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ORIGINAL ARTICLE

Major histocompatibility complex I upregulation in clear cell renal cell carcinoma is associated with increased survival

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Abstract *Objective:* To examine the prognostic value of tumor major histocompatibility complex I (MHCI) expression on survival and recurrence in patients with clear cell renal cell carcinoma (RCC).
Methods: Fifty-three patients that underwent nephrectomy at our institution for clear cell RCC (T1–T3) with ≥4 years of follow-up were queried from our nephrectomy database. Immunohistochemical staining for MHCI was performed on tumor specimens and MHCI expression was quantified with an automated image analysis technique. Patients were divided into high and low MHCI expression groups in order to study the relationship between MHCI expression and prognosis using the Kaplan–Meier method and log-rank test.
Results: Overall survival and recurrence free survival were increased in the high MHCI expression group compared to the low MHCI expression group (log-rank, $p = 0.036$ and $p = 0.028$, respectively). Patients alive at the end of the study had higher MHCI expression (mean positivity score 0.82) than those that died of disease (mean positivity score 0.76, t test, $p = 0.030$). Patients that did not develop recurrence during the study period had higher MHCI expression (mean positivity score 0.83) than those that did develop recurrence (mean positivity score 0.78), but this difference was not significant (t test, $p = 0.079$).

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Conclusion: Our data demonstrate that high MHCI expression confers improved overall and recurrence free survival in patients with clear cell RCC and could serve as an important prognostic tool in identifying high-risk patients.

1. Introduction

With a growing incidence over the past decades, renal cell carcinoma (RCC) afflicts the lives of almost 64 000 patients and claims approximately 13 500 lives annually in the United States [1]. Of these cases, two-thirds have localized disease on initial presentation with potential for curative nephrectomy. However, despite prognostic tools such as TNM staging and Fuhrman Nuclear Grade (FNG), accurate assessment of prognosis post-nephrectomy remains inadequate with one-third of these patients developing metastases and eventually succumbing to disease [2—5]. Further, a recent validation study of the TNM staging system for RCC showed overlapping prognoses between TNM substages as well as insufficient ability to differentiate high-risk disease [6]. Accordingly, more rigorous indicators for disease progression and recurrence are required to effectively stratify patients to determine appropriate modes of treatment and surveillance, and potentially for accrual into clinical trials.

With recent advancements in cancer immunology, the immune system has been well established as an integral factor in tumor progression in various malignancies, but a better understanding of the host anti-tumor immune response is still needed to identify molecular markers able to predict prognosis and survival [7,8]. Characterizing the intratumoral immune microenvironment into an "immunoscore" has been shown to be an effective tool to assess prognosis, even outperforming traditional histopathological tools in patients with colorectal cancer [9—11]. In RCC, mechanisms for tumor immune evasion of cytotoxic T lymphocytes (CTLs) have been studied [12]. Major histocompatibility complex class I (MHCI) expression plays a critical role in tumor antigen recognition and CTL activation, thus it is no surprise that loss of tumor cell MHCI expression has been associated with worse outcomes in RCC [12—14]. In an investigation of MHCI expression in RCC, Kitamura et al. [12] and Yuan et al. [15] found that patients with downregulated MHCI expression had decreased recurrence-free survival. Further studies have also shown that decreased tumor MHCI expression is associated with larger tumor size and increased metastatic potential [13]. These findings suggest that MHCI expression could serve as a prognostic marker to better characterize disease progression and recurrence.

Though recent studies have evaluated the role of the host immune response in cancer progression, the utilization of immunologic biomarkers for postoperative surveillance in patients with RCC has yet to be fully explored. In a previous study evaluating 34 RCC patients with automated image analysis, we found that higher tumor MHCI expression can help predict survival after nephrectomy and even after recurrence [14]. In this study, we continue to investigate tumor MHCI expression as a prognostic tool in a larger cohort and over an increased follow-up interval.

