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Morphological aspects of recurrent prostate cancer

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Chapter 5



Correlation of ^{11}C -choline PET/CT with time to treatment and disease-specific survival in men with recurrent prostate cancer after radical prostatectomy.

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ABSTRACT

Aim

Radiotherapy following radical prostatectomy should be considered in men with high risk features who have a life expectancy of more than 10 years. So far no effect on prostate cancer specific survival has been proven by 3 randomized controlled trials (RCTs) on adjuvant radiotherapy. At present the optimal timing of radiotherapy is not defined. Identifying the site of recurrence is difficult at low PSA levels. ¹¹C-choline PET/CT studies in biochemical recurrent prostate cancer after prostatectomy show a higher frequency of (false) negative cases compared to restaging after EBRT. It is uncertain if this reflects low volume of disease and/or low grade as biopsies fail to prove recurrent cancer in 50% of cases. We followed the clinical course of men with recurrent prostate cancer after radical prostatectomy and investigated treatment and survival. PET/CT data were correlated with clinical data, PSA kinetics and disease specific and overall survival. We also studied relative survival comparing an age matched group from the Central Dutch Statistical Office (CBS).

Methods

64 patients underwent ¹¹C-choline PET/CT on PSA relapse. All patients were initially treated with radical prostatectomy and reached PSA nadir of <0.1ng/mL. Recurrent disease was defined as PSA increase <0.2ng/mL after nadir. Patients were either treated with watchful waiting, salvage radiotherapy and/ or androgen deprivation therapy based on individual assessments by the treating urologists. Statistic: Chi-square, log-rank and Mann-Whitney-U tests were used to compare the ¹¹C-choline PET/CT groups.

Results

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 PSAvel (median 3.09 ng/mL/yr versus 10.17, p= 0.002) and shorter PSADT (med 4.83 mo vs 0.53, 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).

Conclusions

¹¹C-choline PET/CT 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 optimum timing (adjuvant or early salvage) must be answered in running trials before adjuvant RT is used as standard of care.

INTRODUCTION

Prostate cancer accounts for 25% (192280) of all the newly diagnosed cancers in American men and is second (9%; 27360) among the 10 leading cancer-related causes of death for men in the United States in 2008 (1). A rise in PSA or biochemical recurrence (BCR) is the first sign of recurrent prostate cancer after curative treatment. 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% to 46% experience recurrence of disease as detected by a rise in PSA, which is usually the first sign of recurrent prostate cancer after curative treatment (2).

The time-interval between treatment and BCR as well as the PSA doubling time are used as an indicator for a local or a distant recurrence (3). Definitions of recurrent disease are unequivocal and widely accepted. After radical prostatectomy BCR is defined as two consecutive rises above a nadir of 0.2ng/mL. Conventional imaging modalities are limited in their ability to localize the site of recurrence with a high accuracy. Reports on CT and MRI (with or without an endorectal coil) show widely differing results in showing presence of local and regional or distant metastases (4). PSA kinetics might be used to predict the outcome in both localized and advanced prostate cancer. Some groups have shown that the pretreatment PSA velocity can predict high-grade cancer, biochemical relapse (BCR) and survival after RP and EBRT. For patients with 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 (5). Although transrectal ultrasound and prostate biopsies can identify local recurrence after radical prostatectomy, this will not provide enough information for clinical decision making with respect to salvage EBRT. To correctly select patients for a local therapy, adequate re-staging is of paramount importance. ¹¹C-choline and ¹⁸F-choline positron emission tomography (PET) has proven to be an accurate technique for re-staging after EBRT but clinically less accurate after RP (6-10). The threshold of PSA at time of PET and PSA kinetics in patients with BCR after RP

have been suggested as predictive parameters for an abnormal scan and can be used for patient selection [8]. In general, at BCR residual tumor volume after prostatectomy is low. Men with poorly differentiated cancer, non-organ-confined disease, and positive surgical margins are at the highest risk. Currently salvage radiotherapy is used to treat local recurrence on BCR without evidence for metastases. However, it is unclear if better clinical outcomes will be achieved administering adjuvant RT to all patients at increased risk for recurrent PCa who have an undetectable postoperative PSA level compared to close observation and timely salvage RT at the earliest indications of BCR (11). There have been 3 randomized clinical trials published so far on adjuvant RT after radical prostatectomy which are the basis for a recent Cochrane review (12). The review showed an improved overall survival and reduced rate of distant metastases in one trial only with a follow up of 12.5 years. No effect on prostate cancer specific survival was reported. At 5 and 10 years adjuvant RT did improve local control and did reduce the risk of biochemical failure. However this reduction of biochemical failure is not a clinical endpoint. This is underscored by the long lead time from a biochemical recurrence after radical prostatectomy to the development of clinical symptoms which is long and approximately 8-13 years (13-15). One of the questions which remained unanswered in the 3 trials is the timing of the radiotherapy. As trials designs were different and not all men in the control arm were treated with a planned salvage, the optimal timing is unclear. To answer the question on timing, 3 randomized trials RADICALS, NCT00667069 and RAVES are ongoing. In these trials adjuvant versus planned salvage RT are studied in combinations with additional ADT schemes (16).

