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Original Article

Comparative performances of nomograms and conditional survival after resection of adrenocortical cancer

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Abstract

Background: Adrenocortical carcinomas (ACCs) carry a poor prognosis. This study assessed the comparative performance of existing nomograms in estimating the likelihood of survival, along with the value of conditional survival estimation for patients who had already survived for a given length of time after surgery.

Methods: This was an observational study based on a prospectively developed departmental database that recorded details of patients operated for ACC in a UK tertiary referral centre.

Results: Of 74 patients with ACC managed between 2001 and 2020, data were analysed for 62 patients (32 women and 30 men, mean(s.d.) age 51(17) years) who had primary surgical treatment in this unit. Laparoscopic (9) or open adrenalectomies (53) were performed alone or in association with a multivisceral resection (27). Most of the tumours were left-sided (40) and 18 were cortisol-secreting.

Overall median survival was 33 months, with 1-, 3- and 5-year survival rates of 79, 49, and 41 per cent respectively. Age over 55 years, higher European Network for Study of Adrenal Tumours stage, and cortisol secretion were associated with poorer survival in univariable analyses. Four published nomograms suggested widely variable outcomes that did not correlate with observed overall survival at 1, 3 or 5 years after operation. The 3-year conditional survival at 2 years (probability of surviving to postoperative year 5) was 65 per cent, compared with a 5-year actuarial survival rate of 41 per cent calculated from the time of surgery.

Conclusion: Survival of patients with ACC correlates with clinical parameters but not with published nomograms. Conditional survival might provide a more accurate estimate of survival for patients who have already survived for a certain amount of time after resection.

Introduction

Adrenocortical carcinoma (ACC) is a rare disease with a dismal prognosis. Complete tumour resection is the only curative treatment for non-metastatic ACC. Surgery is also recommended for those with oligometastatic disease in an attempt to provide local control, and allow time for chemotherapy to act on systemic disease[1]. Patients with morbidity from the biochemical disturbances associated with excess hormone secretion or locally advanced disease treated without surgery have poor survival. In a cohort of 320 patients registered in the Surveillance, Epidemiology, and End Results (SEER) database, the 1-year survival rate for stage III (local invasion but no metastases) was only 13 per cent if not operated and 77 per cent after surgical treatment; for metastatic disease (stage IV), respective figures were 16 and 54 per cent[2]. For a disease with a poor prognosis, it is imperative to stratify patients at the time of initial diagnosis and make decisions about their treatment based on expected prognosis.

An initial risk stratification of ACC was developed three decades ago by the French Association of Endocrine Surgery based on 156 patients treated over 12 years[3]. These authors showed that outcome was better in patients younger than 35 years of age, and in those with androgen-secreting or non-secreting tumours. As expected, tumour stage and completion of resection allowed further stratification into risk groups, but none of these factors can quantify personal long-term outcome for an individual patient. Nomograms to provide survival estimates have been proposed by several groups. In 2009, a model was developed in 205 patients with ACC, and validated externally using another 207 patients identified in the 1973–2004 SEER database[4]. Three variables (age,

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stage, and surgical status) were included in the nomogram, which predicted cancer-specific and all-cause mortality. In an external validation cohort, the nomograms achieved between 72 and 80 per cent accuracy for prediction of cancer-specific or all-cause mortality at 1–5 years after either surgery or diagnosis of ACC for non-surgical patients[4]. Four more nomograms have been developed in the past 5 years[5–8], each using slightly different parameters to generate a points-based score that can be translated into likelihood of overall survival at 1, 3, and 5 years.

For cancers with a very poor prognosis, the overall survival likelihood might be underestimated by standard prognostic plots because of a disproportionate influence of the large number of patients who die within the first few years. The probability of later survival is likely to change for patients who have already survived for a certain time after resection. Conditional survival (CS) estimates have been proposed as a useful adjunct to traditional measures of survival probability, whereby survival probability is calculated only for individuals who have already survived for a predefined length of time[9–11].

The aim of the present study was to assess the comparative performance of nomograms currently used for ACC[5–8], and to evaluate CS for patients who had already survived for a given length of time after ACC resection.

