

Tumor B7-H1 Is Associated with Poor Prognosis in Renal Cell Carcinoma Patients with Long-term Follow-up

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Abstract

B7-H1 participates in T-cell costimulation functioning as a negative regulator of immunity. Recent observations suggest that B7-H1 is expressed by renal cell carcinoma (RCC) tumor cells and is associated with poor prognosis. However, outcome analyses have been restricted to patients with fresh-frozen tissue and limited follow-up. We report the clinical effect of B7-H1 in RCC patients with a median of 10 years of follow-up. Between 1990 and 1994, 306 patients underwent nephrectomy for clear cell RCC and had paraffin tissue available for review. We did immunohistochemistry with anti-B7-H1 and conducted outcome analyses. Among the 306 patients, 73 (23.9%) harbored tumors with B7-H1 expression. Patients with tumor B7-H1 were at a significantly increased risk of both death from RCC [risk ratio (RR), 3.92; $P < 0.001$] and overall mortality (RR, 2.37; $P < 0.001$). The 5-year cancer-specific survival rates were 41.9% and 82.9% for patients with and without tumor B7-H1, respectively. In a multivariate model, tumor B7-H1 remained associated with cancer-specific death even after adjusting for tumor-node-metastasis stage, grade, and performance status (RR, 2.00; $P = 0.003$). In the subset of 268 patients with localized RCC, tumor B7-H1 was significantly associated with metastatic cancer progression (RR, 3.46; $P < 0.001$) and death from RCC (RR, 4.13; $P < 0.001$) even after adjusting for stage, grade, and performance status (RR, 1.78, $P = 0.036$). RCC patients with tumor B7-H1 are at significant risk of rapid cancer progression and accelerated rates of mortality. B7-H1 may function as a key determinant in RCC, abrogating immune responses directed against this immunogenic tumor. (Cancer Res 2006; 66(7): 3381-5)

Introduction

Several observations suggest that renal cell carcinoma (RCC) is capable of undermining host antitumor immunity (1–3). Elucidating mechanisms responsible for lymphocyte dysfunction noted within the tumor microenvironment may provide potential avenues for therapeutic manipulation. Within the last decade, it has become evident that T-cell activation, T-cell inactivation, and T-cell death are ultimately governed by the balance between positive and negative T-cell costimulatory signaling (4). B7-H1

represents a recently discovered T-cell costimulatory molecule that has been implicated as a potent negative regulator of antitumor immunity (5–7). Constitutive expression of B7-H1 (also known as PD-L1) is typically limited to macrophage-lineage cells (5) although aberrant B7-H1 has also been described in a number of human malignancies (6, 8, 9). For this reason, we examined B7-H1 in RCC specimens hypothesizing that B7-H1 contributes to the profile of immunosuppression observed in some RCC patients. We previously reported that B7-H1 is aberrantly expressed in human RCC and that patients with B7-H1 positive tumors were at significant risk of cancer-specific mortality (10, 11). Our analyses in this previous study were restricted to fewer than 200 patients with fresh-frozen tissue and relatively short-term follow-up (10, 11). Using an antigen retrieval method, we now report the results of B7-H1 immunohistochemical staining in paraffin-embedded specimens and the clinical effect of tumor B7-H1 expression in more than 300 RCC patients with >10 years of follow-up.

Materials and Methods

Patient selection. On approval from the Institutional Review Board, we reviewed the Mayo Clinic Nephrectomy Registry, which contains more than 4,000 patients treated surgically since 1970. A registered nurse abstractor assigned to the Registry reviews the medical records of all patients annually to ascertain the date of detection and location of metastases in patients with RCC who were treated at our institution. If a patient has not returned to Mayo within a year, the abstractor mails the patient a disease status questionnaire. If metastatic disease is documented in the returned questionnaire, the abstractor contacts the patient's local physician to verify the date and location of the progression. Vital status is similarly updated on an annual basis through correspondence with patients and local physicians. To date, <3% of patients in the Registry have been lost to follow-up.

From this Registry, we identified 427 patients treated with nephrectomy for unilateral, sporadic clear cell RCC between 1990 and 1994. Of these, 306 (71.7%) had archived paraffin-embedded tissue available for study. There was no difference in patient outcome between patients with and without tissue available for study ($P = 0.965$, log-rank test). The cancer-specific survival rates (SE, number still at risk) at 5 years for patients with and without tissue available for study were 73.2% (2.7%, 188) and 78.1% (3.9%, 81), respectively.

