Integrating translational research and clinical practice to refine risk stratification in renal cell carcinoma

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The incidence of renal cell carcinoma (RCC) has been increasing over recent decades[1,2]. Worldwide, there are over 400,000 new cases of RCC and over 170,000 deaths due to RCC each year[3]. The five-year survival rate of RCC that is confined to the kidney is 93% while it is only 13% in metastasized disease[4]. In the Netherlands, 58% of RCC patients are diagnosed in stage 1 versus 20% of patients in stage 4 (https://www.kanker.nl). For newly diagnosed patients with localized disease, surgical intervention (i.e. a partial of radical nephrectomy) is the first-choice treatment[5,6]. Other treatment options include targeted therapies, immunotherapies and radiation[7]. After surgical intervention, RCC patients become part of a follow-up regimen consisting of surveillance with ultrasound and intravenous contrast-enhanced CT scans[8]. The exact frequency and protocols of these follow-up activities can depend on the treatment center as currently, there is no consensus on the surveillance guidelines after radical or partial nephrectomy[8-11]. In the Netherlands, the updated 2022 EAU RCC guidelines are used for the management of RCC patients[8].

To guide treatment decisions for RCC patients, clinicians usually rely on a combination of various clinical and pathological characteristics. These include the tumor subtype, tumor stage and tumor grade (ISUP grade)[4,12-15]. Next to these, several prognostic models such as the TNM staging system, the Stage, Size, Grade, and Necrosis (SSIGN) Risk Score, and the University of California Los Angeles Integrated Staging System (UISS) are available[16-18]. Though these tools are widely used in clinical practice[19-21], these models are still suboptimal in predicting patient outcome and clinicians are confronted with the fact that up to 30% of RCC patients develop a metastasis during follow-up. Approximately 10% of these patients die due to disease progression within five years after surgery[22].These numbers indicate that risk stratification in RCC should be enhanced to guide RCC clinical management and improve patients' outcome.

In this thesis, we have proposed a prognostic biomarker model that integrates methylation data from *GREM1*, *GATA5*, *LAD1*, *NEFH*, and *NEURL*, along with clinicopathological characteristics. Additionally, we underscored the importance of carefully selecting methylation assays during the biomarker identification process and highlighted the necessity of updating existing datasets to facilitate comparisons among biomarker studies. Here, we discuss the potential benefits that the findings outlined in this thesis can offer to both RCC patients and clinicians. Additionally, we explore how this current research can assist other researchers in the methylation biomarkers field.

Clinical impact

To improve risk stratification in RCC, studies have been focusing on biomarkers that can complement current prognostic models. Methylation biomarkers have been considered as promising in this regard, and the incorporation of these markers into current prognostic models might enhance these models[24]. Improved RCC risk stratification could enable clinicians to tailor treatment strategies based on individual disease risk. Patients at high risk of recurrence or metastasis may benefit from early interventions and/or more intensive monitoring[23] while for low-risk patients less intensive follow-up could be sufficient. A tailored individual follow-up plan could therefore improve the overall survival of the RCC patients and minimize unnecessary follow-up burden such as frequent post operative imaging and treatment-related side effects. In addition, it could facilitate shared decision-making regarding treatment and follow-up options and potential risks. This could also enable patients to take into consideration their personal preferences and help to avoid anxiety, depression and fear, thereby ultimately improving quality of life. For clinicians, enhanced risk stratification models can aid to prevent over- or under-treatment (or over- or under-surveillance) by selecting the most appropriate routine for specific patients based on their risk profile. Furthermore, integrating methylation markers into current prognostic models may be especially important for the assessment of biopsies when other prognostic factors are not easily assessed. A more accurate risk stratification could also lead to a decreased (financial) burden for both hospitals and society as unnecessary tests and imaging procedures that also take time and effort from specialized staff, could be avoided.