Methods

Consecutive patients operated for ACC between 2001 and 2020 were identified from a prospectively developed database at a tertiary endocrine referral centre (Oxford University Hospitals NHS Foundation Trust, UK). This review study was approved by the institutional review board of Oxford University Hospitals NHS Foundation Trust. Patients were discussed in an established multidisciplinary meeting, and underwent detailed endocrine investigations to characterize functional tumours, along with preoperative thoracoabdominal CT. More recent patients underwent preoperative [^{18}F]fluorodeoxyglucose PET. Tumour stage was determined according to international guidelines published by the European Network for the Study of Adrenal Tumours (ENSAT) (*Table 1*)[12]. Completeness of resection was assessed as R0 (clear microscopic margins), R1 (incomplete tumour capsule, tumour at the resection margin) or R2 (macroscopic tumour remnant). Throughout the study there was a variable practice of reporting either the mitotic rate or the proliferation marker Ki-67.

Table 1 Staging for adrenocortical cancer proposed by the European Network for the Study of Adrenal Tumours

	Description
Tumour category	
T1	≤ 5 cm
T2	> 5 cm
T3	Tumour infiltrating surrounding tissue
T4	Tumour invasion into adjacent organs or tumour thrombus in vena cava or renal vein
Node category	
N0	No positive lymph nodes
N1	Positive lymph node(s)
Metastasis category	
M0	No distant metastases
M1	Presence of distant metastases
ENSAT stage	
I	T1 N0 M0
II	T2 N0 M0
III	T1–2 N1 M0
	T3–4 N0–1 M0
IV	T1–4 N0–1 M1

ENSAT, European Network for the Study of Adrenal Tumours.

Open radical adrenalectomy with *en bloc* resection of the tumour and ipsilateral kidney was the standard approach, with further decisions about multiorgan resection made on an individual basis. Laparoscopic surgery was performed when the preoperative diagnosis of incidentaloma was made in patients with a tumour smaller than 6 cm in diameter, and the diagnosis of ACC was established only after operation.

Adjuvant therapy with mitotane was considered for all patients with ENSAT stage I or II tumours. Patients with ENSAT stage III or IV tumours started mitotane treatment within 4–8 weeks after operation with monitoring of plasma levels (target level 14–20 mg/dl). Follow-up cross-sectional imaging and/or FDG-PET was done according to clinical protocols.

Survival was estimated using four published nomograms (*Table 2*). For patients who had died, observed survival was compared with the likelihood of survival for 1, 3 or 5 years as predicted by each nomogram. The 1-, 3- and 5-year survival rates predicted from each nomogram were compared using ANOVA. Wilcoxon test was used when two nomograms had a similar average rank on ANOVA.

CS was calculated using the Kaplan–Meier estimates of survival[13]. Mathematically, the probability of surviving (S) an additional 3 years, for example, for a patient who has already survived *x* years, can be represented as $S_{(3+x)}/S_{(3)}$.

Statistical analysis

Normally distributed data, presented as mean(s.d.), were compared using Student's *t* test. Values with a non-normal distribution are presented as median (range), and were analysed using Mann–Whitney and Kruskal–Wallis tests. Factors associated with survival were examined in univariable Cox regression analyses. Hazard ratios (HRs) and the 95 per cent confidence intervals were estimated. Multivariable analysis was not deemed feasible owing to the relatively small number of included patients. $P < 0.050$ was considered significant. All statistical analyses were done using StatPlus® for Macintosh® version 7 (AnalystSoft, Walnut, California, USA) or SPSS® for Macintosh® version 23.0 (IBM, Armonk, New York, USA).

Results

Between February 2001 and May 2020, a total of 74 patients with ACC were managed in this unit. Of these, 12 patients were excluded from further analysis because they underwent surgery elsewhere, had missing data, or presented with recurrent disease, or with advanced disease resulting in only palliative treatment.

