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11C-Choline Pet/Ct in the Detection of Prostate Cancer Relapse in Patients After Radical Treatment With Psa Level < 10 Ng/Ml

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Abstract

Purpose: To evaluate the usefulness of 11C-Choline PET/CT in the detection of recurrent prostate cancer (PCa) in patients with biochemical relapse after radical treatment.

Materials and methods: This retrospective study included 217 PCa patients who underwent 11C-Choline PET/CT in the Department of Nuclear Medicine of Bakoulev Scientific Centre. All patients had biochemical relapse 3±2 years after radical treatment for locally advanced PCa (T1–3 N0–1 M0): radical prostatectomy (n = 159) and radiation therapy (n = 58). The mean PSA value in the group was 2.1±2.5 (0.2–9.7) ng/ml, median – 1.9 ng/ml. Imaging was performed on PET/CT scanner (Biograph-64, Siemens) 10 min after injection of ^{11}C-Choline (400–550 Mbq).

Results: Overall, according to 11C-Choline PET/CT results PCa relapse was detected in 56% (121/217) of cases: in 50% (80/159) after radical prostatectomy and in 71% (41/58) after radiation therapy.

The mean PSA value in PET-positive cases was 3.1±2.2 (0.2–9.7) ng/ml, while in PET-negative cases – 1.8±1.7 (0.2–4.6) ng/ml. The majority – 68% (65/96) patients with PET-negative scan had low PSA levels (< 2 ng/ml).

PET/CT results were positive in 43% (50/115) patients with PSA of < 2 ng/ml, in 63% (45/72) with PSA of 2 to 5 ng/ml, and in 87% (26/30) with PSA of > 5 ng/ml.

Local relapse was detected in 51% (62/121) patients, distant metastases – in 28% (34/121) of cases, both local and distant metastases – in 21% (25/121) of cases.

Lymph node metastases were detected in 38% (86/217) of all patients included in the analysis, of which 28% (24/86) had lesions in lymph node of normal size (median 7 mm).

Of all PET-positive patients bone metastases were detected in 33% (40/121), of which 60% (24/40) had isolated skeletal involvement. Importantly, that 27% (11/40) of PET-positive patients with bone metastases had no structural abnormalities on CT images (CT-negative cases), corresponding to isolated involvement of bone marrow. And half of these CT-negative patients (5/11) had single lesions. The mean PSA value in patients with bone metastases was 5.0±3.7 (0.4–9.1) ng/ml, median – 3.8 ng/ml.

According to 11C-Choline PET/CT results oligometastatic PCa recurrence was revealed in 38% (82/217) of all patients, of which 62% (51/82) had local relapse only. Distant oligometastatic lesions were detected in 38% (31/82), of which 13% (4/31) were presented by normal-size lymph nodes and 19% (6/31) – by early bone marrow metastases.

48% (58/121) of PET-positive results were confirmed by data of repeated PET/CT examinations.

Conclusion: 11C-Choline PET/CT has been shown to be a single noninvasive accurate technique for detection of recurrent PCa in patients with rising PSA after radical treatment, which allows to differentiate patients with local and distant metastases in one study, as well as identify oligometastatic process, and therefore was useful in determining the further personalized therapeutic approach.

Keywords: prostate cancer, PET/CT, 11C-Choline, biochemical recurrence, PSA.

1. Introduction

Prostate cancer (PCa) is one of the most common malignancies in men over 50 years. Annually, more than 1 million men worldwide are diagnosed with PCa, of which about 2/3 of cases (70%) – in developed countries [1]. The incidence rate of the disease in Russian Federation has steadily increased over the last decade: in 2003 it was 16,51 cases per 100,000 males, and in 2013 – 34,62 cases per 100,000 males (average annual growth rate of 7,09%) [2]. Currently PCa is the second leading cause of cancer-related death in men [3].

The most common treatment options for PCa are: radical prostatectomy (RP) and radiation therapy (RT), including external beam RT and brachytherapy [3, 4]. Recurrence rate within 5 years after primary treatment is quite high – from 10% up to 53% [3, 5]. This fact determines the importance of early detection of PCa relapse and makes it a crucial issue in oncourology.

