Published in final edited form as:

Hum Pathol. 2015 June ; 46(6): 820–826. doi:10.1016/j.humpath.2015.02.013.

Succinate Dehydrogenase B (SDHB): A New Prognostic Biomarker in Clear Cell Renal Cell Carcinoma

Kristine M. Cornejo, MD^{1,2,*}, Min Lu, MD PhD^{1,2,3,*}, Ping Yang, MD PhD^{1,2,4}, Shulin Wu, MD^{1,2}, Chao Cai, MD^{5,6}, Wei-de Zhong, MD⁵, Aria Olumi, MD⁶, Robert H. Young^{1,2}, and Chin-Lee Wu, MD PhD^{1,2,6}

¹James Homer Wright Pathology Laboratories, Massachusetts General Hospital

²Department of Pathology, Harvard Medical School, Boston, MA

³Department of Pathology, School of Basic Medical Sciences, Peking University Health Science Center, Beijing, P.R. China

⁴Department of Pathology, Sun Yat-sen University Cancer Center, Guangzhou, P.R. China

⁵Department of Urology, Guangzhou First Municipal People's Hospital, Guangzhou Medical College, Guangzhou, China

⁶Department of Urology, Massachusetts General Hospital

Abstract

Succinate dehydrogenase B (SDHB) is a mitochondrial enzyme complex subunit. Loss of SDHB protein expression has been found to correlate with *SDHx* gene mutations. Little is known about its expression in subtypes of renal cell carcinoma (RCC), and whether it's a prognostic indicator. Four-hundred-fifty renal epithelial neoplasms were analyzed for SDHB, comprising of clear cell RCC (CCRCC) (n=240), papillary RCC (PRCC) (n=84), chromophobe RCC (ChRCC) (n=49), renal oncocytoma (RO) (n=47), clear cell papillary RCC (CCPRCC) (n=19) and von Hippel Lindau (VHL)- associated CCPRCC-like tumors (n=11). SDHB expression was graded based upon staining intensity using a 4-tiered system (0–3+), in which 3+ was strongest and complete absence was 0. Neoplasms were further categorized based upon staining extent into SDHB-weak (1–2+) and strong (3+). SDHB was strongly preserved in 131/240 (55%) CCRCCs, 84/84 (100%) PRCCs, 49/49 (100%) ChRCCs, 1/19 (5%) CCPRCC, 5/11 (45%) VHL-associated CCPRCC-like tumors and 47/47 (100%) ROs. The remaining 109 CCRCCs (45%), 18 CCPRCCs and 6 VHL-associated CCPRCC-like tumors had weak but preserved SDHB. SDHB expression in CCRCCs with high International Society of Urological Pathology (ISUP) nucleolar grade (G3–G4) correlated significantly with survival (log rank P=0.0004). SDHB is variably expressed in RCCs

© 2015 Published by Elsevier Inc.

Corresponding Author: Chin-Lee Wu MD PhD, Massachusetts General Hospital, Department of Pathology, Warren Building 225, 55 Fruit Street, Boston, MA 02114, Phone: 617-726-8454, Fax: 617-726-7474, cwu2@partners.org.

*These authors contributed equally to this study.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

with clear cell morphology and strongly preserved in most other neoplasms. Therefore, weak staining, particularly in clear neoplasms, should not be misinterpreted as negative. Finally, SDHB expression in CCRCCs with high nucleolar grade (G3-G4) is significantly associated with survival, indicating it may be both a diagnostic and prognostic marker in RCC.

Keywords

Renal cell carcinoma; clear cell; succinate dehydrogenase B; immunohistochemistry; oncocytoma; prognosis

Introduction

Succinate dehydrogenase (SDH)/mitochondrial complex II is a key respiratory enzyme located in the inner mitochondrial membrane that links the Krebs tricarboxylic acid cycle to oxidative phosphorylation [1]. The SDH complex, comprised of 5 proteins (SDHA, SDHB, SDHC, SDHD and SDHAF2), are encoded by five nuclear genes known as *SDHx* complex genes. Mutations in *SDHx* genes are associated with the development of hereditary pheochromocytoma/paranglioma (PHEO/PGL) syndrome, and less commonly gastrointestinal stromal tumors (GIST) and renal cell carcinoma (RCC) [2–4]. A mutation or inactivation in any *SDHx* gene results in the degradation of the SDH complex and is associated with negative succinate dehydrogenase B (SDHB) protein expression [2,3,5].

