Pattern, timing and predictors of recurrence after surgical resection of chromophobe renal cell carcinoma

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ABSTRACT

Purpose

Currently there are no specific guidelines for the post-operative follow-up of chromophobe renal cell carcinoma (chRCC). We aimed to evaluate the pattern, location and timing of recurrence after surgery for non-metastatic chRCC and establish predictors of recurrence and cancer-specific death.

Methods

Retrospective analysis of consecutive surgically treated non-metastatic chRCC cases from the Royal Free London NHS Foundation Trust (UK, 2015 to 2019) and the international collaborative database RECUR (15 institutes, 2006 to 2011). Kaplan-Meier curves were plotted. The association between variables of interest and outcomes were analysed using univariate and multivariate Cox proportional hazards regression models with shared frailty for data source.

Results

295 patients were identified. Median follow-up was 58 months. The five and ten-year recurrence-free survival rates were 94.3% and 89.2%. Seventeen patients (5.7%) developed recurrent disease, 13 (76.5%) with distant metastases. 54% of metastatic disease diagnoses involved a single organ, most commonly the bone. Early recurrence (<24 months) was observed in 8 cases, all staged ≥pT2b. 30 deaths occurred, of which 11 were attributed to chRCC. Sarcomatoid differentiation was a rare (n=4) but associated with recurrence and cancer-specific death on univariate analysis. On multivariate analysis, UICC/AJCC T-stage ≥pT2b, presence of

coagulative necrosis, and positive surgical margins were predictors of recurrence and cancer-specific death.

Conclusion

Recurrence and death after surgically resected chRCC are rare. For completely excised lesions ≤pT2a without coagulative necrosis or sarcomatoid features, prognosis is excellent. These patients should be reassured and follow-up intensity curtailed.

Keywords

Renal cell carcinoma, chromophobe renal cell carcinoma, nephrectomy, follow-up, survival

INTRODUCTION

Renal cell carcinoma (RCC) represents the sixth most diagnosed cancer in men and the 10th in women[1]. RCC is characterized by distinct histologic subtypes[2]. While clear cell RCC (ccRCC) is the most frequent cortical renal malignancy, chromophobe RCC (chRCC) is a rarer subtype, accounting for roughly 5% of cases.

Loss of chromosomes 1, 2, 6, 10, 13, and 17 are common genetic changes in chRCC[3]. Mitochondrial DNA sequencing revealed potential driver mutations in a nicotinamide adenine dinucleotide dehydrogenase (NADH) subunit[3]. Nevertheless, prognostic molecular markers have not been described for chRCC. In addition, known RCC post-operative prognosticators, such as the Leibovich classification[4] or the UCLA Integrated Staging System (UISS)[5] are not applicable to chRCC, as both use nuclear grading, which has not been approved for clinical use in chRCC[6,7]. To date, no clinical prognostic models are available for chRCC[8,9]. Nonetheless, studies have shown a more favourable clinical course than for the other RCC subtypes, suggesting a low metastatic potential[10-12].

We analysed contemporary data from the largest UK tertiary referral centre and a European registry[13] to study recurrence patterns of patients with chRCC and give recommendations regarding follow-up for this RCC subtype.

METHODS

Data sources

The Specialist Centre for Kidney Cancer (SCKC) at Royal Free London NHS Foundation Trust was established in 2014 and is one of the largest kidney cancer centres in the UK with approximately 1000 referrals/year. The SCKC surgical database was queried for non-metastatic surgical cases with a diagnosis of chRCC from January 2015 to May 2019. Cases with at least one postoperative scan were included (n=90). No other exclusions were made.

The RECUR consortium combined data from 15 institutes across 10 European countries[13]. RECUR collected data from 3426 patients with localised RCC that underwent surgery with curative intent from January 2006 to December 2011, allowing for a minimum of 4 years of follow-up for patients still alive. All RECUR data were audited for quality and completeness by a urological surgeon (SD). After exclusions, the RECUR study population consisted of 3024 patients, of which 205 with a final diagnosis of chRCC were selected. A consort diagram is available in Supplementary Figure 1.

Outcomes

The primary objectives were to evaluate the timing, pattern and location of recurrence and to establish predictors of recurrence and cancer-specific death for chRCC.

Evaluated parameters

Demographic and clinical variables, staging, tumour size, histopathological features, recurrence and survival were evaluated. Both data sources coded TNM staging according the 2010 criteria[14,15].

Potential recurrence and death predictors were UICC/AJCC tumour stage (dichotomised into ≤pT2a and ≥pT2b), presence of coagulative necrosis, presence of sarcomatoid differentiation, and positive surgical margins. UICC/AJCC node stage was excluded as a potential predictor as lymph node disease was present at diagnosis in only one patient.