Asymptomatic rising of prostate specific antigen (PSA) is usually the first sign of recurrent disease after curative treatment, so its monitoring is the primary and the best tool for early detection of PCa relapse. Isolated PSA levels increasing after primary therapy are defined as biochemical relapse (BCR) [3, 4].

In patients with BCR, the goal is to distinguish between loco-regional recurrence and the presence of distant metastases. Although PSA is the most sensitive tool for detection of PCa relapse, it doesn't allow localize the site of recurrence, which plays a key role in further therapeutic approach [3, 4–6].

Currently several conventional imaging modalities for PCa relapse evaluation are available, including transrectal ultrasonography with or without biopsy, bone scintigraphy, computed tomography and magnetic resonance imaging [3]. However, there's no gold standard of PCa relapse detection, and all of above noted modalities have shown limited diagnostic performance, especially in patients with low PSA values.

Recently, positron-emission tomography combined with computed tomography (PET/CT) has been introduced in clinical practice. This modality allows to simultaneously evaluate structural and metabolic changes in tissues and organs, so it has become one of the leading diagnostic imaging modalities used in clinical oncology. An important advantage of PET/CT is a whole-body scan, which allows to detect local relapse, as well as distant metastases within single examination [7, 8]. In the last years several radiotracers have been used to evaluate patients with suspected PCa relapse. To date, Choline, labelled with either ^{11}C or ^{18}F, is one of the most commonly used tracers in the clinical practice. Choline is a substrate for the synthesis of phosphatidylcholine, which is the major phospholipid of cell membrane. In PCa the biosynthesis of cell membrane is particularly increased what leads to accumulation of Choline in malignant cells [7, 8].

The aim of the current study was to evaluate the usefulness of ^{11}C-Choline PET/CT in the detection of recurrent PCa in patients with biochemical relapse after radical treatment.

2. Methods and materials

This retrospective study included 217 PCa patients who underwent 11C-Choline PET/CT in the Department of Nuclear Medicine of Bakoulev Scientific Centre over the period from January 2013 to May 2017. All patients had biochemical relapse 3±2 years after radical treatment for locally advanced PCa (T1–3 No–1 Mo) with different Gleason score

(4–9): after RP (n = 159) and RT (n = 58), including 29 patients after brachytherapy. The mean age of patients was 64 ± 6,4 (range, 50–79) years old.

All patients had achieved minimal PSA level after radical treatment. Study inclusion criteria was the presence of BCR with PSA level less than 10 ng/ml.

The results of serum PSA dated not earlier than 1 month before examination were taken into account. The mean PSA value in total group was 2.1 ± 2.5 (range, 0.2 –9.7) ng/ml, median – 1.9 ng/ml; in patients after RP – 1.9 ± 2.2 ng/ml; in patients after RT – 2.3 ± 3.5 ng/ml. For further analysis, results were divided into three groups, according to PSA level: less than 2.0 ng/ml (n = 115), from 2.0 to 5.0 ng/ml (n = 72) and more than 5.0 ng/ml (n = 30). 91 of 217 (42%) cases had rapid PSA kinetics: PSA doubling time less than 6 months.

Scans were performed on the hybrid system PET/CT "Biograph–64" True Point (Siemens). Prior to the PET/CT study, patients were fasted for 5–8 hours with exception of products containing proteins. Patients underwent the PET/CT scan 10 minutes after intravenous injection of 11C-Choline (400–550 MBq) with following emptying of bladder.

A whole-body PET/CT scan consisting of helical CT scanning (170 mA, 120 kV, FOV 700 mm, slices thickness 5 mm) from the level of orbits through the pelvis was followed by PET acquisition (7–8 bed positions, 3 min per bed position). Immediately after being acquired, PET/CT images were reconstructed automatically: CT images were used to produce attenuation correction values for PET emission reconstruction and fused PET/CT presentation.