Recently, we described negative SDHB immunohistochemical staining in papillary renal cell carcinomas (PRCC) associated with tuberous sclerosis complex (TSC). Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder that can affect in varying degrees, nearly every organ system, including the brain, skin, heart, lungs, and kidneys. A mutation in either *TSC1* (chromosome 9q34), encoding the protein hamartin, or *TSC2* (chromosome 16p13), encoding the protein tuberlin, can be identified. These proteins act together as tumor suppressors and are components of the mTOR (mammalian target of rapamycin) signaling pathway [6]. These tumors have been uniquely found to be negative for SDHB protein expression, despite being associated with *TSC* gene mutations and not *SDHx* gene mutations [7]. TSC-associated PRCCs contain overlapping morphologic features with clear cell (tubulo) PRCCs (CCPRCC) and von-Hippel Lindau-associated CCPRCC-like tumors, as they also contain papillary architecture lined by cells with clear cytoplasm. Immunohistochemically, they were found to be uniquely negative for SDHB in addition to being positive for CD10, CK7 and CAIX, making them distinct [7].

SDHB immunohistochemical staining has not been well documented in renal epithelial neoplasms, with most studies focusing on *SDHx*-mutation associated RCC. In addition, SDHB expression has not been studied as a possible independent prognostic biomarker in RCC. To better characterize SDHB protein expression in renal epithelial neoplasms, we performed immunohistochemical analysis on a total of 450 renal tumors. We found that SDHB protein expression was preserved in all renal epithelial neoplasms analyzed, albeit in varying intensities, as described below. In addition, we tried to validate the prognostic significance of SDHB expression in CCRCC.

Materials and Methods

Case Selection

A total of 420 surgically resected renal epithelial tumors were selected from the case archives of the Department of the Pathology at the Massachusetts General Hospital (MGH) from 1992 to 2003. The patient demographics and follow-up data were obtained from the medical records with approval of the Institutional Review Board. The gross findings, including the laterality, number and size of the tumors, were noted from the pathology reports.

Histologic subtypes of RCCs were reviewed and reclassified according to the ISUP Vancouver Classification of Renal Neoplasia and evaluated for the ISUP nucleolar grade [8,9]. All 420 tumors contained remaining formalin-fixed and paraffin-embedded tissue in which four- μ m sections of each tumor were obtained for immunohistochemical analysis and tissue microarray (TMA) studies.

Tissue Microarray (TMA)

Microarrays of renal epithelial neoplasms (n=420) were constructed from CCRCC (n= 240), PRCC (n=84), chromophobe RCC (ChRCC) (n=49), renal oncocytoma (RO) (n=47) and normal kidney tissue taken adjacent to tumor (n=15). Four 1.0 mm or 0.6mm diameter cores were obtained from paraffin-embedded tissue for each tumor tested.

CCPRCC

Hematoxylin and eosin stained slides, including RCCs selected by TMA together with RCCs resected from 2004 to 2012 at MGH were reviewed for morphologic features of CCPRCC. One representative paraffin block from each case was selected for immunohistochemical staining. The combination of characteristic morphologic features and immunohistochemical staining resulted in a total of 19 CCPRCCs.

VHL-associated CCPRCC-like Tumors

A total of 11 VHL-associated CCPRCC-like tumors were included in this study. The diagnosis of VHL disease was based either on a known family history or a combination of tumors diagnostic of VHL disease including capillary hemangioblastoma of the central nervous system or retina plus another VHL-associated extrarenal tumor.

