Biomarkers Role in Prognosis and Survival Outcomes in Patients with Renal Tumors: Review Article

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Mini Review

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Mahmoud Mohamed*
New York Presbyterian Brooklyn Methodist Hospital, USA

***Corresponding author:** Mahmoud Mohamed, New York Presbyterian Brooklyn Methodist Hospital
New York, NY 11215, USA, Tel: +1 718.780.5616;
Email: ma.elhagagy@gmail.com; mam9629@nyp.org

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Introduction

Renal cell carcinoma (RCC) is one of the most common urological malignancies. In 2016, approximately 62,700 adults (39,650 males and 23,050 females) were diagnosed with RCC in the US and approximately 14,240 individuals died from renal neoplasm [1]. RCC mortality rate can vary between 26% up to 94% according to stage and aggressiveness of the disease [2]. RCC accounts for approximately 3% of solid tumors with high mortality rate due to the absence of curative therapy for advanced disease [3]. RCC can be classified as non-epithelial or epithelial, according to cell origin. The four major types are of epithelial origin includes: clear cell renal carcinoma (ccRCC), papillary, chromophobe renal carcinoma (chRCC) and collecting duct carcinoma. The most common subtype of RCC is ccRCC which accounts for approximately 70-80% of all RCC tumors [4,5]. Chromophobe renal cell carcinoma is accounts for approximately 3-5% with 5-year survival rate up to 94% [6]. The standard treatment of localized ccRCC patients is either partial or radical nephrectomy, however, metastasis has been shown to develop in approximately 30% of patients after surgery [7,8]. Metastatic ccRCC may require immunotherapy, targeted therapy, and/or radiation therapy but with low success rate which typically leaves no other option except for surgery [7].

Considering metastatic ccRCC has a low 5-year disease free survival rate (<10%), early diagnosis and prognostic data is critical in order to achieve the full benefit of surgery and increase the survival outcomes [7,9]. Prognosis for ccRCC can be determined by many factors including; cancer grade, stage, response and resistance to treatment. With current imaging modalities, renal tumors including ccRCC can be easily identified at early stage; however, these imaging modalities cannot identify the tumor stage [7].

The potential for utilizing immunohistochemistry in RCC subtypes classification has shown valuable diagnostic and prognostic significance [10]. However, currently there is no consensus in regard to what biomarker should be used in RCC classification [10]. Various RCC associated biomarkers have been studied including PAX-2/PAX8, CAIX, adipophillin (ADP), CD10, and monoclonal antibody RCC marker (RCCma) [11]. PAX, CAIX and vimentin are biomarkers that might be promising in RCC prognostic significance nowadays.

In particular, PAX-2 and PAX-8 have high sensitivity and specificity for RCC tumors. PAX-2 and PAX-8 are members of paired box gene family which consists of nine members where each one encodes a transcription factor that is expressed during fetal development [12-14]. These transcription factors play an important role in the formation of organs and tissues during embryonic development and subsequent maintenance of certain cells after birth [12,13]. PAX-8 oversees renal and thyroid organogenesis [14]. Specifically, PAX-2 and PAX-8 are generously expressed by renal blastemal cells during nephrogenesis. In adulthood, this expression mostly disappears or is present only in few parenchymal cells; however, expression is increased in RCC [12,13]. Recent studies evaluated the sensitivity and specificity for each marker has a diagnostic value for ccRCC. The study contained 26 cases of ccRCC and 51 cases of non-renal cancer with clear cell morphology. PAX-2 was positive to ccRCC by 81% and was positive in 24% of clear cell morphology group. PAX-8 in ccRCCgroup was 100% positive and was 39% positive in the clear cell morphology group [11]. The study concluded that PAX-2 and PAX-8 are sensitive markers to ccRCC and they lose their specificity in the presence of mullerian tumor cells [11].

