Morphological aspects of recurrent prostate cancer

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Chapter 3

^{11}C-choline Positron Emission Tomography for the intraprostatic tumor characterization and localization in recurrent prostate cancer after EBRT.

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ABSTRACT

Aim

This study focuses on the potential role of ^{11}C-choline positron emission tomography (PET) for the intraprostatic tumor characterization and localization in recurrent prostate cancer after EBRT.

Methods

This retrospective study was conducted in patients who were being followed up after EBRT for histological proven prostate cancer. We selected the patients with a local recurrence by ^{11}C-choline PET/CT fusion. The results of PET were compared with the results of histology and with clinical follow up.

Results

Forty-two patients with a local recurrence suggested by PET were included in this study. 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.

Conclusion

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. The accuracy is too low for the routine use of this modality in the present scenario.

INTRODUCTION

Prostate cancer is a highly prevalent disease throughout the world. It accounts for about 25% of all the newly diagnosed cancers in American men and is second (10%; 28 660) among the 10 leading cancer-related causes of death for men in the United States in 2008.[1] Despite many years of study and effort, the best way of detection, diagnosis and treatment remains uncertain.

Radiation therapy is commonly used in prostate cancer treatment. It may be used instead of surgery in early stage prostate cancer, or after surgery in locally advanced stages as adjuvant radiotherapy. An increasing prostate specific antigen (PSA) level after external beam radiation therapy (EBRT) is the earliest sign of cancer recurrence in about three-quarters of patients.[2,3] If biochemical recurrence is combined with biopsy after EBRT, substantially more patients will be identified with local failure after EBRT.[4]

Zagars reported that 80% of men treated with radiation therapy for localized prostate cancer had an increasing PSA level at a mean follow-up of 5 years.[5]

The main reason why whole-gland therapy has been the standard of care for so long is, that prostate cancer has always been regarded as multifocal. Histological studies, however, have shown that a considerable number of men diagnosed in a contemporary setting have unilateral or unifocal disease. In men undergoing radical prostatectomy, 10–40% have unilateral disease and 10–44% have unifocal tumors. These data raise the possibility that half-gland treatment (hemiablation) or focal ablation of tumor foci alone might be possible for between 10% and almost 50% of patients who would currently receive whole-gland treatment. [6]

At this time, there is not an imaging modality that can determine the exact localization of recurrent prostate cancer. CT and MRI scans 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%.[7] Studies are ongoing to identify novel diagnostic techniques to improve imaging of recurrent prostate cancer. 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 cancer recurrence after EBRT.[8-11] Carbon-11-choline is one of the most commonly applied PET tracers for prostate cancer imaging.[12] In a recent study a high sensitivity of ^{11}C-choline PET was reported in the detection of the site of recurrence in a large cohort of patients with PSA relapse after EBRT.[13]

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.

The aim of this study was to investigate the potential role of ^{11}C-choline PET for the intraprostatic tumor characterization and localization in recurrent prostate cancer after EBRT.

MATERIALS AND METHODS

Patients

This retrospective study was conducted in patients who were being followed up after EBRT for histological proven prostate cancer. All patients were eligible if they showed a biochemical recurrence as defined by the ASTRO consensus criteria 1997. For this study we selected the patients with a local recurrence visualized by PET. No adjuvant hormonal therapy was allowed within 1 year prior to ^{11}C-choline PET. All patients were informed and signed written consent forms prior to participation in the study. The hospital's ethics committee approved the study. All patients were treated according to current guidelines on prostate cancer.[14]

Histology

Primary staging was done using TNM-classification of 1997. In patients with a biochemical recurrence and a palpable/visible tumor transrectal ultrasound guided prostate biopsies were taken. Primary and recurrent histological diagnosis and determination of the Gleason sum were performed on haematoxylin and eosin-stained sections.

^{11}C-choline PET tracer synthesis and PET scan

The ^{11}C-choline was produced using a cyclotron system by the method described by Hara.[15] ^{11}C-choline was produced 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 performed using either an ECAT 951/31 (until 2004) or 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 ^{11}C-choline. 3D-mode data acquisition was started at 5 min after injection over the same area for 7 min per bed position. The prostate bed was included in the first bed position. PET images were fused with a CT scan of the abdomen made separately and fused using Standard Esoft Software to improve tumor localization within the pelvic region.