Among 62 patients who underwent resection of ACC, the sex distribution was equal (32 women and 30 men) (*Table 3*). The mean(s.d.) age was 51(17) years and there was a preponderance of left-sided tumours (40 on the left, 21 on the right, 1 bilateral). Endocrine assessment demonstrated excess secretion of cortisol (18), androgen (7), aldosterone (2), and insulin-like growth factor 1 (1), whereas 34 patients had non-functioning tumours. Mean(s.d.) maximum diameter of tumour assessed on CT was 128(53) mm. [^{18}F]FDG-PET was performed in 16 patients treated in the past decade and all showed intense adrenal uptake with a median maximum standardized uptake value of 17.9 (range 8.6–59.2).

Forty-seven patients who presented with non-metastatic ACC were staged as having ENSAT stage I (5), stage II (24) or stage III

Table 2 Nomograms used for analysis of survival

Reference	Data set used	Variables included
Kim *et al.*[5]	148 patients operated in 13 major institutions in USA (1994–2014)	Tumour size, nodal status, T stage, capsular invasion and cortisol-secreting tumour
Kong *et al.*[6]	404 patients from SEER database (1988–2015); validated externally using the Cancer Genome Atlas set (82 patients, 1998–2012) and a Chinese multicentre cohort data set (82 patients, 2002–2018).	Age, T category, N category, M category
Li *et al.*[7]	751 patients from SEER database (1973–2015)	Age, year of diagnosis, histological grade, stage, chemotherapy
Zhang *et al.*[8]	855 patients from SEER database (1975–2016)	Age, tumour grade, surgical treatment (yes/no), T category, N category, M category

SEER, Surveillance, Epidemiology and End Results.

Table 3 Demographic and clinical data for 62 patients who had surgery for adrenocortical carcinoma

	Non-metastatic ACC ($n=47$)	Metastatic ACC ($n=15$)	$P^{\dagger}$
Age (years)*	52(18)	55(14)	>0.05‡
Sex ratio (F : M)	21 : 26	11 : 4	0.08
Tumour site			>0.05
Left	30	10	
Right	17	4	
Bilateral	0	1	
Tumour size (mm)*	121(50)	147(65)	>0.05‡
Extent of resection			>0.05
Adrenalectomy only	25	4	
+ Ipsilateral nephrectomy	18	9	
+ Splenectomy	13	6	
+ Distal pancreatectomy	4	1	
+ IVC resection	5	5	
Resection margin			>0.05
R0	34	8	
R1	12	5	
R2	1	2	

* Values are mean(s.d.). ACC, adrenocortical carcinoma; IVC, inferior vena cava. † For comparing categorical data, the $\chi 2$-test, or if deemed appropriate Fisher's exact test, was used. ‡ For comparing continuous data, Student's t-test was used.

(18) disease. Metastatic ACC (ENSAT stage IV) was diagnosed in 15 patients.

Nine patients had laparoscopic adrenalectomy for tumours measuring 30–95 mm, of whom five had a preoperative diagnosis of incidentaloma smaller than 6 cm. Open operation was performed in 53 patients: 20 patients had adrenalectomy alone and the remainder underwent *en bloc* ipsilateral nephrectomy (27), and/or splenectomy (19) or distal pancreatectomy (5). Tumour thrombus was removed from the inferior vena cava in 10 patients.

Lymph nodes were identified in 23 patients, of whom nine had lymph node metastases. Resection status was deemed R0 (42 patients), R1 (17) or R2 (3). Proliferation marker Ki-67 was reported in 25 patients, with a median Ki-67 index of 10 (range 2–50) per cent.

Mitotane chemotherapy was given to 44 patients. Of the 18 patients who did not receive mitotane, 12 with earlier stages of disease refused therapy and the other six had associated complex medical problems.

During follow-up, patients who developed oligometastatic disease were considered for further surgical intervention. Multiple operations for recurrent disease were performed in 12 patients for local recurrence (5), liver metastases (5), lung metastases (2) or isolated peritoneal deposits (1), at a median of 13 (range 2–86) months after the initial operation. Two patients had more than one reoperation for metastatic disease.

Overall median survival for the entire cohort was 33 months. The 1-, 3- and 5-year survival rates were 79, 49, and 41 per cent respectively. At the time of last follow-up, 20 patients were alive without disease a median of 70 months after the original operation; three of these patients had survived for more than 10 years. A further eight patients were alive with recurrent/metastatic disease at a median of 28 months after initial surgical treatment.

