









Outcome and prognosis after adrenal metastasectomy: nationwide study

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Abstract

Background: Data regarding adrenal metastasectomy are limited. Here, clinical outcomes, safety, and prognostic factors in patients undergoing adrenal metastasectomy were evaluated in a large nationwide study.

Methods: Patients undergoing adrenal metastasectomy between 2000 and 2018 were identified in the Danish National Pathology Registry. Medical records were reviewed to confirm eligibility and to collect clinical data. The primary outcome was overall survival (OS). Cox multivariable regression analyses were adjusted for baseline factors.

Results: In total, 435 patients underwent adrenal metastasectomy; the primary cancer origins were renal ($n=195$, 45 per cent), lung ($n=121$, 28 per cent), colorectal ($n=50$, 11 per cent), and other ($n=69$, 16 per cent). The median (interquartile range; i.q.r.) age was 66 (59–71) years, and 280 (64 per cent) were men. The 5-year OS was 31 per cent. The 30-day mortality was 1.8 per cent. Complications were more frequent and severe in patients who underwent open surgery compared with laparoscopic surgery (Clavien–Dindo III–V, 31.5 per cent versus 11.8 per cent respectively, $P<0.001$). Factors associated with poor survival included non-radical pR2 resection (hazard ratio (HR) 3.57, 95 per cent c.i. 1.96 to 6.48), tumour size more than 50 mm (HR 1.79, 95 per cent c.i. 1.26 to 2.52), lung cancer origin (HR 1.77, 95 per cent c.i. 1.31 to 2.40), open surgical approach (HR 1.33, 95 per cent c.i. 1.04 to 1.71), presence of extra-adrenal metastases (HR 1.31, 95 per cent c.i. 1.01 to 1.71), and increasing Charlson comorbidity index factors (HR 1.14 per one-point increase, 95 per cent c.i. 1.03 to 1.27).

Conclusion: Adrenal metastasectomy is safe and may result in long-term survival in a subset of patients. Non-radical resection, large tumour size, lung cancer origin, open approach, presence of extra-adrenal metastases, and co-morbidity were associated with inferior outcomes.

Introduction

The adrenal gland is a common metastatic site for lung, kidney, breast, and gastrointestinal tract cancers^{1–6}; adrenal metastasis was found to be present in 3.1 per cent of deceased patients². With increasing use of imaging techniques, the detection of adrenal metastases during staging or follow-up is increasing⁷. When metastasized to the adrenal gland, the cancer is defined as stage IV disease; a condition that until recently was considered incurable^{8,9}. Today, the approach is changing. A patient with a solitary metastasis in an adrenal gland is now considered potentially curable, if the primary tumour has been resected, or can be offered a potentially curable treatment, and the adrenal metastasis technically can be resected with clear margins¹⁰.

The evidence supporting the benefit of adrenal metastasectomy is limited¹¹. Studies have reported long-term survival after adrenal

metastasectomy^{2,4,12–20}, but these studies have shown heterogeneous results. It is unclear which patients achieve long-term survival, and detailed knowledge of prognostic factors is lacking. Such data are imperative for patient counselling and selection for optimal preoperative planning, including the decision between open and laparoscopic adrenalectomy.

Therefore, we sought to determine clinical outcomes, safety, and prognostic factors in patients undergoing adrenal metastasectomy in a large nationwide study.

Methods

Study design

This was a population-based, retrospective, cohort study, comprising all patients operated on for adrenal metastases in Denmark between 1 January 2000 and 31 December 2018. Results were reported according to the RECORD (reporting of

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studies conducted using observational routinely collected data) statement²¹. The study was approved by the Danish Health Authorities (reference 3-3013-1021/2).

Setting

The unique civil registration number that each patient uses in every contact with health authorities, made it possible to link an individual's data from multiple health registries, such as the National Patient Registry and the National Pathology Registry. Healthcare in Denmark is covered by taxes and universally available; these health registries are reliable, have high completeness, and have almost no loss to follow-up²². The Danish population was 5.33 million in 2000 and 5.78 million in 2018 (mean population 5.52 million individuals, 104.9 total person-years of follow-up).

Study cohort

Patients were identified in the Danish National Pathology Register; patients who had received both a pathology code²³ for 'adrenal gland' (T93) and 'metastasis' (MXXXX6) were considered eligible for inclusion. Pathology reports were manually reviewed to confirm the presence of an adrenal metastasis, and that the patient had undergone adrenalectomy, or had the adrenal metastasis removed as part of a larger resection (such as in combination with nephrectomy). Patients were excluded if they only underwent adrenal biopsy without adrenalectomy, had inconclusive pathological examinations, or were diagnosed at autopsy only. Patients were also excluded if only partial resection of the adrenal metastasis was performed. For

confirmed cases, medical records were reviewed to extract clinical information.

Outcomes

The primary outcome was overall survival following adrenal metastasectomy. Vital status and date of death or emigration was obtained from the Danish Central Person Registry (available up until 26 July 2019). The secondary outcomes were predictors of survival and surgical complications following adrenal metastasectomy.

