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Прецизионная брахитерапия рака предстательной железы под контролем ПСМА-рецепторной молекулярной визуализации

П.В. Свиридов¹, П.О. Румянцев², М.В. Дегтярев³, С.С. Серженко³, Д.Б. Санин^{1, 4}, С.В. Стыров¹, Д.Ю. Агибалов¹, С.В. Корнев⁵

¹ Медицинский центр «Доктор Плюс», Обнинск, Российская Федерация;

² Группа клиник «Мой медицинский центр», Санкт-Петербург, Российская Федерация;

³ Национальный медицинский исследовательский центр эндокринологии, Москва, Российская Федерация;

⁴ Национальный медицинский исследовательский центр радиологии, Обнинск, Российская Федерация;

⁵ Балтийский федеральный университет имени Иммануила Канта, Калининград, Российская Федерация

АННОТАЦИЯ

Одним из методов лечения локализованного рака предстательной железы без признаков прорастания капсулы железы и в отсутствии признаков метастазов (стадия cT1-T2N0M0) является брахитерапия с имплантацией микроисточников на основе изотопа ¹²⁵I. Методы структурной визуализации (ультразвуковое исследование; компьютерная томография, КТ; магнитно-резонансная томография, МРТ) не обладают высокой специфичностью в дифференциальной диагностике рака предстательной железы. Гибридные технологии лучевой визуализации (однофотонная эмиссионная компьютерная томография + компьютерная томография, ОФЭКТ/КТ; позитронно-эмиссионная томография + компьютерная томография, ПЭТ-КТ; позитронно-эмиссионная томография + магнитно-резонансная томография, ПЭТ/МРТ) сочетают в себе достоинства высокой чувствительности кросс-секционных методов структурной визуализации (КТ и МРТ) и высокой специфичности методов молекулярной визуализации (ОФЭКТ, ПЭТ) с туморотропными радиофармацевтическими лекарственными препаратами.

В данной работе на 7 клинических наблюдениях локализованного рака предстательной железы (шкала Глисона 6–7) показано, что прецизионность низкодозной брахитерапии микроисточниками ¹²⁵I локализованных карцином предстательной железы, равно как и прицельной биопсии, может быть повышена при использовании гибридных методов ПСМА-рецепторной (простатспецифический мембранный антиген) молекулярной визуализации (ОФЭКТ/КТ, ПЭТ/КТ). Метод ОФЭКТ/КТ более доступен, чем ПЭТ/КТ, и при наличии холодных наборов (HYNIC-PSMA) позволяет выполнять исследование в любой лаборатории радиоизотопной диагностики, располагающей соответствующими сканерами.

Инновационная технология ПСМА-навигационной биопсии и брахитерапии под контролем гибридной молекулярной визуализации может применяться при первичных и рецидивных случаях локализованного рака предстательной железы, увеличивает точность и снижает травматичность процедур, повышает медико-экономическую эффективность низкодозной брахитерапии микроисточниками ¹²⁵I.

Необходимы дальнейшие исследования для совершенствования технологии и оценки отдалённых результатов лечения на многочисленной группе пациентов.

Ключевые слова: брахитерапия низкодозная прецизионная; йод-125; простатспецифический мембранный антиген; ПСМА; однофотонная эмиссионная компьютерная томография, совмещённая с компьютерной томографией; ОФЭКТ/КТ; позитронно-эмиссионная томография, совмещённая с компьютерной томографией; ПЭТ/КТ.

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Precision low-dose brachytherapy of prostate cancer under PSMA-receptor molecular visualization

Pavel V. Sviridov¹, Pavel O. Rumiantsev², Mikhail V. Degtyarev³, Sergey S. Serzhenko³, Dmitry B. Sanin^{1, 4}, Sergey V. Styrov¹, Dmitry Yu. Agibalov¹, Sergey V. Korenev⁵

¹ Medical center "Doctor Plus", Obninsk, Russian Federation;

² Clinics group "My Medical Center", Saint Peterburg, Russian Federation;

³ Endocrinology Research Centre, Moscow, Russian Federation;

⁴ National Medical Research Radiological Center, Obninsk, Russian Federation;