Immunohistochemical Staining

Series of 4- μ m sections were cut from formalin-fixed, paraffin-embedded tissue blocks and SDHB immunohistochemistry was performed (Abcam Inc, Cambridge, MA; clone 21A11AE7; 1:1000 dilution). SDHB immunostaining was first performed on TMA samples of renal epithelial neoplasms. For confirmation, SDHB immunohistochemistry was performed on one whole slide in 50 randomly selected cases from SDHB-weak CCRCC on TMA. Non-neoplastic renal parenchyma was used as a positive control. For negative controls, primary antibodies were omitted from the dilution buffer.

Scoring System

The intensity and extent of immunohistochemical staining was evaluated microscopically. Granular cytoplasmic and/or membranous staining in either TMA or whole sections was considered to be SDHB positive. Staining intensity was graded as 0, 1+, 2+, or 3+. In normal renal parenchyma, SDHB stain is strongest in proximal convoluted tubules and less strong in the distal tubules. Staining in tumor cells comparable to the proximal convoluted tubules was given a grade of 3+ and when similar to the distal tubules as 2+. Staining which showed intensity weaker than that in the distal tubules was designated as 1+. Complete absence of staining was designated as 0.

TMA staining was further divided by relative extent into two groups (weak and strong). If at least one of four cores showed strong staining (3+), the sample was designated as SDHB-strong. Any sample showing less extensive/strong staining was designated as SDHB-weak. SDHB expression on whole slides was ranked as 0 to 3+ according to the intensity of staining which involved the greatest area of tumor tissue.

Statistical Analysis

Age, sex, tumor size, stage, grade, metastasis and SDHB status were recorded as baseline data variables. The distribution of every baseline variable was compared for SDHB-weak and SDHB-strong subgroups, and the Wilcoxon rank sum test for continuous variables together with the Chi-square or Fisher's exact test for categorical variables were used to analyze this data.

Overall survival was measured from the date of nephrectomy (radical or partial) to the date of last follow-up or death. Overall survival in 240 patients with clear cell RCC was estimated by the Kaplan-Meier method and assessed by the use of the log-rank test. All tests were two-sided with statistical significance set at $p < 0.05$. Statistical analysis was carried out with STATA, version 12.0.

Results

Tissue Microarray (TMA)

Immunohistochemistry for SDHB was carried out on all 420 cases of sporadic renal cell neoplasia using TMA. SDHB was strongly expressed in 84 PRCC (100%), 49 ChRCC (100%) and 47 RO (100%) (Table 1). Strong expression was defined by at least one of four cores showing 3+ staining (Figure 1). In CCRCCs, we found SDHB expression could be both cytoplasmic as well as membranous which has not been previously described (Figure 2). The intensity of SDHB expression varied from 1+ to 3+ (Figure 3). None (0%) of the cases were negative for SDHB immunohistochemistry. Cytoplasmic and membranous staining was often interpreted as strong and weak, respectively.

Of the 240 CCRCCs, 131 cases (55%) showed strong SDHB expression, while 109 cases (45%) showed weak SDHB expression (Table 1). One-hundred fifty-six (65%) patients were male and 84 (35%) were female, with a mean age of 62.6 (mean 33–92) years. The median

tumor size was 5 cm (IQR: 3.5–7.5 cm) and the median follow-up period was 98 (IQR: 41–138) months (Table 2).

To determine whether SDHB expression was an independent prognostic biomarker, we compared SDHB expression in CCRCCs with ISUP grade, TNM stage, metastasis and overall survival. There was no significant correlation of SDHB expression with ISUP grade ($p=0.30$), TNM stage ($p=0.98$), the presence of metastasis ($p=0.64$) or overall survival (log rank $p=0.13$) (Table 2). To determine whether SDHB expression correlated with survival in high ISUP grade (G3-G4) CCRCCs ($n=92$), a Kaplan-Meier survival analysis was performed. There was a statistically significant correlation between the SDHB-strong ($n=55$) and SDHB-weak ($n=37$) expression groups (log rank $p=0.0004$) and overall survival (Figure 4).

