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## Morphological aspects of recurrent prostate cancer

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# Chapter 6



## **Clinical impact of $^{11}\text{C}$ -choline PET/CT in selection of patients for salvage cryoablation in recurrent prostate cancer.**

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## **ABSTRACT**

<sup>11</sup>C-choline PET/CT has proven to be a sensitive technique for re-staging after radiation therapy (RT). The aim of this study was to analyze the clinical impact of <sup>11</sup>C-choline PET/CT in the selection of patients with biochemical recurrence (BCR) after RT for salvage cryoablation of the prostate.

### *Methods*

This prospective study was conducted between November 2006 and February 2012 on patients considered as candidates for salvage cryoablation. 74 patients, mean age 69.2 years, median – 70.3 years (range 49-79), who were being followed up after RT for histological proven prostate cancer (according to ASTRO-Phoenix) were included. Until 2009 we used PET/CT fusion, but from 2009 all patients were examined with an integrated PET/CT system. After receiving 400 MBq <sup>11</sup>C-choline intravenously, a whole body scan was made. As reference we used biopsy-proven histology from site of suspicion, confirmative imaging modalities (bonescan, CT) or clinical follow-up. PSA doubling time and velocity was calculated.

### *Results*

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).

### *Conclusion*

<sup>11</sup>C-choline PET/CT could be useful for the selection of patients with BCR after RT for salvage cryoablation of the prostate. <sup>11</sup>C-choline PET/CT was decisive and led to therapy change in 32% of cases.

## INTRODUCTION

Biochemical recurrence (BCR) after radiation therapy (RT) is not uncommon incident (1,2). Several studies reported that 30-50% of men treated with RT for localized prostate cancer had an increasing PSA level at a mean follow-up of 5 years (3,4).

Choosing an adequate salvage treatment for the patients with BCR should be the next step, but it depends on localization of the recurrence: is it local or distant (lymph nodes, bone). Some patients with the local recurrence could be candidates for local salvage treatment like high intensity focused ultrasound (HIFU) or cryoablation and may avoid androgen deprivation treatment (ADT). Thorough diagnostics are needed for the selection of such patients.

Prostate-specific antigen (PSA) is the most sensitive tool for detection of the recurrence, but it cannot distinguish between local-regional recurrences and the presence of distant metastases after treatment (5). During the last few years, several studies have shown PSA velocity and PSA doubling time to be good predictors of failure after treatment by either surgery or radiotherapy, as well as predictors of prostate cancer-specific survival (6-10). PSA kinetics might be used to predict the outcome in both localized and advanced prostate cancer. However, the best way of using PSA kinetics still has to be identified and the research is in progress.

Computed tomography (CT) and magnetic resonance imaging (MRI) are not sensitive in the detection of a local recurrence but can be used for the detection of lymph node metastases with a sensitivity of 30-80% (11).

<sup>11</sup>C-choline positron emission tomography (PET) has already proven to be a sensitive technique for re-staging after external beam radiotherapy (EBRT) (12-15). Combined PET/CT further improved clinical accuracy by fusion of functional and morphological diagnostic imaging (16,17).

The aim of this study was to analyze the clinical impact of <sup>11</sup>C-choline PET/CT in the selection for salvage cryoablation of the prostate in patients with BCR after RT.

## MATERIALS AND METHODS

### *Patients*

This prospective study was conducted between November 2006 and February 2012 in patients considered as candidates for salvage cryoablation. A total of 74 patients, who were being followed up after EBRT or brachytherapy for histological proven prostate cancer were included. Patients were eligible, if they showed a BCR as defined by the ASTRO Phoenix consensus conference (18). No adjuvant hormonal therapy was allowed within 1 year prior to

$^{11}\text{C}$ -choline PET/CT. 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.

### *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 prostate. Histological diagnosis and determination of the Gleason sum were performed on haematoxylin and eosin-stained sections.

### *$^{11}\text{C}$ -choline PET tracer synthesis and PET scan*

The  $^{11}\text{C}$ -choline was produced using a cyclotron system by the method described by Hara (19) 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 in combination with a low dose CT scan for anatomical references. PET/CT fusion images were reconstructed using the Leonardo post processing software (Siemens Medical Solutions, 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  $^{11}\text{C}$ -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.