2. Patients and methods

2.1. Patient selection

Our Nephrectomy Database was queried for patient selection. Inclusion criteria were a history of localized clear cell RCC at presentation and at the time of nephrectomy, and at least 4 years of clinical follow-up information without loss to follow-up. Patients that died of their disease prior to 4 years were still included in the study. All cases were pathologically confirmed by a fellowship trained Urologic Pathologist to be clear cell RCC and were graded and staged according to current guidelines. Patients with T4 disease, clinically suspicious or pathologically confirmed nodal disease, or metastatic disease on presentation were excluded. Subjects that died during the follow-up period due to causes unrelated to RCC and patients that received immunotherapy were excluded from the study. Patients under the age of 18 years were excluded as well.

The follow-up period was the interval between nephrectomy and the subject's most recent follow-up status. Follow-up information on each subject was obtained retrospectively in the electronic medical records, the National Death Index, the Social Security Death Index, or by calling the patients' primary care physicians or other medical providers; or the patients/families themselves were contacted if necessary. All subjects that developed metastases underwent tyrosine kinase inhibitor treatment according to standard of care. Our Institutional Review Board approved the study.

2.2. Immunohistochemistry (IHC)

Paraffin-embedded tissue blocks containing both tumor and adjacent normal kidney parenchyma were used. Normal parenchyma in each sample was stained and observed to account for batch variation. No difference in staining intensity of normal parenchyma was observed between samples. The IHC stainings were performed with an MHCI antibody (clone EMR 8-5; Abcam, Cambridge, UK) following the previously described protocol used at our institution [16]. The obtained slides were then captured on a Nikon Eclipse E400 microscope (Nikon, Tokyo, Japan) using SPOT Flex 15.2 64 Mp Shifting Pixel Camera and SPOT software

(Diagnostic Instruments Inc., Sterling Heights, Michigan, USA) for whole slide digital scanning.

2.3. Automated image and statistical analyses

The digital images were then analyzed with the Aperio image analysis software (Leica Biosystems, Wetzlar, Germany) for quantification of MHCI expression using a previously validated method with modifications [17]. The positive pixel count (PPC) is an algorithm of the Aperio image analysis software that provides the absolute number of pixels positive for the MHCI staining in a pre-determined area divided by the total number of pixels (meaning all the positive and the negative pixels) in the analyzed area. The obtained numerical value is called the "positivity score" and it quantifies MHCI expression. Positive pixels were determined with the parameters of the PPC algorithm including color (of the antibody's staining) and minimal and maximal intensity (the brightness of the staining). Five boxes of 2500 pixels by 2500 pixels were selected in representative areas of tumor and the PPC algorithm was applied to these boxes. The same process was repeated for the adjacent normal kidney parenchyma. Patients were divided into high and low MHCI expression groups in order to study the relationship between MHCI expression and prognosis using the Kaplan—Meier method and log-rank test. Student's *t* test, ANOVA, Mantel—Cox test or non-parametric Kruskal—Wallis test were all conducted as indicated in the text. Statistical analyses were performed with JMP 12 (SAS, Cary, NC, USA). Univariate and multivariate Cox proportional survival analysis was performed with SAS (SAS, Cary, NC, USA).

3. Results

3.1. Cohort description

Fifty-three patients comprised the study cohort, which is described in Table 1. Mean age at the beginning of the study was 62.5 years (range 35—89 years). Tumor stages were evenly distributed within the cohort with 18/53 (34.0%) patients with stage T1 cancer, 14/53 (26.4%) with stage T2, and 21/53 (39.6%) with stage T3. However, FNGs were unevenly distributed within the cohort with 19/53 (35.8%) patients with FNG 2, 26/53 (49.1%) with FNG 3, and 8/53 (15.1%) with FNG 4. Of note, a fellowship-trained pathologist changed the FNG of four patients from 3 to 4 on review. The subjects were followed after nephrectomy as described in the methods section, and mean and median clinical follow-up was 73.3 and 63 months respectively (range: 3—225 months, $n = 53$). Of the study cohort, 36/53 (67.9%) subjects were alive and 17/53 (32.1%) deceased due to clear cell RCC at the end of the study. Further, 28/53 (52.9%) patients developed metastases during the study, of which 17/28 (60.7%) succumbed to their disease. The remaining 25/53 (47.1%) patients were alive at the end of the study and had no radiographic or clinical evidence of recurrence (Table 2).