Local recurrence was defined as disease progression in the renal bed or remaining kidney after radical (RN) and partial nephrectomy (PN), respectively. New renal lesions observed in the contralateral kidney were classified as multifocal metachronous disease, and not as disease recurrence. All extra-renal foci of disease detected during follow-up were classified as distant recurrences.

Follow-up was defined as time from date of surgery to last known imaging scan date. Recurrence free survival (RFS) was defined as time from surgery to date of first unequivocal radiological or clinical evidence of recurrence (local or distant). Early recurrence was defined as local or distant recurrence occurring less than 24 months after surgery. Cancer specific survival (CSS) was defined as time from surgery to chRCC related death. Overall survival (OS) was defined as time from surgery to death from any cause.

Statistical analyses

Descriptive analysis of data from both sources. Continuous variables were compared using Mann-Whitney U test. Categorical variables were compared using Chi-squared test. Kaplan-Meier plots were used to depict cumulative survival functions for the

outcomes of interest. Univariate predictor factor analysis was conducted using Cox regression. Cox proportional hazard regression model with shared frailty for data source was used to study the association between variables of interest and recurrence and cancer-specific death and account for potential heterogeneity in outcomes between the two databases. Sarcomatoid differentiation was not included in the regression model due to missing data and it being a rare event. Proportionality assumption was tested using Schoenfeld residuals. Significance threshold was set at p=0.05. All analyses were performed using Stata SE 16.0.

RESULTS

In total, 295 surgically treated patients with chRCC were identified. Demographic and clinical characteristics are in Table 1. With the exception of follow-up duration and incidence of deaths, demographic and clinical characteristics were similar between patients from the two databases.

During a median follow-up of 58 months (range 1.4 to 149.7), 17 disease recurrences were noted (Supplementary Figure 2A). The five and ten-year RFS rates were 94.3% and 89.2%, respectively. At the time of recurrence, 13 (76.5%) patients were diagnosed with metastatic disease and 4 (23.5%) had isolated local recurrence. Of 13 metastatic cases, 2 had both local and distant recurrences and 10 had distant recurrence only, full information for one metastatic case was missing. Individual patient data on recurrences and management is documented in Supplementary Table 1.

Pattern and location of distant recurrences

Metastatic disease diagnoses involved a single organ in 53.8% (7/13) of patients (bone (n=4), lung, liver and brain). Overall, sites affected by metastatic disease included the bone (n=5), lung (n=4), liver (n=3), retroperitoneal lymph nodes (n=2), pleura (n=1), adrenal gland (n=1), and brain (n=1). The patient with metastatic brain disease was symptomatic, as were all with bone metastases.

Timing of recurrence

Recurrences occurred after a median of 26.5 months (range 1 to 81) following surgery. In 8 cases, recurrence was detected due to symptoms. Distant recurrences

were diagnosed earlier than local ones (median 22.3 versus 47.9 months). Early recurrence (<24 months after surgery) was observed in 8 cases (2.7% of all cases, 47.1% of recurrences), all staged ≥pT2b. Except for one, all patients with early recurrence had distant disease and died a median of 4 months (range 0.7 to 30) after recurrence.

Management of recurrences

Single renal bed recurrences were treated with surgical excision (n=3). Two of the surgically treated cases were also exposed to systemic therapy. One intrarenal recurrence was treated with cryoablation.

Of the 13 cases diagnosed with distant disease, 2 were treated solely with skeletal radiotherapy with curative intent. Another patient received both radiotherapy and systemic treatment for oligometastatic bone disease. The remaining 9 patients were treated with anti-VEGF agents (n=3), received no local or systemic treatment (n=3), or were subject to best supportive care (n=3). Treatment information was missing for 1 patient. None of the patients that developed metastatic disease were surgically treated.

Cancer specific and overall survival

During follow-up 30 deaths (10.2% of all cases) were registered, of which 11 (3.7% of all cases) were attributed to chRCC (Supplementary Figure 2B) and the remaining to other causes. The five-year CSS is 96%, and the ten-year CSS is 92.6%. Death from chRCC occurred at a median of 25.3 months after surgery (range 1.4 to 88.1) and a median of 7.1 months (range 0.5 to 30) after initial diagnosis of recurrence. Of

note, 2 patients died during the first 90 days following surgery, both with large tumours with sarcomatoid differentiation.