Complications were retrieved from the medical records. Complications were classified by way of the Clavien-Dindo classification²⁴ and were graded according to the most severe event.

Prognostic factors

Data collected from medical records included patient characteristics (sex, age, BMI, and Charlson co-morbidity index), tumour characteristics (cancer origin, tumour size, location of metastasis, mode of discovery, and extra-adrenal disease), and surgical management (surgical approach, extent, radicality (R0 versus R1/R2), and duration). Data were collected in a REDCAP database²⁵. Medical records were reviewed from 3 months before adrenalectomy and until death or 26 July 2019 (the date when review of medical records was completed). The database was designed to evaluate medical records chronologically with data on complications and mortality collected last, to minimize the risk of hindsight bias.

Data on co-morbidities was collected from the preoperative surgical, medical, and anaesthetic assessments. Co-morbidities

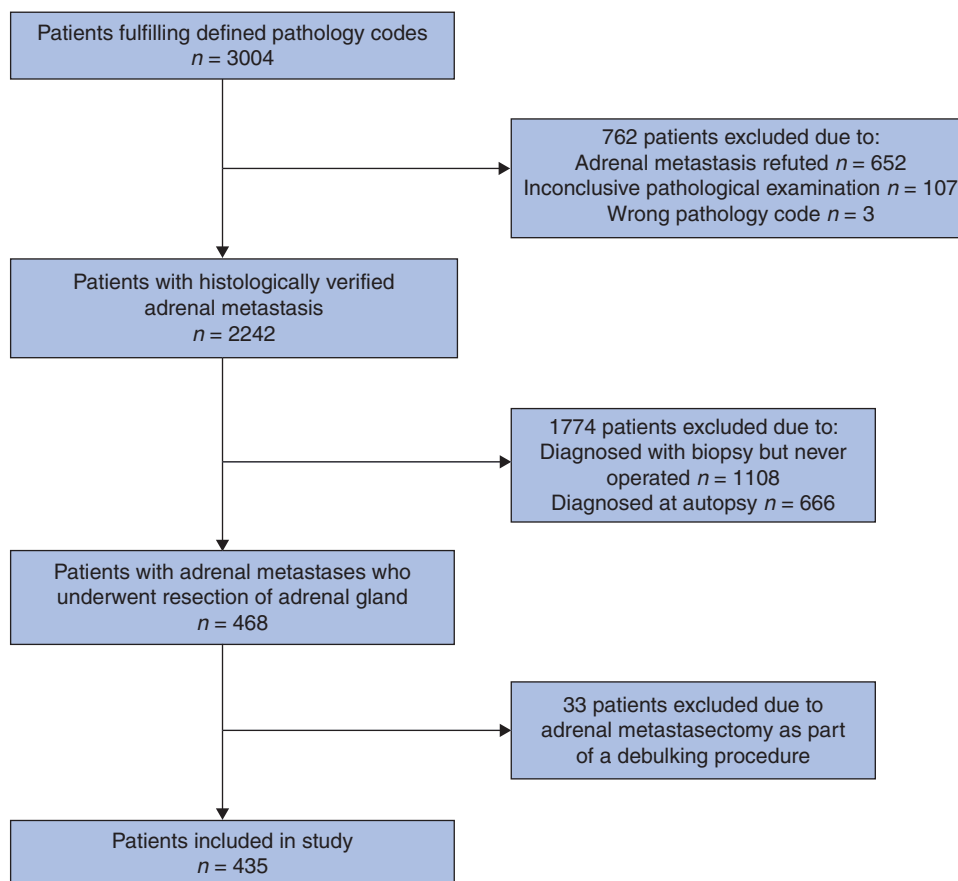


Fig. 1 Flow chart illustrating of all phases of patient identification

Table 1 Patient and tumour characteristics and surgical management by primary cancer