3.2. Automated positive pixel counting on IHC to assess MHCI expression

In this study we used the automated PPC algorithm of the Aperio software to assess the degree of MHCI expression in each tumor slide. The numerical value obtained was called the "positivity score", the ratio of positively stained pixels

Table 1 Patient demographics.

Parameter	Outcome			
	Alive without disease ($n = 25$)	Alive with disease ($n = 11$)	Dead with disease ($n = 17$)	All ($n = 53$)
Age at intervention (year)[a]	59.5 ± 11.3	62.1 ± 11.3	67.2 ± 13.9	62.5 ± 12.5
Gender[b]				
Female	14 (56.0)	4 (36.4)	6 (35.3)	24 (45.3)
Male	11 (44.0)	7 (63.6)	11 (64.7)	29 (54.7)
Race[b]				
African American	3 (12.0)	0 (0.0)	4 (23.5)	7 (13.2)
American Indian	1 (4.0)	0 (0.0)	0 (0.0)	1 (1.9)
Asian	1 (4.0)	1 (9.1)	0 (0.0)	2 (3.8)
Caucasian	19 (76.0)	10 (90.9)	13 (76.5)	42 (79.2)
Hispanic	1 (4.0)	0 (0.0)	0 (0.0)	1 (1.9)
Stage[b]				
T1	11 (44.0)	2 (18.2)	5 (29.4)	18 (34.0)
T2	7 (28.0)	4 (36.4)	3 (17.6)	14 (26.4)
T3	7 (28.0)	5 (45.4)	9 (53.0)	21 (39.6)
FNG[b]				
2	14 (56.0)	4 (36.4)	1 (5.9)	19 (35.8)
3	11 (44.0)	5 (45.4)	10 (58.8)	26 (49.1)
4	0 (0.0)	2 (18.2)	6 (35.3)	8 (15.1)

FNG, Fuhrman nuclear grade.
[a] Values are presented as mean ± SD.
[b] Values are presented as *n* (%).

(i.e. pixels that are stained by the MHCI antibody) over the total amount of pixels analyzed, allowing objective quantitation of MHCI expression with IHC. Visually, antibody staining (brown) was localized to tumor cell membranes and diffusely distributed throughout the specimen. The tumor MHCI positivity score for the entire cohort was 0.80 ± 0.01 (mean ± SE, $n = 53$) and median MHCI expression was 0.81 (range 0.40—0.92). The normal kidney parenchyma MHCI positivity score for the entire cohort was 0.46 ± 0.02 (mean ± SE, $n = 53$) and median MHCI expression was 0.47 (range 0.06—0.71). Mean MHCI expression was significantly higher in tumor than in normal kidney parenchyma (t test, $p < 0.0001$). To investigate the impact of MHCI on patient prognosis, the subjects were categorized, according to tumor MHCI positivity score, into the low (below the mean of 0.80) MHCI expression group or the high (above the mean of 0.80) MHCI expression group. Of the study cohort, 22/53 (41.5%) patients had low MHCI expression and 31/53 (58.5%) had high expression as seen in Table 2.