Immunohistochemistry. Tumor sections were deparaffinized in xylene and rehydrated in a graded series of alcohols. Slides were unmasked in Target Retrieval Solution (DakoCytomation, Glostrup, Denmark) using a Decloaking Chamber (Biocare Medical, Walnut Creek, CA). Following unmasking, slides were blocked for endogenous peroxidase for 5 minutes with a peroxidase blocking solution (DakoCytomation), rinsed in TBS with 0.1% Tween 20 (TBST), and incubated for 30 minutes with 1.5% normal horse serum in TBST (DakoCytomation). Slides were rinsed in TBST and blocked for endogenous avidin and biotin using an Avidin/Biotin Blocking kit (Vector Laboratories, Burlingame, CA). Slides were then incubated

Note: J.C. Cheville and E.D. Kwon contributed equally to this work.

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overnight at 4°C with anti-B7-H1 (clone 5H1) at 1:100. This step was followed by 30 minutes of incubation with biotinylated horse anti-mouse immunoglobulin G and avidin/biotin complex (ABC) reagent from a Vectastain Elite ABC kit (Vector Laboratories). Slides were amplified using a Tyramide Signal Amplification Biotin System (Perkin-Elmer, Boston, MA) and incubated in 3-amino-9-ethylcarbazole chromogen (Biocare Medical). Irrelevant isotype-matched antibodies were used to control for nonspecific staining.

To validate the specificity of 5H1 for B7-H1 in paraffin specimens, we did immunohistochemical blocking studies in a competition assay. These studies were done by pre-exposing anti-B7-H1 (clone 5H1) with a B7-H1 fusion protein (5) before immunohistochemical staining. Paraffin-embedded, B7-H1-transduced 624mel melanoma cells (positive control), non-B7-H1-transduced parental melanoma cells (negative control), and RCC tumor specimens were immunohistochemically stained with unblocked anti-B7-H1 as well as fusion protein-blocked anti-B7-H1 antibody. These studies show that B7-H1 staining on RCC as well as B7-H1-transduced melanoma is eliminated by blocking using the fusion protein (Fig. 1). Thus, the anti-B7-H1 antibody employed in our study shows an appropriate level of specificity for the B7-H1 protein in paraffin-embedded tumor specimens.

Pathologic features and quantification of B7-H1. The original tumor sections were reviewed by a single urologic pathologist (J.C.C.) for the

pathologic features of histologic subtype, primary tumor classification (T), regional lymph node involvement (N), distant metastases (M), tumor size, nuclear grade, and coagulative tumor necrosis. The percentages of tumor cells that stained positive for B7-H1 were reviewed independently by two urologic pathologists (J.C.C. and T.J.S.). The tumor was considered positive for B7-H1 if there was histologic evidence of cell-surface membrane staining. Cases with <5% tumor staining were considered negative. When there was a discrepancy in scoring, the cases were reviewed by both pathologists for a consensus using a double-headed microscope. At all times, the pathologists were blinded to clinical outcome.

Statistical methods. Associations of B7-H1 expression with pathologic features of interest [tumor-node-metastasis (TNM) stage groupings, tumor size, nuclear grade, and tumor necrosis] were evaluated using χ^2 tests. Cancer-specific and progression-free survival were estimated using the Kaplan-Meier method. Causes of death other than RCC were censored for the estimation of cancer-specific survival. The associations of B7-H1 expression with outcome were evaluated using Cox proportional hazards regression models univariately and after adjusting for 2002 TNM stage (analyzed using three indicator variables for stages II, III, and IV, with stage I as the reference), nuclear grade (analyzed using two indicator variables for grades 3 and 4, with grades 1 and 2 as the reference), and Eastern Cooperative Oncology Group (ECOG) performance status (analyzed using one indicator