Scientific impact

Despite the promising outlook of methylation biomarkers for risk stratification in RCC, none of these biomarkers have reached the clinic yet[25,26]. Several reasons for this lack of clinical translation have been described in the previous chapters of this thesis, but among the main reasons are the lack of validation, the high degree of heterogeneity in clinical aspects (e.g. differences in populations, studied RCC subtypes and used clinical outcomes) and the high degree of technical heterogeneity of previous studies. This latter form of heterogeneity could be an overlooked issue in biomarker research. Previously, the exact genomic location of measured DNA methylation[27] and the suboptimal design of the assay have been highlighted as factors hindering progression of potential DNA methylation biomarkers[28], but also the technique to measuring DNA methylation as well as the sample type should be taken into account. Different methylation-specific PCR (MSP) variants, such as the conventional MSP or the quantitative MSP, are often used interchangeably in biomarker studies and directly compared to each other, sometimes when using different sample types (e.g. fresh-frozen versus formalin-fixed paraffin-

embedded). This could lead to inaccurate conclusions about the biomarkers' prognostic value. To enable head-to-head comparisons, which are crucial to advance the prognostic biomarker research field, researchers should acknowledge the impact of this technical application heterogeneity. This does not imply that all research on DNA methylation markers should be conducted according to one standardized approach or using one preferred technical method. Instead, researchers should consider their technical choices upfront, weighing (dis)advantages of several techniques in the context of the sample type they are using. Besides, in their considerations, previous results on DNA methylation biomarkers and techniques used to obtain these results, should be taken into account as well, to ensure that new studies will have complementary value to existing ones. Although this is mainly the responsibility of the researchers, scientific journals and funding organizations could stimulate this by enforcing the listing of technical considerations in publications and/or grant applications or by mandating researchers to explain a rationale for their choice of methylation assay and/or sample type. Additionally, researchers should see the value in using existing data and this should also be encouraged by scientific journals and funding organizations[29]. While the discovery of novel biomarkers is undoubtedly very valuable, there is also a wealth of data already available. The use of this data, after necessary optimization, re-evaluation, or updates according to novel clinical insights, could provide crucial information on potential biomarkers and should therefore be endorsed. Furthermore, in doing so, the scientific community, in collaboration with the clinical field, can contribute more effectively to the development and implementation of robust, clinically relevant tools for risk assessment in RCC patients. Eventually, this could positively impact quality of life for RCC patients and reduce health system costs.