At low serum PSA levels imaging and locating the site of recurrent prostate cancer can be difficult (17). Because digital rectal examinations (DRE) have very low accuracy transrectal ultrasound is often employed. Sensitivity of traditional grey-scale transrectal (TR) sonography is high (95 %) in the detection of small tumours, but specificity is poor (18,19). Non-invasive imaging in men who have undergone radical prostatectomy and have rising PSA levels is therefore needed to determine the presence of local recurrence or systemic disease, as this could affect treatment choices. We studied the effect of ¹¹C-choline PET/CT findings in relation to time to treatment, disease specific and overall survival in biochemically recurrent prostate cancer after radical prostatectomy.

MATERIALS AND METHODS

Patients

This prospective study was conducted in 64 patients who were in follow-up after RP for prostate cancer. All 64 patients 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 serum PSA determination and digital rectal examination. All patients also underwent an ^{11}C -choline PET. No patients had received adjuvant (hormonal) therapy at time of ^{11}C -choline PET.

Histology

Primary staging was done using the TNM-classification of 1997. In patients with biochemical recurrence and if palpable/ visible, finger or TRUS-guided biopsies were taken from the prostatic fossa. Primary histological diagnosis and determination of the Gleason sum were performed on haematoxylin and eosin-stained sections.

^{11}C -choline tracer synthesis and scan

^{11}C -choline was produced using a cyclotron system by the method described by Hara (12). ^{11}C -choline was produced with a specific activity of $>3,700$ GBq/mmol and dissolved in 4 ml of sterile saline. The solution was isotonic, colourless 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 performed using an ECAT Exact HR+ PET camera (Siemens/CTI, Knoxville, TN, USA). A transmission scan was performed over 3-5 bed positions (10 min per position), covering the pelvis and lower part of the abdomen, immediately followed by an intravenous injection of 400 MBq ^{11}C -choline. 3D-mode data acquisition was started at 5 min after injection over the same area (in reverse order) for 7 min per bed position. The prostate was included in the first bed position. Using rigid software fusion on the Leonardo workstation PET and CT images could be overlain.

Image reconstruction and data analysis

3D-attenuation-corrected images were obtained using an iterative reconstruction algorithm (ordered subset expectation maximisation). PET images were analysed by an independent experienced nuclear physician, who was blinded for the clinical data. The location of each lesion was marked on case record forms and qualitatively scored as 0 (no uptake), 1 (benign uptake, just above background), 2 (uncertain benign, clearly above background) or 3 (probably malignant uptake), 4 (malignant uptake).

Further patient evaluation

All patients underwent serum PSA assessment every 6-12 months. In patients with a biochemical recurrence evaluation was done using DRE and/or TRUS with or without

biopsies. CT, MRI or bone scan were performed only on clinical indication using current European guidelines. Patients were defined as having recurrent disease in case of biopsy-proven histology from the site of suspicion, clinical indication (i.e. significant serum PSA rise after nadir or significant PSA doubling time or velocity), and/ or positive findings with other imaging modalities, which were used as a composite reference, as well as response to local salvage therapy expressed through PSA decline. We followed the clinical course of men with recurrent prostate cancer after radical prostatectomy and investigated additional hormonal treatment and disease specific survival. PET/CT data were correlated with clinical data, PSA kinetics and disease specific and overall survival. We also studied relative survival comparing an age matched group from the Central Dutch Statistical Office (CBS).

Prostate specific antigen, velocity and doubling times

Serum PSA was determined using an automated Chemiluminescent Microparticle Immunoassay on an Architect platform (Abbott Diagnostics Division). PSA doubling times and velocities were calculated using the Memorial Sloan-Kettering Medical Center prostate cancer prediction tool (<http://www.mskcc.org/mskcc/html/10088.cfm>).