Evaluation of factors associated with survival indicated that advanced age had a negative impact (HR 4.29, 95 per cent c.i. 2.07 to 8.87; $P<0.001$) (*Table 4*). Median survival was 33 months for patients aged under 55 years and 19 months for those aged 55 years or more ($P<0.001$) (*Fig. 1a*). Tumour size did not affect survival, but advanced T category was associated with shorter survival (HR 3.52, 1.58 to 7.82; $P=0.002$). Positive nodal status had a strong negative impact on the chances of prolonged postoperative survival (HR 5.5, 1.49 to 20.44; $P=0.010$). The presence of metastatic disease was not associated with survival (HR 1.89, 0.77 to 4.65; $P=0.158$), although only a small subgroup (15 patients) presented with metastatic disease at the time of surgery. Although the presence of a hormone-secreting functional tumour overall was not associated with survival, the survival of patients with non-functioning tumours was significantly better than that of patients with a cortisol-secreting tumour (median 64 *versus* 12 months) (*Fig. 1b*). The presence of a positive resection margin (R1 or R2 *versus* R0) bordered on having a statistically significant influence on survival (HR 1.88, 0.94 to 3.76; $P=0.076$).

ENSAT stage correlated with survival. Median survival was 145 months for those with localized disease (ENSAT I–II), and 36 months for those with locally advanced (ENSAT III) or metastatic disease (ENSAT IV) (*Fig. 1c*).

Owing to the relatively small number of patients for whom Ki-67 index was available, analysis was done based on whether the Ki-67 index was below 10 per cent (11 patients) or 10 per cent and higher (14). With this cut-off, there was no statistically significant difference in survival between groups (HR 3.60, 0.89 to 14.5; $P=0.072$) (*Fig. 1d*). The mean survival for patients with a Ki-67 index of less than 10 per cent was 71 months, compared with 57 months for those with a higher value ($P=0.057$).

Predicted survival using published nomograms

For each nomogram, the scores and likelihood of survival were calculated by two independent observers. There was good interobserver correlation ($r^2=0.90$–0.98).

Predicted 1-, 3- and 5-year survival rates from each nomogram were compared, and found to be significantly different. The lack of correlation between survival rates predicted by different nomograms is illustrated in Fig. 2, which shows predicted 1-year (Fig. 2a) and 3-year (Fig. 2b). survival.

Using the observed survival in the cohort, the Kong nomogram indicated that patients who died within 1 year had a median likelihood of 12-month survival ranging from 15 to 94 per cent (median 70 per cent) (Fig. 3a). Patients who died within 3 years had a median likelihood of a 3-years predicted survival of 30 (range 0–77) per cent on the Zhang nomogram (Fig. 3b). Similar wide ranges for predicted 5-year survival rates were observed in patients who died within the first 5 years after ACC resection.

Table 4 Univariable Cox regression analyses of factors proposed to be associated with survival after resection of adrenocortical carcinoma

	Hazard ratio
Age ≥ 55 years at time of presentation	4.29 (2.07, 8.87)
Male sex	0.95 (0.48, 1.85)
Hormonally functional tumour	1.57 (0.80, 3.09)
Tumour site: left	1.34 (0.64, 2.88)
Type of resection: laparotomy	1.02 (0.36, 2.91)
T category of tumour	
T1–2	1.00 (reference)
T3–4	3.52 (1.58, 7.82)
N category of tumour	
N0	1.00 (reference)
N1	5.5 (1.49, 20.44)
Nx	1.64 (0.56, 4.76)
Metastatic disease at time of surgery	1.89 (0.77, 4.65)
Size ≥ 12 cm in largest diameter on histopathology	0.91 (0.46, 1.81)
Positive resection margin	1.88 (0.94, 3.76)
Ki-67 index >10%	3.60 (0.89, 14.5)
ENSAT stage	
I–II	1.00 (reference)
III–IV	2.64 (1.26, 5.54)
Adjuvant mitotane treatment	0.69 (0.33, 1.46)

Values in parentheses are 95 per cent confidence intervals. ENSAT, European Network for the Study of Adrenal Tumours.