⁵ I. Kant Baltic Federal University, Kaliningrad, Russian Federation

ABSTRACT

Brachytherapy with implantation of micro sources based on isotope ¹²⁵I is a preferred treatment for localized prostate cancer without signs of germination of the gland capsule and in the absence of signs of metastases (stage cT1-T23aN0M0). Structural imaging methods (ultrasound, computed tomography, and magnetic resonance imaging) do not have high specificity in the differential diagnosis of prostate cancer. Hybrid technologies of radiation imaging (single-photon emission computed tomography/computed tomography, positron emission tomography/computed tomography, and positron emission tomography/magnetic resonance imaging) combine the advantages of high sensitivity of cross-sectional structural imaging methods (computed tomography and magnetic resonance imaging) and high specificity of molecular imaging methods (single-photon emission computed tomography and positron emission tomography) with tumorotropic radiopharmaceuticals. In this original clinical study, based on seven observations of localized prostate cancer (Gleason 6–7), it was shown that the precision of low-dose brachytherapy using ¹²⁵I micro sources of localized prostate carcinomas, along with targeted biopsy, can be increased using hybrid methods of PSMA-receptor molecular imaging (single-photon emission computed tomography/ computed tomography, positron emission tomography/ computed tomography). The single-photon emission computed tomography/ computed tomography method is more accessible than positron emission tomography/ computed tomography. Moreover, when coupled with cold kits (HYNIC-PSMA), it allows research within any radioisotope diagnostics laboratory equipped with single-photon emission computed tomography/ computed tomography. The innovative technology of PSMA-navigation biopsy and brachytherapy, under the control of hybrid molecular imaging, can be used in primary and recurrent cases of localized prostate cancer, increases the accuracy and reduces the traumatic nature of procedures, and increases the medical and economic efficiency of low-dose brachytherapy with ¹²⁵I micro sources. Further research is needed to improve the technology and evaluate its long-term results.

Keywords: brachytherapy low-dose rate precision; ¹²⁵I; prostate-specific membrane antigen; PSMA; single-photon emission computed tomography / computed tomography; positron emission tomography / computed tomography.

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在PSMA受体分子成像控制下的前列腺癌精确近距离照射

Pavel V. Sviridov¹, Pavel O. Rumiantsev², Mikhail V. Degtyarev³, Sergey S. Serzhenko³, Dmitry B. Sanin^{1,4}, Sergey V. Styrov¹, Dmitry Yu. Agibalov¹, Sergey V. Korenev⁵

¹ Medical center "Doctor Plus", Obninsk, Russian Federation;

² Clinics group "My Medical Center", Saint Peterburg, Russian Federation;

³ Endocrinology Research Centre, Moscow, Russian Federation;

⁴ National Medical Research Radiological Center, Obninsk, Russian Federation;

⁵ I. Kant Baltic Federal University, Kaliningrad, Russian Federation

简评

治疗无腺囊萌发迹象和无转移迹象（cT1-T2N0M0期）的局部前列腺癌的方法之一是植入基于同位素¹²⁵I的微源近距离照射。结构成像方法（超声检查、电子计算机断层扫描（CT）、磁共振成像（MRI））在前列腺癌的鉴别诊断中特异性不高。混合放射成像技术（单光子发射计算机断层扫描+电子计算机断层扫描，SPECT/CT；正电子发射计算机断层扫描+电子计算机断层扫描，PET/CT；正电子发射断层扫描+磁共振成像，PET/MRI）结合了结构成像的横断面方法（CT和MRI）的高灵敏度和分子成像方法（SPECT、PET）的高特异性与肿瘤放射治疗物的优点。

在这项研究中，7例局部前列腺癌（格里森评分为6-7分）的临床观察结果表明了，通过使用PSMA受体（前列腺特异性膜抗原）分子成像（SPECT/CT、PET/CT）的混合方法，可以提高使用微源¹²⁵I对局部前列腺癌进行低剂量近距离照射以及靶向活检的精确度。SPECT/CT比PET/CT更经济实惠，而且在存在冷试剂盒（HYNIC-PSMA）的情况下，允许在任何拥有适当扫描仪的放射性同位素诊断实验室进行检查。

