Commentary

Clinomics—an underutilized resource?

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Comment on: Freedland SJ, Choeurng V, Howard L, *et al.* Utilization of a Genomic Classifier for Prediction of Metastasis Following Salvage Radiation Therapy after Radical Prostatectomy. Eur Urol 2016. [Epub ahead of print].

Submitted Mar 04, 2016. Accepted for publication Mar 08, 2016.
doi: 10.21037/tcr.2016.03.08
View this article at: http://dx.doi.org/10.21037/tcr.2016.03.08

Biochemical recurrence after radical prostatectomy for prostate cancer can be seen in 30–50% of the cases depending on stage, PSA and Gleason score. About 50% of the recurrences become apparent within 2 years after surgery with local failure being the predominant pattern. It is therefore obvious that early post-operative adjuvant radiotherapy (ART) or PSA-triggered salvage radiotherapy (SRT) are frequently considered in these patients and improve outcome. Open questions regarding the optimal mode of treatment at biochemical recurrence especially the combination of radiotherapy with antihormonal therapy and/or other systemic agents are currently investigated. In addition current studies demonstrated the value of dose-escalated SRT especially in patients with R+ disease (1).

The current paper by Freedland *et al.* (2) helps to shed some light on the challenge to identify patients who may benefit from more aggressive therapy in order to "hit early and hit hard". In a retrospective analysis, tumor material from a cohort of 170 men receiving SRT (median 66.6 Gy) after radical prostatectomy was analysed. Twenty patients (12%) developed metastases after a median follow-up of 5.7 years. The genomic classifier (GC) based on expression of 22 predefined biomarkers (affymetrix oligonucleotide microarray) predicted the risk of metastases better than established scores [CAPRA-S (3), Briganti *et al.* (4)] and identified a group of patients with a high risk of metastases (33.1%). On univariate analysis Gleason score 7 and higher, extraprostatic extension and pre-SRT PSA as well as GC significantly predicted post-SRT-metastases. GC remained an independent predictor after adjusting for clinical variables.

This study adds to our knowledge and represents an important milestone in personalizing treatment in order to deliver more aggressive treatment for selected patients. However, there are several open questions which need to be addressed in future analyses.

- What would have been the role of early adjuvant RT in these high risk patients as identified by the GC? Wouldn't it be better to treat these patients with upfront radiotherapy in order to stop metastases at the source? The time delay between surgery and the initiation of SRT (median 12.4 mon) allows selected tumor cells to leave the prostatic fossa and either migrate to lymph nodes or beyond. Factors favouring early adjuvant RT were present in a high percentage of the patients (extraprostatic extension 52.7%, seminal vesicle invasion 26.6%, positive surgical margin 80.6%). So why not treat early as long as the tumor is restricted to the prostatic fossa and can be cured by RT alone?
- Focussing the genetic analyses only on tumor tissue without having normal tissue sensitivity in mind may not allow to properly increase the aggressiveness of the treatment. The therapeutic index has to be kept in mind. i.e., increasing the radiation dose or administering combined modality treatment in a sensitive subgroup of patients may induce unacceptable toxicity;
- Clinomics, which is defined as the total clinical information about the patient, is heavily underutilized in investigations like this. We are well aware, that especially regarding radiation response and toxicity life style factors like smoking habits, body mass index, use of herbal additives etc. significantly influence the outcome. Like epigenetic regulation and post-translational modifications, clinical factors (the

"clinome") may influence the microenvironment. Because the mechanisms of radiation response in tissues are predominantly mediated via reactive oxygen species (ROS) e.g., smoking can lower the chance of overall survival by up to 20% (5,6) and significantly increase the risk of side effects (7).

Future studies should not put an isolated focus on genetic predictors but investigate the complete picture including the genome, the epigenome, the transcriptome, the proteome, the metabolome and last but not least the clinome.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Peng Zhang (Department of Urology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China).

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.03.08). Wenz F serves as an unpaid editorial board member of Translational Cancer Research from Jun 2012 – May 2019.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Cite this article as: Wenz F. Clinomics—an underutilized resource? Transl Cancer Res 2016;5(2):206-207. doi: 10.21037/tcr.2016.03.08

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