Evaluation of PET scan

Attenuation-corrected images were made using an iterative reconstruction algorithm (ordered subset expectation maximization). Two independent experienced PET physicians, blinded for the clinical data, analyzed the PET images. A local recurrence was suspected when any increased uptake occurred within the prostate contour. Lesions 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 0 and 1 points were considered negative. Lesions with level 2 and 3 uptake were defined as positive and considered malignant. Intraprostatic recurrent prostate cancer was classified as focal – defined as a single circumscriptive area of uptake, or “diffuse”, when there was heterogeneous uptake of ^{11}C-choline along the prostate. Next, the SUV’s of ROI were measured using the SUV-70% threshold of SUV max to delineate the ROI. PET results were compared with the results of prostate biopsies and/or with clinical follow up after local salvage treatment.

Reference test and further patient evaluation

According to protocol, all follow-up patients undergo (half-) yearly serum PSA determination. In patients with biochemical recurrence further evaluation was performed using digital rectal examination and transrectal ultrasound guided prostate biopsies.

Patients and localization of recurrence in the prostate were deemed true positive based on the biopsy findings when stated as malignant. Biopsies stated as indeterminate or radiation changes were classified as negative. We used conventional imaging studies (CT, MRI) and bone scintigraphy on clinical indication only. In addition we used clinical follow-up data, i.e., response to salvage therapy with PSA decline < 1.0 ng/ml in five cases with negative prostate biopsies.

Prostate specific antigen

Serum PSA was determined using an automated chemiluminescent microparticle immunoassay on an architect platform (Abbott Diagnostics Division, Abbott Park, IL, USA).

RESULTS

We included 42 patients with a biochemical recurrence after EBRT and with a local recurrence suggested by PET in this study. The patient characteristics are presented in Tables I, II. 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). Of the remaining 10 patients, three patients also showed distant metastases on PET, all confirmed by CT or bone scans, two received hormonal treatment for rapid progressive disease and five were treated with cryoablation and their PSA response was sustained <1.0 ng/ml as indication of a complete response. Overall 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 results of PET and histology of transrectal prostate biopsies regarding the intraprostatic location of the tumor (either unilateral or bilateral) are presented in Table III. The mean time between PET and biopsies was 29 days. The concordance of the intraprostatic distribution of the tumor with PET with histology from median 7 (range 4-12) prostate biopsies was 47% (7/15) in unilateral cases and 41% (11/27) in bilateral cases. No significant differences were seen between the two groups in serum PSA at time of PET (p=0.509) and SUV (p=0.739) using Student's *t*-test.

TABLE I. *Patient characteristics (Number of patients = 42)*

	Mean (range)		
Age at PET (years)	70.4 (50-81)		
Initial PSA (ng/ml)	21.3 (5-132)		
PSA at PET (ng/ml)	11.6 (0.6-47)		
Biopsies (№)	7 (4-12)		
Initial stage	T1	T2	T3
	15	12	15
Gleason score	4-6	7	8-10
	12	23	7

