

University of Groningen

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 8



Summary.

Detection and staging of recurrent prostate cancer is still one of the important clinical problems in prostate cancer. A rise in PSA or biochemical recurrence (BCR) is the first sign of recurrent prostate cancer after curative treatment. Although PSA is the most sensitive tool for detection of the recurrence, it cannot distinguish between locoregional recurrences and the presence of distant metastases after treatment. At this time, there is not an imaging modality that can determine the exact localization of small volume prostate cancer. Studies are ongoing to identify novel diagnostic techniques to image prostate cancer. Molecular imaging is the main area of research on this aspect. Possible imaging technologies are functional MRI techniques (diffusion-weighted MRI (DWI), MR spectroscopy (MRS), dynamic contrast-enhanced MRI (DCE-MRI)) and positron emission tomography (PET). PET has already been identified as promising imaging technique for detecting prostate cancer recurrence after EBRT. Carbon-11-choline is one of the most commonly applied PET tracers for prostate cancer imaging. With a growing interest in focal treatment of recurrent prostate cancer by ablative treatments like high intensity focused ultrasound (HIFU) and cryoablation, patient selection could be improved if the site of recurrence and its extent could be visualized. Focal therapy can involve the local application of therapy to a specific area, and if done under real-time imaging, it then becomes 'image-guided focal therapy'.

In this thesis the potential role of ^{11}C -choline PET/CT for the intraprostatic tumor characterization and localization in recurrent prostate cancer after EBRT was explored. The effect of total PSA and PSA kinetics on the detection rates of ^{11}C -choline PET in recurrent prostate cancer after radical prostatectomy or external beam radiotherapy was evaluated. The correlation between ^{11}C -choline PET/CT, time to treatment and disease specific and overall survival in biochemically recurrent prostate cancer after radical prostatectomy was studied. Also we analyzed the clinical impact of ^{11}C -choline PET/CT in the selection of patients with biochemical recurrence after radiation therapy for salvage cryoablation of the prostate. Finally we investigated the expression of prostate-specific membrane antigen (PSMA), epithelial cell adhesion molecule (EpCAM), vascular endothelial growth factor (VEGF) and gastrin-releasing peptide receptor (GRPR) in locally recurrent prostate cancer after brachytherapy or external beam radiotherapy and analyzed their adequacy for targeted imaging. A variety of new PET tracers are under study for targeting specific antigens/receptors, such as gastrin releasing peptide receptor (GRPR), prostate-specific membrane antigen (PSMA), prostate stem cell antigen (PSCA), Knowledge about expression of the receptors in recurrent cancer could improve selection of one of these new tracers in recurrent prostate cancer in future.

Chapter 2 provides a review about the technologic aspects of different imaging techniques and the clinical results for intraprostatic tumor characterization. Conventional CT and FDG PET are not able to detect prostate cancer foci <5mm within the prostate. Based

on the preliminary studies, dynamic contrast-enhanced (DCE)-CT may be a useful tool in for localization of prostate tumors and perhaps more importantly, quantification of therapeutic response in prostate cancer. However validation work is required to define its accuracy and role in therapeutic paradigms such as focal therapies, particularly given the current accuracy of MRI. In the future, combining DCE-CT with CT or ^{11}C -choline PET/CT may be an alternative to MRI, offering a combination of quantitative parameters which may correlate to tumor prognosis as well as cancer localization for focal therapy.

Chapter 3 describes a study which focuses on the potential role of ^{11}C -choline PET for the intraprostatic tumor characterization and localization in patients with recurrent prostate cancer after external beam radiation therapy (EBRT). This retrospective study was conducted in 42 patients with histological proven prostate cancer treated by EBRT and showing a biochemical recurrence as defined by the ASTRO consensus criteria 1997. Forty-two patients with a local recurrence suggested by PET were included. The results of PET were compared with the results of histology and with clinical follow up. According to PET results: of the 42 patients, 15 (36%) had a focal recurrence, 27 (64%) showed a diffuse recurrence. The overall concordance of PET with histology concerning detection of recurrence was 76% (32 patients had positive PET results and positive biopsies). We confirmed the local recurrence as visualized by PET in 37/42 (88 %) patients using a composite reference with histology and clinical follow up after local salvage treatment. The concordance of the intraprostatic distribution of the tumor with PET with histology from transrectal prostate biopsies (median biopsies 7, range 4-12) was 47% (7/15) in unilateral cases and 41% (11/27) in bilateral cases. No significant differences were seen between the 2 groups in serum PSA at time of PET ($p=0.509$) and SUV ($p=0.739$) using Student's *t*-test. Our study shows that intraprostatic characterization of recurrent prostate cancer after EBRT with ^{11}C -choline PET is feasible at present but shows a moderate concordance with routine transrectal prostate biopsies. Therefore the use of this modality to select patients for a focal treatment is not recommended in the present scenario due to its low accuracy.