Outcome Predictors

Combined analysis revealed that 15 of the 17 (88.3%) recurrences occurred in patients with tumours staged pT2b or higher. During the median follow-up of 58 months, incidence of recurrence was 0.9% (2/221) for tumours staged pT1a to pT2a, and 20.3% (15/74) for those staged pT2b or higher. Two local recurrences were noted following surgery for T1a tumours. In one patient, a 30mm tumour was excised by RN after conversion from an attempted laparoscopic PN. Surgical margins were negative. Local recurrence was noted and histologically confirmed after incomplete excision 5 years later. Local progression led to 2 lines of systemic therapy (Sunitinib followed by Sorafenib) and distant progression to therapy change to Everolimus. The patient has remained on Everolimus for 5 years with stable disease. In the second case, positive surgical margins were documented after laparoscopic PN for a 19mm tumour. Local recurrence was documented four years after surgery and managed with cryoablation. Five years after ablation, the patient remains disease-free.

Sixty-one cases were found to be associated with coagulative necrosis (20.7%). Recurrence was observed in ten of these cases (16.4%) and death from disease in seven (11.5%).

Positive margins were noted in 17 cases (5.8%), 14 after PN and 3 after RN. Notwithstanding, recurrence after this microscopic finding was only seen in 3 cases.

Sarcomatoid differentiation was noted in 4 cases (1.3%), all of which recurred. It was also associated with dismal outcomes for 3 cases, with metastatic recurrence and death from disease 1.4, 2.5 and 28 months after surgery respectively. On univariate

analyses sarcomatoid differentiation depicted a HR of 107.4 (95%CI 29.4 to 391.4, p<0.001) and of 39.1 (95%CI 9.9 to 154.4, p<0.001) for recurrence and cancer-specific death associated with the presence of sarcomatoid differentiation, respectively (Figure 1A and 2A).

Final predictors incorporated in the model were UICC/AJCC T stage (Figure 1B and 2B), coagulative necrosis (Figure 1C and 2C), and surgical margins (Figure 1D and 2D). The 3 factors were deemed predictors of recurrence and cancer-specific death (Supplementary Table 2, Supplementary Figure 3). Analyses depicted a HR of 10.1 (95%CI 3.1 to 32.8, p<0.001) and of 13.5 (95%CI 2.7 to 66.2, p=0.001) for, respectively, recurrence and cancer-specific death associated with UICC/AJCC T stage. The presence of coagulative necrosis was associated with a HR of 6.3 (95%CI 2.0 to 19.6, p=0.001) and of 6.0 (95%CI 1.4 to 25.5, p=0.014) for, respectively, recurrence and cancer-specific death. Positive surgical margins were associated with a HR of 7.2 (95%CI 1.7 to 29.4, p=0.006) and of 8.0 (95%CI 1.4 to 46.0, p=0.020) for, respectively, recurrence and cancer-specific death.

DISCUSSION

The European Association of Urology (EAU) RCC Guidelines Panel established a collaborative multicentre consortium (RECUR) to investigate evidence-based follow-up recommendations for localized RCC. In contrast to previously published follow-up studies, RECUR focuses on further management and outcome after a recurrence is detected[16,13]. With data from the Specialist Centre for Kidney Cancer, the largest number of contemporary patients diagnosed with chRCC were collected with detailed information about location, dynamics and pattern of recurrences as well as subsequent management.

We observe that after a median follow up of 5 years, recurrence and cancer-specific death are rare events for surgically treated chRCC. Adverse outcomes are more likely in tumours staged pT2b and above, with coagulative necrosis, sarcomatoid differentiation or positive surgical margins. Metastatic disease is the more frequent first presentation of recurrence and the bone the most affected site. Early recurrence occurred only for tumours staged pT2b and above and were associated with early cancer-specific death.

Our analyses are validated by a previously published series on 496 chRCC treated at the Memorial Sloan Kettering Cancer Center (MSKCC)[17]. In this study spanning 26 years, larger tumour size, sarcomatoid differentiation, and higher T-stage were significantly associated with adverse RFS and overall survival in chRCC. Metastatic recurrence was 5% for chRCC. No specific follow-up recommendations were made. A retrospective analysis of 291 patients from the Surveillance and Treatment Update on Renal Neoplasms (SATURN) project reported similar outcomes[10]. At a median follow-up of 44 months, 8.6% patients had disease recurrence and 6.2% died from

disease. The 5-year RFS and CSS were 89.3% and 93%, respectively. T stage and sarcomatoid differentiation were independent predictors of RFS and CSS at multivariable analysis. Again, no risk adapted follow-up recommendations were given. Better outcomes compared to clear cell RCC were also reported in a Korean cohort of 166 patients with chRCC which included a pooled analysis of 10 other retrospective series[18] and a propensity score matched analysis of 109 chRCC cases collected over a period of 40 years[11].

