CANCER UROLOGY 3'2016 VOL. 12

Biomolecular prognostic factors in renal cell carcinoma: a literature review

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While analyzing data from domestic and foreign literature, we looked at various molecular factors of kidney tumors, some of which may be considered as diagnostic and prognostic markers of the clinical course of the cancer process. Here presented also is an assessment of the possible use of these indicators, in conjunction with other classic factors, in the prognosis of survival and the evaluation of the risk of metastasis in renal cancer.

Key words: *biomolecular markers, prognostic factors of tumor progression, survival, renal cell carcinoma*

DOI: 10.17650/1726-9776-2016-12-3-45-50

Renal cell carcinoma (RCC) is a considerable challenge in urology. In the structure of malignant neoplasms, RCC comprises 2–3 % [1]. About 46,000 new diagnoses are made annually in the USA, and 13,000 patients die of the disease [2]. Morbidity is 12 cases per 100,000 people a year, ratio between men and women with RCC remains constant: 3:2 [3]. Morbidity is 10–20 % higher in black people [4]. Since 1970, RCC morbidity increases on average by 3 % a year in people of the Caucasian race, and by 4 % in black people [4]. This tendency correlates with increased frequency of incidentally detected tumors and improved 5-year survival in patients with localized RCC [5].

According to data obtained by E.M. Aksel, in 2012 19,675 new cases were registered in Russia. Compared to 2007, the increase in the total number of patients was 16.1 % for men and 19.0 % for women. Among men aged 40–54 years morbidity reached 7.2 % (3rd ranked place), among men 55–69 years it reached 5 % (6th ranked place). In the CIS countries, percentage of RCC in the structure of oncological morbidity in men is 2.0–5.8 %, in women – 1.8–3.8 %. Mean age of patients fluctuates between 54 and 59 years in Kyrgyzstan, Azerbaijan, and Kazakhstan, between 61 and 66 years in Russia, Belarus, and Armenia [6]. According to Apolikhin et al., in 2012 percentage of malignant neoplasms of the kidney comprised 3.7 % of all malignant neoplasms in Russia, which amounts to the 10th ranked place in the structure of oncological morbidity in both sexes. In men, it comprises 4.5 %, in women – 3.1 %. In 2012 the total number of deaths due to malignant tumors of the kidney in Russia was 8,305 people, which is 4.4 % higher than in 2002. Dynamics of this characteristic during the decade (2002–2012) had peaks and troughs with a small tendency towards growth. Mean age of deaths from RCC in Russia in 2012 was 66.6 years, while in 2002 it was 64.6 years [7–9].

Smoking, excess weight, and arterial hypertension are the main risk factors of RCC, but the exact cause of the disease is still unknown [10]. A small percentage of RCCs result from hereditary genetic abnormalities, the most common of which is the von Hippel-Lindau gene (*VHL*) [11]. Detailed study of metabolic disorders underlying RCC pathogenesis lead to a deeper understanding of molecular mechanisms of the disease and identification of potential biomarkers [12].

Although widespread use of radiological visualization techniques predominantly increased the number of diagnoses of local asymptomatic (incidental) RCCs, radical nephrectomy remains the main method of surgical treatment [13, 14].

Development of effective targeted therapy of metastatic RCC led to studies of its effectiveness as adjuvant therapy in RCC patients with high risk of progression. Currently, identification of such groups is made based on traditional well-researched prognostic factors. Supposedly, in the future molecular markers which currently are being extensively studied will also be used in clinical practice [15].

The study objective was to analyze literature data on molecular markers characterizing RCC prognosis.

RCC markers can be divided into several groups. One of the main groups is tissue biomarkers. This group includes the *VHL* gene, hypoxia-inducible factors (HIFs), vascular endothelial growth factor (VEGF), carbonic anhydrase 9 (CA9) [16].