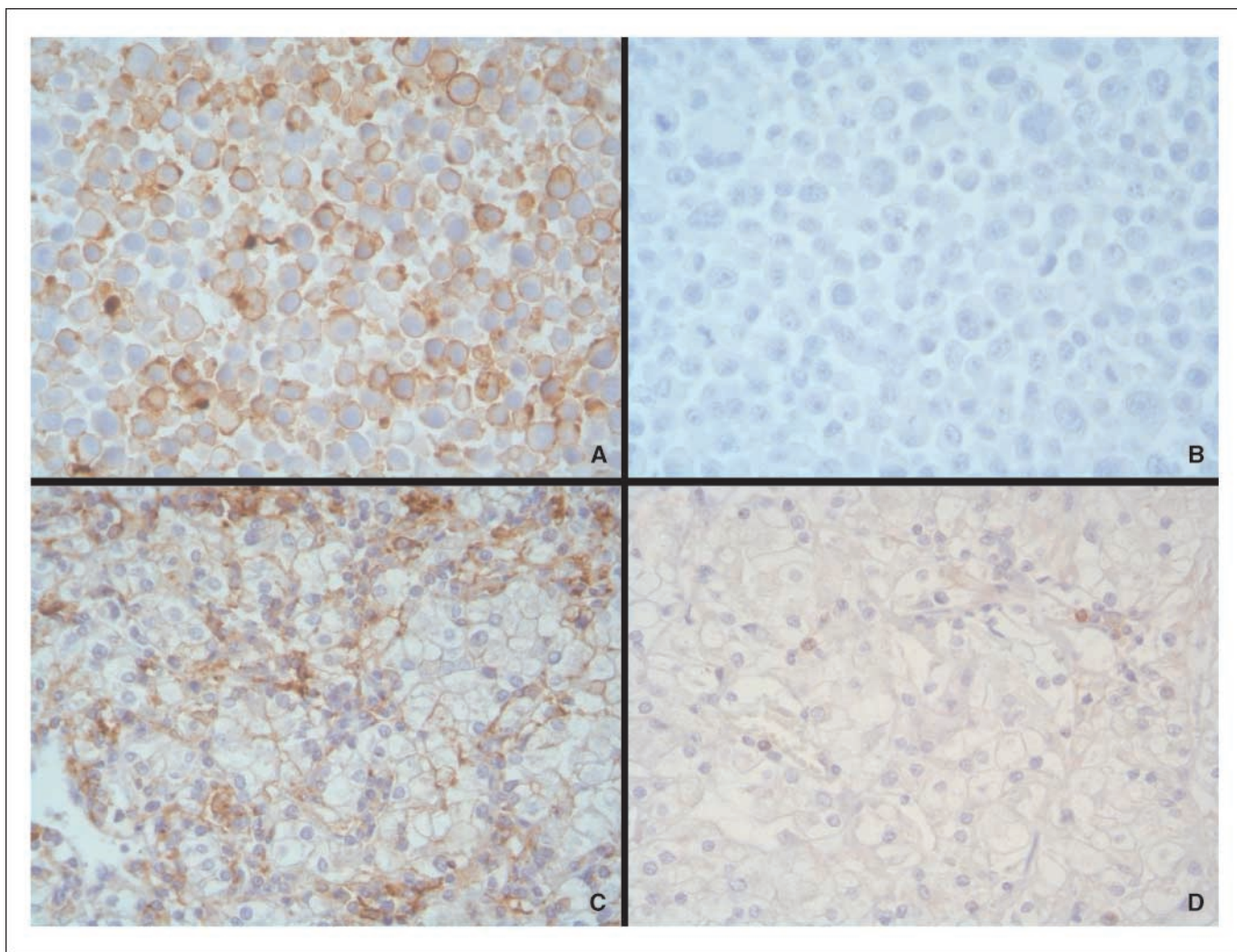


Figure 1. Specificity of anti-B7-H1 (clone 5H1). Paraffin-embedded B7-H1⁺/624mel cells (A) and clear cell RCC (C) are stained with anti-B7-H1 antibody without B7-H1 fusion protein. The cell-surface brown reactivity shows B7-H1 protein expression. On anti-B7-H1 incubation for 30 minutes with B7-H1 fusion protein, cell-surface expression of B7-H1 is completely eliminated in both B7-H1⁺/624mel cells (B) and clear cell RCC (D).