Our study is strengthened by the use of data from a multi-institutional and large dataset (RECUR) and a contemporaneous and detailed cohort (SCKC). The RECUR database provides long follow-up but excludes recurrences within 90 days following surgery. This is offset by the SCKC dataset offering insight into very early chRCC recurrences. Limitations of our study include the retrospective nature with inherent biases as well as a lack of a central pathology review and of a unified follow-up regimen. Heterogeneity in the reporting of positive surgical margins cannot be excluded. The event rate (recurrences and deaths) was low, which limited analysis and precision. In addition, an overall median follow-up of almost 5 years may not be sufficient to provide certainty of an absence of recurrence. Nevertheless, these data provide guidance for follow up recommendations for a subtype which has an overall low recurrence rate.

CONCLUSION

Recurrence of surgically resected chRCC is rare in a contemporary setting. For pT1 and pT2a lesions with negative surgical margins, absence of sarcomatoid features and coagulative necrosis, prognosis is excellent. Patients should be reassured and

follow up intensity can be curtailed. We propose a new and reduced radiological follow up scheme specific for chRCC, whereby the first axial scan covering chest and abdomen is done 2 years after surgery for pT1a to pT2a tumours without sarcomatoid differentiation or coagulative necrosis (Supplementary Table 3).

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CONFLICTS OF INTEREST

GDS has received educational grants from Pfizer, AstraZeneca and Intuitive Surgical, consultancy fees from Merck, Pfizer, EUSA Pharma and CMR Surgical, travel expenses from Pfizer and speaker fees from Pfizer. The remaining authors declare no conflicts of interest.

ETHICS APPROVAL

The study was deemed exempt from research ethics committee approval (UK Health Research Authority decision tool). Informed consent was not sought. Only retrospectively collected clinical data was used for analysis. The study was performed in line with the principles of the Declaration of Helsinki.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68 (6):394-424. doi:10.3322/caac.21492

2. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM (2016) The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. Eur Urol 70 (1):93-105. doi:10.1016/j.eururo.2016.02.029

3. Davis Caleb F, Ricketts CJ, Wang M, Yang L, Cherniack Andrew D, Shen H, Buhay C, Kang H, Kim Sang C, Fahey Catherine C, Hacker Kathryn E, Bhanot G, Gordenin Dmitry A, Chu A, Gunaratne Preethi H, Biehl M, Seth S, Kaipparettu Benny A, Bristow Christopher A, Donehower Lawrence A, Wallen Eric M, Smith Angela B, Tickoo Satish K, Tamboli P, Reuter V, Schmidt Laura S, Hsieh James J, Choueiri Toni K, Hakimi AA, Creighton Chad J, Davis Caleb F, Morgan M, Gunaratne Preethi H, Donehower Lawrence A, Kaipparettu Benny A, Wheeler David A, Gibbs Richard A, Signoretti S, Cherniack Andrew D, Robertson AG, Chu A, Choueiri Toni K, Henske Elizabeth P, Kwiatkowski David J, Reuter V, Hsieh James J, Hakimi AA, Tickoo Satish K, Ricketts C, Linehan WM, Schmidt Laura S, Gordenin Dmitry A, Bhanot G, Seiler M, Tamboli P, Rathmell WK, Fahey Catherine C, Hacker Kathryn E, Smith Angela B, Wallen Eric M, Shen H, Laird Peter W, Shuch B, Muzny D, Buhay C, Wang M, Chao H, Dahdouli M, Xi L, Kakkar N, Reid Jeffrey G, Downs B, Drummond J, Morton D, Doddapaneni H, Lewis L, English A, Meng Q, Kovar C, Wang Q, Hale W, Hawes A, Kalra D, Walker K, Murray