Criteria used to validate PET/CT results were following: histological analysis in 13% of cases, and in 87 % – findings from other imaging techniques, repeated PET/CT, clinical follow-up, further PSA dynamics, treatment response, as well as the combination of all mentioned above within 9 ± 3 (1–12) months after performing PET/CT.

For the statistical analysis, data were computerized and analyzed by the statistical package R version 3.2 [http://www.r-project.org]. The Wilson score method was used to perform 95% confidence interval estimations. Statistical results were considered significant at a p value less than 0.05.

3. Results

Overall, according to 11C-Choline PET/CT results PCa relapse was detected in 56% (121/217) of cases: in 50% (80/159) after RP and in 71% (41/58) after RT. In the rest of cases (n = 96) PET-negative results allowed to rule out clinically significant PCa relapse.

It has to be noted that the majority of these PET-negative results – 68% (65/96) were obtained in patients with low PSA levels (< 2 ng/ml).

The mean PSA value in PET-positive cases was significantly higher than in PET-negative cases (p<0.05): 3.1 ± 2.2 (0.2 – 9.7) ng/ml and 1.8 ± 1.7 (0.2 – 4.6) ng/ml, respectively. Similar results were obtained in each group – after RP and after RT (table 1). Although the median PSA value was significantly higher in PET-positive than in PET-negative patients (2.4 ng/ml vs 1.4 ng/ml, p < 0.05), PET/CT confirmed its ability to detect relapse in patients with low PSA levels (from 0.2 ng/ml).

TABLE 1: Mean PSA values in the analyzed groups.

PET/CT results	after RP	after RT	TOTAL
PET-positive: mean PSA, range, median	2.1 ± 2.8 0.2 – 9.0 2.1	2.3 ± 3.7 0.6 – 9.7 3.5	3.1 ± 2.2 0.2 – 9.7 2.4
PET-negative: mean PSA, range, median	1.4 ± 1.5 0.2 – 3.7 1.2	1.9 ± 2.9 0.9 – 4.6 2.2	1.8 ± 1.7 0.2 – 4.6 1.4
TOTAL	1.9 ± 2.2 0.2 – 9.0 1.7	2.3 ± 3.5 0.6 – 9.7 2.8	2.1 ± 2.5 0.2 – 9.7 1.9

PET/CT results were positive in 43% (50/115) patients with PSA of < 2 ng/ml, in 63% (45/72) with PSA of 2 to 5 ng/ml, and in 87% (26/30) with PSA of > 5 ng/ml. The results in groups after RP and RT are presented in table 2. A strong positive correlation between 11C-Choline PET/CT detection rate of relapse and PSA serum level was revealed (r = 0.9; p < 0.05).

TABLE 2: Correlation between PSA level and 11C-Choline PET/CT detection rate of relapse.

PET-positive results	PSA level, ng/ml			TOTAL
	< 2.0	**2.0 – 5.0**	**> 5.0**	
after RP	38/98	30/46	12/15	80/159
after RT	12/17	15/26	14/15	41/58
TOTAL	50/115 **(43%)**	45/72 **(63%)**	26/30 **(87%)**	121/217 **(56%)**

11C-Choline PET/CT results were analyzed according to the localization of PCa recurrence. Local relapse was detected in 51% (62/121) patients: prostatic bed (n = 11), prostatic bed and pelvic lymph nodes (n = 7), pelvic lymph nodes (n = 44). Distant

metastases were identified in 28% (34/121) cases: bone (n = 23), extrapelvic lymph nodes (n = 9), lymph nodes and lungs (n = 1), bone and lung (n = 1). Both local and distant metastases were diagnosed in 21% (25/121) cases: regional lymph nodes and bone lesions (n = 11), regional and extrapelvic lymph nodes (n = 9), regional and extrapelvic lymph nodes and bone (n = 5).

