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## Morphological aspects of recurrent prostate cancer

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# Chapter 4



## **Impact of total PSA, PSA doubling time and PSA velocity on detection rates of <sup>11</sup>C-choline Positron Emission Tomography in recurrent prostate cancer.**

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## **ABSTRACT**

### *Purpose*

To evaluate the effect of total PSA (tPSA) and PSA kinetics on the detection rates of <sup>11</sup>C-choline PET in patients with biochemical recurrence (BCR) after radical prostatectomy (RP) or external beam radiotherapy (EBRT).

### *Methods*

We included 185 patients with BCR after RP (PSA > 0.2 ng/ml) or after EBRT (ASTRO definition). After injection of 400 MBq <sup>11</sup>C-choline i.v. a scan was made using the ECAT HR+ PET camera with CT fusion images or Siemens mCT PET/CT. Biopsy-proven histology, confirmative imaging (CT or bone scan) and/or clinical follow-up (PSA) were used as composite reference. Statistical analysis was performed using PASW Statistics 18.

### *Results*

<sup>11</sup>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.

### *Conclusions*

Total serum PSA and PSA velocity have significant effect on the detection rates of <sup>11</sup>C-choline PET/CT in men with a BCR after RP or EBRT.

## INTRODUCTION

Prostate cancer accounts for 25% (192,280) of all the newly diagnosed cancers in American men and is second (9%; 27,360) among the 10 leading cancer-related causes of death for men in the United States in 2009 [1].

Many patients diagnosed with localized prostate cancer are treated with radical prostatectomy (RP) or external beam radiation therapy (EBRT). Of the patients treated with RP, 15-46% experience recurrence of disease as detected by a rise in PSA [2], which is usually the first sign of recurrent prostate cancer after curative treatment.

Agarwal *et al.* [3] reported that 63% of men treated with radiation therapy for prostate cancer had an increasing PSA level at a mean follow-up of 38 months.

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 [4]. 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 [5-9]. For patients with biochemical recurrence (BCR) after curative treatment for localized prostate cancer, PSA doubling time might be useful to identify patients at high risk of dying from the disease, and subsequently to optimize their management [10].

<sup>11</sup>C-choline positron emission tomography (PET) has proven to be an accurate technique for re-staging after EBRT but clinically less accurate after RP [4, 11-14]. The threshold of PSA at the time of PET and PSA kinetics in post-RP patients with BCR have been suggested as predictive parameters for an abnormal scan and can be used for patient selection [8].

The aim of this study was to evaluate the effect of total PSA and PSA kinetics on the detection rates of <sup>11</sup>C-choline PET in recurrent prostate cancer after radical prostatectomy or external beam radiotherapy.

## MATERIALS AND METHODS

### *Patients*

This retrospective study was conducted in patients who were followed after RP or EBRT for histological proven prostate cancer. The patients after EBRT were eligible if they showed a BCR as defined by the ASTRO consensus criteria 1997 [15]. The post-RP patients with a BCR were included with a rising serum PSA >0.2 ng/ml. No adjuvant hormonal therapy was allowed within 1 year prior to <sup>11</sup>C-choline PET. All patients were informed and signed written consent forms prior to participation in the study and for the anonymous

publication of the data. The study was approved by the hospital's ethics committee and conducted according to the Declaration of Helsinki and subsequent revisions.

### *Histology*

Primary staging was performed using the TNM-classification of 1997. In patients with a BCR and a palpable/visible tumor, transrectal ultrasound (TRUS)-guided prostate biopsies were taken from the bladder neck region (after RP) or from the prostate (after EBRT). Histological diagnosis and determination of the Gleason sum were performed on hematoxylin- and eosin-stained sections.

### *<sup>11</sup>C-choline PET tracer synthesis and PET scan*

The <sup>11</sup>C-choline was produced using a cyclotron system by the method described by Hara [16] with an activity of >3,700 GBq/mmol and dissolved in 4 ml of sterile saline. The solution was isotonic, colorless and sterile, with a radiochemical purity of >95%. Prior to the PET study, the subjects were fasted overnight with the exception of water and their usual medication. The PET studies were initially performed using an ECAT Exact HR+ PET camera (Siemens/CTI, Knoxville, TN, USA). A transmission scan was performed over three bed positions (10 min per position), covering the pelvis and lower part of the abdomen, immediately followed by intravenous injection of 400 MBq <sup>11</sup>C-choline. 3D-mode data acquisition was started at 5 min after injection over the same area for 7 min per bed position. The prostatic bed was included in the first bed position. A low dose computed tomography (CT) scan was used for anatomical references, and PET/CT fusion images were reconstructed using the Leonardo post-processing software (Siemens Medical Solutions, Knoxville, TN, USA).

