

METHOD TO USE GENE EXPRESSION TO DETERMINE LIKELIHOOD OF CLINICAL OUTCOME OF RENAL CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority benefit of U.S. provisional application serial no. 61/294,038, filed January 11, 2010 and priority benefit of U.S. provisional application serial no. 61/346,230, filed May 19, 2010.

TECHNICAL FIELD

[0002] The present disclosure relates to molecular diagnostic assays that provide information concerning prognosis in renal cancer patients.

INTRODUCTION

[0003] Each year in the United States there are approximately 51,000 cases of renal cell carcinoma (kidney cancer) and upper urinary tract cancer, resulting in more than 12,900 deaths. These tumors account for approximately 3% of adult malignancies. Renal cell carcinoma (RCC) represents about 3 percent of all cancers in the United States. Predictions for the United States for the year 2007 were that 40,000 new patients would be diagnosed with RCC and that 13,000 would die from this disease.

[0004] The clinical outcome for a renal cell carcinoma patient depends largely on the aggressiveness of their particular cancer. Surgical resection is the most common treatment for this disease as systemic therapy has demonstrated only limited effectiveness. However, approximately 30% of patients with localized tumors will experience a relapse following surgery, and only 40% of all patients with renal cell carcinoma survive for 5 years.

[0005] In the US, the number of adjuvant treatment decisions that will be made by patients with early stage renal cell carcinoma in 2005 exceeded 25,000. The rates in the European Union are expected to be similar. Physicians require prognostic information to help them make informed treatment decisions for patients with renal cell carcinoma and recruit appropriate high-risk patients for clinical trials. Surgeons must decide how much kidney and surrounding tissue to remove based, in part, on predicting the aggressiveness of a particular tumor. Today, cancer tumors are generally classified based on clinical and pathological features, such as stage, grade, and the presence of necrosis. These designations are made by applying standardized criteria, the subjectivity of which has been demonstrated by a lack of concordance amongst pathology laboratories. Biological markers have been identified for diagnosis of aggressive versus non-aggressive CC-RCC, such as genes that are up-regulated in non-aggressive CC-RCC tumour tissue relative to normal tissue (US 2006/088823). Gene expression profiling

using primary CC-RCC specimens, metastatic specimens and non-cancerous unmatched cortical specimens has identified nucleic acid sequences (WO 2006/124022). Y. Masahiro, et al., (Int J Cancer 123:5 (2008)), developed a three-gene expression signature model to predict clinical outcome of CC-RCC, and showed that VCAM1, EDNRB and RGS5 were associated with cancer-specific survival and that higher expression correlated with better outcome.

SUMMARY

[0006] The present disclosure provides biomarkers, the expression of which has prognostic value in renal cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] Figures 1a-1c: Consistency between Stage I and III for exemplary genes associated with RFI

[0008] Figure 2: Consistent results across endpoints (OS and RFI) for exemplary genes

[0009] Figure 3: Kaplan-Meier curve: Recurrence Free Interval (RFI) by Cleveland Clinic Foundation (CCF) histologic necrosis

[0010] Figure 4: Performance of Mayo prognostic tool applied to CCF data

[0011] Figure 5: Example of using one gene to improve estimate: EMCN in addition to Mayo Criteria

[0012] Figure 6: Example of using one gene to improve estimate: AQP1 in addition to Mayo Criteria

[0013] Figure 7: Example of using one gene to improve estimate: PPAP2B in addition to Mayo Criteria

DETAILED DESCRIPTION

DEFINITIONS

[0014] Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Singleton *et al.*, Dictionary of Microbiology and Molecular Biology 2nd ed., J. Wiley & Sons (New York, NY 1994), and March, Advanced Organic Chemistry Reactions, Mechanisms and Structure 4th ed., John Wiley & Sons (New York, NY 1992), provide one skilled in the art with a general guide to many of the terms used in the present application.

[0015] One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Indeed, the present invention is in no way limited to the methods and materials described. For purposes of the present invention, the following terms are defined below.

Claims

1. A method comprising:

(a) measuring, in a biological sample obtained from a cancer patient with renal cell carcinoma, an expression level of an RNA transcript of PPAP2B, or its expression product;

(b) normalizing the expression level to obtain a normalized expression level; and

(c) (i) determining a likelihood of recurrence of renal cell carcinoma for the patient by comparing the normalized expression level of PPAP2B to gene expression data obtained from a renal cell carcinoma sample from a population of patients with known clinical outcome with respect to recurrence of renal cell carcinoma-based on the normalized expression level of the RNA-transcript of PPAP2B, or its expression product, wherein the increased normalized expression level of PPAP2B is negatively correlated with a risk of a recurrence of cancerrenal cell carcinoma; or

(ii) determining a likelihood of an increased tumor tumour stage for the patient by comparing the normalized expression level of PPAP2B to gene expression data obtained from a renal cell carcinoma sample from a population of patients with known clinical outcome with respect to stage of the tumour, based on the normalized expression level of the RNA-transcript of PPAP2B, or its expression product, wherein the increased normalized expression level of PPAP2B is negatively correlated with increased stage of the tumour; or