Bradley A, Sougnez C, Saksena G, Carter Scott L, Schumacher Steven E, Tabak B, Zack Travis I, Getz G, Beroukhim R, Gabriel Stacey B, Meyerson M, Ally A, Balasundaram M, Birol I, Brooks D, Butterfield Yaron SN, Chuah E, Clarke A, Dhalla N, Guin R, Holt Robert A, Kasaian K, Lee D, Li Haiyan I, Lim E, Ma Y, Mayo M, Moore Richard A, Mungall Andrew J, Schein Jacqueline E, Sipahimalani P, Tam A, Thiessen N, Wong T, Jones Steven JM, Marra Marco A, Auman JT, Tan D, Meng S, Jones Corbin D, Hoadley Katherine A, Mieczkowski Piotr A, Mose Lisle E, Jefferys Stuart R, Roach J, Veluvolu U, Wilkerson Matthew D, Waring S, Buda E, Wu J, Bodenheimer T, Hoyle Alan P, Simons Janae V, Soloway Mathew G, Balu S, Parker Joel S, Hayes DN, Perou Charles M, Weisenberger Daniel J, Bootwalla Moiz S, Triche T, Jr., Lai Phillip H, Van Den Berg David J, Baylin Stephen B, Chen F, Coarfa C, Noble Michael S, DiCara D, Zhang H, Cho J, Heiman David I, Gehlenborg N, Voet D, Lin P, Frazer S, Stojanov P, Liu Y, Zou L, Kim J, Lawrence Michael S, Chin L, Yang L, Seth S, Bristow Christopher A, Protopopov A, Song X, Zhang J, Pantazi A, Hadjipanayis A, Lee E, Luquette Lovelace J, Lee S, Parfenov M, Santoso N, Seidman J, Xu Andrew W, Kucherlapati R, Park Peter J, Kang H, Lee J, Roberts Steven A, Klimczak Leszek J, Fargo D, Lang M, Choi Y-L, Kim Sang C, Lee J-K, Park W-Y, Wang W, Fan Y, Ahn J, Akbani R, Weinstein John N, Haussler D, Ma S, Radenbaugh A, Zhul J, Biehl M, Lichtenberg Tara M, Zmuda E, Black Aaron D, Hanf B, Ramirez Nilsa C, Wise L, Bowen J, Leraas Kristen M, Hall Tracy M, Gastier-Foster Julie M, Kaelin William G, Thorne L, Boice L, Huang M, Vocke C, Peterson J, Worrell R, Merino M, Czerniak Bogdan A, Aldape Kenneth D, Wood Christopher G, Spellman Paul T, Atkins Michael B, Cheville J, Thompson RH, Jensen Mark A, Pihl T, Wan Y, Ayala B, Baboud J, Velaga S, Walton J, Liu J, Chudamani S, Wu Y, Sheth M, Mills Shaw Kenna R, Demchok John A, Davidsen T, Yang L, Wang Z, Tarnuzzer

Roy W, Zhang J, Eley G, Felau I, Zenklusen Jean C, Hutter Carolyn M, Guyer Mark S, Ozenberger Bradley A, Sofia Heidi J, Chin L, Meyerson M, Kucherlapati R, Park W-Y, Robertson AG, Laird PW, Henske EP, Kwiatkowski DJ, Park PJ, Morgan M, Shuch B, Muzny D, Wheeler DA, Linehan WM, Gibbs RA, Rathmell WK, Creighton CJ (2014) The Somatic Genomic Landscape of Chromophobe Renal Cell Carcinoma. Cancer Cell 26 (3):319-330. doi:10.1016/j.ccr.2014.07.014

4. Leibovich BC, Blute ML, Cheville JC, Lohse CM, Frank I, Kwon ED, Weaver AL, Parker AS, Zincke H (2003) Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. Cancer 97 (7):1663-1671. doi:10.1002/cncr.11234

5. Zisman A, Pantuck AJ, Wieder J, Chao DH, Dorey F, Said JW, deKernion JB, Figlin RA, Belldegrun AS (2002) Risk group assessment and clinical outcome algorithm to predict the natural history of patients with surgically resected renal cell carcinoma. J Clin Oncol 20 (23):4559-4566. doi:10.1200/jco.2002.05.111

6. Meskawi M, Sun M, Ismail S, Bianchi M, Hansen J, Tian Z, Hanna N, Trinh QD, Graefen M, Montorsi F, Perrotte P, Karakiewicz PI (2013) Fuhrman grade [corrected] has no added value in prediction of mortality after partial or [corrected] radical nephrectomy for chromophobe renal cell carcinoma patients. Mod Pathol 26 (8):1144-1149. doi:10.1038/modpathol.2012.230

7. Delahunt B, Cheville JC, Martignoni G, Humphrey PA, Magi-Galluzzi C, McKenney J, Egevad L, Algaba F, Moch H, Grignon DJ, Montironi R, Srigley JR (2013) The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. Am J Surg Pathol 37 (10):1490-1504. doi:10.1097/PAS.0b013e318299f0fb

8. Siddiqui SA, Frank I, Cheville JC, Lohse CM, Leibovich BC, Blute ML (2009) Postoperative surveillance for renal cell carcinoma: a multifactorial histological subtype specific protocol. BJU Int 104 (6):778-785. doi:10.1111/j.1464-410X.2009.08499.x