Conditional survival

Fig. 4 shows actuarial survival and CS for patients included in the study. Overall, 3-year CS probabilities increased as a function of time already survived after the initial operation. The actuarial survival rate at 5 years after ACC resection was 41 per cent, whereas the 3-year CS rate at 2 years was 65 per cent.

With increasing number of years already survived by the patient, the difference in the relative survival probabilities for actuarial survival *versus* CS estimates became more pronounced. For instance, the actuarial survival rate at 8 years after ACC resection was 35 per cent, whereas the 3-year CS rate at 5 years was 86 per cent.

Discussion

The overall results of this study are in line with those of other observational studies relating to ACC. The mean age of patients in this cohort was 51 years, comparable to data from large national reports[14,15]. The present analysis showed that patients aged less than 55 years had significantly better survival than those aged 55 years or more, corroborating a previous report[16] from the National Cancer Data Base. Half of the patients had non-functional tumours and their survival was better than that of patients with cortisol-secreting tumours, confirming observations in the Mayo Clinic series[17], where patients with functioning adrenocortical carcinomas (53 per cent of cohort) had shorter survival (median 22 *versus* 66 months).

Staging was assessed using the ENSAT classification[12]. This was originally proposed based on data from 492 patients from

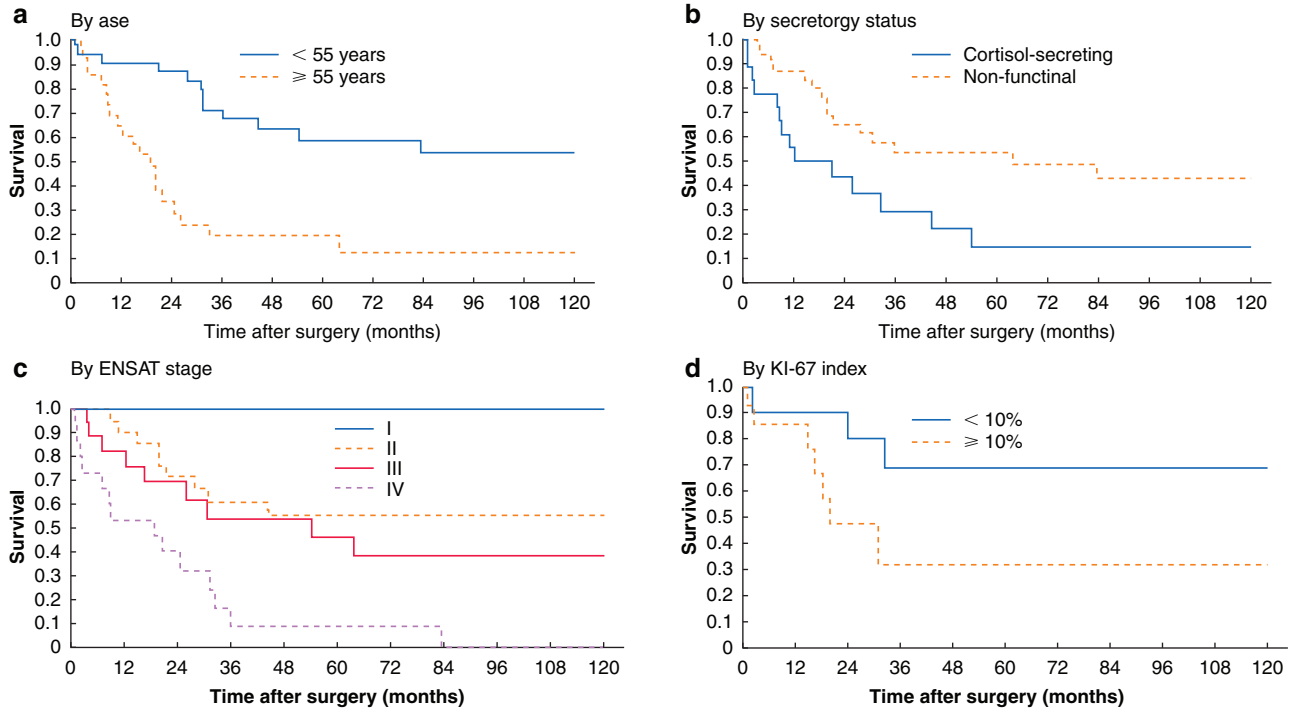

Fig. 1 Kaplan–Meier overall survival curves for the cohort, stratified by age, secretory status, European Network for the Study of Adrenal Tumours stage, and Ki-67 index