To confirm the findings from the TMA studies, SDHB immunohistochemistry was repeated on randomly selected whole sections from 50 SDHB weak CCRCC cases. In these 50 cases, sections showed heterogeneity of SDHB expression ranging from 1+ to 3+, but all were found to express SDHB. In most instances where weak staining occurred, it was noted to be in a membranous staining pattern.

Discussion

Recently, we described TSC-associated PRCCs which display prominent papillary architecture lined predominantly by cells with clear cytoplasm. A hallmark of these tumors are the higher nucleolar grades, prominent complex papillary branching and delicate eosinophilic cytoplasmic thread-like strands that occasionally aggregate to form eosinophilic globules [7]. In addition, these tumors commonly lack foamy macrophages and psammoma bodies. Morphologically, these tumors are similar to CCPRCCs and VHL-associated CCPRCCs as they all contain papillary architecture lined by clear cells.

Immunohistochemically, these neoplasms are predominantly positive for CK7 and CAIX and negative for AMACR and TFE3, similar to CCPRCCs and most VHL-associated CCPRCCs. However, these tumors are CD10 positive and uniquely SDHB negative [7]. Interestingly, the lack of SDHB protein expression was previously reported in RCCs associated with germline *SDHx* mutations. Renal cell carcinomas associated with *SDHB* and rarely *SDHA* and *SDHC* mutations contain distinct morphologic features of cuboidal cells with bubbly and vacuolated eosinophilic cytoplasm, and cytoplasmic inclusions with eosinophilic fluid-like material, arranged in tubules or nests surrounding central cystic spaces [10–12]. They have also been found to contain conspicuous intratumoral mast cells which may be a helpful histologic clue, although it is not specific [11].

Immunohistochemically, they are negative for SDHB and CAIX and variably positive for CD10 and AMACR [10,11].

Renal cell carcinomas with other morphologies have also been rarely reported in addition to the characteristic features. RCCs associated with *SDHB* and *SDHC* mutations have occasionally been reported to display clear cell and rarely papillary features, making identification of *SDHx* mutation-associated RCCs difficult based upon morphology alone [12–15]. This emphasizes the importance of adequately evaluating SDHB protein

expression. A helpful clue is that most of these neoplasms occur in younger individuals (<45 years of age), although the age range can vary, and evaluation with an SDHB immunostain in these instances seems appropriate [13].

The data is limited on the prognosis of *SDHx* mutation-associated RCCs, but it appears tumors detected at a low stage without sarcomatoid differentiation have a relatively good outcome [10,11,13]. However, a subset of patients with *SDHx* mutation-associated RCC have been associated with poorer outcomes and more aggressive behavior [11,13]. In this study, the loss of SDHB immunostaining appears to be a prognostic indicator in CCRCCs with high ISUP nucleolar grade as there was a significant difference in overall survival in patients with SDHB-weak in comparison to SDHB-strong immunostaining (log rank $p=0.0004$). The role of SDH mitochondrial enzyme dysfunction in the pathogenesis of renal neoplasia is unclear, but likely related to the stabilization of hypoxic-inducible factors (HIFs), resulting in the transcription of genes essential for cell growth, survival and angiogenesis [16]. The correlation between the loss of protein and prognosis may be related to their role in tumorigenesis.

In this study, we analyzed the pattern of expression of SDHB in a large number of renal epithelial neoplasms. Our data has shown that all 84 (100%) PRCCs, 49 (100%) ChRCCs and 47 (100%) ROs contained strongly preserved SDHB immunostaining on TMA. Of the 240 CCRCC cases, 131 (55%) contained strong SDHB positivity on TMA. Fifty of the remaining 109 (45%) cases that contained weak SDHB protein expression were randomly selected for re-examination of SDHB immunostaining on whole slides and all (100%) were confirmed to contain preserved staining.

Evaluation of SDHB protein expression may result in a weak or more importantly false negative result due to the lack of typical granular cytoplasmic staining seen in SDHB protein expression. SDHB highlights proteins in the mitochondria and due to the abundant cytoplasmic lipid and glycogen in RCC with clear cell morphology, only membranous staining may occur, resulting in a weak or false negative result. Therefore, interpretation in tumors which appear to contain loss of staining should be done: 1) with caution, 2) with careful high-power evaluation and 3) in the context of internal positive controls.