9. Leibovich BC, Lohse CM, Cheville JC, Zaid HB, Boorjian SA, Frank I, Thompson RH, Parker WP (2018) Predicting Oncologic Outcomes in Renal Cell Carcinoma After Surgery. Eur Urol 73 (5):772-780. doi:10.1016/j.eururo.2018.01.005

10. Volpe A, Novara G, Antonelli A, Bertini R, Billia M, Carmignani G, Cunico SC, Longo N, Martignoni G, Minervini A, Mirone V, Simonato A, Terrone C, Zattoni F, Ficarra V (2012) Chromophobe renal cell carcinoma (RCC): oncological outcomes and prognostic factors in a large multicentre series. BJU Int 110 (1):76-83. doi:10.1111/j.1464-410X.2011.10690.x

11. Frees S, Kamal MM, Knoechlein L, Bell R, Ziesel C, Neisius A, Thomas C, Brenner W, Jager W, Thuroff JW, Roos FC (2016) Differences in Overall and Cancer-specific Survival of Patients Presenting With Chromophobe Versus Clear Cell Renal Cell Carcinoma: A Propensity Score Matched Analysis. Urology 98:81-87. doi:10.1016/j.urology.2016.05.048

12. Daugherty M, Sedaghatpour D, Shapiro O, Vourganti S, Kutikov A, Bratslavsky G (2017) The metastatic potential of renal tumors: Influence of histologic subtypes on definition of small renal masses, risk stratification, and future active surveillance protocols. Urol Oncol 35 (4):153.e115-153.e120. doi:10.1016/j.urolonc.2016.11.009

13. Dabestani S, Beisland C, Stewart GD, Bensalah K, Gudmundsson E, Lam TB, Gietzmann W, Zakikhani P, Marconi L, Fernandez-Pello S, Monagas S, Williams SP, Torbrand C, Powles T, Van Werkhoven E, Meijer R, Volpe A, Staehler M, Ljungberg B, Bex A (2019) Intensive Imaging-based Follow-up of Surgically Treated Localised

Renal Cell Carcinoma Does Not Improve Post-recurrence Survival: Results from a European Multicentre Database (RECUR). Eur Urol 75 (2):261-264. doi:10.1016/j.eururo.2018.10.007

14. Sobin LH, Gospodarowicz MK, Wittekind C (2009) TNM classification of malignant tumours (UICC International Union Against Cancer). 7th edn. Wiley-Blackwell,

15. Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A (2011) AJCC cancer staging manual. 7th edn. Springer,

16. Dabestani S, Beisland C, Stewart GD, Bensalah K, Gudmundsson E, Lam TB, Gietzmann W, Zakikhani P, Marconi L, Fernandez-Pello S, Monagas S, Williams SP, Torbrand C, Powles T, Van Werkhoven E, Meijer R, Volpe A, Staehler M, Ljungberg B, Bex A (2019) Long-term Outcomes of Follow-up for Initially Localised Clear Cell Renal Cell Carcinoma: RECUR Database Analysis. Eur Urol Focus 5 (5):857-866. doi:10.1016/j.euf.2018.02.010

17. Casuscelli J, Becerra MF, Seier K, Manley BJ, Benfante N, Redzematovic A, Stief CG, Hsieh JJ, Tickoo SK, Reuter VE, Coleman JA, Russo P, Ostrovnaya I, Hakimi AA (2019) Chromophobe Renal Cell Carcinoma: Results From a Large Single-Institution Series. Clin Genitourin Cancer 17 (5):373-379.e374. doi:10.1016/j.clgc.2019.06.011

18. Jiang HM, Wei JH, Zhang ZL, Fang Y, Zhou BF, Chen ZH, Lu J, Liao B, Zhou FJ, Luo JH, Chen W (2016) Does chromophobe renal cell carcinoma have better survival than clear cell renal cell carcinoma? A clinical-based cohort study and meta-analysis. Int Urol Nephrol 48 (2):191-199. doi:10.1007/s11255-015-1161-3

