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## Morphological aspects of recurrent prostate cancer

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*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

2015

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Rybalov, M. (2015). *Morphological aspects of recurrent prostate cancer: on molecular imaging for local salvage treatment*. [Thesis fully internal (DIV), University of Groningen]. [S.n.].

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# Chapter 11



**Conclusions and future perspectives.**

This thesis reports on the clinical value and potential of  $^{11}\text{C}$ -choline PET/CT in recurrent prostate cancer imaging. The results of the clinical studies showed that  $^{11}\text{C}$ -choline PET/CT has a high overall sensitivity in detection of a local recurrence in the prostate after EBRT on a patient based analysis. Our results suggest that  $^{11}\text{C}$ -choline PET/CT could be useful for the selection of patients with a biochemical recurrence after radiotherapy for salvage cryoablation of the prostate. By accurately identifying the patients with nodal or distant metastases,  $^{11}\text{C}$ -choline PET/CT impacts the therapeutic decision-making for those who would not benefit from local salvage treatment.

It was shown that total serum PSA and PSA velocity have significant effect on the detection rates of  $^{11}\text{C}$ -choline PET/CT in men with a biochemical recurrence after both radical prostatectomy and EBRT. Also a negative PET/CT correlates with a higher disease specific survival and a lower treatment rate in men with a biochemical recurrence after radical prostatectomy.

At the same time the accuracy of  $^{11}\text{C}$ -choline PET/CT for the intraprostatic tumor characterization and localization in patients with recurrent prostate cancer after EBRT is too low to use this imaging technique routinely for this indication. It means that  $^{11}\text{C}$ -choline PET/CT is not able to improve the localization of recurrent small focal prostate tumors. So it cannot contribute to the 'image-guided focal therapy' application in recurrent prostate cancer after EBRT.

Most tracers which are currently used for molecular imaging of the prostate cancer like choline in our studies are not (prostate) cancer-specific. The main goal now is the development of radiopharmaceuticals targeting tumour specific antigens and receptors. The adequacy of prostate-specific membrane antigen (PSMA), epithelial cell adhesion molecule (EpCAM), vascular endothelial growth factor (VEGF) and gastrin-releasing peptide receptor (GRPR) for targeted imaging is analyzed in this dissertation. The results suggest that PSMA, EpCAM and VEGF can be used for targeted imaging of locally recurrent prostate cancer based on their high tumour distinctiveness. PSMA showed the best characteristics for imaging of recurrent prostate cancer.

PSMA or glutamate carboxypeptidase II is an enzyme that in humans is encoded by the FOLH1 (folate hydrolase 1) gene. PSMA is strongly expressed in the human prostate, being a hundredfold greater than the expression in most other tissues. It is upregulated in expression in prostate cancer, with increase of 8- to 12-fold over the noncancerous prostate. PSMA is the target of an approved imaging agent for prostate cancer, capromabpentide, ProstaScint<sup>®</sup>. However, for routine use in clinical practice, the sensitivity of ProstaScint<sup>®</sup> is not high enough, because the antibody targets the intracellular epitope of PSMA, thereby probably targeting only damaged or necrotic/apoptotic cells [1]. Several second-generation antibodies and low-molecular-weight ligands for imaging and therapy are being developed,

but most studies are still in a preclinical phase [1].  $^{68}\text{Ga}$ -PSMA PET/CT already showed significantly higher detection rate of lesions in patients with recurrent prostate cancer compared to  $^{18}\text{F}$ -fluoromethylcholine PET/CT even at low PSA levels [2].

Recent developments in MRI have improved the diagnostic process of prostate cancer. Multiparametric MRI is considered a promising technique to improve the detection and staging of prostate cancer and its application has emerged during last few years. The integration of diffusion weighted imaging (DWI), dynamic contrast enhanced (DCE) imaging, and spectroscopic (functional) imaging in combination has allowed radiologists to better identify areas of benign and potentially malignant disease. There are ongoing efforts to combine MR methods in multiparametric formats to improve the performance characteristics of the detection and localization of prostate cancer. Future additions may include diffusion tensor imaging, multi-component diffusion analysis, MR elastography, or new spectroscopic methods, which are currently in pre-clinical investigation [3].

For molecular imaging PET/CT is now widely available. It provides both anatomical and metabolic information. PET/MRI is another hybrid imaging modality, which already received great attention not only in its emerging clinical applications but also in the preclinical field. Research studies are actively conducted at the moment to understand benefits of the new PET/MRI diagnostic method. First clear advantage is lower radiation exposure using PET/MRI. According to several studies PET/MRI may increase the accuracy using simultaneous acquisition of high-resolution morphologic and functional data. In the comparison study PET/MRI was able to accurately detect recurrent prostate cancer clarifying unclear findings by PET/CT [4]. Studies with appropriate radiotracers targeting the specific antigens are required to choose the most appropriate technique in the future.

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## ACKNOWLEDGEMENTS

I would like to thank everyone involved in my research project.

Special thanks for organizing this opportunity to International Offices of Pavlov First Medical University and University of Groningen, especially to Prof. Dr. Salman Al-Shukri, Dr. Sergei Borovets and Drs. R.J. van Groningen.

Thanks to Prof. Dr. Igle Jan de Jong for his kind supervision, encouragement and useful advices throughout all the years of the research.

Thanks to Prof. Dr. R.A.J.O. Dierckx for his kind assistance.

Thanks to Prof. Dr. J.M. Nijman for his guidance.

Thanks to Dr. Anton Breeuwsma for all his help in research and everything.

Thanks to Dr. Hildo Ananias for his help and friendly support.

Thanks to Drs. Hilde Hoving for her assistance in our immunohistochemistry research.

Thanks to all other researchers I met during all these years.

Thanks to my co-authors Prof. Dr. Jan Pruijm, Dr. Stefano Rosati, Dr. Henk van der Poel, Dr. Annemarie Leliveld.

Thanks to the Department of Urology in the University Medical Center Groningen.

Thanks to the International Office in the University Medical Center Groningen.

Thanks to Alice Tigchelaar for her assistance during the finishing and printing of the thesis.

Спасибо всем сотрудникам кафедры урологии ПСПбГМУ им. акад. И.П. Павлова.

Спасибо всем сотрудникам международного отдела ПСПбГМУ им. акад. И.П. Павлова.

Thanks to my parents and brother for their support.

Спасибо всем большое.

Dank u allen hartelijk.

## **CURRICULUM VITAE**

Maxim Rybalov was born in Leningrad, USSR on April 23, 1983. He attended the Second Saint-Petersburg Gymnasium and graduated in 2000. In the same year he started studying medicine at the Pavlov Saint Petersburg State Medical University and graduated in 2006 with the Diploma of Physician. He went through a one-year surgical internship at the Djanelidze Research Institute of Emergency Medicine, Saint Petersburg under supervision of Prof. Dr. A. Belyaev and received the Certificate of Surgery. In 2007 he went to study urology at the Department of Urology of the Pavlov Saint-Petersburg State Medical University under supervision of Prof. Dr. S. Al-Shukri. In 2009 he became a PhD student at the Department of Urology of University Medical Center Groningen, University of Groningen under supervision of Prof. Dr. I.J. de Jong Groningen, The Netherlands (studies in collaboration with the Pavlov State Medical University). In 2013 he received the Certificate of Urology at the First Pavlov Saint Petersburg State Medical University.

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