Attenuation-corrected images were made using an iterative reconstruction algorithm (ordered subset expectation maximization). From 2009 we have used a 64-slice mCT (PET/CT) camera (Siemens CTI), with 2-mm spatial resolution with an emission time of 3 min (approximately 8 bed positions) per bed position and a transmission CT scan for attenuation correction.

All scans and quantifications were obtained according to the guidelines for tumor PET of the European Association of Nuclear Medicine [17]. Scans were reconstructed with a Gaussian filter of 5 mm in full width at half maximum, and iterative reconstruction methods were used with 3 iterations and 24 subsets. PET images were assessed qualitatively and quantitatively by a nuclear medicine physician. When in the field of view, CT data were used to allocate PET-positive lesions to an anatomic substrate.

### *Evaluation of PET scan*

Two independent experienced PET physicians with over 100 scans evaluated per physician, blinded for the clinical data, analyzed the PET images. A local recurrence was defined as any focal increased uptake within the prostate contour. Regional lymph nodes and skeleton were evaluated using a four point scale (0 – no uptake, 1 – uptake at background level, 2 – marked uptake above background level and 3 – high uptake). Lesions with level 2 and 3 uptake were defined as abnormal and considered malignant. Patients were grouped according to the PET/CT fusion results as negative (no pathological uptake) or positive (abnormal uptake in prostate region, prostate, pelvic nodes or skeleton).

### *Reference test and further patient evaluation*

According to protocol, all follow-up patients undergo serum PSA measurements at six-month interval during 3 year, and then annual PSA determination. In patients with BCR, further evaluation was performed using digital rectal examination and TRUS-guided biopsies from the bladder neck region (after RP) or from the prostate (after EBRT). Lymph node metastases were confirmed by histology after *pelvic lymph node dissection* (PLND) or biopsy or by confirmatory imaging on the CT. Bone scans were used to confirm bone metastases on PET/CT. In addition, we used follow-up data, that is, response to local salvage therapy with PSA decline as composite reference.

### *Prostate specific antigen velocity and doubling times*

Serum PSA was determined using an automated Chemiluminescent Microparticle Immunoassay on an Architect platform (Abbott Diagnostics Division). The last 3 (half) yearly measurements prior to the PET/CT scan were used for the calculations of the PSA kinetics, covering 12–24 months in time. PSA velocity was calculated by the absolute increase of PSA level in ng/mL per year using first and last PSA according.

PSA doubling time was calculated by natural log of 2 (0.693) divided by the slope of the relationship between the log of PSA and time of PSA measurements [18].

Calculation was performed using the Memorial Sloan-Kettering Medical Center prostate cancer prediction tool (<http://www.mskcc.org/mskcc/html/10088.cfm>).

## Statistics

ROC analysis was performed using PASW Statistics 18. Differences in distribution of PSA and PSA kinetics between the PET/CT groups were analyzed using Mann-Whitney *U* and *t* test with  $p < 0.05$  considered significant.

## RESULTS

Patient characteristics are shown in Table 1.  $^{11}\text{C}$ -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 regional metastases on PET/CT (pelvic nodes, skeleton). The positive PET scans were confirmed by histology from prostate biopsies and/or pelvic lymph node dissections in 87/124 (70%), by confirmatory imaging (CT scan or bone scan) in 34/124 (28%) and by clinical follow-up after salvage treatment in 3 (2%) cases. For local recurrences, the sensitivity was 80%, specificity 65% and false negative rate 19%. For metastases the sensitivity was 95% and the false negative rate was 4%. No false positive scans were observed. Total PSA, PSA kinetics and detection rates of  $^{11}\text{C}$ -choline PET are summarized in Table 2. Both tPSA and PSA velocity were correlated with an increase in detection rate of  $^{11}\text{C}$ -choline PET. The ROC analysis to detect recurrence sites 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.

TABLE 1. Patient characteristics.