3.3. High MHCI expression is associated with improved survival and decreased recurrence

Mean MHCI positivity score for the "alive" subgroup (positivity score 0.82 ± 0.02 (mean ± SE), $n = 36$) was significantly higher than in the "deceased" subgroup (positivity score 0.76 ± 0.02 (mean ± SE), $n = 17$, t test, $p = 0.030$). To further evaluate the effect of MHCI expression on patient survival, overall survival was compared in the high (above the mean of 0.80) *vs.* low (below the mean of 0.80) MHCI expression groups. Time-to-death was significantly longer in the high MHCI expression group (log-rank, $p = 0.036$; Fig. 1A). Median time-to-death for censored and non-censored subjects was 78.7 months and 28.4 months, respectively. Further, only 6/31 (19.4%) subject deaths occurred in the group of patients with high MHCI scores while 11/22 (50.0%) subjects of the low MHCI group died (Table 2). Univariate analysis showed that MHCI expression and FNG were significant factors influencing overall survival (log-rank, $p = 0.036$ and $p < 0.001$, respectively), however TNM stage was not (log-rank, $p = 0.440$). In multivariate analysis, only FNG was a significant and independent factor influencing overall survival ($p = 0.028$).

Decreased MHCI expression also correlated with the development of metastases post-nephrectomy. Mean MHCI positivity score of the subjects that did not recur (0.83 ± 0.02 (mean ± SE), $n = 25$) during the study was higher than the mean MHCI positivity score of those that did recur (0.78 ± 0.02 (mean ± SE), $n = 28$), but this difference was not significant (t test, $p = 0.079$). Furthermore, time-to-recurrence was longer in patients in the high MHCI expression group (log-rank, $p = 0.028$; Fig. 1B). Median time-to-recurrence for censored and non-censored subjects was 74.0 months and 11.3 months, respectively. In the low MHCI group, 15/22 (68.2%) subjects recurred within the follow-up time, while only 13/31 (41.9%) subjects developed metastases in the high MHCI group (Table 2). Univariate analysis showed that MHCI expression and FNG were significant factors influencing recurrence-free survival (log-rank, $p = 0.028$ and $p < 0.001$, respectively). In multivariate analysis, only FNG was a significant and independent factor influencing recurrence-free survival ($p = 0.035$).

Finally, to compare MHCI expression with commonly used prognostic tools in the clinical setting, the mean MHCI scores of subjects with FNG 2, 3 and 4, and stages T1, T2 and T3 were compared (Table 3). No collinearity was found between FNG and tumor MHCI expression (ANOVA, $F = 0.12$, $p = 0.88$) or between stage at presentation and tumor MHCI expression (ANOVA, $F = 0.39$, $p = 0.68$).

Table 2 High *vs.* low MHCI expression.

Parameter	High *vs.* low MHCI expression		
	Low MHCI ($n = 22$)	High MHCI ($n = 31$)	All ($n = 53$)
Stage[a]			
T1	4 (18.2)	14 (45.2)	18 (34.0)
T2	7 (31.8)	7 (22.6)	14 (26.4)
T3	11 (50.0)	10 (32.2)	21 (39.6)
FNG[a]			
2	7 (31.8)	12 (38.7)	19 (35.8)
3	10 (45.5)	16 (51.6)	26 (49.1)
4	5 (22.7)	3 (9.7)	8 (15.1)
Outcome[a]			
Alive without disease	7 (31.8)	18 (58.0)	25 (47.1)
Alive with disease	4 (18.2)	7 (22.6)	11 (20.8)
Dead with disease	11 (50.0)	6 (19.4)	17 (32.1)
Tumor positivity[b]	0.7 ± 0.1	0.9 ± 0.0	0.8 ± 0.1

MHCI, major histocompatibility complex I.
[a] Values are presented as n (%).
[b] Values are presented as mean ± SD.