FIGURES

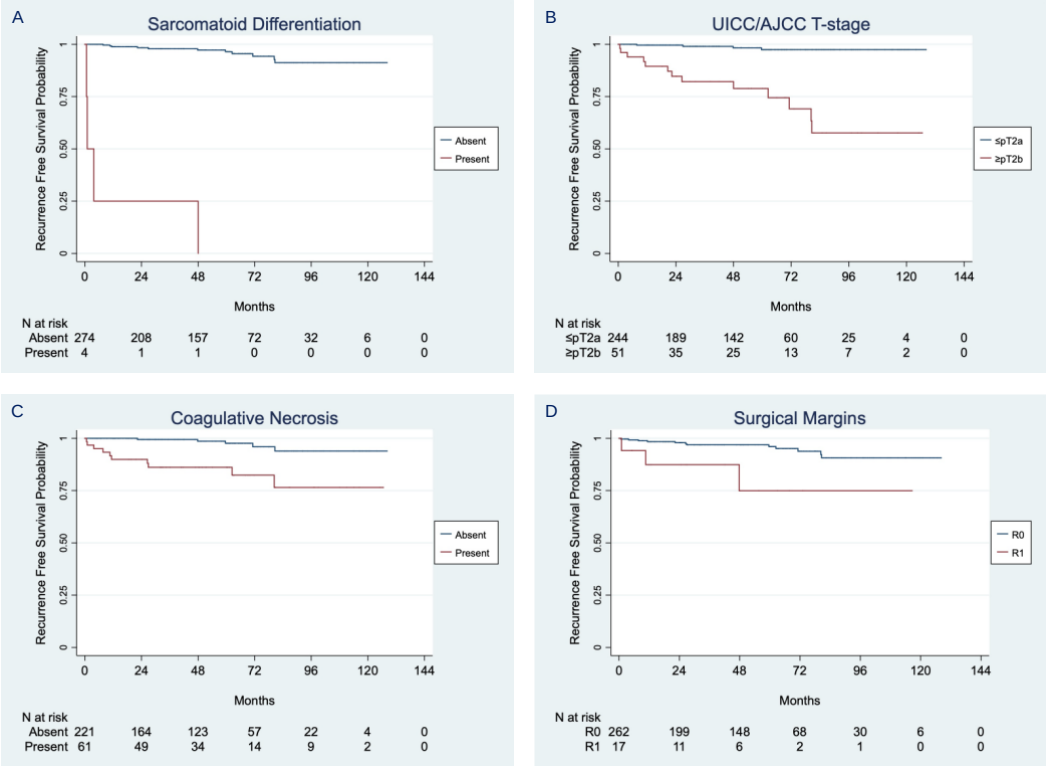

Figure 1 - Kaplan Meier plots for Recurrence-Free Survival by presence of sarcomatoid differentiation (A), UICC/AJCC T-stage (B, dichotomised into ≤pT2a and ≥pT2b), presence of coagulative necrosis (C), and surgical margins (D). R0: negative surgical margins, R1: positive surgical margins.