	Total	Renal cancer	Lung cancer	Colorectal cancer	Other cancer*
Patients, n	435	195	121	50	69
Sex					
Female, n (%)	155 (36)	62 (32)	58 (48)	12 (24)	23 (33)
Male, n (%)	280 (64)	133 (68)	63 (52)	38 (76)	46 (67)
Age at surgery					
under 60 years, n (%)	116 (27)	55 (28)	31 (26)	8 (16)	22 (32)
60–70 years, n (%)	184 (42)	76 (39)	61 (50)	19 (38)	28 (41)
More than 70 years, n (%)	135 (31)	64 (33)	29 (24)	23 (46)	19 (28)
Age at surgery in years, mean(s.d.)	65.0(9.3)	65.3(9.6)	64.2(8.0)	68.5(8.8)	63.4(10.3)
BMI in kg/m², mean(s.d.)	26.1(4.8)	26.8(4.8)	24.9(4.8)	26.4(4.4)	26.5(4.8)
CCI, mean(s.d.)	0.6(1.0)	0.7(1.2)	0.6(0.9)	0.5(1.0)	0.6(0.9)
Doctor's delay in days, median (i.q.r.)#	65 (40–124)	51 (29–83)	69 (48–117)	94 (50–155)	84 (57–166)
Tumour size (n = 369)					
under 25 mm, n (%)	127 (34)	75 (47)	31 (28)	10 (23)	11 (19)
25–50 mm, n (%)	143 (39)	54 (34)	45 (41)	19 (43)	25 (44)
More than 50 mm, n (%)	99 (27)	29 (18)	34 (31)	15 (34)	21 (37)
Size in mm, median (i.q.r.)	35 (20–54)	25 (16–44)	40 (22–55)	45 (30–64)	40 (30–72)
Location of metastasis (n = 421)					
Left, n (%)	253 (60)	112 (61)	70 (58)	28 (58)	43 (63)
Right, n (%)	152 (36)	62 (34)	48 (40)	20 (42)	22 (32)
Bilateral, n (%)	16 (4)	11 (6)	2 (2)	-	3 (4)
Mode of discovery (n = 405)					
Synchronous, n (%)	160 (40)	106 (57)	41 (36)	6 (12)	7 (12)
Metachronous, n (%)	245 (60)	80 (43)	72 (64)	43 (88)	50 (88)
Extra-adrenal metastases at time of surgery (n = 391)					
No, n (%)	282 (72)	113 (69)	92 (80)	35 (73)	42 (65)
Yes, n (%)	109 (28)	50 (31)	23 (20)	13 (27)	23 (35)
Surgical approach (n = 395)					
Laparoscopic, n (%)	237 (60)	73 (45)	93 (79)	31 (65)	40 (61)
Conversion to open, n (%)	22 (6)	11 (7)	8 (7)	1 (2)	2 (3)
Open, n (%)	136 (34)	80 (49)	16 (14)	16 (33)	24 (36)
Surgical extent (n = 429)					
Only adrenalectomized, n (%)	247 (58)	66 (34)	102 (85)	34 (71)	45 (65)
Extended surgery, n (%)	182 (42)	126 (66)	18 (15)	14 (29)	24 (35)
Radicality					
R0 resection, n (%)	279 (64)	135 (69)	79 (65)	28 (56)	37 (54)
R1 resection, n (%)	140 (32)	55 (28)	36 (30)	20 (40)	29 (42)
R2 resection, n (%)	16 (4)	5 (3)	6 (5)	2 (4)	3 (4)
Duration of surgery in min (n = 246)					
Laparoscopic, median (i.q.r.)	100 (70–153)	143 (88–200)	85 (60–121)	109 (69–146)	103 (70–141)
Open, median (i.q.r.)	176 (113–233)	182 (124–226)	160 (129–261)	229 (117–295)	111 (96–178)

CCI, Charlson co-morbidity index; i.q.r., interquartile range. For variables, where data could not be found for all 435 patients, the number of patients with available information is specified in brackets (n = x). Details on histopathological subtypes of renal, lung, and colorectal cancer are available in [Supplementary Table S1](#). *Other types of cancers, see [Table S1](#). #Doctor's delay is defined as the time from discovery of adrenal metastasis until surgery.

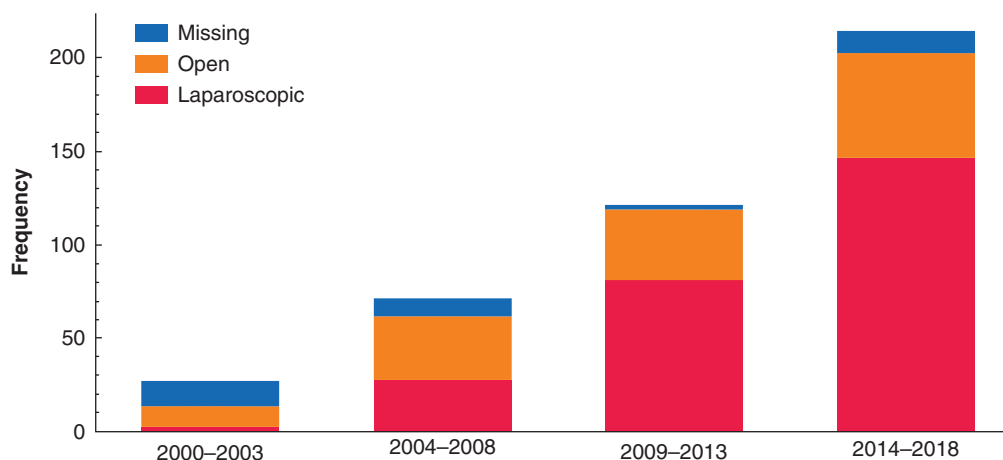


Fig. 2 Adrenal metastasectomy in Denmark, 2000 to 2018

Bars are coloured according to the surgical approach. The first column to the left only includes 4 years, whereas the remaining columns include 5 years. Laparoscopic surgery includes patients who were converted to open surgery.