Table 1. Comparison of pathologic features by tumor B7-H1 expression, *n* (%)

Feature	Tumor B7-H1 expression		<i>P</i>
	Negative (<i>n</i> = 233)	Positive (<i>n</i> = 73)	
2002 TNM classification			
I	156 (67.0)	24 (32.9)	<0.001
II	14 (6.0)	5 (6.9)	
III	41 (17.6)	31 (42.5)	
IV	22 (9.4)	13 (17.8)	
Primary tumor size (cm)			
<5	103 (44.2)	18 (24.7)	<0.001
5 to <7	57 (24.5)	11 (15.1)	
7 to <10	37 (15.9)	21 (28.8)	
≥10	36 (15.5)	23 (31.5)	
Nuclear grade			
1	31 (13.3)	5 (6.9)	<0.001
2	133 (57.1)	10 (13.7)	
3	59 (25.3)	35 (48.0)	
4	10 (4.3)	23 (31.5)	
Coagulative tumor necrosis			
Absent	188 (80.7)	24 (32.9)	<0.001
Present	45 (19.3)	49 (67.1)	

variable for ECOG ≥1, with ECOG 0 as the reference), and after adjusting for the Mayo Clinic Stage, Size, Grade, and Necrosis Score (TNM stage, tumor size, nuclear grade, and coagulative tumor necrosis), a prognostic composite score developed specifically for patients with clear cell RCC (ref. 12; analyzed as a continuously scaled variable). Statistical analyses were done using the SAS software package (SAS Institute, Cary, NC). All *P* values were two sided and *P* < 0.05 was considered statistically significant.

Results

Patient follow-up. At last follow-up, 173 of the 306 patients studied had died, including 96 patients who died from RCC at a median of 2.2 years (range, 0-13 years) following nephrectomy. Among the 133 remaining patients, the median duration of follow-up was 11.2 years (range, 0-15 years); 106 (80%) of these patients had at least 10 years of follow-up. Cancer-specific survival rates (SE, number still at risk) at 1, 5, and 10 years following nephrectomy were 90.4% (1.7%, 258), 73.2% (2.7%, 188), and 67.7% (2.9%, 127), respectively.

Tumor B7-H1 expression. Seventy-three (23.9%) patients had positive tumor B7-H1 staining. To evaluate the association of B7-H1 with tumor biology, a comparison of the pathologic features correlated with B7-H1 is shown in Table 1. Patients with tumor B7-H1 were more likely to exhibit adverse pathologic features including 2002 TNM stage III or IV, tumor size of ≥5 cm, nuclear grade 3 or 4, and coagulative tumor necrosis (*P* < 0.001 for all). There was not a statistically significant difference in ECOG performance status between patients with and without tumor B7-H1 expression (*P* = 0.435).

By univariate analysis, patients with a B7-H1-positive tumor were nearly four times more likely to die from RCC compared with patients with a B7-H1-negative tumor [risk ratio (RR), 3.92; 95% confidence interval (95% CI), 2.61-5.88; *P* < 0.001]. The 5-year cancer-specific survival rates were 41.9% for patients with B7-H1-positive tumors and 82.9% for patients with B7-H1-negative

tumors (Fig. 2). In a multivariate model, tumor B7-H1 remained significantly associated with cancer-specific death after adjusting for TNM stage, nuclear grade, and ECOG performance status (RR, 2.00; 95% CI, 1.27-3.15; *P* = 0.003) and after adjusting for the Stage, Size, Grade, and Necrosis Score (RR, 2.13; 95% CI, 1.41-3.22; *P* < 0.001). In addition, patients with B7-H1-positive tumors were also at increased risk of death from any cause compared with patients with B7-H1-negative tumors (RR, 2.37; 95% CI, 1.72-3.28; *P* < 0.001).

To determine the association of B7-H1 with cancer progression, we also studied the subset of 268 patients with localized (pN₀/pN_x pM₀) clear cell RCC at nephrectomy, of whom 66 (24.6%) progressed to distant metastases at a median of 1.6 years (range, 0-12 years) following nephrectomy. In this subset, aberrant tumor B7-H1 expression was significantly associated with cancer progression (RR, 3.46; 95% CI, 2.11-5.69; *P* < 0.001). The 5-year progression-free survival rates were 56.5% for patients with B7-H1-positive tumors and 86.4% for patients without tumor B7-H1 expression (Fig. 3). The median times to progression were 0.7 and 2.9 years for patients with B7-H1-positive and B7-H1-negative tumors, respectively. Furthermore, for this subset of patients, aberrant tumor B7-H1 expression was significantly associated with death from RCC univariately (RR, 4.13; 95% CI, 2.49-6.86; *P* < 0.001) after adjusting for the TNM stage, nuclear grade, and ECOG performance status (RR, 1.78; 95% CI, 1.04-3.06; *P* = 0.036) and after adjusting for the Stage, Size, Grade, and Necrosis Score (RR, 1.72; 95% CI, 1.00-2.93; *P* = 0.049).