(iii) determining a likelihood of an increased tumour grade for the patient by comparing the normalized expression level of PPAP2B to gene expression data obtained from a renal carcinoma sample from a population of patients with known clinical outcome with respect to grade of the tumour, based on the normalized expression level of the RNA-transcript of PPAP2B, or its expression product, wherein the increased normalized expression level of PPAP2B is negatively correlated with increased grade of the tumour; or

(iv) determining the presence of necrosis for the patient by comparing the normalized expression level of PPAP2B to gene expression data obtained from a renal carcinoma sample from a population of patients with known clinical outcome with respect to presence of necrosis, based on the normalized expression level of the RNA-transcript of PPAP2B, or its expression product, wherein the increased normalized expression level of PPAP2B is negatively correlated with the presence of necrosis;
or

(v) determining a nodal status of the patient by comparing the normalized expression level of PPAP2B to gene expression data obtained from a renal carcinoma sample from a population of patients with known clinical outcome with respect to nodal invasion, based on the normalized expression level of the RNA-transcript of PPAP2B, or its expression product, wherein the increased normalized expression level of PPAP2B is negatively correlated with nodal invasion.

2. —A method as claimed in claim 1, wherein the method is for determining a likelihood recurrence of

~~cancer for the patient, wherein the method comprises measuring, in a biological sample obtained from the patient, an expression level of an RNA transcript of PPAP2B, or its expression product, and determining the likelihood that the patient will have recurrence of cancer based on the normalized expression level, wherein expression of PPAP2B is negatively correlated with a risk of recurrence of cancer.~~

~~2. A method as claimed in claim 1, wherein the method is that specified in Parts (a), (b) and c(i).~~

~~3. A method as claimed in claim 2, further comprising generating a report based on the score.~~

~~4. A method as claimed in claim 2, wherein the recurrence of cancer is recurrence of renal cell carcinoma.~~

~~53. A method as claimed in claim 4 2, wherein the biological sample is obtained from a tumour.~~

~~64. A method as claimed in claim 1, wherein the biological sample is a fixed, paraffin-embedded tissue sample.~~

~~75. A method as claimed in claim 2, wherein expression levels from PPAP2B and at least one other gene, or its expression product are measured, wherein the at least one other gene or its expression product is selected from ENNRB, APOLD1, NOS3, EIFEBP1, LMNB1, TUBB2A, CCL5, CX3CL1, CEACAM1, or IL6, and/or any other gene, or its expression product selected from Tables 3a, 3b, 8a, or 8b.~~

~~86. A method as claimed in claim 7 5, wherein PPAP2B and the at least one other gene, or its expression product, are from one or more gene subsets.~~

~~97. A method as claimed in claim 8 6, wherein the one or more gene subsets is angiogenesis, immune response, transport, cell adhesion/extracellular matrix, cell cycle, or apoptosis genes.~~

~~108. A method as claimed in claim 1, wherein the method is that specified in Parts (a), (b) and c(ii) for determining a likelihood of an increased tumour stage for the patient, wherein the method comprises measuring, in a biological sample obtained from the patient, an expression level of an RNA transcript of PPAP2B, or its expression product, and determining the likelihood of an increased tumour stage based on the normalized expression level, wherein the normalized expression level of PPAP2B is negatively correlated with increased stage of the tumour.~~

~~119. A method as claimed in claim 1, wherein the method is that specified in Parts (a), (b) and~~

~~c(iii).for determining a likelihood of an increased tumour grade in the patient, wherein the method comprises measuring, in a biological sample obtained from the patient, an expression level of an RNA transcript of PPAP2B, or an expression product, and determining the likelihood of increased tumour grade based on the normalized expression level, wherein the normalized expression level of PPAP2B is negatively correlated with increased grade of the tumour.~~

~~4210. A method as claimed in claim 1, wherein the method is that specified in Parts (a), (b) and c(iv).for determining presence of necrosis in a biological sample obtained from the patient, wherein the method comprises measuring, in the biological sample, an expression level of an RNA transcript of PPAP2B, or its expression product, and determining the presence of necrosis of the tissue based on the normalized expression level, wherein the normalized expression level of PPAP2B is negatively correlated with the presence of necrosis.~~

~~4311. A method as claimed in claim 1, wherein the method is that specified in Parts (a), (b) and c(v).for determining nodal status of the patient, wherein the method comprises measuring, in a biological sample obtained from the patient, an expression level of an RNA transcript of PPAP2B, or its expression product, and determining the nodal status of the cancer patient based on the normalized expression level, wherein the normalized expression level of PPAP2B is negatively correlated with nodal invasion.~~

~~4412. A method as claimed in any one of the preceding claims, wherein the expression level of the RNA transcript is measured using a PCR-based method.~~

~~13. A method as claimed in any one of the preceding claims, wherein the expression level of the RNA transcript of PPAP2B is measured.~~

~~14. A method as specified in any one of Parts (a), (b) and c(i) of claim 1 and claims 2 to 7, wherein the expression level of the RNA transcript of PPAP2B is measured.~~