n = 95$)	4.5 ± 2.7 (3.8; 0.7–18.0)
Size of adrenal gland (cm) ($n = 137$)	5.4 ± 3.7 (4.7; 0.4–21.0)
Site of primary tumor ($n = 164$) (%)	
Kidney	60 (37)
Lung	24 (15)
Colon	15 (9)
Pancreas	13 (8)
Neuroendocrine	7 (4)
Sarcoma	7 (4)
Leiomyosarcoma	6 (4)
Liposarcoma	6 (4)
Melanoma	6 (4)
Liver	5 (3)
Gastrointestinal tract	4 (2)
Breast	2 (1)
Lymphoma	2 (15)
Ovary	2 (1)
Thyroid	2 (1)
Cholangiocarcinoma	1 (1)
Endometrium	1 (1)
Tonsils	1 (1)
Interval: primary Dx to adrenalectomy ($n = 153$) (%)	
≥6 months	92 (60)
<6 months	61 (40)
Interval: primary Dx to adrenalectomy ($n = 153$) (%)	
≥1 years	80 (52)
<1 year	73 (48)
Interval: primary Dx to adrenalectomy ($n = 153$) (%)	
≥2 years	55 (36)
<2 years	98 (64)
Site of metastases ($n = 154$) (%)	
Solitary adrenal	55 (36)
Bilateral adrenal	3 (2)
Adrenal + other site	96 (62)
Type of adrenalectomy (%)	
Laparoscopic	29 (17)
Open	46 (28)
Combined	91 (55)
Persistent disease following adrenalectomy ($n = 151$) (%)	
No	106 (70)
Yes	45 (30)

Dx diagnosis
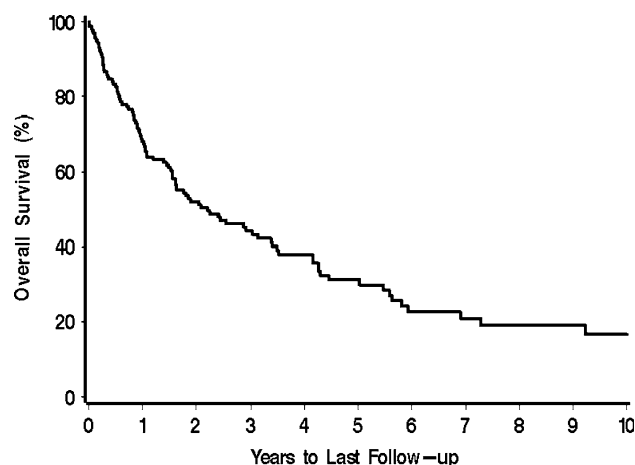
Fig. 1 Estimated overall survival ($n = 166$)

The median OS for the two groups occurred at 5.8 and 1.3 years, respectively (Table 3; Fig. 2).

Kidney

Estimated overall survival rates (95% CI, number still at risk) at 1, 2, and 3 years following the primary kidney tumor diagnosis were 86% (78–96; 52), 80% (70–91; 45), and 72% (62–85; 38), respectively, for the 59 patients treated with ADX for metastasis arising from the kidney cancer compared with 55% (53–57; 1209), 37% (35–39; 530), and 27% (25–29; 200), respectively, for the 2869 patients with stage IV kidney cancer from the SEER database ($p < 0.001$). The median OS for the two groups occurred at 8.4 and 1.3 years, respectively (Fig. 3).

Lung

Estimated overall survival rates (95% CI, number still at risk) at 1, 2, and 3 years following the primary lung tumor diagnosis were 91% (79–100; 19), 69% (51–93; 12), and 52% (33–81; 9), respectively, for the 21 patients treated with ADX for metastasis arising from the lung cancer compared with 52% (49–54; 984), 34% (32–37; 430), and 25% (23–28; 162), respectively, for the 2420 patients with stage IV lung cancer from the SEER database ($p = 0.002$). The median OS for the two groups occurred at 3.5 and 1.1 years, respectively (Fig. 4).