Discussion

In the last decade, the field of immunology has achieved significant understanding of the fundamental regulatory mechanisms directing host immune cell activation, with particular emphasis on T-cell costimulation. To our knowledge, B7-H1 is the only T-cell costimulatory molecule reported to significantly correlate with survival in a human malignancy. Our data show that

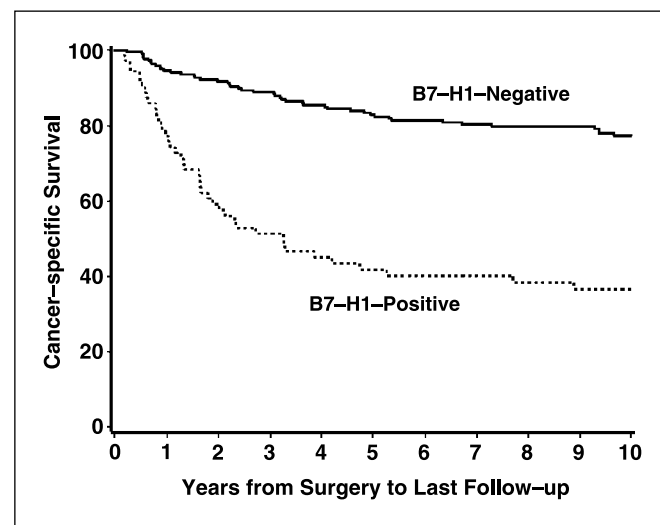


Figure 2. Association of tumor B7-H1 expression with death from RCC for 306 patients with clear cell RCC (RR, 3.92; 95% CI, 2.61-5.88; *P* < 0.001). Cancer-specific survival rates (number still at risk) at 1, 5, and 10 years following nephrectomy were 77.3% (53), 41.9% (26), and 36.7% (16), respectively, for patients with positive tumor B7-H1 expression compared with 94.6% (205), 82.9% (162), and 77.4% (111), respectively, for patients with negative tumor B7-H1 expression.

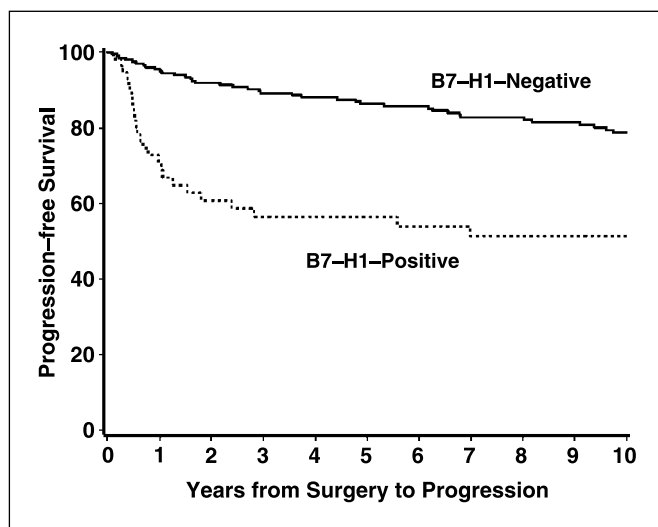


Figure 3. Association of tumor B7-H1 expression with progression to distant metastases for 268 patients with localized (pN₀/pN_x pM₀) clear cell RCC (RR, 3.46; 95% CI, 2.11-5.69; $P < 0.001$). Progression-free survival rates (number still at risk) at 1, 5, and 10 years following nephrectomy were 70.9% (36), 56.5% (23), and 51.4 (15)% respectively, for patients with positive tumor B7-H1 expression compared with 95.5% (186), 86.4% (149), and 78.7% (97), respectively, for patients with negative tumor B7-H1 expression.

RCC patients with B7-H1-positive tumors are at significant risk of cancer progression, cancer-specific death, and overall mortality. Our work underscores the fact that B7-H1 is independently associated with poor outcome in clear cell RCC and improves prognostication over currently used features. In addition, our data are consistent with the expanding body of literature indicating that B7-H1 negatively regulates antitumor immunity (4–6, 13–15).