The *VHL* gene was first identified and described as a tumor suppressor gene in chromosome 3p resulting in deficient protein isoforms pVHL19 and pVHL30. *VHL* is inactivated in almost all patients with the von Hippel-Lindau syndrome and in about 70 % of patients with sporadic clear cell RCC [17]. Presence of *VHL* changes (mutations or hypermethylation) predicts increased progression-free survival and decreased mortality for stage I and III clear cell RCC ($p = 0.024$ and $p = 0.023$, respectively) [17]. Research suggests that angiogenesis regulation and RCC proliferation do not directly depend on the mutation of *VHL*. J. Dagher

et al. discovered that *VHL* changes in kidney cancer significantly corresponded to high Furhman's grade, more frequent metastasis, presence of a sarcoma-like component in the tumor, as well as higher level of VEGF expression [18].

Hypoxia-inducible factor (HIF). HIF-α is accumulated either in hypoxia conditions or due to *pVHL* gene deficiency. Increased HIF-α expression was identified in 75 % (24 of 32) of cases of clear cell RCC and only in 38 % (3 of 8) of cases of non-clear cell RCC [19]. It was shown, that HIF-α paralogs – HIF-1α and HIF-2α – have opposite effects on tumor development and progression. HIF-1α acts as a tumor suppressor, while HIF-2α carries oncogenic potential [20].

Vascular endothelial growth factor (VEGF) is a dimeric glycoprotein, one of platelet-derived growth factors. It affects angiogenesis in normal and pathological conditions. Angiogenesis in tumors is governed by VEGF. In clear cell RCC, VEGF mRNA is activated due to abnormal HIF-1α regulation and is a result of VHL protein loss and environmental hypoxia. Large tumors have insufficient blood flow, which leads to further hypoxia and additional VEGF activation. Increased VEGF expression was identified in 29 % of patients with clear cell RCC and 67 % of patients with papillary RCC ($p = 0.02$) [21]. In clear cell RCC, VEGF expression correlates with tumor size ($p = 0.05$) [21], Fuhrman's grade ($p = 0.002$), tumor necrosis ($p = 0.001$), tumor stage ($p = 0.006$) [22], microvessel invasion ($p = 0.01$) [60], rate of disease progression ($p = 0.01$) [22], and cancer-specific survival [21–23].

Carbonic anhydrase 9 (CA9) is a HIF-1α-regulated transmembrane protein associated with aggressive phenotype and poor risk in a large number of tumors in humans [24, 25]. CA9 helps regulate intracellular and extracellular pH levels in response to tumor hypoxia and subsequent anaerobic metabolism. CA9 expression is observed in more than 80 % of RCC cases (in 90 % of clear cell RCCs). It was noted that in localized and metastatic RCCs high CA9 expression is associated with favorable prognosis [26, 27]. The level of CA9 staining is inversely proportional to RCC metastasis potential ($p = 0.036$), and high CA9 expression suggested longer survival in a multivariable analysis taking into account such prognostic factors as T stage, Fuhrman's grade, and general state ($p \leq 0.005$) [27].

The next group of biomarkers is **mTOR**. It includes ribosomal protein S6 (pS6), protein kinases B (pAkt), phosphatase and tensin homolog (PTEN). The mTOR metabolic pathway regulates cell growth. Its positive activation in tumors promotes such important cellular functions as protein degradation and angiogenesis [28]. The prognostic role of mTOR as a biomarker is still controversial and poorly understood. Nevertheless, mTOR inhibitors (temsirolimus [29], everolimus [30]) are the drugs of choice in treatment of metastatic RCCs.

Ribosomal protein S6 (pS6) is overexpressed in clear cell carcinoma and is associated with mTOR activation in its metabolic pathway [31]. pS6 is a predictor of survival in both localized (risk ratio (RR) 3.14; $p = 0.002$) and metastatic RCCs (RR 1.55; $p = 0.04$) [31]. High expression of the S6 kinase ($p = 0.02$) predicted response to temsirolimus in 20 of 32 patients [32]. Measurement of the S6 expression level is useful for prognosis of optimal biological doses of mTOR inhibitors in treatment of RCC [33].