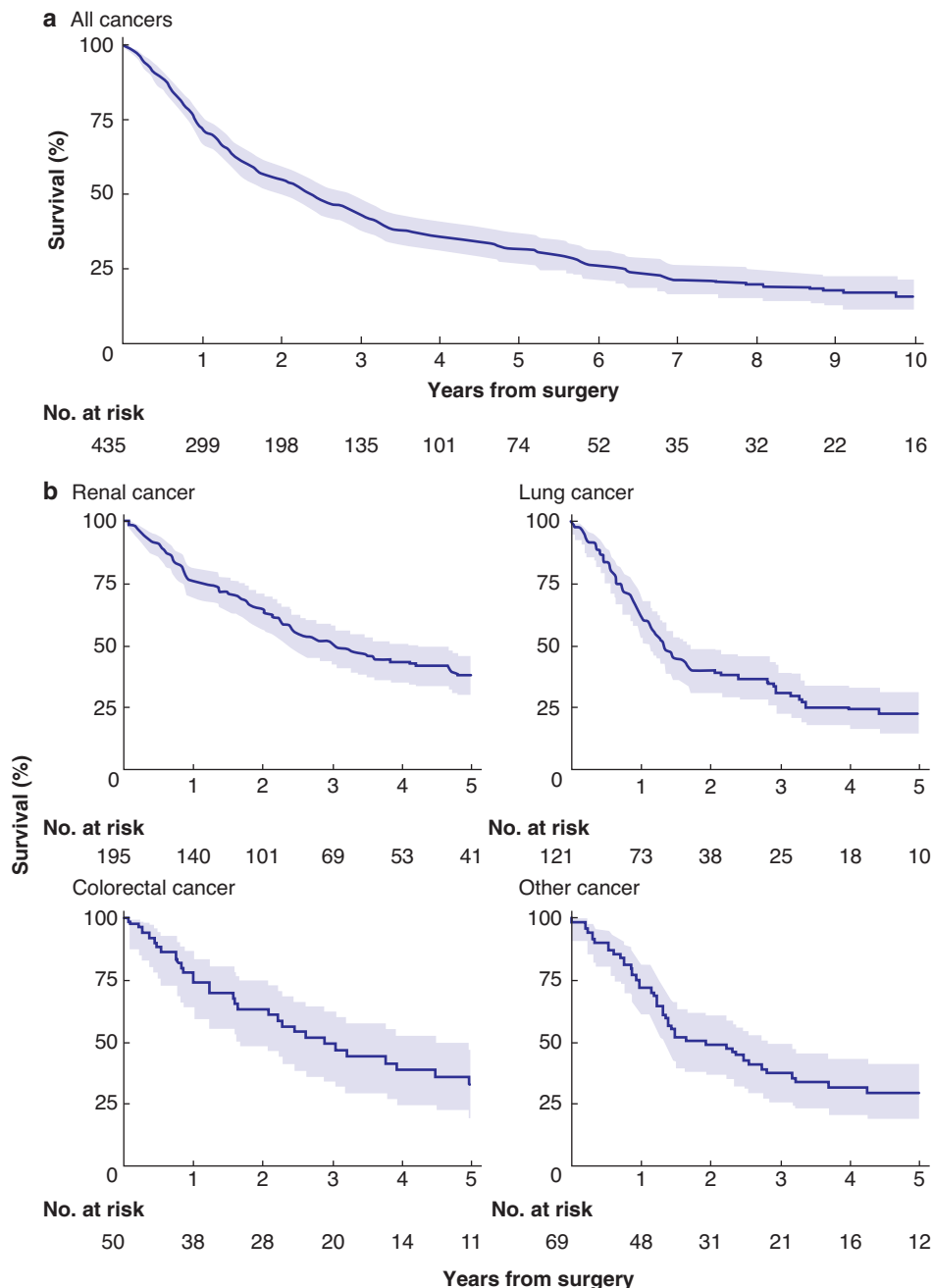


Fig. 3 Kaplan-Meier curve showing survival after adrenal metastasectomy

a All patients combined. **b** By primary cancer. The faded area represents the 95 per cent confidence interval. Patients at risk are shown below graphs.

were categorized according to potential impact on mortality and quantified as the sum of those weights (from 0 to 6) by way of the Charlson co-morbidity index²⁶, but excluded the current cancer (but included any other previous cancers) from calculations.

Tumour size was defined as the largest diameter of the metastasis. As preoperative imaging was often unavailable or had been performed several months before surgery, we used the postoperative pathological measurement to define tumour size. For patients with bilateral adrenal metastases, tumour size was based on the largest metastasis. Cancer origin was determined based on histopathological examination of the metastases and grouped into renal cancer, lung cancer, colorectal cancer, and other types of cancer. Metastases were defined as synchronous

if detected within 6 months after treatment of the primary tumour, and metachronous if discovered >6 months after treatment of the primary tumour. Adrenal metastases were considered solitary if patients had no other known metastatic lesions, including lymph node metastases.