We also formulated a 4-tiered grading system to evaluate RCCs with clear cell features for SDHB expression, and allowed them to be placed into two categories based upon relative extent of staining, SDHB-strong and weak. One challenge when determining the overall grade, mainly for those with clear cell morphology, was the heterogeneity of staining. In a whole slide, there could be areas of 3+ staining adjacent to areas with 1+ staining. The grade of intensity was given based upon the highest score present, but may not have been representative of the majority of the tumor. Therefore, whole slides and especially small biopsies that are negative for SDHB staining should be repeated. More importantly, one should note a negative result may not be entirely representative, albeit all tumors in our study revealed positive staining on both TMA and whole slides.

The immunoexpression of SDHB in renal epithelial neoplasms has recently been described in one study [17]. Of the 711 renal epithelial neoplasms examined, 4 were found to contain a

loss of SDHB by immunohistochemistry (0.6%). Morphologically, one was clear cell, one was papillary type 2, and the remaining two were of unclassified types. One of the unclassified RCCs was from a patient with SDH-deficient gastrointestinal stromal tumor. None of the tumors were CCPRCC or CCPRCC-like RCCs and they were not tested for *SDHx* mutation analysis [17]. A pitfall of the study was the lack of detail in the scoring system used to evaluate the SDHB protein expression. Some of the cases that were reported to be negative may have actually contained membranous or focal staining leading to a false-negative result. In addition, the negative CCRCC may have represented an *SDHC*-mutation associated RCC.

In summary, we report our experience with SDHB immunohistochemistry and our interpretation of its protein expression. We used a 4-tiered grading system in which 3+ intensity was similar to staining in proximal tubules, 2+ intensity was comparable to staining in distal tubules, and any staining with less intensity than 2+ was considered 1+. Complete absence of staining was graded as 0. The tumors were then separated based upon the relative extent of staining into SDHB-strong which included 3+ tumors, and SDHB-weak which included the 1–2+ tumors. We have found the staining pattern of SDHB to be cytoplasmic and/or membranous making interpretation much more difficult. Truly negative staining has clinical implications as it may help to identify *SDHx* mutation-associated RCCs, particularly those with clear cell morphology, or a TSC-associated PRCC, making accurate interpretation important.

We also analyzed the expression of SDHB in renal epithelial neoplasms, including CCPRCCs and VHL-associated CCPRCC-like tumors which have not been previously described. We found strongly preserved SDHB immunostaining in PRCCs, ChRCCs, and ROs. Clear cell papillary RCCs, VHL-associated CCPRCCs and CCRCCs also contained SDHB immunostaining, albeit in varying intensities. The 4-tiered grading system appears to only be applicable to RCCs with clear cell morphology, as all other forms of renal epithelial neoplasms tested, excluding the TSC-associated PRCCs, had strongly preserved protein expression. Therefore, one should not over-interpret SDHB immunostaining in RCC with clear cell features. In addition, it should not be used routinely as a diagnostic biomarker in RCC with clear cell morphology given SDHB was preserved. Lastly, SDHB expression correlated with survival in patients with CCRCCs with high ISUP nucleolar grade (G3-G4). Therefore, SDHB may serve as a prognostic marker in RCC. Additional studies utilizing the SDHB immunostain may help to provide further insight into their diagnostic and prognostic utility in RCCs.

Acknowledgments

Conflict of Interest and Source of Funding: Supported by National Institutes of Health Grant CA120964 to C.-L. Wu.