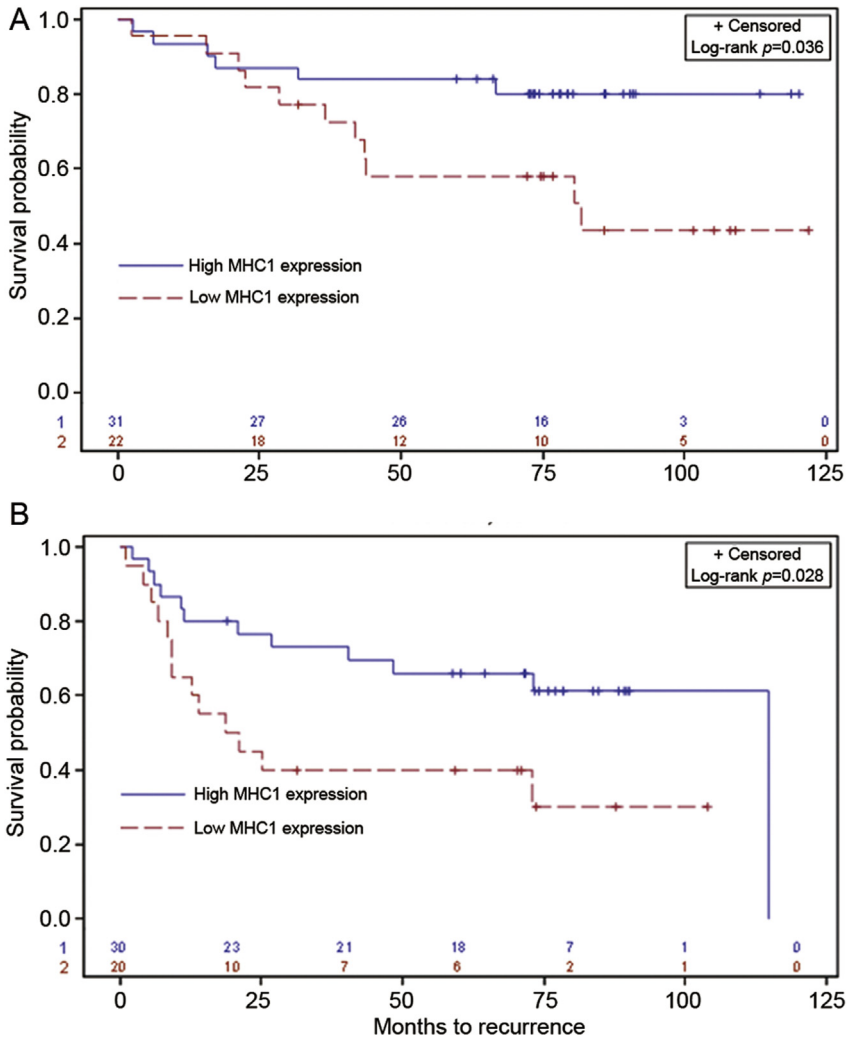

Figure 1 High MHCI expression is associated with increased survival and decreased recurrence. (A) Increased survival seen in patients with high MHCI expression; (B) Increased time until recurrence in patients with high MHCI. MHCI, major histocompatibility complex class I.

Table 3 MHCI expression (mean ± SD).

	Outcome			
	Alive without disease	Alive with disease	Dead with disease	All
All	0.83 ± 0.07	0.81 ± 0.09	0.76 ± 0.12	0.80 ± 0.10
Stage				
T1	0.81 ± 0.08	0.87 ± 0.06	0.81 ± 0.10	0.81 ± 0.08
T2	0.82 ± 0.10	0.83 ± 0.07	0.63 ± 0.20	0.78 ± 0.14
T3	0.86 ± 0.03	0.77 ± 0.10	0.77 ± 0.08	0.80 ± 0.08
FNG				
2	0.80 ± 0.09	0.80 ± 0.04	0.81 ± 0.04	0.80 ± 0.08
3	0.86 ± 0.04	0.81 ± 0.13	0.74 ± 0.14	0.81 ± 0.12
4	N/A	0.82 ± 0.06	0.77 ± 0.10	0.78 ± 0.09

FNG, fuhrman nuclear grade; MHCI, major histocompatibility complex class I.