Pancreas

Estimated overall survival rates (95% CI, number still at risk) at 1, 2, and 3 years following the primary pancreatic tumor diagnosis were 79% (56–100; 7), 56% (32–100; 5), and 45% (22–93; 4), respectively, for the 11 patients treated with ADX for metastasis arising from the

Table 2 Univariate associations of clinical, surgical, and pathologic features with death for 166 patients

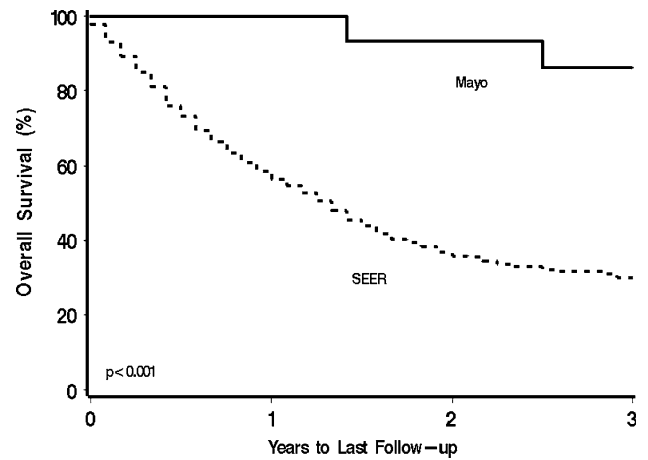| Feature	Hazard ratio (95% CI)	p
Age at surgery (10-year increase)	1.09 (0.92–1.29)	0.33
Sex		
Female	1.0 (reference)	
Male	1.13 (0.75–1.69)	0.56
Site of primary tumor ($n = 164$)		
Kidney	1.0 (reference)	
Lung	1.54 (0.83–2.83)	0.17
Colon	1.55 (0.71–3.38)	0.27
Pancreas	2.13 (1.01–4.46)	0.046
All others	1.86 (1.16–3.00)	0.011
Interval: primary Dx to ADX ($n = 153$)		
≥0.5 year	1.0 (reference)	
<0.5 year	1.24 (0.82–1.89)	0.31
Interval: primary Dx to ADX ($n = 153$)		
≥1 years	1.0 (reference)	
<1 year	1.32 (0.87–2.00)	0.19
Interval: primary Dx to ADX ($n = 153$)		
≥2 years	1.0 (reference)	
< 2 years	1.81 (1.14–2.88)	0.012
Site of metastases ($n = 154$)		
Solitary or bilateral adrenal	1.0 (reference)	
Adrenal + other site	1.99 (1.28–3.07)	0.002
Type of ADX		
Laparoscopic	1.0 (reference)	
Open	1.66 (0.83–3.35)	0.15
Combined	2.02 (1.06–3.85)	0.032
Size of metastases (1-cm increase; $n = 95$)	1.10 (0.99–1.23)	0.09
Size of adrenal (1-cm increase; $n = 137$)	1.10 (1.03–1.17)	0.006
Intent of ADX ($n = 161$)		
Cure	1.0 (reference)	
Palliation	1.64 (1.09 – 2.47)	0.017
Persistent disease following ADX ($n = 151$)		
No	1.0 (reference)	
Yes	1.85 (1.16 – 2.94)	0.010

Fig. 2 Estimated overall survival for patients with metastatic sarcoma. *SEER* surveillance epidemiology and end results
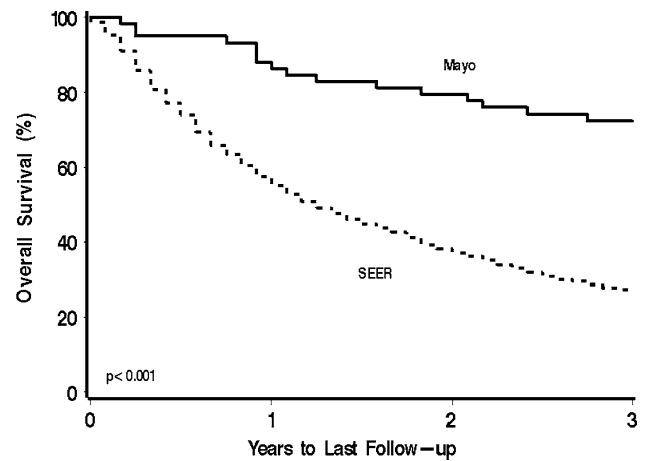