References

1. Rustin P, Munnich A, Rotig A. Succinate dehydrogenase and human diseases: new insights into a well-known enzyme. *Eur J Hum Genet.* 2002; 10:289–291. [PubMed: 12082502]
2. Gill AJ, Benn DE, Chou A, Clarkson A, Muljono A, Meyer-Rochow GY, et al. Immunohistochemistry for SDHB triages genetic testing of SDHB, SDHC, and SDHD in

paraganglioma-pheochromocytoma syndromes. *Hum Pathol.* 2010; 41:805–814. [PubMed: 20236688]

3. Gill AJ, Chou A, Vilain R, Clarkson A, Lui M, Jin R, et al. Immunohistochemistry for SDHB divides gastrointestinal stromal tumors (GISTs) into 2 distinct types. *Am J Surg Pathol.* 2010; 34:636–644. [PubMed: 20305538]
4. Barletta JA, Hornick JL. Succinate dehydrogenase-deficient tumors: diagnostic advances and clinical implications. *Adv Anat Pathol.* 2012; 19:193–203. [PubMed: 22692282]
5. van Nederveen FH, Gaal J, Favier J, Korpershoek E, Oldenburg RA, de Bruyn EM, et al. An immunohistochemical procedure to detect patients with paraganglioma and pheochromocytoma with germline SDHB, SDHC, or SDHD gene mutations: a retrospective and prospective analysis. *Lancet Oncol.* 2009; 10:764–771. [PubMed: 19576851]
6. Narayanan V. Tuberous sclerosis complex: genetics to pathogenesis. *Pediatr Neurol.* 2003; 29:404–409. [PubMed: 14684235]
7. Yang P, Cornejo KM, Sadow PM, Cheng L, Wang M, Xiao Y, et al. Renal cell carcinoma in tuberous sclerosis complex. *Am J Surg Pathol.* 2014; 38:895–909. [PubMed: 24832166]
8. Srigley JR, Delahunt B, Eble JN, Egevad L, Epstein JI, Grignon D, et al. The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. *Am J Surg Pathol.* 2013; 37:1469–1489. [PubMed: 24025519]
9. Delahunt B, Cheville JC, Martignoni G, Humphrey PA, Magi-Galluzzi C, McKenney J, et al. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. *Am J Surg Pathol.* 2013; 37:1490–1504. [PubMed: 24025520]
10. Gill AJ, Pachter NS, Chou A, Young B, Clarkson A, Tucker KM, et al. Renal tumors associated with germline SDHB mutation show distinctive morphology. *Am J Surg Pathol.* 2011; 35:1578–1585. [PubMed: 21934479]
11. Williamson SR, Eble JN, Amin MB, Gupta NS, Smith SC, Sholl LM, et al. Succinate dehydrogenase-deficient renal cell carcinoma: detailed characterization of 11 tumors defining a unique subtype of renal cell carcinoma. *Mod Pathol.* 2015; 28:80–94. [PubMed: 25034258]
12. Gill AJ, Lipton L, Taylor J, Benn DE, Richardson AL, Frydenberg M, et al. Germline SDHC mutation presenting as recurrent SDH deficient GIST and renal carcinoma. *Pathology.* 2013; 45:689–691. [PubMed: 24150194]
13. Ricketts CJ, Shuch B, Vocke CD, Metwalli AR, Bratslavsky G, Middleton L, et al. Succinate dehydrogenase kidney cancer: an aggressive example of the Warburg effect in cancer. *J Urol.* 2012; 188:2063–2071. [PubMed: 23083876]
14. Ricketts C, Woodward ER, Killick P, Morris MR, Astuti D, Latif F, et al. Germline SDHB mutations and familial renal cell carcinoma. *J Natl Cancer Inst.* 2008; 100:1260–1262. [PubMed: 18728283]
15. Malinoc A, Sullivan M, Wiech T, Kurt Werner S, Jilg C, Straeter J, et al. Biallelic inactivation of the SDHC gene in renal carcinoma associated with paraganglioma syndrome type 3. *Endocr Relat Cancer.* 2012; 19:283–290. [PubMed: 22351710]
16. Gill AJ. Succinate dehydrogenase (SDH) and mitochondrial driven neoplasia. *Pathology.* 2012; 44:285–292. [PubMed: 22544211]
17. Miettinen M, Sarlomo-Rikala M, McCue P, Czapiewski P, Langfort R, Waloszczyk P, et al. Mapping of succinate dehydrogenase losses in 2258 epithelial neoplasms. *Appl Immunohistochem Mol Morphol.* 2014; 22:31–36. [PubMed: 23531856]

Figure 1. SDHB expression in sporadic renal cell neoplasms on TMA. Routine H&E staining (x100) in A) non-neoplastic kidney, C) PRCC, E) ChRCC, G) RO. Strong (3+) cytoplasmic SDHB expression (x100) in B) non-neoplastic kidney, D) PRCC, F) ChRCC, and H) RO.