Since 2009 a whole body PET/CT scan using the integrated Biograph mCT system was performed. A low dose CT scan was used for transmission scanning as well as for anatomical references, followed by intravenous injection of 400 MBq  $^{11}\text{C}$ -choline. 3D-mode data acquisition was started at 5 min after injection (Siemens/CTI, Knoxville, TN, USA).

### *Evaluation of PET scan*

Attenuation-corrected images were made using an iterative reconstruction algorithm (ordered subset expectation maximization, OSEM). 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 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 (half-) yearly serum PSA determination. In patients with BCR further evaluation was performed using digital rectal examination and TRUS guided prostate biopsies. 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 i.e. 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. 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 (20). Calculation was performed using the Memorial Sloan-Kettering Medical Center prostate cancer prediction tool (<http://www.mskcc.org/mskcc/html/10088.cfm>).

#### *Statistics*

Descriptive statistics were performed using SPSS-19 software package. Differences between groups were compared using ANOVA with p less than 0.05 considered significant.

## **RESULTS**

The patient characteristics are presented in table 1. Figure 1 shows the complete breakdown of the reference test. 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 scans were confirmed by histology from prostate biopsies and/or pelvic lymph node dissections in 38/60 (63%) of the cases, by confirmatory imaging (CT scan or bone scan) in 14/60 (23%) and by clinical follow up after salvage treatment in 8/60 (14%) cases. There were 13 false negative cases. No false positive scans were observed.

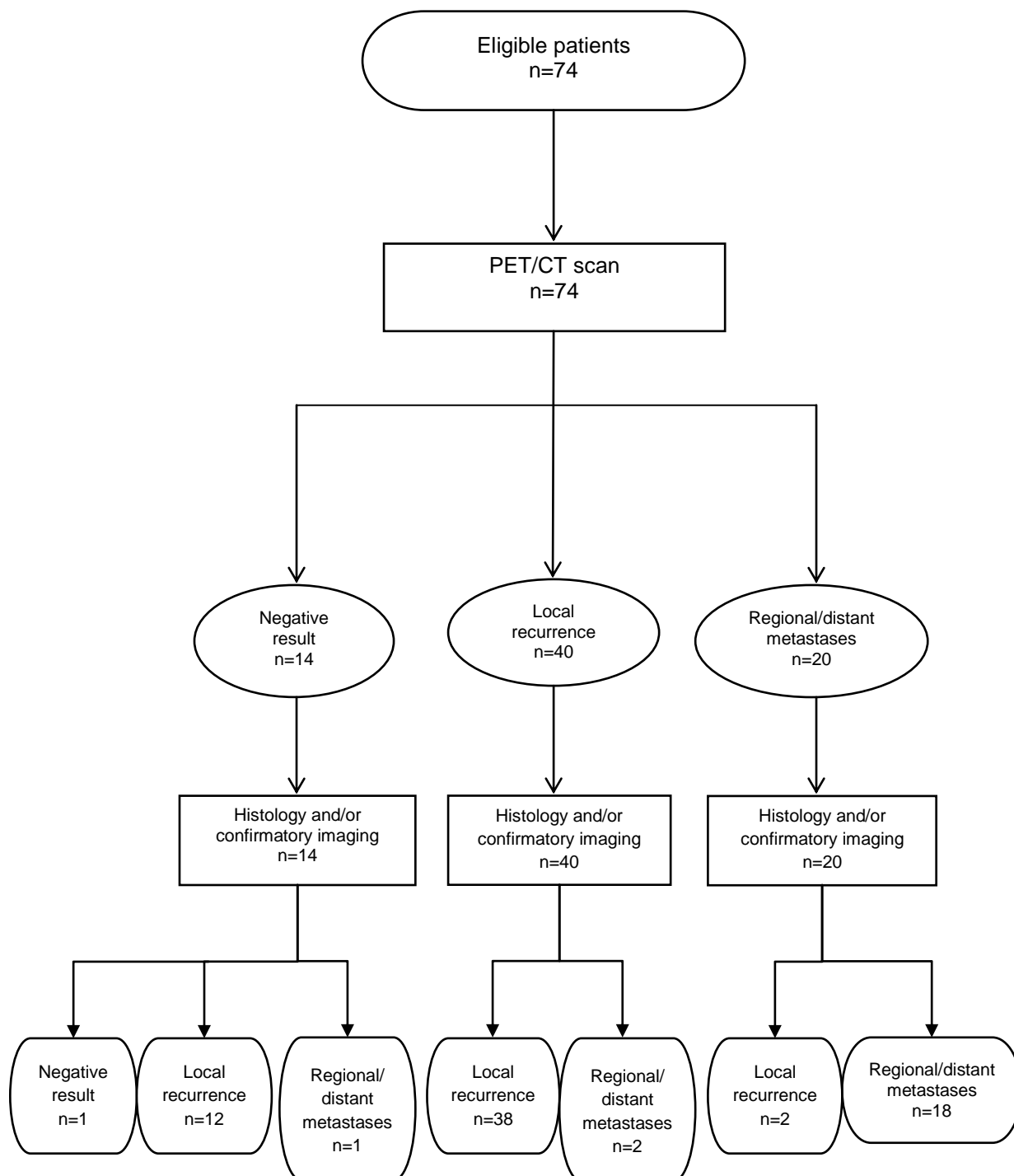
The results of PET/CT, PSA distribution at PET and salvage treatment is shown in table 2. Cryoablation was performed in 50/74 (68%) patients only. In 24/74 (32%) patients the decision for salvage cryoablation was abandoned. Treatment was changed to active surveillance or ADT based on the results of the PET/CT scans in combination with histology and/or confirmatory imaging. The comparison of the groups with different outcome shown by <sup>11</sup>C-choline PET/CT using ANOVA is presented in table 3.