Statistics

The PSA and PSA derived kinetics were compared with PET results (Kruskal-Wallis test, $p < 0.05$ considered significant, Chi-square, log-rank and Mann-Whitney-U tests with $p < 0.05$ considered significant). Cox single and multiple regression analysis was performed to study different factors in treatment free survival.

RESULTS

Sixty-four patients were included. Median PSA of 1.4ng/mL. Median follow-up period of patients was 50 (6-124) months. Scan results are presented in Table I.

Ten patients died during the course of follow-up of which 5 due to metastasized prostate cancer. Age of patients at death from the whole group did not differ from the age of death in an age matched group.

A total of 23 of the 64 patients with a biochemical recurrence (median PSA 2.2 ng/ mL; mean PSA 7.4), proved true positive for a local recurrence and/ or loco-regional and/ or distant metastases on ^{11}C -choline PET (sensitivity 36%).

Twelve of these patients had a local recurrence only, as defined by uptake of ^{11}C -choline in the prostatic bed only. In 8 of these patients, biopsies of the prostatic bed were performed. In only 2 of these patients was prostate cancer proven. Of the 12 patients with

local recurrence only on ¹¹C-choline PET 9 underwent EBRT and all had a serum PSA drop <0.3 ng/mL. In 2 cases watchful waiting was applied because of low PSA (<0.8ng/mL). In the remaining patient hormonal therapy was given on the basis of patients' inability to withstand curative treatment schedule.

Table I. *Clinical parameters of patients with biochemical recurrence and scan results.*

	Scan results		
	Negative (n= 41)	Local recurrence (n= 12)	Regional/ distant metastases (bone) (n= 11)
Mean age (y)	67	65	65
Mean initial serum PSA (ng/ml)	15.1	14.2	10.0
T stage			
T2	19	6	7
T3	20	6	4
T4	2	N/A	N/A
Gleason sum			
≤6	16	7	5
7	23	5	6
8-10	2	N/A	N/A

The other 11 patients showed uptake of ¹¹C-choline outside the prostatic fossa only. In 6 of these 11, prostatic bed biopsies were taken, which were all positive for local recurrence. Consequently, ¹¹C-choline PET yielded 6 false negative scans in the prostatic fossa. In 4 of the 11 patients, histological verification of lymph node metastases was obtained, through

pelvic lymph node dissection. In 3 of patients with metastasised disease, on ¹¹C-choline PET also showed bone metastases. These were confirmed by bone scans in all cases.

In the other 41 patients with a biochemical recurrence (median PSA 1.4 ng/ mL; mean PSA 3.1 at recurrence), ¹¹C-choline PET showed no uptake. Twenty-six of these patients received subsequent treatment despite the negative PET findings. In the 22 patients of these 26 ¹¹C-choline PET scans, who underwent radiotherapy on the prostatic bed 17 had serum PSA drop < 0.1 ng/ mL after radiotherapy (average follow-up 70 months); 4 patients had PSA < 2.0 ng/ mL (average follow-up 48 months); and one was lost to follow-up. Four patients were treated with hormonal treatment. In 15/41 patients deferred treatment was decided upon based on low serum PSA values. Overall positive and negative predictive values and accuracy of ¹¹C-choline PET are 1.0, 0.14 and 0.32 respectively. The factors significant in treatment free survival are shown in Table II.

Table II. *Cox-regression Analysis Treatment Free Survival.*

Univariate	HR (95%CI)	p-value
Age at PET	1.00 (0.95;1.04)	0.882
PSA at BCR	1.76 (0.92;3.39)	0.089
PSADT(median)	0.48 (0.25;0.94)	0.031
PSAV(median)	1.84 (0.94;3.60)	0.076
Gleason sum	0.80 (0.44;1.46)	0.471
PET (negative)	2.80 (1.40;5.59)	0.004
Multivariate		
PET (negative)	2.80 (1.40;5.59)	<0.05

Using the PSA subgroups PSA <1 ng/ mL, 1-3 ng/ mL and > 3 ng/ mL the sensitivity of detection of any recurrent tumour is shown in table III.

Table III. PET/CT scan results by PSA group.

	Patients	Negative scan	Local recurrence	Metastases	Sensitivity
<1	n= 24	18	6	0	25%
1-3	n= 20	13	6	1	35%
>3	n= 20	10	0	10	50%

Figure 1 shows therapy free survival in ¹¹C-choline PET/CT negative versus positive cases. Further, figure 2 shows mortality age at death (2A) and relative mortality (2B).