The prevalence of local relapse was observed in each of the analyzed groups (after RP and after RT), and thus, did not depend on the type of primary treatment (Fig.1).
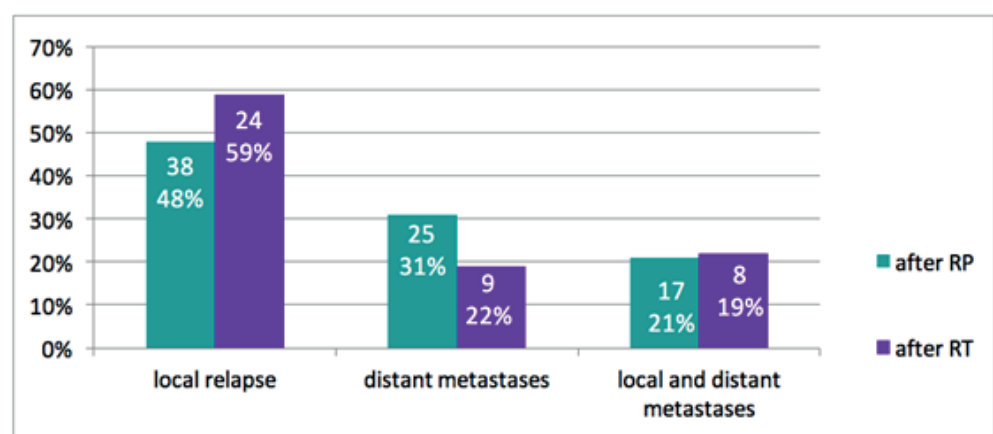

Figure 1: Distribution of PET-positive results according to PCa relapse localization in groups after RP and after RT, n = 121.

Lymph node metastases were detected in 38% (86/217) of patients included in the analysis, which made up 71% (86/121) of all revealed PCa relapses by PET/CT. Of all cases with lymph node metastases, 27% (23/86) had lesions in extrapelvic nodes and 28% (24/86) – in nodes of normal size (median 7 mm). The mean PSA value in patients with revealed lymph node metastases was 2.7±2.0 (0.2–8.6) ng/ml, median –2.0 ng/ml, and did not significantly differ in groups after RP and after RT. 35% (30/86) of patients with PET-positive lesions had PSA doubling time less than 6 months.

Bone metastases were detected in 18% (40/217) of patients included in the analysis, which made up 33% (40/121) of all revealed PCa relapses by PET/CT. Of all cases with bone metastases, 60% (24/40) had isolated skeletal involvement and 63% (25/40) – single lesions. Importantly, that 27% (11/40) of PET-positive patients with bone metastases had no structural abnormalities on CT images (CT-negative cases), corresponding to isolated involvement of bone marrow. And half of these CT-negative patients (5/11) had single lesions. The mean PSA value in patients with revealed bone metastases was 5.0±3.7 (0.4 – 9.1) ng/ml, median – 3.8 ng/ml. 53% (21/40) of patients with PET-positive bone metastases had PSA doubling time less than 6 months.

11C-Choline PET/CT results allowed to detect oligometastatic PCa recurrence in 38% (82/217) of patients included in the analysis, which made up 68% (82/121) of all revealed PCa relapses by PET/CT. Of all cases with oligometastatic recurrence 62% (51/82) had local relapse only. Distant oligometastatic lesions were detected in 38% (31/82), of which 13% (4/31) were presented by normal-size lymph nodes and 19% (6/31) – by early bone marrow metastases.