TABLE II. The clinical data of patients with PET and histology results

Patient №	Age at PET	Stage	Initial PSA	PSA at PET	PET findings	SUV mean	Biopsies №	Histology
1	75	T1 N0 M0	132	14	Unifocal; left	1,72	6	recurrence left and right Gleason 7
2	77	pT1c Nx Mx	13	17	Diffuse; asymmetrical; left	3,03	12	changes due to radiotherapy
3	78	T1c Nx M0	8,5	4	Diffuse; symmetrical	2	6	recurrence left Gleason 8
4	65	T2b N0 M0	8,2	15,3	Diffuse; symmetrical	2,54	5	changes due to radiotherapy
5	75	T3 pN0 M0	130	3,50	Diffuse; symmetrical	2,45	4	changes due to radiotherapy, no adenocarcinoma
6	72	T2b pN0 M0	15	4,2	Diffuse; symmetrical	5,83	8	recurrence left and right Gleason 8
7	72	T2N0M0	21,5	29,7	Diffuse; symmetrical	7,94	8	recurrence left Gleason 7 and right Gleason 8
8	67	T3 pN0 M0	24	3,6	Diffuse; symmetrical	1,04	6	recurrence right, left - no recurrence
9	58	T3	22	1,2	Unifocal; left	4,06	12	changes due to radiotherapy, no adenocarcinoma
10	72	T1c N0 M0	27	11,3	Diffuse; asymmetrical; right	2,86	5	recurrence right Gleason 6, left - no recurrence
11	65	T2 N0 M0	10,9	3,3	Unifocal; left	1,8	8	recurrence left Gleason 6, right - no recurrence
12	74	T3b N0 M0	21	24	Diffuse; asymmetrical; right	3,74	6	recurrence right Gleason 7, left - no recurrence
13	74	T1c N0 M0	13	18,2	Diffuse; symmetrical	2,34	4	recurrence right Gleason 6
14	73	T1c pN0 M0	35,8	12,5	Diffuse; symmetrical	3,42	10	recurrence left Gleason 6 and right Gleason 7
15	71	T1c N0 M0	18,4	20	Unifocal; left	3,01	6	multifocal recurrence Gleason 7
16	71	T1c N0 M0	42	3,6	Diffuse; symmetrical	3,01	4	recurrence right Gleason 7
17	74	T3b pN0 M0	22	14	Unifocal; left	5,65	6	recurrence left and right Gleason 8
18	74	T1c	10,7	21,4	Unifocal; left	3,55	7	recurrence left Gleason 8
19	72	T1c N0 M0	17	12,8	Diffuse; symmetrical	6,23	6	recurrence left and right Gleason 8
20	74	T2a	13,4	2,9	Unifocal; left	3,2	8	no recurrence
21	74	T2a N0 M0	58	4,2	Diffuse; symmetrical	2,58	9	recurrence left Gleason 8, right - changes due to radiotherapy
22	68	T2a N0 M0	7,8	8,3	Unifocal; right	2,37	4	recurrence right Gleason 6, left - no recurrence
23	71	T3 N0 M0	8,2	4,1	Unifocal; left	4,08	8	recurrence left Gleason 9, right - no recurrence
24	57	T3 N0	28	5,4	Diffuse; symmetrical	2,83	12	recurrence left Gleason 9, right - changes due to radiotherapy
25	70	T2a N0 M0	11	47	Diffuse; symmetrical	4,07	4	recurrence left and right Gleason 8
26	50	T2a G2	7,3	2,2	Unifocal; right	3,59	4	recurrence right Gleason 7
27	80	T2 pN0 M0	15	22	Diffuse; asymmetrical; left	4,13	9	recurrence left and right Gleason 10
28	74	T1c N0 M0	27	11	Diffuse; asymmetrical; right	4,58	8	recurrence left and right Gleason 6
29	67	cT3 pN0 M0	39	9,2	Diffuse; symmetrical	2,47	6	recurrence left Gleason 6 and right Gleason 7
30	72	T3a pN1 M0	34	6,2	Diffuse; asymmetrical; right	2,65	9	recurrence right Gleason 8
31	71	T2 N0 M0	5	9,3	Unifocal; right	3,31	12	recurrence left and right Gleason 7
32	53	T3 N0 M0	51	2,2	Unifocal; right	3,65	6	recurrence left Gleason 9, right - no recurrence
33	76	T1c Nx Mx	7	7,6	Diffuse; asymmetrical; right	3,96	12	recurrence left and right Gleason 8
34	73	T3 pN0 M0	41	25,5	Diffuse; asymmetrical; right	2,39	7	no recurrence
35	81	cT3 Nx Mx	34	2,7	Diffuse; symmetrical	3,03	12	recurrence left and right Gleason 9
36	65	T1c N0 M0	6,3	6	Unifocal; left	2,63	4	recurrence left Gleason 8, right - no recurrence
37	66	T1c N0 M0	14	7,9	Diffuse; symmetrical	4,37	6	changes due to radiotherapy
38	69	T3 pN1 M0	22,7	13,8	Diffuse; symmetrical	6,1	8	recurrence left and right Gleason 8
39	73	T1c Nx M0	14,5	0,6	Diffuse; symmetrical	1,17	n.a.	changes due to radiotherapy
40	69	T2 N0 M0	29	31,4	Unifocal; left	n.a.	n.a.	recurrence left Gleason 7
41	72	pT3 N0 M0	10	20,2	Diffuse; symmetrical	2,17	9	left and right atrophy, no recurrence
42	73	T3 pN0 M0	15,3	2,9	Unifocal; right	3,36	8	no recurrence

TABLE III. PET results vs. results of biopsies, SUV, PSA

	PET	
	Diffuse	Focal
Biopsy		
- Negative	2	3
- Changes due to radiotherapy	5	1
- Unilateral tumor	9	7
- Bilateral tumor	11	4
PSA at PET (mean) ng/ml	12,98	10,70
SUV	3,44	3,28