Overall survival by **a** age, **b** secretory status, **c** European Network for the Study of Adrenal Tumours (ENSAT) stage, and **d** Ki-67 index

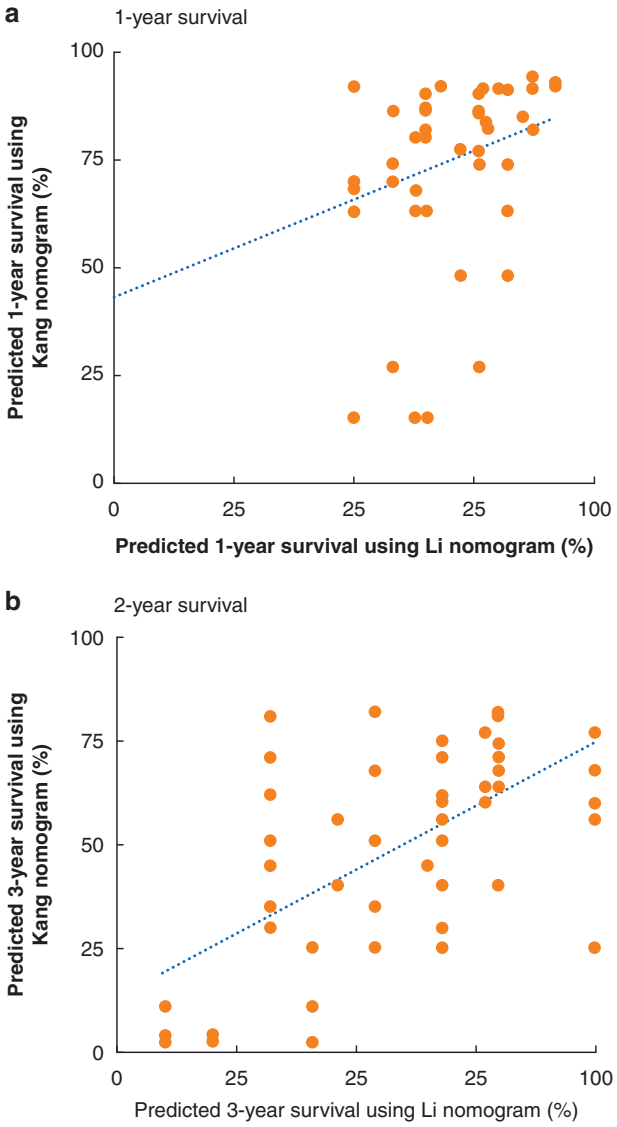

Fig. 2 Comparison of 1- and 3-year likelihood of survival using different nomograms for adrenocortical carcinoma

Likelihood of **a** 1-year survival (y =0.4548x+43.072, R^2=0.098) and **b** 3-year survival (y =0.6121x+13.088, R^2=0.380)

the German ACC registry[12], and showed high accuracy in predicting recurrence and survival rates when validated in a North American population-based cohort of 573 patients[18]. In the present study, survival was dependent on ENSAT stage, similar to data already published[18].

The proliferation marker Ki-67 index has also been reported to be an independent prognostic factor for ACC[19], although variability in Ki-67 scoring assessment is well recognized. Another study[20] reported wide variation when Ki-67-stained slides from 76 ACCs were analysed independently by 14 observers, each according to their preferred method, including eyeballing, formal manual counting, and digital image analysis. The present study did not identify a statistically significant difference in survival based on Ki-67 index, possibly owing to the small number of patients for whom this marker was available.