Radicality was based on pathology and classified as: micro- and macroscopic tumour-free margins with at least 1 mm (pR₀-resection); microscopically uncertain or non-tumour-free margins, but macroscopically tumour-free margins (pR₁-resection); and macroscopic-positive margins (pR₂-resection). Surgical procedures and complications were entered from the surgical records; conversions were accounted for as laparoscopic procedures. Doctor's delay (time from adrenal lesion detection to

Table 2 Prognosis by primary cancer

	n died/ n total	Crude HR (95% c.i.)	Adjusted HR (95% c.i.)*	Median (i.q.r.) survival months	1-year survival % (95% c.i.)
Cancer origin					
Renal cancer	122/195	1.00	1.00	36.5 (13.0–82.3)	76 (69–81)
Lung cancer	86/121	1.64 (1.24–2.17)	1.77 (1.31–2.40)	16.2 (8.4–48.0)	62 (53–70)
Colorectal cancer	34/50	1.12 (0.77–1.65)	1.19 (0.79–1.79)	34.7 (12.2–83.0)	78 (64–87)
Other cancer	51/69	1.27 (0.91–1.76)	1.43 (1.01–2.04)	23.2 (11.6–65.9)	72 (60–81)

i.q.r., interquartile range; HR, hazard ratio. *Adjusted for age, sex, and Charlson co-morbidity index.

Table 3 Prognostic factors by primary cancer

	Renal cancer crude HR (95% c.i.)	Lung cancer crude HR (95% c.i.)	Colorectal cancer crude HR (95% c.i.)	Other cancer crude HR (95% c.i.)
Sex				
Female	1.28 (0.88–1.85)	0.95 (0.62–1.46)	0.92 (0.40–2.14)	0.77 (0.42–1.40)
Male	1.00	1.00	1.00	1.00
Age (per 10 years)	1.16 (0.96–1.40)	0.73 (0.55–0.98)	1.52 (0.95–2.41)	1.05 (0.78–1.42)
Age at surgery				
Under 60 years	1.00	1.00	1.00	1.00
60–70 years	1.10 (0.71–1.72)	0.66 (0.41–1.07)	1.45 (0.48–4.32)	0.72 (0.36–1.43)
More than 70 years	1.26 (0.79–2.01)	0.50 (0.27–0.93)	3.16 (1.07–9.30)	1.55 (0.78–3.08)
CCI (per 1)	1.12 (0.98–1.28)	1.25 (0.99–1.59)	1.19 (0.80–1.77)	1.29 (0.92–1.80)
BMI in kg/m² (per 1)	0.97 (0.93–1.02)	0.99 (0.95–1.04)	1.07 (0.97–1.17)	0.97 (0.90–1.03)
Tumour size				
Under 25 mm	1.00	1.00	1.00	1.00
25–50 mm	1.00 (0.62–1.60)	1.32 (0.72–2.42)	1.54 (0.55–4.34)	0.75 (0.33–1.71)
More than 50 mm	1.58 (0.91–2.72)	2.66 (1.44–4.89)	2.16 (0.76–6.16)	1.12 (0.49–2.57)
Size (per 10 mm)	1.04 (0.97–1.13)	1.08 (1.02–1.15)	1.05 (0.94–1.17)	1.03 (0.95–1.10)
Mode of discovery				
Synchronous	2.17 (1.47–3.20)	1.33 (0.84–2.10)	0.98 (0.37–2.58)	3.83 (1.53–9.55)
Metachronous	1.00	1.00	1.00	1.00
Extra-adrenal metastases at time of surgery				
No	1.00	1.00	1.00	1.00
Yes	1.21 (0.81–1.83)	1.79 (1.07–3.01)	1.41 (0.66–3.00)	1.71 (0.96–3.04)
Surgical approach				
Laparoscopic	1.00	1.00	1.00	1.00
Open	2.07 (1.38–3.09)	1.27 (0.69–2.36)	1.11 (0.53–2.31)	2.00 (1.12–3.58)
Radicality				
R0 resection	1.00	1.00	1.00	1.00
R1 resection	1.79 (1.24–2.60)	2.35 (1.51–3.65)	1.90 (0.92–3.90)	0.83 (0.46–1.50)
R2 resection	3.02 (0.93–9.74)	2.47 (0.98–6.25)	4.58 (0.99–21.17)	3.60 (1.07–12.10)

i.q.r., interquartile range; CCI, Charlson co-morbidity index; HR, hazard ratio. Cox proportional regression analysis was used for overall survival after adrenal metastasectomy for each primary cancer.

surgery), was defined as number of days between the first description of a suspicious adrenal mass in records and the date of adrenalectomy.

Statistical methods

Efficacy and safety outcomes were summarized descriptively. For descriptive analyses, categorical values were presented as number of patients and percentages, and continuous variables as mean with s.d. or median with interquartile range (i.q.r.; 25th–75th percentile) as appropriate.

Overall survival and survival by cancer origin were calculated from date of surgery until date of death, emigration, or last date of available data on vital status (26 July 2019) and were plotted with Kaplan–Meier survival analysis.