4. Discussion

In this study we show that MHCI expression varies widely in patients with clear cell RCC and that upregulation of tumor MHCI expression is associated with increased overall survival and recurrence-free survival post-nephrectomy. Further, patients that survived at the end of the study had a significantly higher mean MHCI positivity score compared to those who died from their disease. Similarly, those who did not have recurrence at the end of the study had a higher mean MHCI positivity score compared to those who developed metastatic disease, however this difference was not statistically significant. Together, these data suggest that MHCI expression could serve as a powerful prognostic tool capable of differentiating high-risk disease and help direct post-operative care in patients with clear cell RCC.

Our study also evaluated the relationship between MHCI expression on tumor characteristics, including TNM stage

and FNG. Consistent with previous results, our data show no collinearity between MHCI expression, FNG, and TNM staging. These findings demonstrate that MHCI expression influences cancer pathogenesis independent of FNG and TNM stage, suggesting that effective immune recognition of RCC by the host immune system plays a critical role in disease progression that might not otherwise be captured by traditional histopathological prognostic tools.

Several studies have looked into the role of MHCI expression in patients with RCC as well as other malignancies. Brasnac et al. [13] first reported that approximately 15% of patients with RCC had down regulation of HLA class I and that this pattern was associated with increased tumor size and advanced tumor stage. These findings were later confirmed by Atkins et al. [20] who went on to propose down regulation of HLA class I expression as an immune escape mechanism. With Japanese and Chinese cohorts, subsequent studies have found that down-regulation of tumor MHCI expression is associated with decreased survival [12,15]. With an American cohort consisting of mainly Caucasians and African Americans, we confirm these previous findings and expand upon a previous study by our group with a larger sample size and increased follow-up period.

The improved prognosis with MHCI upregulation in our cohort could be explained via modulation of the tumor immune microenvironment with increased infiltration of CTLs. The exact role of MHCI expression in tumor immune evasion and RCC progression has yet to be further studied. Previous studies have shown that tumor cell growth and MHCI expression are closely linked by shared gene activation pathways [17,18]. In addition, others have found that certain MHCI haplotypes and differential expression of MCHI associated antigen processing molecules in RCC tumor tissue allows for immune escape and disease progression [19,20]. The therapeutic potential of targeted immunotherapies used in RCC and in other solid organ malignancies is another argument for using MHCI expression quantification and other immune scoring systems [21,22]. In fact, conventional chemotherapy and targeted therapies in advanced RCC have other relevant immune effects and could have an effect on MHCI expression, further underlying the need for immune biomarkers [23,24].

It is important to note that in contrast to the previous study by Kitamura et al. [12], we found that MHCI expression was not an independent and significant predictor of overall survival or recurrence free survival in multivariate analysis. This difference could be due to several factors such as our exclusion criteria of patients with T4 disease as well as genetic and racial differences between our patient populations. Despite this finding, MHCI expression still provides crucial information in the management of patients with RCC in adjunct with other prognostic tools. While TNM stage and FNG characterize tumor aggressiveness, MHCI expression is a marker of the antigen processing and presentation machinery within tumor cells. With the expanding use of immune checkpoint blockade, neoantigen based therapeutics, and other immunotherapies that hinge on the effector function of CTLs, developing a detailed understanding of tumor cell antigen processing and presentation will become increasingly important.

The findings of this study suggest that MHCI could be a potent prognostic tool in patients with RCC after undergoing nephrectomy. In addition, the automated image analysis technique used in this study allowed for objective quantification of MHCI tumor expression, differing from the pathologist-dependent semi-quantitative technique used in previous studies [12,15]. In fact, an automated pixel count of MHCI IHC staining could be an ideal technique for the larger multi-center prospective studies that are needed to determine if MHCI is a practical clinical biomarker to predict survival in RCC.

5. Conclusion

Our data demonstrate that upregulation of MHCI expression on tumor cells confers improved overall survival and recurrence-free survival in patients undergoing nephrectomy for localized clear cell RCC. Therefore, MHCI expression could serve as an important prognostic tool in differentiating patients with high-risk disease and determining appropriate modes of post-operative management.

Conflicts of interest

The authors declare no conflict of interest.

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