Only one-third of patients (23 of 62) had nodal status assessed formally in the present series. For the majority of patients, the histology report did not mention any lymph nodes encountered in the resection specimen. Despite controversy over the value of lymphadenectomy[21–23], it remains difficult to understand the inability to retrieve a reasonable yield of lymph nodes, especially when an *en bloc* dissection includes the ipsilateral kidney. One recent study[24] identified recurrent lymphatic metastases in the renal hilum, perirenal fat cranial and caudal to the renal hilum, and para-aortic and aortocaval areas, and such data reinforce the concept that a more extended lymph node dissection is beneficial. This remains an area of surgical practice in need of urgent improvement.

Survival data from this cohort of patients were used to assess the performance of four nomograms reported in the past 5 years. Although equally large data sets of several hundred patients were used in their development (*Table 2*), each nomogram identified slightly different clinical parameters that influence survival. For example, age is not mentioned in the Kim nomogram[5], is classified into groups in another (less than 39, 40–59, over 60 years)[7], and is a continuous variable in a third[6]. Only Li's nomogram[7] stratified patients based on year of diagnosis and the use of chemotherapy. TNM stage is included in three nomograms, but only Kim's nomogram refers to functional aspects of the tumour (*Table 2*). None of these publications comment on the different outcomes reached following similar analysis undertaken by other groups using nearly identical data sets derived from the SEER database. None of the nomograms have been validated in institutional data sets, and so it remains impossible to choose any one of them in support of clinical practice.

The present analysis found that the information provided by each of the nomograms was contradictory, and there was no correlation between likelihood of survival estimated by each one. These nomograms should not be used to influence clinical decision-making or in response to patient concerns regarding long-term outcome.

Long-term outcomes of patients with various types of malignancy have been examined using CS[11,25–27]. The main rationale for using CS is that survival should be viewed as a non-static variable. For aggressive malignancies with a high early death rate, the influence of time already survived should not be overlooked. Therefore, rather than basing estimations solely on initial risk factors determined at the time of surgery, CS is able to provide a more dynamic assessment of a patient's survival probability. For patients undergoing resection of ACC, data on CS are limited. One study[28] examined the difference between CS and actuarial survival estimates among 641 patients from the SEER registry. Similar to findings in the present cohort, the analysis showed that CS appeared to better reflect patients' survival. These authors also showed that the diminished survival for patients with more advanced disease stage disappeared when follow-up was longer. Once patients have survived for a defined length of time, CS could provide a better estimate of prognosis than that based on factors at the time of surgery. The potential for bias during CS analysis needs to be acknowledged[29], as there is a need for sufficiently long follow-up to allow reliable estimation of CS and the sample must be large enough.

The present study has several limitations reflecting the experience of a single unit and a relatively small number of patients. The small sample size limits statistical power and inferences as well as precluding meaningful subgroup analyses. Based on recent evidence for volume–outcome correlation in adrenal surgery, the European Society of Endocrine Surgeons[30] has recommended that the care of ACC should continue in centres performing at least 12 adrenal operations per year. As this is an