混合分子成像控制下的PSMA引导活检和近距离照射创新技术可用于原发性和复发性的局部前列腺癌病例，提高准确度，减少检查创伤性，提高微源¹²⁵I低剂量近距离照射的医疗和经济效益。

还需要进一步的研究来改进这种技术，并对大量患者的长期治疗效果进行评估。

关键词：精确低剂量近距离照射；碘125；前列腺特异性膜抗原；PSMA；联合电子计算机断层扫描的单光子发射计算机断层扫描；SPECT/CT；联合电子计算机断层扫描的正电子发射计算机断层扫描；PET/CT。

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BACKGROUND

Prostate cancer is the second most common malignant neoplasm in males and the fifth most common cause of death in the world [1]. Screening for prostate cancer based on the level of prostate-specific antigen (PSA) in the blood increases the number of prostate carcinomas detected at an early stage, significantly improving the prognosis of patient survival [2].

One method for treating localized prostate cancer without signs of capsule germination and without metastases (cT1-T2N0M0) is brachytherapy with implantation of ^{125}I -based microspheres [3–8].

In brachytherapy, the radiation dose is achieved by spatial distribution of microspheres during implantation in the projection of primary prostate carcinoma guided by computed tomography (CT) or ultrasound (US). Implanted microspheres are fixed in the tissue, protecting surrounding healthy tissue from irradiation. Simultaneously, safe irradiation borders (2–3 mm) along the periphery of microspheres do not lead to side irradiation of risk organs, such as the urethra, bladder, and rectum, which are inevitably affected during prostatectomy, external beam radiation therapy, and high-dose brachytherapy. Some studies of prostate cancer patients at low and moderate risk of tumor recurrence showed better tumor ablation than external beam radiotherapy [4, 5]. The effectiveness of low-dose brachytherapy in patients with localized prostate cancer (pT1-2N0M0) is at least noninferior compared with any other current treatment method, whereas patient tolerability and quality of life are significantly higher [9]. While in the early 2000s, low-dose brachytherapy was combined with external beam radiation therapy for boosting in a moderate risk group, in recent decades, this method has been used more frequently [10].

The brachytherapy method has several advantages, including its low invasiveness (puncture technology), the ability to control the process of installing microspheres using structural imaging methods (ultrasound and CT), and the low frequency and low severity of adverse effects [11].

Hybrid radiation imaging technologies, such as single photon emission CT combined with CT (SPECT/CT), positron emission tomography combined with CT (PET/CT), and positron emission tomography combined with magnetic resonance imaging (PET/MRI), combine the high sensitivity of cross-sectional structural imaging methods (CT and MRI) and high specificity of molecular imaging methods (SPECT and PET) with tumor tropic radiopharmaceuticals (RPs).

Prostate-specific membrane antigen (PSMA) in humans is encoded by the *FOLH1* gene, which is involved in folate metabolism. It is a zinc-containing transmembrane glycoprotein produced in prostate epithelial cells and known as N-acetyl-L-aspartyl-L-glutamate peptidase or glutamate carboxypeptidase II. Its expression is significantly higher in malignant cells and closely related to tumor aggressiveness, particularly in castration-resistant and metastatic prostate cancer [12].

PSMA-receptor molecular imaging techniques (SPECT and PET) provide additional advantages in determining tumor stage and selecting targets for precision biopsy and brachytherapy of prostate carcinoma [13]. PET/CT with ^{68}Ga -PSMA-11 and ^{18}F -PSMA-1007 and SPECT/CT with $^{99\text{m}}\text{Tc}$ -HYNIC-PSMA (small-molecule PSMA inhibitors) are accessible in Russian clinical practice. The latter appears highly promising because of its greater availability (significantly more SPECT/CT scanners than PET/CT scanners), easy operation, lower cost, and technological advantages to ensure high precision in biopsy and brachytherapy of localized prostate cancer.