	(n=185)
Mean age (year)	69
Initial Mean PSA (ng/ml)	18,45
Initial Stage	
T1	35
T2	77
T3	70
T4	3
Initial Gleason sum	
$\leq 6$	68
7	96
8-10	21

TABLE 2. Total PSA, PSA DT and PSA velocity at time of PET and detection rates.

PSA (ng/ml)	Total	PET POS (local/metastases)	PET NEG	Detection rate (%)
0-1	25	6 (6/0)	19	24
1-2	15	5 (4/1)	10	33
2-3	16	12 (11/1)	4	75
3-4	18	14 (10/4)	4	78
4-5	15	11 (7/4)	4	73
5-10	50	37 (20/17)	13	74
10-20	32	26 (13/13)	6	81
> 20	14	13 (8/5)	1	93
PSADT (months)	Total	PET POS (local/metastases)	PET NEG	Detection rate (%)
0-3	14	11 (3/8)	3	79
3-6	35	24 (8/16)	11	69
6-9	33	23 (14/9)	10	70
9-12	31	19 (11/8)	12	61
12-24	47	32 (30/2)	15	68
> 24	25	15 (13/2)	10	60
PSA Velocity (ng/ml/year)	Total	PET POS (local/metastases)	PET NEG	Detection rate (%)
< 1	60	24 (22/2)	36	40
1-2	34	24 (19/5)	10	71
2-4	31	26 (15/11)	5	84
4-6	21	18 (12/6)	3	86
6-10	23	18 (8/10)	5	78
>10	16	14 (3/11)	2	88



## DISCUSSION

This study shows that tPSA and PSA kinetics have an effect on the detection rates of <sup>11</sup>C-choline PET in patients with BCR.

Our results on PSA kinetics in post-RP group are in line with the study from Castellucci *et al.* [8], who demonstrated a significant correlation between <sup>11</sup>C-choline PET detection rates and PSA kinetics in patients with BCR after RP. The authors showed that the detection rate of <sup>11</sup>C-choline PET/CT was significantly higher when PSA velocity was >1.1 ng/mL/year or PSADT was <3.4 months.

Recently, Giovacchini *et al.* [9] also demonstrated that PSA doubling time is an independent predictor of <sup>11</sup>C-choline PET/CT findings. In their study in patients with a BCR after RP, the <sup>11</sup>C-choline PET/CT was positive in 75 of 170 patients (44%). In the multivariate logistic regression analysis, PSA and PSA doubling time were significant ( $p < 0.05$ ) predictors of positive <sup>11</sup>C-choline PET/CT. For tPSA, the odds ratio (OR) was 1.43 (95% CI, 1.15-1.78), and for PSA doubling time, the OR was 1.12 (95% CI, 1.04-1.21). The difference in mean tPSA at the time of PET/CT could explain the fact that tPSA did have an effect on the detection of a local recurrence compared to our study. In our study the mean tPSA at the time of PET was 4.8 ng/ml, at which level detection rates did not improve further [14].

PSA doubling time was different between patients with pathological uptake in the prostatectomy bed and those with increased <sup>11</sup>C-choline uptake in distant sites. tPSA did not differentiate between local or regional recurrence (data not shown). In a study by Giovacchini, a PSA doubling time of 3-6 months correlated with a 61% likelihood of lesions on the <sup>11</sup>C-choline PET/CT [9]. This increases to 81% in patients with a PSA doubling time of <3 months. In the group of patients with a PSA doubling time of <3 months, no case of a local recurrence in the prostate was identified.

In a recent study by Breeuwsma [4], the authors demonstrated that PSA doubling time and PSA velocity were significantly different in patients with a negative scan versus local and distal recurrences. In this cohort of men with BCR after EBRT, a PSA doubling time of approximately 4 months showed a significant correlation with distant metastases identified on <sup>11</sup>C-choline PET.

Our analysis showed a clear correlation between both tPSA and PSA velocity and a positive scan. Our results differ from the study by Giovacchini *et al.* [9]. In their study the likelihood for a positive scan was increased in patients with a tPSA at the time of PET <2.4 ng/mL in combination with a PSA doubling time <3.4 months and/or a PSA velocity higher than 1 ng/ml/year, respectively. In patients with a tPSA at the time of PET/CT higher than 2.4 ng/ml, the authors could not demonstrate any additional effect of PSA kinetics. The authors

discuss that they did not include patients with a high risk for metastases in order to be able to detect any influence of PSA kinetics in the low PSA ranges. However, with a comparable mean tPSA at the time of PET/CT, their reported detection rate was substantially lower in the PSA < 2 ng/ml compared to other series in the literature. It is not clear whether selection of patients with low to intermediate risk of metastasis is a bias. However, a short PSA doubling time was correlated with an increased detection rate.