TABLE 1. Patient characteristics (Number of patients = 74)

	<b>Median (range)</b>		
Age at PET (years)	70.3 (49-79)		
Initial PSA (ng/ml)	13.2 (1.8-58)		
PSA at PET (ng/ml)	6.1 (1.7-17.9)		
Radiation dose (Gy)	70 (60-78)		
Initial stage	T1	T2	T3
	16	30	28
Gleason score	4-6	7	8-10
	27	36	11

TABLE 2. PSA distribution at PET and salvage treatment

PSA at PET	№	PET/CT			Treatment		
		Neg	Loc	Met	Cryo	ADT	Act Surv
0-4 ng/ml	20	3 (15%)	15 (75%)	2 (10%)	19 (95%)	1 (5%)	0 (0%)
4-10 ng/ml	42	8 (19%)	21 (50%)	13 (31%)	27 (64%)	14 (33%)	1 (3%)
>10 ng/ml	12	3 (25%)	4 (33%)	5 (42%)	4 (33%)	6 (50%)	2 (17%)
All	74	14 (19%)	40 (54%)	20 (27%)	50 (68%)	21 (28%)	3 (4%)



**FIGURE 1. PET results and results of histology and confirmatory imaging**

**TABLE 3. Total PSA at PET, PSA kinetics and <sup>11</sup>C-choline PET/CT results.**

	PET/CT neg	PET/CT loc	PET/CT met	p value
Total PSA at PET (ng/ml)	6,6	6,0	8,1	,080
PSA DT (month)	17,1	20,2	10,3	,052
PSA Velocity (ng/ml/year)	2,6	2,3	4,6	,005



## DISCUSSION

This study shows that  $^{11}\text{C}$ -choline PET/CT is a useful tool for the selection of patients with BCR after RT for salvage cryoablation of the prostate.  $^{11}\text{C}$ -choline PET/CT was decisive and led to therapy change in 32% of cases.

As this study is one of the first reported on the clinical impact of  $^{11}\text{C}$ -choline PET/CT in the selection of patients for salvage cryoablation, a comparison cannot be made with those from other groups.

Although cryoablation is a universally recognized therapeutic option for prostate cancer, no consensus has been reached on guidelines for indications or patient selection for either primary or salvage cryoablation. Patient inclusion criteria at different medical centers vary.