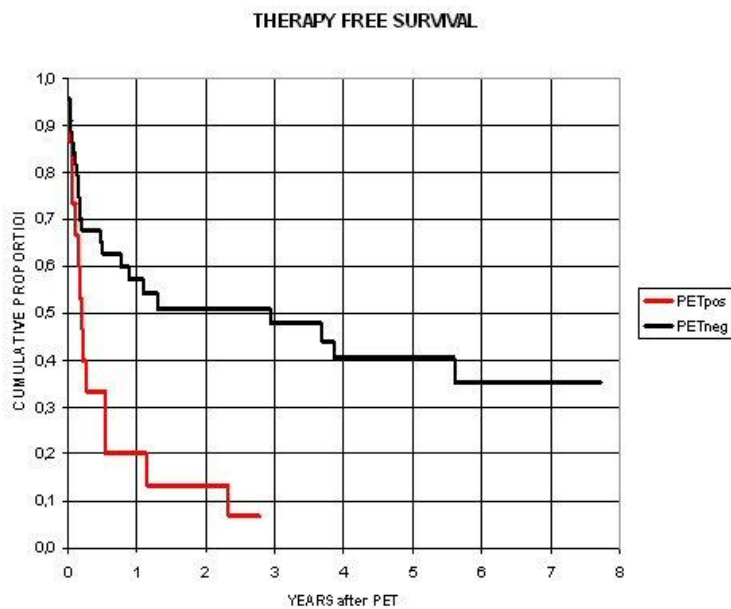


Figure 1. Treatment free survival in ¹¹C choline PET/CT negative versus positive cases

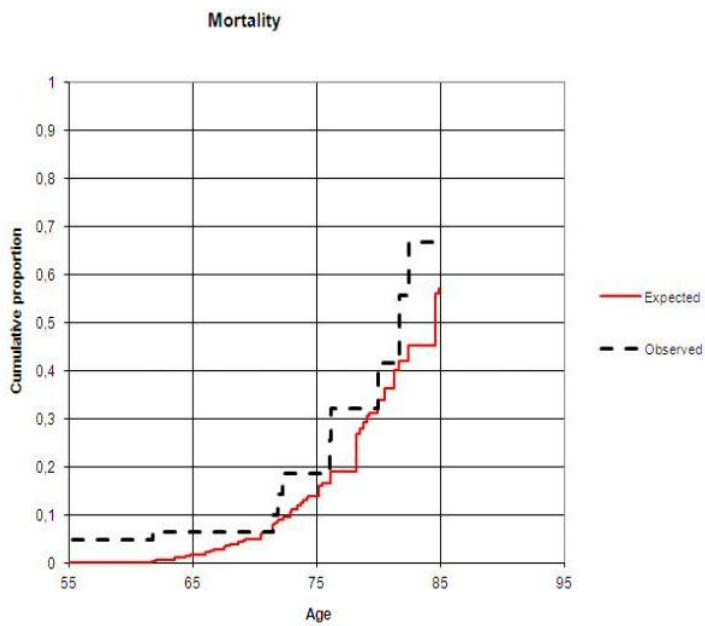
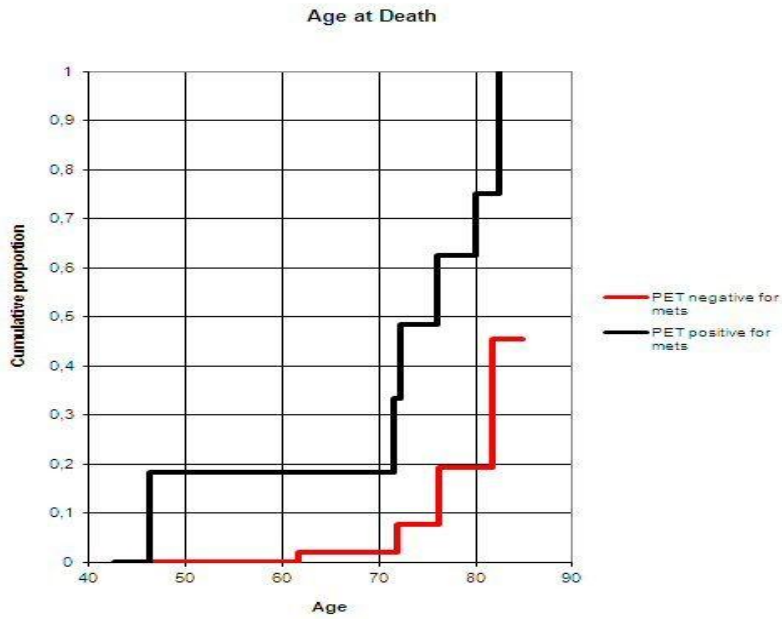


Figure 2. Mortality age at death (A) and relative mortality (B). Observed 6; Expected 4,73 Standardized Mortality Ratio 1,26 (95%CI 0,26 - 2,06) χ^2 0,12 (p-value = 0,7).