Potential prognostic factors for survival were examined with Cox proportional hazard regression models and presented as hazard ratio (HR) with 95 per cent confidence intervals (c.i.). Two different models were applied: first, a univariate Cox regression for each variable separately, and second, a

multivariate model where each variable was adjusted for sex, age, and Charlson co-morbidity index. Both models were applied to the total patient cohort combined, and to each category of cancer origin separately. Tumour size was categorized in three intervals in the overall analysis. Age groups were analysed as a category and as a continuous (per 10 years) variable. The Charlson co-morbidity index was analysed as a continuous variable. The assumption of proportionality of hazards was assessed with log–log plots. In cases of doubt, Schoenfeld residuals was used for assumption testing with a cutoff of 0.05. All analyses were performed in Stata Statistical Software, release 16.1 (StataCorp, College Station, Texas, USA).

Results

Patient cohort

A total of 3004 patients were identified in the Danish National Pathology Registry. After exclusions, 435 patients, who had an adrenal metastasectomy performed, were included in the study

Table 4 Surgical complications by surgical approach

	Total	Laparoscopic *	Open
No complications	198 (50.6)	161 (62.6)	37 (27.6)
Clavien–Dindo I or II, n (%)	115 (29.4)	63 (24.5)	52 (38.8)
Bleeding, n	40	12	28
Superficial capsular lesion of organ (without intervention), n	28	17	11
Tumour leakage, n	14	7	7
Wound infection (including abscesses drained at bedside), n	10	6	4
GI problems (obstipation/diarrhoea), n	10	3	7
Urinary tract infection, n	6	6	0
Pneumonia (without sepsis or ICU), n	5	4	1
Lung atelectasis, n	1	1	0
Other, n	37	20	17
Clavien–Dindo III, n (%)	43 (11.0)	21 (8.2)	22 (16.4)
Conversion, n	15	15	0
Unplanned organ resection due to lesion, n	11	3	8
Abscess requiring intervention, n	4	1	3
Pleura exudate, n	5	2	3
Unplanned organ resection due to adherence, n	5	1	4
Re-operation due to bleeding, n	4	2	2
Lesions of organs (requiring intervention wo/resection), n	2	1	1
Bleeding ulcer, n	2	0	2
Other, n	4	2	2
Clavien–Dindo IV, n (%)	28 (7.2)	9 (3.5)	19 (14.2)
Biliary lesions, n	10	3	7
Renal insufficiency, n	3	1	2
Delirium, n	3	2	1
Abdominal catastrophe, n	1	0	1
Cardiac events (excluding AFIB), n	2	1	1
Circulatory collapse from bleeding, n	2	2	0
Sepsis, n	2	1	1
Kidney infarction, n	1	0	1
Adrenal insufficiency, n	1	0	1
Other, n	5	0	5
Clavien–Dindo V, n (%)	7 (1.8)	3 (1.2)	4 (3.0)
Death with 30 days, n	7	3	4

AFIB, atrial fibrillation; GI, gastrointestinal; ICU, intensive care unit. *Including patients perioperatively converted from laparoscopic to open surgery. Patients were only counted once in the Clavien–Dindo classification according to their most severe complication. Within a Clavien–Dindo category, a patient could be counted more than once if they had multiple complications of the same severity. Adrenal insufficiency after bilateral adrenalectomy was not considered a complication, but adrenal insufficiency after unilateral adrenalectomy was.

(Fig. 1). The majority of patients ($n=375$, 86.2 per cent) had surgery performed at the five main departments of adrenal surgery, whereas the remaining patients ($n=60$, 13.8 per cent) had surgery performed at 21 different departments across 17 hospitals. The procedures were centralized to university hospitals during the study interval. The primary cancer origin was renal cancer ($n=195$, 44.8 per cent), lung cancer ($n=121$, 27.8 per cent), colorectal cancer ($n=50$, 11.5 per cent), and other ($n=69$, 12.9 per cent) (Table 1 and Table S1). The median (i.q.r.) age was 66 (59–71) years, and 280 (64 per cent) patients were men. Mean(s.d.) BMI was 26.1(4.8), and mean(s.d.) Charlson co-morbidity index was 0.6(1.0). Age, BMI, and Charlson co-morbidity index varied minimally across the different cancer origins.

The metastasis was in the left adrenal gland in 253 (60 per cent) patients, right gland in 152 (36 per cent) patients, and bilateral in 16 (4 per cent) patients. The metastasis was found synchronously in 160 (40 per cent) patients and metachronously in 245 (60 per cent) (Fig. S1). There was presence of extra-adrenal metastatic disease at time of surgery in 109 (28 per cent) patients, whereas the remaining 282 (72 per cent) had a solitary metastasis. Location of the metastasis and presence of extra-adrenal metastatic disease was similar across various cancer origins. Median (i.q.r.) time from adrenal lesion detection to treatment (doctor's delay) was 65 (40–124) days (Table 1). Patients with renal cancer had the shortest doctor's delay, whereas patients with colorectal cancer had the longest (51 versus 94 days; $P < 0.001$).