Protein kinases B (pAkt) regulate cell growth and survival mechanisms by phosphorylating a large number of substrates in the cytoplasm and nucleus [34]. In one-factor analysis, increased pAkt immunostaining was associated with lower differentiation grade ($p = 0.04$), faster metastasis ($p = 0.004$), and decreased cancer-specific survival ($p = 0.01$) [35]. Other studies have demonstrated a favorable prognosis for localized RCC with high pAkt expression (RR 0.66; $p = 0.3$), and inversely a poor prognosis for high cytoplasmic pAkt expression in metastatic RCC (RR 1.31; $p = 0.2$) [35].

Phosphatase and tensin homolog (PTEN) is a tumor suppressor protein coded by a tumor suppressor gene *PTEN*. PTEN phosphatase regulates the mTOR metabolic pathway by inhibiting and phosphorylating pAkt [36]. Although *PTEN* mutations are rare, its loss during carcinogenesis is associated with poor RCC prognosis [36]. PTEN expression is higher in tumors with initial T stage of localized non-clear cell RCC. According to A.J. Pantuck, PTEN expression improves survival for RCC (RR 0.74; $p = 0.3$) [31].

Alternative biomarkers group. An important representative of this biomarker group is **survivin**. Carcinogenesis is associated with apoptosis deregulation promoting acquirement of harmful characteristic in cancer cells, including loss of tumor suppressor genes, angiogenic changes, and immortalization [37]. Survivin is a representative of the apoptosis inhibitors family. It controls mitosis progression and causes changes in expression of genes associated with tumor invasion. Survivin is overexpressed in all types of cancer in humans including RCC [38].

Alterative biomarkers group also includes the **p53 protein**, a DNA-binding protein which plays a role in cell cycle arrest [39] and serves as a marker of apoptosis regulation [40, 41]. Overexpression of p53 in papillary, chromophobe, and clear cell RCC was observed in 70, 27, and 12 % of tumors, respectively. Overexpression of p53 is an independent predictor of improved metastasis-free survival in patients with localized clear cell RCC ($p = 0.01$) [42].

This group also includes **matrix metalloproteases (MMP)**, a family of enzymes consisting of important proteases of extracellular matrix remodeling. Their activity was observed in a number of crucial normal and pathological processes. The later include tumor growth, progression and metastasis, as well as dysregulation of angiogenesis and associated processes. Some studies prove increased expression of MMP-2 and MMP-9 in 67–76 and 43 % of RCC cases, respectively. According to reports of N. Kawata et al., over-

expression of MMP-2 and MMP-9 is more common in clear cell RCC, and it correlates with aggressive behavior, tumor differentiation grade, and survival [43, 44].

Another representative of the alternative biomarkers group is **insulin-like growth factor II mRNA-binding protein (IMP3)**. IMP3 is an oncofetal RNA-binding protein regulating transcription of insulin-like growth factor II mRNA in developing epithelial, muscle, and placenta cells at the early stages of embryogenesis in humans and mice. In adults, its level is very low or undetectable. IMP3 expression is governed by cell proliferation and invasion during various cancers. In RCC, IMP3 expression correlates with later stage, low tumor differentiation grade, sarcoma-like transformation, and increased cancer-specific survival. In a study including 371 patients with localized clear cell, papillary, and unclassified RCC, Z. Jiang et al. have shown that IMP3 expression in tumor cells significantly corresponds to disease progression, distant metastases, and increases death rate. Their multivariate analysis took into account patient age, sex, tumor size, stage and differentiation grade, RCC histological variant [45].

Another alternative biomarker **Ki-67** is a marker of cell proliferation [46]. Ki-67 expression correlates with aggressive phenotype in clear cell RCC [47–49]. High Ki-67 expression predicts early recurrences (RR 1.05; $p = 0.02$) [50] and short survival (RR 1.95; $p < 0.001$) [51, 52].

Vimentin is another representative of this group. Vimentin is a cytoplasmic intermediate filament which is not normally expressed in epithelial cells. Vimentin expression is observed in clear cell (26–51 %) and papillary RCCs (61 %) [53]. Vimentin overexpression (30–53 %) predicts poor prognosis ($p < 0.007$) irrespectively of the T stage or tumor differentiation grade [54].