Six were observed 6 whereas 4,73 were expected which leads to a standardized mortality ratio 1,26 (95%CI 0,26 - 2,06) Chi-square 0,12 (p-value = 0,7).

DISCUSSION

To assess candidates for salvage treatment it is necessary to determine the extent and the location of prostate cancer. For patients to successfully benefit from local salvage radiotherapy after RP the maximum serum PSA of 0.5 to 1.0 ng/mL is currently used (20). This study in patients with recurrent prostate cancer after RP shows that ^{11}C -choline PET is not an accurate molecular imaging technique to localise the site of recurrent disease. In this group of 64 patients with a biochemical recurrent prostate cancer after RP only 23 showed abnormal uptake on ^{11}C -choline PET scan.

Our results are in concordance with the results obtained by several authors (7,21-24). Earlier studies, however, have incorporated different retrospective cohorts of patients using heterogeneous patient groups that have undergone different treatment modalities (i.e. prostatectomy, radiotherapy and/ or hormonal therapy). We feel this factor will have influenced the overall reported accuracy. Especially, on BCR after radical prostatectomy the accuracy of ^{11}C -choline PET is reported to be low by several authors (21,25). Also, inclusion criteria are different between studies that could be an explanation for the high accuracy of studies that included a high number of patients with palpable and/ or visible lesions. This study aimed to recruit patients uniformly and prospectively according to preset accrual. The results in this study must be seen in the light of the low PSA levels and the definition of recurrence. Especially in low PSA levels the PET detection rates seem to drop from almost 80% in PSA levels ≥ 3 ng/ mL to 36% in PSA < 1.0 ng/ mL. We report a detection rate of 25% in our study in the < 1.0 PSA group. This corroborates earlier reports (21). Although retrospective studies have identified PSA doubling time as a strong predictor for progression in patients failing initial local treatment, the need for validation of these cut off points for PSA doubling time is clear (26). Our preliminary results on PSA and PSA kinetics in the context of PET imaging should therefore be interpreted with care and restriction. Patients without recurrent prostate cancer showed no significant uptake of ^{11}C -choline, the 41 patients with a false negative PET scan do need special consideration. One explanation for the false negative cases could be that the volume of recurrent disease after RP, shown through its low serum PSA, is limited and below the detection range of PET (± 4 -5mm). Furthermore, it is plausible that tumour volume does influence ^{11}C -choline uptake quantitatively and therefore may affect detectability on PET. Slow PSA rise may also be caused by lower rates of proliferation and progression of prostate cancer tissue. However, proliferation seems to be independent of ^{11}C -choline uptake as expressed through standardised uptake values (27). Further, it seems reasonable to assume that PET/CT would be more accurate in identifying lymph node metastases. Physiological uptake in the intestinal tract can complicate detection of pelvic lymph nodes. Morphological orientation in the pelvic area would also be more

accurate. One study using ^{11}C -choline PET in staging de novo prostate cancer showed that 12/15 patients with histologically proven lymph node metastases were PET positive (28). When PET/CT was used, this value increased to 19/21 patients (29).

A limitation in this study is that histological proof of local and regional/ distant recurrence after RP was not obtained, although a significant number of local recurrences can be missed on biopsy. However, lymph node staging was performed successfully in one study and it was already shown that choline is taken up by these metastases in recurrent prostate cancer (29). Another limitation is that we used software fused PET with CT for most patients. PET/CT integrated systems seems to have higher detection rates than PET alone. It remains to be determined if ^{11}C -choline PET/CT imaging can play a role in the selection of patients for adjuvant or salvage therapy after RP. Current trigger for salvage therapy in all studies is serum PSA. The rationale for this is that low serum PSA values mostly reflects recurrence at local site and less so at pelvic lymph nodes or distant sites. Especially, for curative (salvage) treatment to be effective the local recurrence alone is important. Radiotherapy following radical prostatectomy in men with high risk features should be considered for men who have a life expectancy of more than 10 years. The optimum timing (adjuvant or early salvage) is unknown (12).

CONCLUSIONS

Radiotherapy following radical prostatectomy should be considered in men with high risk features who have a life expectancy of more than 10 years. Bioimaging using ^{11}C -choline PET/CT 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 optimum timing (adjuvant or early salvage) must be answered in running trials before adjuvant RT is used as standard of care.

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