On the other hand, carbonic anhydrase IX (CAIX) is released under hypoxic conditions caused by the upstream hydroxylation of hypoxia-inducible factor 1-alpha (HIF-1alpha) and subsequent binding to the Von Hippel Lindau (VHL) protein [15,16]. Over-expression of CAIX is therefore associated with various tumor malignancies including ccRCC [17,18]. CAIX is expressed in both high grade and low grade RCC. The CAIX immunohistochemical membrane staining pattern for ccRCC is circumferential while pRCC typically lacks tumor cell apical surface staining and is positive for basolateral membrane outlining [19,20]. Low grade ccRCC immunohistochemical testing can include KIM-1, vimentin, and CAIX. Low grade renal neoplasms that exhibit both clear cell/granular features typically have a negative CAIX expression result which can be diagnostic for chromophone renal cell carcinoma (ChRCC) and oncocytoma [20]. Given its diagnostic association with RCC, the prognostic value of CAIX has received attention. Specifically, several studies have suggested that high CAIX expression (≥75%) may be able to predict prognostic outcomes in patients with ccRCC [16,21,22,23]. In addition, high CAIX

expression has also been cited as an independent predictor for improved interleukin-2 therapy response [24]. Conversely, low CAIX expression (<75%) was associated with higher mortality and a greater chance of lymphatic spread [15,16].

By examining tumor pathologic features, some studies have found inconsistent results for CAIX expression and patient survival [16,24,25]. Survival outcomes in patients with RCC can be affected by patient background, clinical symptoms, and tumor pathologies such as tumor necrosis and nuclear grade [16,26]. Variations in the findings of many reported studies in results continue to generate controversy over CAIX expression and patient prognosis significance [16]. Finally, vimentin, which is a type III intermediate filament that is expressed in normal mesenchymal cells and helps provide resistance to stress [27]. In addition to renal tubular and renal stromal cells, Vimentin expression is recognized in broad scope of other cell types including Sertoli cell, trophoblasts, giant cells, pancreatic cells, endothelial cells, fibroblast, macrophages, neutrophils, leukocytes and mesangial cells [28,29]. Overexpression of vimentin has been detected in prostate cancer, lung cancer, gastrointestinal cancer, and malignant melanoma. Although vimentin has been used for diagnosing and classifying renal neoplasms, there is currently no consensus regarding which immunomarker can be used as standards for renal neoplasm classification. Moreover, little is known regarding vimentin's prognostic value in renal tumors. Considering the identification of specific renal tumor type is crucial in determining treatment and prognosis, biomarkers capable of differential diagnosis and prognostic valueare of great interest.

Vimentin is reported to be an essential marker for epithelial-mesenchymal transition (EMT). EMT is associated with numerous tumorigenic incidents, which vimentin overexpression occurs. However, vimentin exact role remains unknown [4,30]. EMT is also related to tumor invasion, proliferation and metastasis [31]. Over expression of vimentin is associated with epithelial cancers including ccRCC and correlates with tumor growth, invasion, and poor prognosis; however, its role in cancer progression remains uncertain [27]. Vimentin is considered as a potential molecular target for cancer therapy but its specific role remains unclear as well [4,27]. Moreover, vimentin is used as a reliable biomarker in differentiating certain types of renal cell carcinomas [32]. It has been shown that vimentin is expressed in the majority of clear cell and papillary renal cell carcinomas; however, it is rarely expressed in oncocytoma and chromophobe renal cell carcinomas [32,33]. Therefore, vimentin may assist in confirming diagnoses and having a prognostic value regarding each subtype of RCC. Vimentin overexpression was specific to ccRCC in comparison to other chRCC and oncocytoma. A study presented at the American Association of Cancer research (AACR) annual conference in 2016included 66 patients with ccRCC, 11 patients with Oncocytoma and 11 patients with chRCC reported that Vimentin overexpression may be a marker of metastatic disease in patients with ccRCC [34]. Vimentin expression was not significant for tumor grade, pathologic stage, or presence of sarcomatoid features in ccRCC [34].

Conclusion

The efficiency and accuracy of biomarkers studies using immunohistochemical and tissue microarray techniques are still variable and unclear in regards to prognostic significance and survival outcomes in patient with renal tumors. Multiple biomarkers shown to be significant to assess diagnosis and prognosis in these patients and other were not significant. Studies with larger sample sizes and more specific to each biomarker will be needed to validate the results and confirm the usefulness of biomarkers in regards to prognostic significance in patients with renal tumors.

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