Fig. 3 Estimated overall survival for patients with kidney cancer

pancreatic cancer compared with 33% (29–38; 129), 20% (16–25; 51), and 12% (9–17; 15), respectively, for the 490 patients with stage IV pancreatic cancer from the SEER database ($p = 0.011$). The median OS for the two groups occurred at 2.5 and 0.6 years, respectively (Fig. 5).
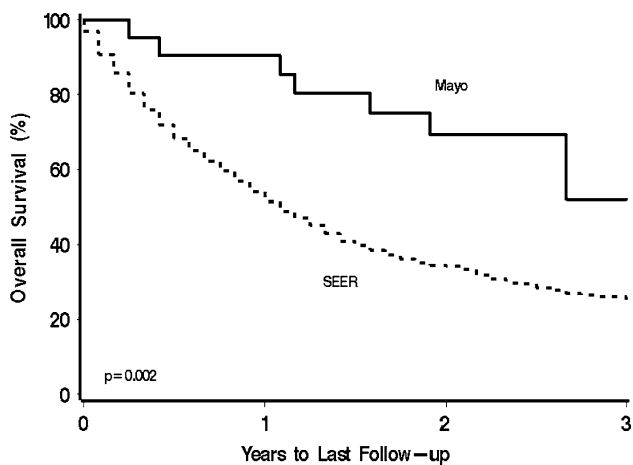
Table 3 Comparisons of estimated overall survivals

Primary site	OS for Mayo cohort				OS for SEER cohort			
	1 year (%)	2 years (%)	3 years (%)	Median survival (years)	1 year (%)	2 years (%)	3 years (%)	Median survival (years)
Kidney	86	80	72	8.4	55	37	27	1.3
Lung	91	69	52	3.5	52	34	25	1.1
Sarcoma	100	93	86	5.8	57	36	30	1.3
Pancreas	79	56	45	2.5	33	20	12	0.6

OS overall survival

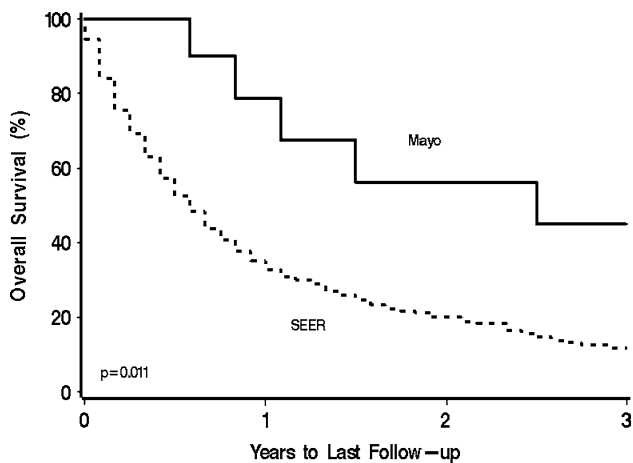**Fig. 4** Estimated overall survival for patients with lung primary cancer

Fig. 5 Estimated overall survival for patients with metastatic pancreatic cancer

Discussion

The adrenal gland is one of the most common organs involved in metastatic disease. The increased used of computed tomography, magnetic resonance imaging, and positron emission tomography for routine surveillance of patients with known malignancy has led to an increased prevalence of asymptomatic adrenal masses [14]. The presence of adrenal metastasis purveys a poor prognosis to those patients treated nonsurgically. It continues to represent a significant challenge to physicians as the indications for ADX in cases of metastatic adrenal tumors remains a topic of controversy. The indications for surgery and a survival benefit have not been clearly defined because of small series of reported patients with many different primary malignancies.