Median (i.q.r.) pathologic tumour size was 35 (20–54) mm. Tumour size varied; patients with renal cancer origin had the smallest metastasis compared with patients with colorectal cancer origin who had the largest metastasis (25 versus 45 mm; $P < 0.001$).

Surgical management

Adrenal metastasectomy procedures increased seven-fold from 2000 and 2003 to 2014 and 2018, with increasing use of laparoscopic procedures (Fig. 2). Laparoscopic approach was used in 237 (60 per cent) patients, open laparotomy in 137 (35 per cent) patients, and 21 (5 per cent) procedures were converted from laparoscopic to open surgery. The use of laparoscopy was evenly distributed across the different cancer types except in patients with renal cancer origin, where almost half of the patients (49 per cent) underwent open laparotomy. Adrenalectomy was either performed alone ($n=247$, 58 per cent) or as part of an extended operation ($n=182$, 42 per cent), with removal of the primary tumour, lymph nodes, and/or other metastasis (Table 1). Patients with renal cancer origin had extended surgery in 126 (66 per cent) patients, whereas patients with lung, colorectal, and other cancer origin had adrenalectomy performed alone in most (more than 65 per cent) patients. pR0 resection was achieved in 279 (64 per cent) patients, pR1 resection was achieved in 140 (32 per cent), and pR2 resection in 16 (4 per cent) patients. Median (i.q.r.) operating time was 99 (70–153) min in patients undergoing laparoscopic surgery, and 178 (112–236) min in patients undergoing open laparotomy (P

< 0.001). The median duration of hospital stay was longer after open surgery (6 versus 2 days $P < 0.001$).

Overall survival

Median (i.q.r.) follow-up time was 21 (18–24) months. On database cutoff, 293 (67 per cent) patients were dead. Median (i.q.r.) survival time after adrenal metastasectomy was 28 (11–75) months. Overall survival at 1, 5, and 10 years was 72 per cent, 31 per cent, and 16 per cent respectively. Survival differed by cancer origin (Fig. 3). Patients with renal and colorectal cancer origin survived the longest with a median (i.q.r.) survival time of 37 (13–82) months and 35 (12–83) months respectively. Patients with other cancer origin had a median (i.q.r.) survival time of 23 (12–66) months, and patients with lung cancer had median (i.q.r.) survival time of 16 (8–48) months (Table 2).

Prognostic factors

Sex and BMI did not affect survival. Older age did not impact survival except in patients with colorectal cancer older than 70 years, HR 3.16 (95 per cent c.i. 1.07 to 9.30). In patients with lung cancer, age above 70 years was associated with improved survival outcomes, HR 0.50 (95 per cent c.i. 0.27 to 0.93) (Table 3).

Overall, factors associated with poor survival included lung cancer origin (HR 1.77, 95 per cent c.i. 1.31 to 2.40) (Table S2), increasing numbers of Charlson co-morbidity index factors (HR 1.14 per one-point increase, 95 per cent c.i. 1.03 to 1.27), tumour size above 50 mm (HR 1.79, 95 per cent c.i. 1.26 to 2.52), presence of extra-adrenal metastases (HR 1.31, 95 per cent c.i. 1.01 to 1.71) (Fig. S2), open surgical approach (HR 1.33, 95 per cent c.i. 1.04 to 1.71) and non-radical pR2-resection (HR 3.57, 95 per cent c.i. 1.96 to 6.48) (Table 3 and Fig. S3).

Surgical complications and mortality

The majority (50.6 per cent) did not have surgical complications. The most common minor surgical complications (Clavien–Dindo I or II) were bleeding ($n = 40$, 10.2 per cent), superficial lesions of organs ($n = 28$, 7.1 per cent), tumour leakage ($n = 14$, 3.7 per cent), and wound infection ($n = 10$, 2.5 per cent). Major complications (Clavien–Dindo III or IV) included conversion ($n = 15$, 3.8 per cent), unplanned organ resection due to lesions ($n = 11$, 2.8 per cent), abscess requiring intervention ($n = 4$, 1.0 per cent), biliary lesion ($n = 10$, 2.5 per cent), pleura exudate ($n = 5$, 1.3 per cent), and re-operation due to bleeding ($n = 4$, 1.0 per cent) (Table 4).

Complications varied depending on type of surgery. Complications were more frequent and severe in patients who underwent open surgery compared with patients undergoing laparoscopic surgery (Clavien–Dindo III–V, 31.5 per cent versus 11.8 per cent respectively, $P < 0.001$).

The 30-day mortality was 1.8 per cent. Three patients died from surgical complications, one from rapid tumour progression, one patient died from sudden cardiac failure, and one patient, who had both adrenal glands removed, from Addison crisis.

Discussion

This is one of the largest retrospective nationwide studies of survival, prognostic factors, and complications in patients undergoing adrenal metastasectomy. The main findings were that approximately one-third of patients achieved long-term 5-year survival after adrenal metastasectomy, and that the procedure was safe. Second, several prognostic factors for short overall survival were identified, including non-radical resection, large tumour size, lung cancer origin, open

approach, presence of extra-adrenal metastases, and co-morbidity. This information may guide patient counselling and treatment decisions.