The interpretation of PSA doubling time and PSA velocity is complicated and limited by the large biological and inter-assay variability of PSA, and the availability of many methods for its calculation [10]. Even small deviations from the methods can change PSA doubling time for several months, which could lead to errors in patient management in newly diagnosed prostate cancer [10]. In our study we used the models, which have shown to have a high accuracy [19].

An issue that has not yet been solved is the noticeable difference in detection rates of <sup>11</sup>C-choline PET/CT in BCR after RP versus EBRT as reported in the literature so far. One hypothesis is that the tumor volume is the main cause. By definition, recurrent prostate cancer will be detected by a higher total PSA after EBRT compared to RP. The relationship between tumor volume and serum PSA levels were studied by Stamey *et al.* [20]. They found a significant correlation between PSA and volume with a correlation  $r = 0.70$ . A tumor volume of 1 ml was calculated to be responsible for 3.6 ng/ml serum PSA level. This could explain the differences in detection rates of <sup>11</sup>C-choline PET/CT in patients with a PSA <3 versus >3 ng/ml [14]. However, recent studies have questioned the correlation between PSA and volume in early prostate cancer patients treated with a radical prostatectomy [21]. No data are available on role of tumor volume in PSA values in recurrent prostate cancer.

Our study has limitations. We have used the PET/CT fusion for most patients which could have led to lower accuracy in the detection of the recurrent tumors when compared with our current PET/CT hybrid systems.

In preoperative lymph node staging using <sup>11</sup>C-choline PET in de novo prostate cancer, 12/15 (80%) patients with histologically proven lymph node metastases were PET positive [22]. In a recent study using <sup>11</sup>C-choline PET/CT system in recurrent prostate cancer, this seems to increase to 19/21 (90%) patients [23]. Another limitation of our study is the histopathological proof (obtained in 70% of the patients) of all local and regional/distant recurrences after either RP or EBRT. This common drawback has been addressed in the recent study by Giovacchini *et al.* [9], who used histology only in 11% of the cases and confirmatory imaging and clinical follow-up in 89%. As the authors stated, this could have caused over-interpretation and extensive use of confirmatory imaging. Using a per-patient analysis like in our study, this problem is less important when compared with a complex regional analysis in the pelvic region. We believe that only by using standardized histology

(biopsies plus routine PLND) a per-lesion analysis will provide additional information to the per-patient analysis. Importantly, a significant quantity of local recurrences can be missed using prostate or bladder neck biopsies failing to prove true positives. The use of a composite reference with clinical follow-up after local salvage treatment as surrogate end point will validate cases of local recurrences in due course.

In summary, tPSA and PSA kinetics demonstrated a significant effect on the detection rates of <sup>11</sup>C-choline in men with a BCR. Detection rates are <50% in cases with a tPSA <2 ng/ml and/or a PSA velocity <1 ng/ml/year. This could improve patient selection for PET/CT and reduce the number of false negative PET/CT scans.

## **CONCLUSIONS**

Total serum PSA and PSA velocity have significant effect on the detection rates of <sup>11</sup>C-choline PET/CT in men with a BCR after RP or EBRT.

## REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ (2009) Cancer statistics, 2009. *CA Cancer J Clin* 59:225-249.
2. Han M, Partin AW, Pound CR, Epstein JI, Walsh PC (2001) Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience *Urol Clin North Am* 28:555–565.
3. Agarwal PK, Sadetsky N, Konety BR, Resnick MI, Carroll PR (2008) Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE). Treatment failure after primary and salvage therapy for prostate cancer: likelihood, patterns of care, and outcomes. *Cancer* 112(2):307-314.
4. Breeuwsma AJ, Pruim J, Van Den Bergh AC et al (2010) Detection of local, regional and distant recurrence in patients with PSA relapse after external beam radiotherapy using (11)C-choline positron emission tomography. *Int J Radiat Oncol Biol Phys* 77:160-164.
5. Maffezzini M, Bossi A, Collette L (2007) Implications of prostate-specific antigen doubling time as indicator of failure after surgery or radiation therapy for prostate cancer. *Eur Urol* 51:605–613.
6. Palma D, Tyldesley S, Pickles T (2008) Prostate Cohort Outcomes Initiative. Pretreatment prostate-specific antigen velocity is associated with development of distant metastases and prostate cancer mortality in men treated with radiotherapy and androgen-deprivation therapy. *Cancer* 112:1941–1948.
7. Petit JH, Chen MH, Loffredo M, Sussman B, Renshaw AA, D'Amico AV (2006) Prostate-specific antigen recurrence and mortality after conventional dose radiation therapy in select men with low-risk prostate cancer. *Cancer* 107:2180–2185.
8. Castellucci P, Fuccio C, Nanni C et al (2009) Influence of trigger PSA and PSA kinetics on 11C-Choline PET/CT detection rate in patients with biochemical relapse after radical prostatectomy. *J Nucl Med* 50:1394-1400.
9. Giovacchini G, Picchio M, Scattoni V et al (2010) PSA doubling time for prediction of [(11)C]choline PET/CT findings in prostate cancer patients with biochemical failure after radical prostatectomy. *Eur J Nucl Med Mol Imaging* 37:1106-1116.
10. Fitzpatrick JM, Banu E, Oudard S (2009) Prostate-specific antigen kinetics in localized and advanced prostate cancer. *BJU Int* 103:578-587.
11. Picchio M, Messa C, Landoni C et al (2003) Value of 11C choline-positron emission tomography for restaging prostate cancer: a comparison with 18F fluorodeoxyglucose-positron emission tomography. *J Urol* 169:1337–1340.

12. de Jong IJ, Pruijm J, Elsinga PH, Vaalburg W, Mensink HJ (2003) 11C-choline positron emission tomography for the evaluation after treatment of localized prostate cancer. *Eur Urol* 44:32–38.
13. Rinnab L, Mottaghy FM, Blumstein NM et al (2007) Evaluation of [11C]-choline positron-emission/computed tomography in patients with increasing prostate-specific antigen levels after primary treatment for prostate cancer. *BJU Int* 100:786–793.
14. Krause BJ, Souvatzoglou M, Tuncel M et al (2008) The detection rate of [(11)C]choline-PET/CT depends on the serum PSA-value in patients with biochemical recurrence of prostate cancer. *Eur J Nucl Med Mol Imaging* 35:18–23.
15. Consensus statement (1997) Guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *Int J Radiat Oncol Biol Phys* 37:1035-1041.
16. Hara T (2002) 11C-choline and 2-deoxy-2-[18F]fluoro-D-glucose in tumor imaging with positron emission tomography. *Mol Imaging Biol* 4:267-273.
17. Boellaard R, O’Doherty MJ, Weber WA et al (2010) FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging—version 1.0. *Eur J Nucl Med Mol Imaging* 37:181–200.
18. Schmid HP, McNeal JE, Stamey TA (1993) Observations on the doubling time of prostate cancer. The use of serial prostate-specific antigen in patients with untreated disease as a measure of increasing cancer volume. *Cancer* 71:2031-2040.
19. Connolly D, Black A, Murray LJ, Napolitano G, Gavin A, Keane PF (2007) Methods of calculating prostate-specific antigen velocity. *Eur Urol* 52:1044– 1051.
20. Stamey TA, Kabalin JN, McNeal JE et al (1989) Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. II. Radical prostatectomy treated patients. *J Urol* 141:1076-1083.
21. Stamey TA, Johnstone IM, McNeal JE, Lu AY, Yemoto CM (2002) Preoperative serum prostate specific antigen levels between 2 and 22 ng./ml. correlate poorly with post-radical prostatectomy cancer morphology: prostate specific antigen cure rates appear constant between 2 and 9 ng./ml. *J Urol* 167:103-111.
22. de Jong IJ, Pruijm J, Elsinga PH, Vaalburg W, Mensink HJ (2003) Preoperative staging of pelvic lymph nodes in prostate cancer by 11C-choline PET. *J Nucl Med* 44:331-335.
23. Scattoni V, Picchio M, Suardi N et al (2007) Detection of lymph-node metastases with integrated [11C]choline PET/CT in patients with PSA failure after radical retropublic prostatectomy: results confirmed by open pelvic-retroperitoneal lymphadenectomy. *Eur Urol* 52:423-429.