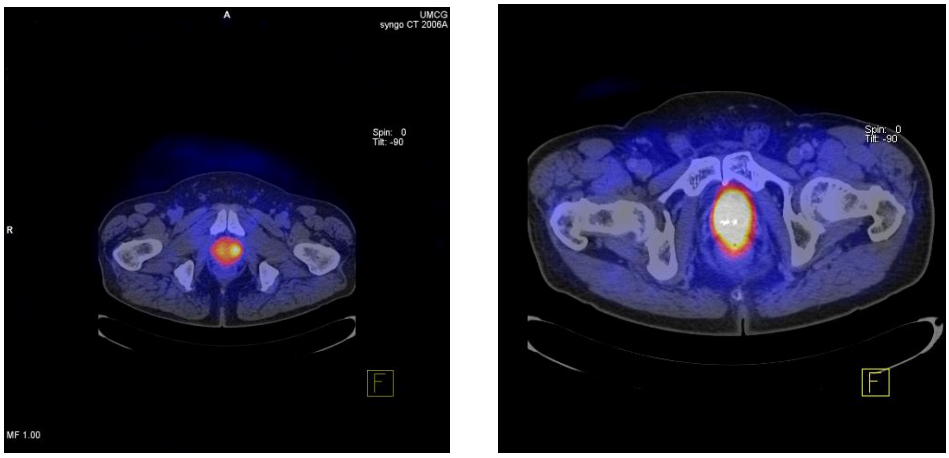

Figure 1 and 2 - Two typical cases of focal(left) and diffuse (right) Chol-PET/CT.

DISCUSSION

In this study we showed that ^{11}C-choline PET has a high overall sensitivity in detection of a local recurrence in the prostate after EBRT on a patient based analysis. This is in concordance with results published by other groups using both carbon-11 and fluor-18 labelled cholines.[9,13,16,17] However on a lesion based analysis the intraprostatic characterization of the tumor was less accurate when compared to histology using prostate biopsies. The concordance between the results of PET and biopsies was 47% in patients with unilateral disease and 41% in patients with bilateral form.

As this study is one of the first reported on the intraprostatic characterization of recurrent prostate cancer with PET, we cannot compare our data with those from other groups. Our results are in line with recent publications on MRI in a comparable group of patients.[18] In this study a local recurrence was verified by prostate biopsies in 12/33 patients with PSA relapse after EBRT. This is lower than in our group but the difference could be explained by the lower mean PSA of 2.1 ng/ml in their cohort *versus* mean PSA of 11.6 ng/ml in our group. In the MRI study the local recurrence could be visualized using T2 weighted images in 58% of the patients with proven local recurrence and in 100% of the patients using DCE-MRI. As this study used the result of prostate biopsies only as reference, a substantial number of false negative cases have to be recognized. Prostate biopsies will not be able to identify all cases of local recurrence, which would influence the reported accuracy of DCE-MRI.

The limitations of transrectal prostate biopsies to identify all tumor sites in PET imaging of primary prostate cancer prior to prostatectomy were described by Farsad *et al*.[19] They studied ^{11}C-choline PET/CT using both sextant biopsies and whole mount specimens after prostatectomy. PET/CT demonstrated focal ^{11}C-choline uptake in 108 sextants (94 of which involved tumor), and 108 sextants showed no abnormal ^{11}C-choline uptake (49 of which were false negative). The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of PET/CT were 66%, 81%, 71%, 87%, and 55%, respectively.

New strategies of so called mapping biopsies are currently studied for their accuracy in identifying intraprostatic tumors. [20,21]

Unfortunately there are also few data on the histopathology of recurrent prostate cancer. Salvage prostatectomies are not performed on a large scale due to the high morbidity with incontinence, rectal injuries and urethral strictures as the main problems.

Recently histological data were presented analyzing radical prostatectomy specimens from 50 patients who underwent salvage radical prostatectomy following radiation therapy between 1994 and 2008.[22] Unifocal tumors were present in 66% of the RPS and the tumor was bilateral in 74% (37/50) of the cases.

This means that rather often the tumor can be unifocal and bilateral at the same time, *i.e.*, a single recurrent tumor which crosses the midline and involves both lobes. Our imaging data correlate with these results, with 27/42(63%) of the patients having recurrent cancer detected in both lobes.