The origin of the primary tumour was clearly important (Table S2). Renal and colorectal cancer origin were associated with favourable survival outcomes, whereas lung cancer origin was related to poor outcome; this was in agreement with previous studies^{5,6,12}. Only two patients with breast cancer and seven patients with oesophageal/cardia cancer had surgery in the present study, even though adrenal metastasis from both cancer origins are frequently found in autopsy studies^{2,27}. Thus, patients with oligometastatic disease from certain cancers seems more frequently selected for surgery than other; this is probably related to inherent tumour biology.

Increasing tumour size was associated with reduced survival. Further, the chance of performing a radical resection was reduced in patients with large adrenal metastases. This agreed with a recent study from the British Association of Endocrine and Thyroid Surgeons' national registry, describing malignant disease, and large tumour size independently associated with mortality²⁸.

Increasing Charlson co-morbidity index factor was negatively associated with survival; a 14 per cent increased rate of death was observed per one-point increase. The impact of Charlson co-morbidity as a prognostic factor in patients with metastases to the adrenal gland has not previously been reported in the literature. This finding may have clinical impact and may help in patient counselling.

Over the last decades both the number of procedures and the frequency of laparoscopic procedures have increased dramatically. Laparoscopic procedure was associated with shorter duration of hospital stay, shorter operating time, and fewer complications. Recent results from a multicentre European study found that survival after adrenalectomy was negatively affected by an open approach²⁰. This agreed with the present findings; however, patients may not be comparable as the laparoscopic approach is used in patients with smaller tumours. There was no difference in the number of pR0 resections depending on surgical approach. This is important, as risk of non-radical resection has been an argument for surgeons to favour an open approach. Major postoperative complications (Clavien–Dindo III–V) in this study were significantly more frequent in patients who had open surgery rather than laparoscopic surgery (31.5 versus 11.8 per cent). Complications were recorded according to the Clavien–Dindo classification, which is probably the reason that complications were more frequent in our study compared with other studies not using this classification^{29,30}. Laparoscopy is now the standard, and should be the first choice unless it is not laparoscopically possible to ensure tumour-free margins^{5,30}.

In the present study, resection margins significantly impacted survival. The strongest negative prognostic factor identified in our study was non-radical pR2 resection, corresponding to a 3.57-times increased rate of death compared with clear margins. This has also been shown in previous studies^{2,4,5} and is never intended. Accordingly, it is a difficult prognostic factor to include in the preoperative counselling with the patient; however, the intention must be to increase surgical margins in metastatic lesions, where growth can be outside the adrenal gland in surrounding fatty tissue in contrast with benign adrenal tumours.

Doctor's delay has not previously been reported in the literature. According to guidelines it is important to rule out

pheochromocytoma before surgery¹⁰; this requires biochemical screening, which should be performed in an early phase in the interests of time. Given the importance of tumour size and radicality, doctor's delay should be reduced to as little as possible and observation with multiple control scans should be avoided. However, synchronous metastatic disease may have a more aggressive tumour biology than metachronous metastatic disease³¹. This was also seen in the present study.

A relatively large number of patients (33 per cent) had extra-adrenal metastatic disease at the time of surgery, which has also been reported in a similar study⁵. This is not recommended by guidelines¹⁰. In our study, these patients had a short median survival of 16 months. This finding was confirmed by a previous study, that found decreased survival with HR of 1.46 in patients with extra-adrenal disease⁵. While there can be diagnostic or palliative reasons for non-radical adrenal metastasectomy, curative-intended surgery should be balanced against the postponement of other oncological treatment induced by surgery.

The main strengths of this study were inclusion of nationwide registries, complete follow-up data, and access to clinical data from medical records, which allowed us to exclude patients undergoing debulking procedures. The main limitations are the retrospective design, long inclusion interval, missing information on smoking, alcohol, or concomitant medication, and lack of a proper control group. We were not able to address a volume–outcome effect due to missing data³². Further, we did have some missing data, which cannot be avoided in a large retrospective study.

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L.R. conceived the study idea. L.R., E.V., and A.E. designed the study with contributions from F.D. and P.L.P. A.E. identified the initial cohort in health registries. E.V. collected data from medical records and confirmed the final cohort with supervision from L.R. E.V. wrote and conducted the statistical analysis plan with assistance from A.E. and L.R. E.V. drafted the first paper. All authors critically revised and approved the final paper. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Disclosure. The authors declare no conflict of interest.

Supplementary material

[Supplementary material](#) is available at *BJS Open* online.

Data availability

The analysis plan was not preregistered in an online independent registry. The Stata code for the analysis is available at <https://github.com/andreasebbehoj/2020-AdrMet-Prognosis-EV>, including history of all changes and the log file. To preserve patient confidentiality and uphold Danish law on data protection, restrictions apply to the availability and exchange of patient data.

Upon request, the corresponding author will detail these restrictions and under certain circumstances access to some of the data may be provided.

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