Prognostic potential of blood biomarker **thrombocytosis** was observed in several studies. Thrombocytosis didn't add any significant information (+0.3 %) to a prognostic model consisting of the TNM stage, age, tumor size, Fuhrman's grade, histological subtype, and preoperative hemoglobin level ($n = 1828$) [55]. Nonetheless, it reaches the status of independent factor (RR 1.49; $p = 0.01$) in prognosis of overall survival in patients with metastatic RCC.

C-reactive protein (CRP). According to T.V. Johnson, CRP was a powerful prognostic factor for tumor metastasis ($p < 0.001$) and increased overall mortality ($p < 0.001$) after nephrectomy in 130 patients with localized RCC [56]. CRP increases prognostic accuracy of several clinical and pathological factors by 3.7 % ($p < 0.001$) [57].

Serum amyloid A (SAA) is another blood biomarker. Human SAA is a high-density lipoprotein playing an important role as an inflammation modulator, and in cholesterol metabolism and transport. SAA is a potentially useful biomarker for monitoring patients with different malignant tumors. In RCC, SAA level is higher in patients with metastases; in [58], SAA level was an independent prognostic factor of overall survival.

Neutrophilic gelatinase-associated lipocalin (NGAL) is a protein activated in damaged tumor cells. NGAL has a protective effect against acute ischemic damage [59]. Its overexpression is observed in several tumors in humans including RCC [60].

Insulin-like growth factor 1 (IGF-1) is a representative of the same group of biomarkers. IGF-1 has various functions, but there's scientific proof that it serves as an important metabolic biomarker. In a group of 256 patients with RCC, serum IGF-1 level correlated with overall survival after correction for the effect of tumor stage [61]. Studies of the prognostic role of IGF in RCC are currently at the early stage.

Urine markers. Urinary nuclear matrix protein (NMP-22) is a biomarker approved by the Food and Drug Administration of the USA (FDA) for screening and monitoring of bladder cancer [62]. Several studies have shown that NMP-22 level is higher in patients with RCC compared to the control group ($p \leq 0.005$) [63].

The last group of biomarkers are immunological markers.

Tumor-infiltrating lymphocytes (TILs). RCC is an immunogenic cancer with pathological samples carrying a large number of TILs [61]. TILs are a manifestation of the host's immune reactions against cancer. It was shown that increased TILs level positively correlates with higher stage of carcinogenesis and tumor differentiation grade [63]. In another study, patients with pronounced TILs (CD8+) expression had earlier recurrences and higher mortality according to a multivariate analysis [64].

Regulatory T cells (Tregs) are also immunological markers. TILs, Tregs, while supporting activation of other T cells, play the main role in suppression of immune response to tumor formation and prevent development of effective antitumor immunity. Increased number of regulatory T cells (> 10 %) in RCC tumor lesions (CD4+, CD25+, Foxp3 –) is associated with a later stage (TNM IV: 22 % vs. 11 %; $p = 0.01$), large tumor size (10 cm: 36 % vs. 20 %; $p = 0.02$), as well as presence of coagulative tumor necrosis (14 % vs. 6 %; $p = 0.03$) [65]. Expression of regulatory T cells also correlates with cancer-specific mortality (RR 1.03; $p = 0.007$) [65].

B7-H1 is a co-regulator of T cells which are a powerful and independent RCC progression factor [66]. Expression of B7-H1 inhibits tumor-specific T cell immunity through induction of apoptosis in T cells, decreases production of cytokines and cytotoxicity of activated T cells [67]. High B7-H1 expression correlated with higher cancer-specific (RR 3.92; $p < 0.001$) and overall mortality (RR 2.37; $p < 0.001$) in a group of 306 patients after nephrectomy for clear cell RCC [68].

Currently, the role of biomolecular markers in the prognosis of RCC progression is not fully understood. A number of studies has shown that some markers can potentially join the ranks of traditional prognostic factors. Further research of prognostic significance of biomolecular markers in RCC is necessary.

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