Figure 2. SDHB membranous immunohistochemical expression in CCRCC. Routine H&E staining (x100) of CCRCC in A) and C). SDHB membranous positivity ranges from 1+ B) to 2+ D) (x100). Normal cells in the intratumoral fibrovascular network show positive 2+ to 3+ staining and serve as a positive intratumoral control.

Figure 3. SDHB immunohistochemical grading in CCRCC on TMA. Routine H&E staining (x100) in a CCRCC in A), C), and E). B) 1+ weak SDHB staining (x100). D) 2+ SDHB staining (x100). F) 3+ strong SDHB staining (x100).

Figure 4. Kaplan-Meier curve of the overall survival in 92 CCRCC patients with high ISUP grade (G3 and G4) stratified by weak vs strong SDHB expression (p=0.0004).

TABLE 1

Expression of SDHB in sporadic renal epithelial neoplasms with TMA and whole section (n=450).

Renal Neoplasm	SDHB -neg (0)	SDHB-weak (1- 2+)	SDHB-strong (3+)
CCRCC (n=240)	0 (0%)	109 (45%)	131 (55%)
PRCC (n=84)	0 (0%)	0 (0%)	84 (100%)
ChRCC (n=49)	0 (0%)	0 (0%)	49 (100%)
CCPRCC (n=19)	0 (0%)	18 (95%)	1 (5%)
VHL-associated CCPRCC-like (n=11)	0 (0%)	6 (55%)	5 (45%)
RO (n=47)	0 (0%)	0 (0%)	47 (100%)
	17		
TSC-associated PRCC ^a [7] (n=17)	(100%)	0 (0%)	0 (0%)
HOCT ^a [7] (n=11)	0 (0%)	0 (0%)	11 (100%)

CCPRCC, clear cell papillary renal cell carcinoma; CCRCC, clear cell renal cell carcinoma; ChRCC, chromophobe renal cell carcinoma; HOCT, hybrid oncocytic/chromophobe tumor; neg, negative; PRCC, papillary renal cell carcinoma; RO, renal oncocytoma; SDHB, succinate dehydrogenase B; TMA, tissue microarray; TSC, tuberous sclerosis complex; VHL, von Hippel Lindau.

^aData from previously published study [7].

TABLE 2

Clinicopathologic characteristics of patients with CCRCC (n=240).

	SDHB- weak	SDHB- strong	p-value
Sex, patients (%)			
Female	49 (58.3%)	35 (41.7%)	0.003
Male	60 (38.5%)	96 (61.5%)	
Age, years			
Mean (SD)	63.0 (11.7)	62.2 (12.4)	0.61
Tumor size, cm			
Median (IQR)	5.1 (3.1–8.5)	5.0 (3.5–7.1)	0.69
ISUP grade, patients (%)			
1	18 (60.0%)	12 (40.0%)	0.30
2	54 (45.8%)	64 (54.2%)	
3	33 (40.7%)	48 (59.3%)	
4	4 (36.4%)	7 (63.6%)	
AJCC pStage, patients (%)			
I	65 (45.1%)	79 (54.9%)	0.98
II	17 (48.9%)	22 (51.1%)	
III	26 (47.3%)	29 (52.7%)	
IV	1 (50%)	1 (50%)	
Metastasis, patients (%)			
No	86 (46.2%)	100 (53.8%)	0.64
Yes	23 (42.6%)	31 (57.4%)	

AJCC, American Joint Committee on Cancer; CCRCC, clear cell renal cell carcinoma; cm, centimeter; IQR, interquartile range; ISUP, International Society of Urological Pathology; SD, standard deviation; SDHB, succinate dehydrogenase B.