Several studies have shown PSA kinetics to be a good predictor of failure after treatment by either surgery or radiotherapy, as well as a predictor of prostate cancer-specific survival. In **Chapter 4** the effect of total PSA (tPSA) and PSA kinetics on the detection rates of ^{11}C -choline PET in recurrent prostate cancer after radical prostatectomy (RP) or EBRT was evaluated. 185 patients with biochemical recurrence after RP (PSA > 0.2 ng/ml) or after EBRT (ASTRO definition) were included and underwent an ^{11}C -choline PET (with CT fusion images) or PET/CT scan. Biopsy-proven histology, confirmative imaging (CT or bone scan) and/or clinical follow-up (PSA) were used as composite reference. ^{11}C -choline PET was positive in 124/185 cases (65%) (in 22/61 (36%) after RP, 102/124 (82%) after EBRT). In 79 patients a local recurrence was identified, and 45 patients showed locoregional

metastases on PET/CT. In 20 cases a proven false-negative PET scan was observed. Positive PET scans were confirmed by histology in 87/124 (70%) cases, by confirmatory imaging in 34/124 (28%) and by clinical follow-up after salvage treatment in 3 (2%) cases. The ROC analysis to detect a recurrence showed significant difference in area under the curve (AUC) of tPSA 0.721 ($p < 0.001$) and PSA velocity 0.730 ($p < 0.001$). PSA doubling time showed no significant difference with an AUC of 0.542 ($p = 0.354$). Detection rates are $< 50\%$ in tPSA < 2 ng/ml and/or PSA velocity < 1 ng/ml/year. This study shows total serum PSA and PSA velocity to have significant effect on the detection rates of ^{11}C -choline PET/CT in men with a BCR after RP or EBRT.

The effect of ^{11}C -choline PET/CT findings in relation to time to treatment, disease specific and overall survival in biochemically recurrent prostate cancer after radical prostatectomy is studied in **Chapter 5**. This prospective study was conducted in 64 patients who were in follow-up after RP for prostate cancer and had a biochemical recurrence i.e. two consequent serum PSA readings ≥ 0.2 after a nadir < 0.2 ng/ mL after RP. All patients underwent an ^{11}C -choline PET/CT scan. PET/CT data were correlated with clinical data, PSA kinetics and disease specific and overall survival. The 64 patients had median PSA of 1.4ng/mL. Median follow-up period of patients was 50 (6-124) months. Ten patients died during the course of follow-up of which 5 due to metastasized disease. No significant differences were seen in age, time to recurrence, total PSA at recurrence and PET/CT results. Patients with abnormal PET had higher PSA velocity (median 3.09 versus 10.17 ng/mL/year, $p=0.002$) and shorter PSA doubling time (median 4.83 vs 0.53 months, $p=0.016$). Median time to treatment was significantly lower in the PET/CT negative group. Age of patients at death from the whole group did not differ from the age of death in an age matched group. Disease specific survival was significantly higher in the PET/CT negative group ($p=0.05$). Our results showed that a negative PET/CT correlated with a higher disease specific survival and a lower treatment rate in men with a biochemical recurrence after radical prostatectomy. Overall survival of the total group was equal to the age matched cohort emphasizing the limited effect of a biochemical recurrent prostate cancer on overall survival. The clinical impact of ^{11}C -choline PET/CT in the selection of patients with biochemical recurrence after RT for salvage cryoablation of the prostate is analyzed in **Chapter 6**. 74 patients, who were being followed up after RT for histological proven prostate cancer (according to ASTRO-Phoenix) were included and underwent an ^{11}C -choline PET/CT scan. According to the PET/CT results, 40 (54%) patients had a local recurrence, 20 (27%) had regional/distant metastases and 14 (19%) had a negative scan. The positive PET findings were proved by histology from prostate biopsies and/or pelvic lymph node dissections in 63% of cases. Considering PET/CT results: 50/74 (68%) patients received cryoablation, for 24/74 (32%) treatment was changed (active surveillance or

androgen deprivation therapy). ^{11}C -choline PET/CT was decisive and led to therapy change in 32% of cases. Our results suggest that ^{11}C -choline PET/CT could be useful for the selection of patients with BCR after RT for salvage cryoablation of the prostate, identifying patients with nodal or distant metastases who would not benefit from local salvage treatment.

The expression of prostate-specific membrane antigen (PSMA), epithelial cell adhesion molecule (EpCAM), vascular endothelial growth factor (VEGF) and gastrin-releasing peptide receptor (GRPR) in locally recurrent prostate cancer after brachytherapy or external beam radiotherapy is investigated in **Chapter 7**. Also their adequacy for targeted imaging is analyzed as all these antigens are considered promising targets for cancer imaging. Prostate cancer specimens were collected of 17 patients who underwent salvage prostatectomy because of locally recurrent prostate cancer after brachytherapy (4 patients) or external beam radiotherapy (13 patients). Immunohistochemistry with commercially available antibodies was performed. Staining for PSMA was seen in 100% (17/17), EpCAM in 82.3% (14/17), VEGF in 82.3% (14/17) and GRPR in 100% (17/17) of prostate cancer specimens. Staining for PSMA, EpCAM and VEGF was seen in 0% (0/17) and for GRPR in 100% (17/17) of specimens' stromal compartments. In 11.8% (2/17) of cases GRPR staining intensity of prostate cancer was higher than that of stroma, while in the remaining 88.2% (15/17) of cases GRPR staining in cancer and stroma was equal. Our results suggest that PSMA, EpCAM and VEGF can be used as potential target for bioimaging of locally recurrent prostate cancer based on their high tumour distinctiveness.