An example of oligometastatic recurrence detection by 11C-Choline PET/CT is presented in the picture 1.
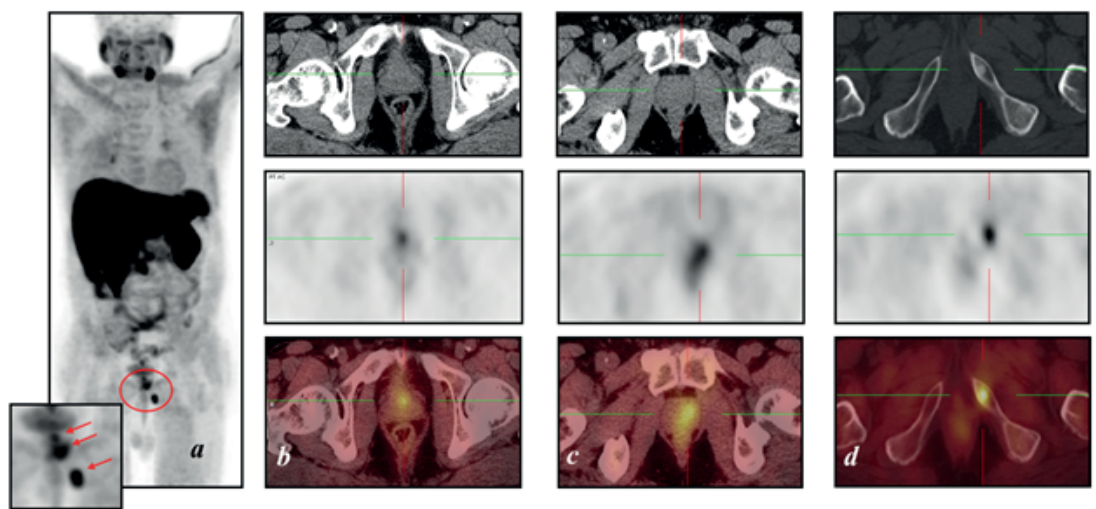
Picture 1: A 64-year-old patient 2 years after radiation therapy for PCa (T3bN0M0, Gleason 7) with rising PSA (current PSA = 3.7 ng/ml).
11C-Choline PET/CT results showed **(a)** oligometastatic recurrence: **(b, c)** two foci in prostate and **(c)** osteoblastic mts in the pubic bone. Thus PET/CT has upstaged the disease and therefore changed its management – radiation therapy on prostatic and single bone mts was performed. One year later repeated 11C-Choline PET/CT (PSA = 0.04 ng/ml) was negative and therefore allowed to confirm the effectiveness of the personalized treatment.

48% (58/121) of PET-positive results were confirmed by repeated PET/CT examinations. Obtained PET/CT results allowed to determine further therapeutic approach of all PCa patients with BCR.

4. Discussion

In PCa patients with BCR the detection of the site of relapse is crucial for further therapeutic approach [3–5]. In patients with revealed local PCa relapse and low PSA level – salvage RT to the prostatic bed is considered effective [3–5]. If distant metastases are present – the systemic therapy has been considered the only option. However, significant number of patients have increasing PSA due to single or minimal (up to

three) number of metastatic lesions – oligometastatic recurrence [6]. And recently and increasing number of studies on metastases-directed therapy (surgery or RT) of PCa relapse in such patients are being published [5, 6]. The results of these studies show that a personalized treatment approach allows to delay the beginning of the systemic treatment [6].

Overall, in the current study 11C-Choline PET/CT results detected PCa relapse in 56% (121/217) of cases. Rodado-Marina et al. analyzed a group with comparable number of patients and reported 48% (111/233) [9]. In other studies, performed on larger and mixed groups of patients (both after RP and RT) as well, 11C/18F-Choline PET/CT results allowed to reveal PCa relapse in 62% (155/250), 65% (124/185), 74% (185/250) and 76% (129/170) [10–13]. Higher rates obtained in the above mentioned studies were, most likely, due to high PSA values: up to 43 ng/ml, 4692 ng/ml and 98 ng/ml, respectively [10, 12, 13]. While PSA values in our group did not exceed 10 ng/ml. Patients with higher PSA levels were excluded from the analysis, as PCa relapse according to PET/CT results was diagnosed in 100% of cases.

Graziani et al. retrospectively analyzed a large group of patients (n = 4426) with similar inclusion criteria to our study: BCR after two main types of primary treatment with mean PSA value 4.9 ng/ml and median 2.1 ng/ml (in current study 2.1 ng/ml and 1.9 ng/ml, respectively). The PET/CT detection rate was 53%, of which distant metastases were revealed in 29% [14]. In our study similar detection rates of 56% and 27%, respectively, were obtained.

In the current study, in patients with rising PSA after RP 11C-Choline PET/CT results allowed to detect PCa recurrence in 50% (80/159) of cases. Other authors, who performed studies on larger groups of patients after RP, reported 44% (75/170) and 45% (161/358) [15, 16].