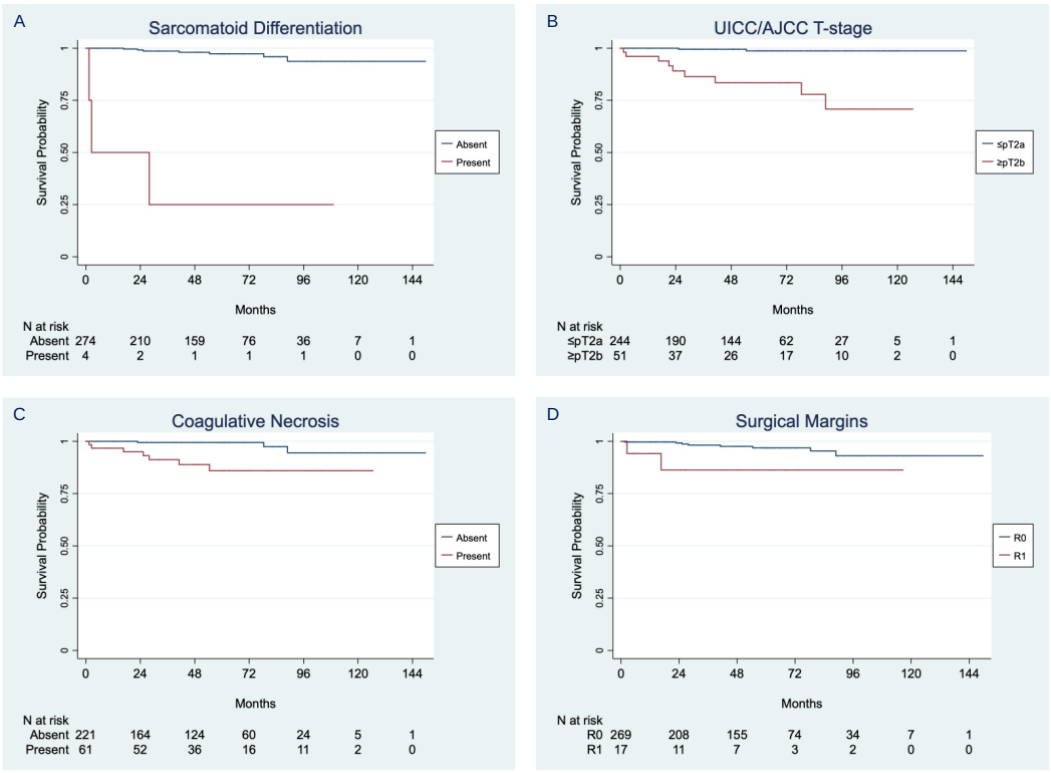

Figure 2 - Kaplan Meier plots for Cancer-Specific Survival by presence of sarcomatoid differentiation (A), UICC/AJCC T-stage (B, dichotomised into ≤pT2a and ≥pT2b), presence of coagulative necrosis (C), and surgical margins (D). R0: negative surgical margins, R1: positive surgical margins.

TABLES

Table 1 – Demographic and clinical characteristics of included patients, by data source

		SCKC		RECUR		SCKC vs RECUR	SCKC + RECUR
						p	
Number of patients		90	*Missing data*	205	*Missing data*	NA	295
Age at diagnosis *(years)*	median (IQR, min, max)	59 (16, 25, 84)	0%	62 (20, 22, 88)	0%	0.18	60 (19, 22, 88)
Male	n (%)	49 (54.4)	0%	120 (58.3)	0%	0.51	169 (57.3)
Left side	n (%)	46 (51.1)	0%	91 (44.4)	3.4%	0.39	137 (46.4)
Multifocal chRCC	n (%)	3 (3.3)	0%	3 (1.5)	3.4%	0.29	6 (2.0)
Surgery							
– Radical nephrectomy	n (%)	53 (58.9)	0%	114 (55.6)	0%	0.26	167 (56.7)
– Partial nephrectomy	n (%)	36 (40.0)	0%	91 (44.4)	0%		127 (43.0)
– Nephroureterectomy	n (%)	1 (1.1)	0%	0 (0)	0%		1 (0.3)

Pathological analysis after surgery							
– *Size (mm)*	median (IQR, min, max)	54.5 (43, 15, 160)	0%	50 (45, 8, 210)	0%	0.77	50 (46, 8, 210)
– T1a	n (%)	31 (34.4)	0%	72 (35.1)	0%	0.63	103 (34.9)
– T1b	n (%)	29 (32.2)	0%	59 (28.8)	0%		88 (29.8)
– T2a	n (%)	6 (6.7)	0%	24 (11.7)	0%		30 (10.1)
– T2b	n (%)	8 (8.9)	0%	15 (7.3)	0%		23 (7.8)
– T3a	n (%)	16 (17.8)	0%	29 (14.1)	0%		45 (15.3)
– T3b	n (%)	0 (0)	0%	4 (2.0)	0%		4 (1.36)
– T3c	n (%)	0 (0)	0%	1 (0.5)	0%		1 (0.3)
– T4	n (%)	0 (0)	0%	1 (0.5)	0%		1 (0.3)
– N0	n (%)	12 (13.3)	NA	49 (23.9)	NA	0.62	61 (20.7)
– N1	n (%)	0 (0)	NA	1 (0.5)	NA		1 (0.3)
– Nx	n (%)	78 (86.7)	NA	155 (75.6)	NA		233 (79)
– Presence of coagulative necrosis	n (%)	13 (14.4)	1.1%	48 (23.4)	5.9%	0.05	61 (20.7)

– Presence of sarcomatoid differentiation	n (%)	2 (2.2)	5.5%	2 (1.0)	5.9%	0.39	4 (1.4)
– Positive surgical margins	n (%)	8 (8.9)	0%	9 (4.4)	4.4%	0.15	17 (5.7)
Total follow up *(surgery to last scan; months)*	median (IQR, min, max)	18 (16, 1.4, 51)	NA	64 (32, .2, 150)	NA	**<0.01**	58 (50, 1.4, 150)
Recurrence rate	n (%)	2 (2.2)	NA	15 (7.3)	NA	0.08	17 (5.8)
Deceased	n (%)	2 (2.2)	NA	28 (13.7)	NA	**<0.01**	30 (10.2)
Deceased from chRCC	n (%)	2 (2.2)	NA	9 (4.4)	NA	0.36	11 (3.7)

chRCC – chromophobe renal cell carcinoma
SCKC – Specialist Centre for Kidney Cancer at Royal Free London NHS Foundation Trust
RECUR – euRopEan association of urology renal cell carcinoma guidelines panel Collaborative multicenter consortium for the studies of follow-Up and recurrence patterns in Radically treated renal cell carcinoma patients
NA – not applicable