By Chin *et al.* (21) for salvage cryoablation of the prostate, all patients should have biochemical evidence of local treatment failure, i.e., rising PSA levels on three consecutive determinations at least 2 years after radical RT, in addition to histologic proof of local cancer recurrence. All patients should have reasonable life expectancy and acceptable anesthetic risks. All should have a negative pelvic and abdominal computed tomography (CT) study as well as radionuclide bone scan. PSA levels preferably should be  $<10$  ng/mL at the time of consideration for cryoablation of the prostate to minimize the probability of occult distant metastatic disease. Patients with serum PSA levels between 10 and 20 ng/mL should have a negative pelvic lymphadenectomy or a negative CT-guided aspiration biopsy of pelvic nodes. An unfavorable biochemical outcome can be predicted by precryoablation PSA levels over 10 ng/mL, initial Gleason score of 8 or greater, and T3/T4 disease. In our series 12 patients were studied with a PSA  $> 10$  ug/L at time of PET/CT. In 5/12 cases metastases were identified, leaving only a minority of patients suitable for salvage cryoablation. These results are in corroboration with the literature and should be considered the upper limit for selection for restaging with PET/CT after radiotherapy or brachytherapy today. It remains to be seen if the patients with PSA  $> 10$  and negative imaging do benefit of salvage cryoablation or if they have early failures due to false negative scans.

Nguyen *et al.* (22) summarized the clinical characteristics of patients who are more likely to present with local only failure after primary RT. These included PSA  $< 10$  ng/mL, Gleason score  $\leq 6$ , clinical T1c or T2a tumor status, pretreatment PSA velocity  $< 2.0$  ng/mL per year at the time of initial presentation, interval to PSA failure  $> 3$  years, PSA-DT  $> 12$  months, negative bone scan and pelvic imaging studies, and positive rebiopsy.

Such patients, who will likely have relatively low-volume and indolent disease with a life expectancy  $> 10$  years, could have a reasonable chance of gaining a benefit from salvage therapy that will justify the toxicity of therapy. In our study in the group of patients

with favorable characteristics for salvage cryoablation,  $^{11}\text{C}$ -choline PET/CT identified metastatic disease in almost 25% of cases. For this  $^{11}\text{C}$ -choline PET/CT was the reason for changing treatment to (delayed) ADT.

Several studies have shown that  $^{11}\text{C}$ -choline PET/CT scan is a sensitive and accurate imaging technique to identify the site of recurrence in patients with BCR after EBRT for prostate cancer. Local recurrences and regional and/or distant metastases can be identified with an overall sensitivity of 80% (5,12-15). Aside from the overall decreased scan time, major clinical advantages of PET/CT include better localization of activity to normal versus abnormal structures, better identification of inflammatory lesions, CT visualization of PET-negative lesions (especially bone lesions), discovery and confirmation of abnormal sites, and improved localization for biopsy or radiotherapy (23).

Still there is a possibility to optimize patient selection using PSA kinetics. Recent studies have shown the influence of PSA kinetics on detection rate of  $^{11}\text{C}$ -choline PET/CT. No other factors seem to have a significant value in predicting the presence of a positive choline PET/CT scan. The only problem is that a commonly accepted method for calculation of PSA kinetics is needed to standardize this promising tool. Optimal application of PSA kinetics could become an important step in improving patient selection.

Limitations of the study include the use of PET/CT fusion until 2009, which could have led to lower accuracy in the detection of the recurrent tumors when compared with our current PET/CT hybrid systems. Another limitation of our study is the histopathological proof obtained in 63% of the patients with local or regional/distant recurrences. However, a significant quantity of local recurrences can be missed using prostate or bladder neck biopsies which fail to prove true positives. The use of a composite reference with clinical follow up after local salvage treatment could validate more cases and make this problem less important.

## **CONCLUSION**

$^{11}\text{C}$ -choline PET/CT could be useful for the selection of patients with BCR after RT for salvage cryoablation of the prostate.  $^{11}\text{C}$ -choline PET/CT was decisive and led to therapy change in 32% of cases.

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