In recent publications by Heidenreich *et al.* in consecutive series of salvage prostatectomies, the authors have used ^{11}C-choline PET/CT prior to prostatectomy in cases with negative biopsies.[23] The authors report a correlation of 90% between the intraprostatic number and spread of tumor foci and PET/CT but did not provide the data, using whole mount specimens as reference.[24] These unique data are of utmost importance to validate the accuracy of ^{11}C-choline PET/CT for intraprostatic characterization of recurrent prostate cancer after EBRT.

Our study has some limitations. First we have used PET/CT fusion for this cohort of patients which could lower the accuracy of the localization of the recurrent tumor(s). Second, with the reference technique using prostate biopsies we accept a mismatch compared to whole organ histology. The lack of whole organ histology will persist as salvage prostatectomy is not routinely performed. At present the literature on salvage prostatectomy series does not exceed 600 patients. By using a composite reference with clinical follow up after local salvage treatment more cases could be validated. Because of these limitations we did not report on sensitivity, specificity and predictive values but only on concordance with the reference. Third, changes in choline uptake in prostate cancer cells monitored by PET after radiotherapy might not exclusively reflect therapeutic success but also altered tracer uptake as a consequence of irradiation. This might be due to metabolic changes associated with initiation of processes that finally cause cell death.[25] So far this mechanism has only been shown in an *in vitro* model. In this study the effects of per dosing irradiation were investigated very shortly after EBRT. As the mean disease free period exceeds six years in our study we believe that this mechanism will not affect our benefits. Only patients with PET positive local findings were included in the study, although the negative result of PET does not always guarantee the absence of disease, as it was in the recent study when 13 patients with defined biochemical recurrence had negative PET.[13]

In recurrent prostate cancer after EBRT the limited data suggests that patterns of local recurrence after radiotherapy are focal in 2/3 of the patients. As whole gland salvage treatments like prostatectomy, cryoablation or HIFU all have shown to have considerable morbidity and complicates rates of > 50%, the need for less toxic treatment is obvious. If imaging could improve delineation of recurrent prostate cancer the option of focal and/or targeted salvage treatment would enable effective cancer control on the one hand and reduction of complications on the other hand. At present ^{11}C-choline PET/CT and DCE MRI are the best candidate techniques for this purpose.

Clinical application of these techniques could be facilitated once so called mapping biopsy strategies with 30-60 template directed biopsies have been validated as reference technique and could replace whole mount histology.

CONCLUSIONS

Intraprostatic characterization of recurrent prostate cancer after EBRT with ^{11}C-choline PET is feasible but at present shows a moderate concordance with routine transrectal prostate biopsies. The accuracy is too low for the routine use of this modality in the present scenario.

REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T et al. Cancer statistics. CA Cancer J Clin. 2008 Mar-Apr;58(2):71-96.
2. Zagars GK, Pollack A, von Eschenbach AC. Prognostic factors for clinically localized prostate carcinoma. analysis of 938 patients irradiated in the prostate specific antigen era. Cancer 1997;79:1370–80.
3. Zietman AL, Coen JJ, Dallow KC, Shipley WU. The treatment of prostate cancer by conventional radiation therapy: an analysis of long-term outcome. Int J Radiat Oncol Biol Phys 1995;32:287–92.
4. De La Taille A, Benson MC, Bagiella E, Burchardt M, Shabsigh A, Olsson CA et al. Cryoablation for clinically localized prostate cancer using an argon-based system: complication rates and biochemical recurrence. BJU Int 2000; 85(3):281-286.
5. Zagars GK. Prostate specific antigen as an outcome variable for T1 and T2 prostate cancer treated by radiation therapy. J Urol. 1994 Nov;152(5 Pt 2):1786-91.
6. Ahmed HU, Pendse D, Illing R, Allen C, van der Meulen JH, Emberton M. Will focal therapy become a standard of care for men with localized prostate cancer? Nat Clin Pract Oncol. 2007 Nov;4(11):632-42.
7. Kane CJ, Amling CL, Johnstone PA, Pak N, Lance RS, Thrasher JB et al. Limited value of bone scintigraphy and computed tomography in assessing biochemical failure after radical prostatectomy. Urology 2003; 61:607-611.
8. Picchio M, Messa C, Landoni C, Gianolli L, Sironi S, Brioschi M et al. Value of [11C] choline-positron emission tomography for restaging prostate cancer: a comparison with [18F]fluorodeoxyglucose-positron emission tomography. J Urol 2003;169:1337–40.
9. de Jong IJ, Pruim J, Elsinga PH, Vaalburg W, Mensink HJ. [11C]-choline positron emission tomography for the evaluation after treatment of localized prostate cancer. Eur Urol 2003;44:32–8.
10. Rinnab L, Mottaghy FM, Blumstein NM, Reske SN, Hautmann RE, Hohl K et al. Evaluation of [11C]-choline positron-emission/computed tomography in patients with increasing prostate-specific antigen levels after primary treatment for prostate cancer. BJU Int 2007;100(4):786–793.
11. Krause BJ, Souvatzoglou M, Tuncel M, Herrmann K, Buck AK, Praus C et al. 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 2008;35(1):18–23.