Case reports and small series have suggested an increased survival for patients who undergo resection of solitary adrenal metastasis for primary tumors of the kidney, lung, gastrointestinal tract, and melanoma. Muth et al. [15] reported a recent series of 30 patients undergoing surgery for metastatic disease and identified the following as independent survival prognostics factors: ADX for potential cure, no previous metastasis surgery, tumor type. Better prognosis was identified in patients suffering from metastatic colorectal carcinoma and renal cell carcinoma [15]. Worse prognosis was found in patients with non-small-cell lung cancer and malignant melanoma [15].

In 1996 we published our experience with ADX for adrenal metastasis from 1983 to 1993. ADX was performed in 52 patients for different types of metastatic cancer, 32 of which were asymptomatic on initial evaluation [1]. A solitary adrenal metastasis was an indication for surgery in 60% of patients, and symptomatic adrenal pain relief was achieved in 11 of 13 patients [1]. Overall survival rates were 73 and 40% at 1 and 2 years, respectively [1]. In 1997, the Memorial Sloan Kettering Cancer Center reported their experience with 37 patients over a 10-year period. In all, 73% of whom were asymptomatic upon presentation [11]. All nine patients presenting with pain had symptomatic relief after surgery [11]. The OS was 24% at 5 years, with a survival median of 21 months.

Several series reporting on metastatic melanoma and metastases from lung and renal carcinomas to the adrenal gland(s) are encouraging. Significant survival improvement has been noted, and some authors even suggest the potential of surgical cure with aggressive interventions in a selected cohort with limited metastatic burden [9, 10]. Furthermore, symptomatic palliation has been achieved in most patients presenting with adrenal pain [1, 11]. Collinson et al. [9] reported increased survival in patients with melanoma, with a median survival of 16 months for patients who underwent ADX compared to 5 months for patients with documented adrenal metastases treated nonsurgically. A recent series reporting outcomes of ADX in cases of solitary metastatic disease originating from renal cell carcinoma showed median long-term survivals of 13.8 and 11.7 years for patients with no evidence of metastatic spread and those with a solitary intraadrenal metastatic lesion, respectively [10].

Thorough multidisciplinary oncologic evaluation, adequate preoperative imaging, and consideration of the patient's functional status are imperative when selecting candidates for these interventions. There is an established role for ADX in the symptomatic palliation setting; surgery must be a consideration for patients presenting with a limited disease burden and adrenal pain [1, 5, 11]. We found no difference in risk of death between laparoscopic and open ADX in this setting. These findings support

multiple recent series reports regarding the feasibility of adequate outcomes with a laparoscopic approach in selected patients with localized, resectable disease [16–19].

Conclusions

Our experience suggests that an aggressive surgical approach for adrenal metastasis results in statistically significant improvement in overall survival in selected patient cohorts with metastatic disease. Statistical significance was encountered in groups with primaries tumors arising from soft tissues ($p < 0.001$), kidney ($p < 0.001$), lung ($p = 0.002$), and pancreas ($p = 0.011$). Though a pancreatic primary purveyed increased risk of death for the patient, we did see improved survival with ADX when compared to SEER stage 4 cohort. Other tumors may benefit, but larger study cohorts are needed to obtain meaningful comparison data. Synchronous disease, tumor type, size, burden, and site are statistically significant risk factors for death and should be considered when selecting patients for ADX.

When establishing guidelines or treatment recommendations, one must be conscious of the lack of randomized controlled trials and the potential of referral bias to avoid misinterpretation of the data. Our biggest limitation and perhaps the caveat of our retrospective project was the lack of a cohort with localized and resectable metastasis treated nonsurgically. The SEER stage 4 cohort's data provided us with the closest available nonsurgical comparison group.

Conflicts of interest The authors declare no conflicts of interest.

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