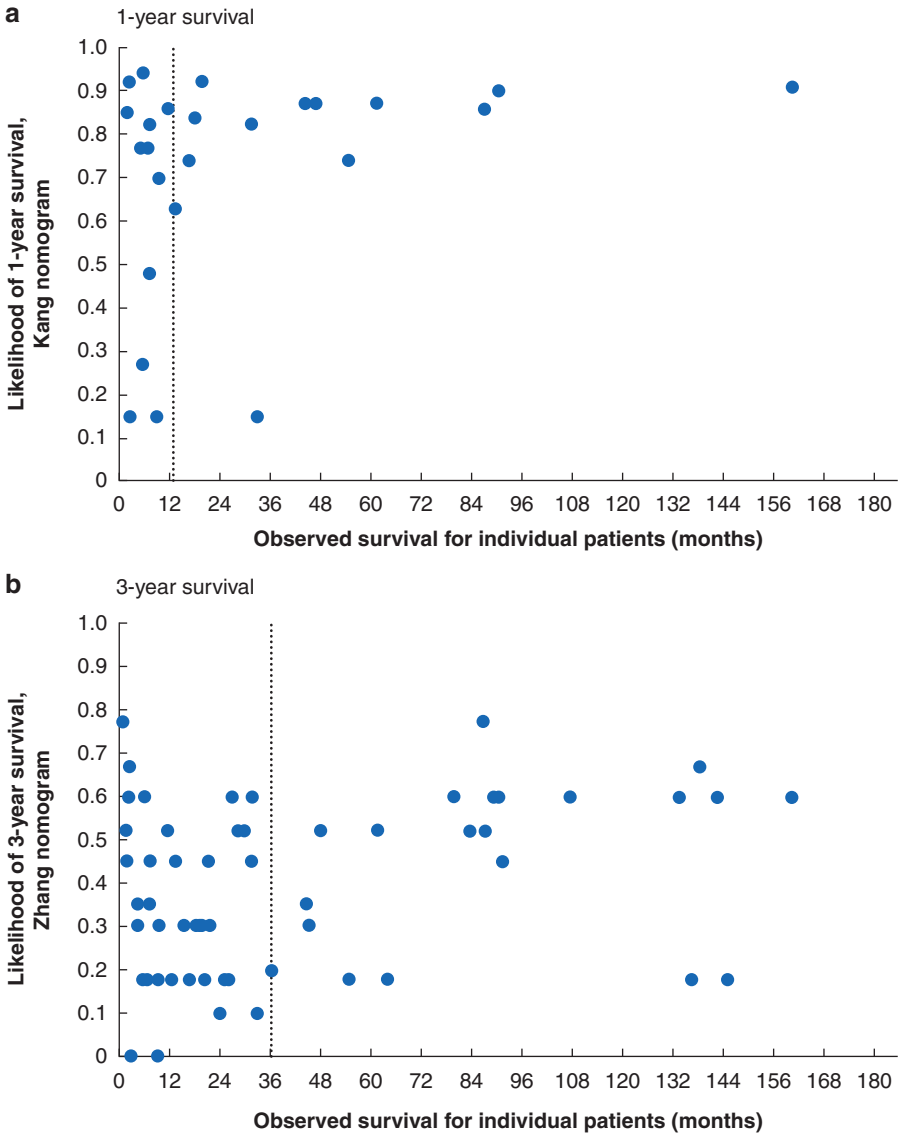

Fig. 3 Likelihood of 1-year and 3-year survival *versus* observed survival in patients with adrenocortical carcinoma

Likelihood of **a** 1-year and **b** 3-year survival *versus* observed survival

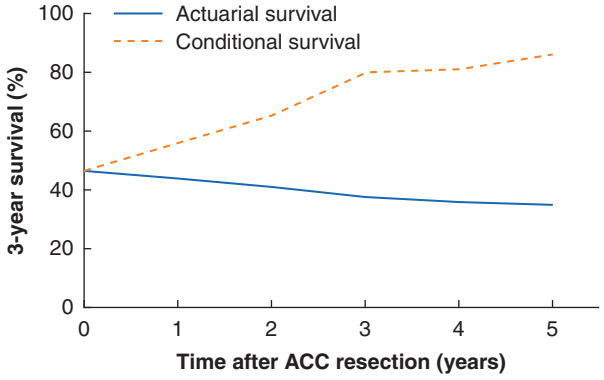

Fig. 4 Comparison of actuarial and conditional survival estimates as a function of time elapsed since surgery

Time 0 corresponds to actuarial survival at 3 years. ACC, adrenocortical carcinoma

observational study, there was some selection bias. Specifically, the study had an unavoidable racial bias, with almost all patients being of Caucasian origin. Patients had surgery over a relatively long period, certain tests were introduced during the study, and some data were missing.

To provide more precise prediction of individualized outcomes, future survival estimates have to be based on a better understanding of the biology of ACC. Pangenomic studies (transcriptome, methylome, chromosome alteration, and mutational profiles) can provide discriminant prognostic models for localized ACC[31,32], and genes associated with prognosis in the ACC tumour microenvironment are also valuable[33]. Such techniques are unlikely to become part of routine clinical practice soon and, until the results of such genomic tests can be integrated in this way, risk stratification based on easily accessible parameters remains paramount.

Disclosure. The authors declare no conflict of interest.

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