12. Farsad M, Schiavina R, Franceschelli A, Sanguedolce F, Castellucci P, Bertaccini A et al. Positron-emission tomography in imaging and staging prostate cancer. Cancer Biomark. 2008;4(4-5):277-84.
13. Breeuwsma AJ, Leliveld AM, Pruim J, Van Den Bergh ACM, Dierckx RA, Nijman JM et al. Detection of local, regional and distant recurrence in patients with PSA relapse after external beam radiotherapy using [11C]-choline positron emission tomography (PET). Int J Radiat Oncol Biol Phys. 2010 May 1;77(1):160-4.
14. Heidenreich A, Aus G, Bolla M, Joniau S, Matveev VB, Schmid HP et al. EAU guidelines on prostate cancer. Eur Urol. 2008 Jan;53(1):68-80.
15. Hara T. [11C]-choline and 2-deoxy-2-[18F]fluoro-D-glucose in tumor imaging with positron emission tomography. Mol Imaging Biol 2002;4:267-273.
16. Schilling D, Schlemmer HP, Wagner PH, Böttcher P, Merseburger AS, Aschoff P et al. Histological verification of [11C]-choline-positron emission/computed tomography-positive lymph nodes in patients with biochemical failure after treatment for localized prostate cancer. BJU Int. 2008 Aug; 102(4):446-51.
17. Cimitan M, Bortolus R, Morassut S, Canzonieri V, Garbeglio A, Baresic T et al. [18F]fluorocholine PET/CT imaging for the detection of recurrent prostate cancer at PSA relapse: experience in 100 consecutive patients. Eur J Nucl Med Mol Imaging. 2006 Dec;33(12):1387-98.
18. Haider MA, Chung P, Sweet J, Toi A, Jhaveri K, Ménard C et al. Dynamic contrast-enhanced magnetic resonance imaging for localization of recurrent prostate cancer after external beam radiotherapy. Int J Radiat Oncol Biol Phys. 2008 Feb 1;70(2):425-30.
19. Farsad M, Schiavina R, Castellucci P. Detection and localization of Prostate cancer: correlation of [11]C-choline PET/CT with histopathologic step-section analysis. J Nucl Med 2005;46(10):1642–1649.
20. Crawford ED, Wilson SS, Torkko KC, Hirano D, Stewart JS, Brammell C et al. Clinical staging of prostate cancer: A computer-simulated study of transperineal prostate biopsy. BJU Int 2005;96(7):999 –1004.
21. Onik G, Barzell W. Transperineal 3D mapping biopsy of the prostate: an essential tool in selecting patients for focal prostate cancer therapy. Urol Oncol. 2008 Sep-Oct; 26(5):506-10.
22. Chiong E, Andino L, Guo CC, Prokhorova IN, Goh JJK, Pisters LL et al. Pathologic features of salvage radical prostatectomy specimens following radiotherapy: implications for focal therapeutic options. J Urol 2009 Apr;181(4) Suppl 1:458.
23. Heidenreich A, Semrau R, Thüer D, Pfister D. Radical salvage prostatectomy: Treatment of local recurrence of prostate cancer after radiotherapy. Urologe A. 2008 Nov; 47(11):1441-6.

24. Ohlmann C, Pfister D, Thüer D, Wille S, Engelmann UH, Heidenreich A. [11C]-choline Positron Emission Tomography/Computerized Tomography for tumor localization of locally recurrent prostate cancer after radiation therapy. Eur Urol Suppl 2007;6(2):229.
25. Holzapfel K, Müller SA, Seidl C, Grosu AL, Schwaiger M, Senekowitsch-Schmidtke R. Effects of irradiation on the [Methyl-3H]choline uptake in the human prostate cancer cell lines LNCaP and PC3. Strahlenther Onkol. 2008 Jun;184(6):319-24.