There are only few publications with detailed analysis of an isolated group of PCa patients after RT. In the current study, the detection rate of 11C-Choline PET/CT in this group of patients was quite high – 71% (41/58) of cases. In other studies performed on larger groups of patients with rising PSA after RT high rates were obtained as well – 78% (65/83), 82% (102/124) and 88% (123/140) [11, 17, 18]. It is noted, that 11C-Choline PET/CT detection rate is significantly higher in patients after RT than after RP [11, 19].

The mean PSA value in PET-positive cases was significantly higher than in PET-negative cases and a strong positive correlation between 11C-Choline detection rate of relapse and PSA serum level ($p < 0.05$ for both) was revealed. Obtained results are in agreement with most of the reported studies [11, 13, 20, 21].

We also performed a detailed analysis of patients with low PSA level (< 2 ng/ml) – a very important cohort for treatment-decision making: if distant metastases are excluded, a salvage RT should be considered, and its effectiveness is higher at PSA level less than 0.5 ng/ml [3]. This group formed up the majority of total cases – 53% (115/217). It's remarkable that in these cases with low PSA values a high rate of PET-negative results was revealed – 57% (65/115). And we believe that this could affect the total PET/CT detection rate of PCa relapse in the current study (56%). Though, PET/CT was able to detect PCa relapse in 43% (50/115) patients with low PSA values (< 2 ng/ml). According to data of other authors, PET/CT showed corresponding rates ranged from 19% to 55% [9, 19, 21–24].

The prevalence of local relapse was observed – in 51% of patients. The same detection rate was reported by Rybalov et al. [11]. Von Eyeben et al. performed a meta-analysis of 26 studies on 11C/18F-Choline PET/CT diagnostic performance in 2348 PCa patients with BCR after RP and the prevalence of local relapse was revealed as well [25]. In the study of Marzola et al. in the majority of cases (66%) distant metastases were detected – we suppose that this may be due to the prevalence of high risk patients (Gleason >8) and high mean PSA value in the group (8.0 ng/ml) [26].

In the current study lymph node metastases were detected in 71% (86/121) of all revealed PCa relapses by PET/CT, according to other studies this rate varies from 47% up to 66% [17, 21, 26]. Importantly, that PET/CT allows to detect metastases to lymph nodes of normal size (less than 10 mm diameter), which cannot be considered pathological according to other imaging modalities.

Bone metastases were detected in 33% (40/121) of all revealed PCa relapses by PET/CT. Other authors obtained similar results – 29% (46/161), 30% (33/111) and 34% (42/123) [9, 21, 27]. PET/CT allowed to detect isolated involvement of bone marrow in 27% of patients with bone metastases; Garcia et al. report 39% [28]. Another important result was the detection of oligometastatic bone lesions in 63%, Ceci et al. obtained similar result – 70% [29].

Overall, 11C-Choline PET/CT results allowed to reveal oligometastatic PCa recurrence in 68% of all detected PCa relapses according to PET/CT data. Similar results were published by Chondrogiannis et al. and Ceci et al. – in both studies this rate was of 63% [10, 18].

5. Conclusions

11C-Choline PET/CT has been shown to be a single noninvasive accurate technique for detection of reccurent PCa in patients with rising PSA after radical treatment. These data allow to differentiate patients with local and distant metastases in one study (in 56%), as well as identify oligometastatic process, and therefore was useful in determining the further personalized therapeutic approach.

A strong positive correlation between PSA level and 11C-Choline PET/CT detection rate of PCa relapse was confirmed (r = 0.9; p < 0.05).

In patients with low PSA value (< 2.0 ng/ml). 11C-Choline PET/CT was able to correctly detect PCa relapse (both local and systemic) in 43% of cases.

11C-Choline PET/CT confirmed its ability to detect PCa metastases lymph nodes of normal size.

11C-Choline PET/CT identified bone metastases in patients with low PSA values (minimal 0.4 ng/ml; median 3.8 ng/ml) and in cases with no morphologic changes on CT.

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