References

1. Bahadoram S, Davoodi M, Hassanzadeh S, Bahadoram M, Barahman M, Mafakher L. Renal cell carcinoma: an overview of the epidemiology, diagnosis, and treatment. G Ital Nefrol. 2022;39(3):2022-vol 3.
2. Makhov P, Joshi S, Ghatalia P, Kutikov A, Uzzo RG, Kolenko VM. Resistance to Systemic Therapies in Clear Cell Renal Cell Carcinoma: Mechanisms and Management Strategies. Mol Cancer Ther. 2018;17(7):1355-64.
3. Tacconi EMC, Tuthill M, Protheroe A. Review of Adjuvant Therapies in Renal Cell Carcinoma: Evidence to Date. Onco Targets Ther. 2020;13:12301-16.
4. Padala SA, Barsouk A, Thandra KC, Saginala K, Mohammed A, Vakiti A, et al. Epidemiology of Renal Cell Carcinoma. World J Oncol. 2020;11(3):79-87.
5. Mittal A, Al-Ezzi E, Li X, Moloney B, Wilson B, Spiliopoulou P, et al. The role of cytoreductive nephrectomy and systemic therapy in the management of tumour thrombus in patients with metastatic renal cell carcinoma. British Journal of Cancer. 2023;128(10):1888-96.
6. Krabbe LM, Bagrodia A, Margulis V, Wood CG. Surgical management of renal cell carcinoma. Semin Intervent Radiol. 2014;31(1):27-32.
7. Chowdhury N, Drake CG. Kidney Cancer: An Overview of Current Therapeutic Approaches. Urol Clin North Am. 2020;47(4):419-31.
8. Ljungberg B, Albiges L, Abu-Ghanem Y, Bedke J, Capitanio U, Dabestani S, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2022 Update. Eur Urol. 2022;82(4):399-410.
9. Follow-up for Clinically Localized Renal Neoplasms- American Urological Association [
10. Dabestani S, Beisland C, Stewart GD, Bensalah K, Gudmundsson E, Lam TB, et al. Increased use of cross-sectional imaging for follow-up does not improve post-recurrence survival of surgically treated initially localized R.C.C.: results from a European multicenter database (R.E.C.U.R.). Scand J Urol. 2019;53(1): 14-20.
11. Motzer RJ, Jonasch E, Agarwal N, Alva A, Baine M, Beckermann K, et al. Kidney Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022;20(1):71-90.
12. Delahunt B, Cheville JC, Martignoni G, Humphrey PA, Magi-Galluzzi C, McKenney J, et al. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. Am J Surg Pathol. 2013;37(10):1490-504.
13. Kim SP, Alt AL, Weight CJ, Costello BA, Cheville JC, Lohse C, et al. Independent validation of the 2010 American Joint Committee on Cancer TNM classification for renal cell carcinoma: results from a large, single institution cohort. J Urol. 2011;185(6):2035-9.
14. Sun M, Shariat SF, Cheng C, Ficarra V, Murai M, Oudard S, et al. Prognostic factors and predictive models in renal cell carcinoma: a contemporary review. Eur Urol. 2011;60(4):644-61.
15. Wagener N, Edelmann D, Benner A, Zigeuner R, Borgmann H, Wolff I, et al. Outcome of papillary versus clear cell renal cell carcinoma varies significantly in non-metastatic disease. PLoS One. 2017;12(9):e0184173.
16. Gerald T, Margulis V. Variability in prognostic models for localized renal cell carcinoma. Nature Reviews Urology. 2022;19(7):385-6.
17. Klatte T, Rossi SH, Stewart GD. Prognostic factors and prognostic models for renal cell carcinoma: a literature review. World Journal of Urology. 2018;36(12):1943-52.
18. Novara G, Ficarra V, Antonelli A, Artibani W, Bertini R, Carini M, et al. Validation of the 2009 TNM version in a large multi-institutional cohort of patients treated for renal cell carcinoma: are further improvements needed? Eur Urol. 2010;58(4):588-95.
19. Downs TM, Schultzel M, Shi H, Sanders C, Tahir Z, Sadler GR. Renal cell carcinoma: risk assessment and prognostic factors for newly diagnosed patients. Crit Rev Oncol Hematol. 2009;70(1):59-70.
20. Ficarra V, Novara G, Galfano A, Brunelli M, Cavalleri S, Martignoni G, et al. The 'Stage, Size, Grade and Necrosis' score is more accurate than the University of California Los Angeles Integrated Staging System for predicting cancer-specific survival in patients with clear cell renal cell carcinoma. BJU Int. 2009;103(2):165-70.
21. Parker WP, Cheville JC, Frank I, Zaid HB, Lohse CM, Boorjian SA, et al. Application of the Stage, Size, Grade, and Necrosis (SSIGN) Score for Clear Cell Renal Cell Carcinoma in Contemporary Patients. Eur Urol. 2017;71(4):665-73.

22. Lerner SE, Hawkins CA, Blute ML, Grabner A, Wollan PC, Eickholt JT, et al. Disease outcome in patients with low stage renal cell carcinoma treated with nephron sparing or radical surgery. 1996. J Urol. 2002;167(2 Pt 2):884-9; discussion 9-90.
23. Grimm MO, Leucht K, Foller S. Risk Stratification and Treatment Algorithm of Metastatic Renal Cell Carcinoma. J Clin Med. 2021;10(22).
24. Joosten SC, Odeh SNO, Koch A, Buekers N, Aarts MJB, Baldewijns M, et al. Development of a prognostic risk model for clear cell renal cell carcinoma by systematic evaluation of DNA methylation markers. Clin Epigenetics. 2021;13(1):103.
25. Kern SE. Why your new cancer biomarker may never work: recurrent patterns and remarkable diversity in biomarker failures. Cancer Res. 2012;72(23):6097-101.
26. Poste G. Bring on the biomarkers. Nature. 2011;469(7329):156-7.
27. Koch A, Joosten SC, Feng Z, de Ruijter TC, Draht MX, Melotte V, et al. Analysis of DNA methylation in cancer: location revisited. Nat Rev Clin Oncol. 2018;15(7):459-66.
28. Massen M, Lommen K, Wouters KAD, Vandersmissen J, van Criekinge W, Herman JG, et al. Technical considerations in PCR-based assay design for diagnostic DNA methylation cancer biomarkers. Clin Epigenetics. 2022;14(1):56.
29. Iain Chalmers D, Prof Michael B Bracken P, Prof Ben Djulbegovic P, Silvio Garattini M, Jonathan Grant P, A Metin Gülmezoglu P, et al. How to increase value and reduce waste when research priorities are set. Lancet. 2014;383(9912):156-65.