Discovered in 1999 by Dong et al. (5), B7-H1 is a cell-surface glycoprotein within the B7 family of T-cell costimulatory molecules. Constitutive expression of B7-H1 is normally restricted to macrophage-lineage cells (5). In contrast, several human cancers, including breast, ovarian, lung, colon, lymphoma, and melanoma, have now been reported to aberrantly express B7-H1 (6, 8, 9). Tumor cell expression of B7-H1 has been shown to inhibit tumor-specific T-cell-mediated immunity by inducing T-cell apoptosis, impairing cytokine production, and diminishing the cytotoxicity of activated T cells (6, 15–17). Furthermore, murine tumors expressing B7-H1 have been reported to abrogate immune-mediated tumor regression following adoptive transfer of tumor antigen-specific CD8⁺ T-cell clones and treatment with agonistic costimulatory antibodies that promote T-cell activation (14). Consistent with this, *in vivo* blockade of B7-H1 can potentiate antitumor T-cell responses directed against immunogenic murine tumors expressing B7-H1 either endogenously or following B7-H1 gene transduction (6, 14, 15). Thus, preclinical studies support that B7-H1 blockade can be used to enhance antitumor immunity in murine cancer models (13, 14).

RCC is regarded as an immunogenic tumor. High levels of infiltrating T cells within RCC tumors are frequently observed but paradoxically associated with diminished cancer-specific patient survival (18). Consistent with this, infiltrating lymphocytes within RCC tumors are often impaired and incapable of mediating tumor destruction (1–3). These observations collectively suggest that RCC tumors possess mechanisms to undermine spontaneous or immunotherapy-induced antitumor immunity. The results of our

study suggest that tumor B7-H1, at least in part, contributes to the profile of immunosuppression observed in RCC patients. As such, blockade of B7-H1 may theoretically permit immune-mediated tumor destruction for this treatment-refractory malignancy.

Our observation that B7-H1 is associated with cancer progression may have important implications for the management of advanced RCC. Currently, TNM stage, nuclear grade, and patient performance status represent the most commonly used clinical predictors of outcome for patients with RCC (19). Survival among RCC patients using these predictive indices, however, tends to be variable, highlighting the heterogeneous behavior of RCC tumors (20). Hence, we and others have reported additional features of RCC, including coagulative tumor necrosis, histologic subtype, and tumor size, which independently predict outcome. In the current study, we show that tumor B7-H1 independently identifies patients at risk for cancer progression. Even among patients with seemingly localized disease, median time to progression was <1 year when B7-H1 was aberrantly expressed by the tumor (0.7 versus 2.9 years, respectively). Thus, the assessment of tumor B7-H1 not only identifies patients at risk for relapse but identifies patients at risk for rapid metastatic dissemination. Prospective studies are now warranted to validate the prognostic value of B7-H1, particularly when used to identify patients for adjunctive therapy.

One limitation of this study merits discussion. The percentage of patients with B7-H1-positive tumors assessed in paraffin-embedded tissue is lower compared with our analysis of fresh-frozen tissue (10, 11). We previously reported that 37% of 196 patients had high tumor B7-H1 expression and that these patients were at significant risk of cancer-specific mortality, albeit with limited follow-up. In the current study, only 24% of 306 patients had B7-H1-positive tumors. This discrepancy may reflect the denaturant effect of formalin fixation on protein, which frequently compromises antigen staining during immunohistochemistry. Thus, we are likely underestimating the presence of B7-H1 in clear cell RCC and possibly underestimating the true association between B7-H1 and survival. However, the associations between tumor B7-H1 and outcome observed in the current study are generally consistent with those we reported using fresh-frozen tissues (10, 11). We believe that B7-H1 staining of paraffin-embedded tissues provides important prognostic information and further study is warranted to determine if manipulation of B7-H1 with therapeutic intent improves outcome for this refractory tumor.

Conclusion

Clear cell RCC patients with tumor B7-H1 are at significant risk of cancer progression and mortality. The basis for these associations may relate to the recognized ability of B7-H1 to inhibit antitumor T-cell-mediated immunity. The assessment of tumor B7-H1 offers additional information for patient prognosis and represents an attractive target for immune manipulation in the multimodal treatment of RCC.

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