CASE REPORTS

Patients

The study examines treatment outcomes in seven patients aged 65–84 yr (mean: 73 yr; 95% confidence interval [95% CI], 66.8–79.2) with histologically diagnosed prostate cancer who underwent brachytherapy using ^{125}I -based microspheres at the Doctor-Plus clinic in Obninsk, Kaluga region, Russia. All patients had histologically confirmed prostate carcinoma with no signs of regional and/or distant metastases. Five patients had primary tumors. Another two patients had local tumor recurrence in 21 and 28 months after receiving brachytherapy with ^{125}I -based microspheres. The tumor stage in two patients was T1N0M0, whereas the stage in four patients was T2N0M0. The stage in one patient was T3aN0M0. In the other case, the patient refused the proposed surgical treatment, which included combined external beam radiation and androgen deprivation therapy.

The Gleason score was 6 (3 + 3) in five cases and 7 (3 + 4) in two cases. Before brachytherapy, blood PSA levels ranged from 2.8 to 12 ng/mL (mean: 8.2 ng/mL).

Methods

Patients with local tumor recurrence were treated with interstitial radiation therapy using ^{125}I -based microspheres in the first stage. The time to progression ranged from 12 to 29 months (24.2 [95% CI, 17.8–30.5]).

Clinical examination included standard measurement of serum PSA levels. A venous blood sample was collected in the morning under fasting conditions and prepared in accordance with study protocols. Serum PSA levels were measured using a chemiluminescent immunoassay (sensitivity limits: 0.008–30.0 ng/mL).

Transrectal ultrasound diagnostics was performed using a B/K Medical scanner (USA) to determine the prostate volume and residual urine. Uroflowmetry was performed to assess the maximum volumetric urine flow rate.

In the excretory phase, a pelvic CT with intravenous contrast enhancement (Omnipaque 350 mg/mL, 30 mL) was performed to better visualize the anatomy of organs at risk using a Somatom Scope multidetector (32 slices) CT scanner (Siemens, Germany) with subsequent data transfer for planning interstitial radiation therapy.

A radionuclide study with ^{99m}Tc -HYNIC-PSMA was performed using a General Electric Discovery NM/CT 670 hybrid scanner. The finished RP was administered intravenously with a vent visor (intranasal control) at a 6.3 MBq/kg b.w rate. A pelvic area was scanned 2 h after RP administration using a SPECT/CT gamma camera; 60 projections with 30-s exposures per projection, matrix 256×256 . CT data acquisition parameters were as follows: tube voltage, 120 kV; current (modulated), 80–400 mA; slice thickness, 3.75 mm with 1.25-mm reconstruction; and couch increment, 1 mm. The resulting 3D SPECT/CT image was analyzed using the General Electric Xeleris 4DR data workstation. The identified prostate lesions of focal RP accumulation were indicated on a schematic PI-RADS prostate sector map.

Without anesthesia, a US-guided biopsy was performed transperineally (using SPECT/CT data with ^{99m}Tc -HYNIC-PSMA) with a Promag 2.0 biopsy needle and gun. If required, a CT-guided biopsy of the prostate gland and seminal vesicles was performed under spinal anesthesia through pararectal access. Histological biopsy specimens were examined in pathological laboratories with Gleason score determination.

Planning and conducting brachytherapy with ^{125}I sources

Topometry and dosimetry planning were performed for pre-implantation planning using a VariSpeed dosimetry

planning system (Varian, USA). That system allowed the DICOM format images of different modalities to be combined.

^{125}I -based microspheres were implanted under a CT guide using a Siemens Somatom Scope (Germany) using a 3D stereotactic machine with a hole increment of 2.5 mm to perform targeted brachytherapy. Under spinal anesthesia, the procedure was performed via pararectal access.

Figure 1 shows an example of pre-implantation brachytherapy planning using ^{125}I sources. Crosses indicate virtual holes in the stereotactic array, which fully corresponds to the array implanted in a patient. Red dots indicate microspheres, whereas colored lines indicate isodose distribution.

^{125}I microspheres in the form of grains (BEBIG LLC, Russia) were used for interstitial implantation. Each source measured 4.5 mm in length and 0.8 mm in diameter. According to the comprehensive examination results and dosimetry planning, the number of sources was ordered individually for each patient (Table 1).

Brachytherapy requires bowel preparation and antibiotic therapy. Spinal anesthesia with lidocaine/bupivacaine was administered to relieve pain.

The implantation was performed in accordance with 2014 recommendations [12]. During control scans and

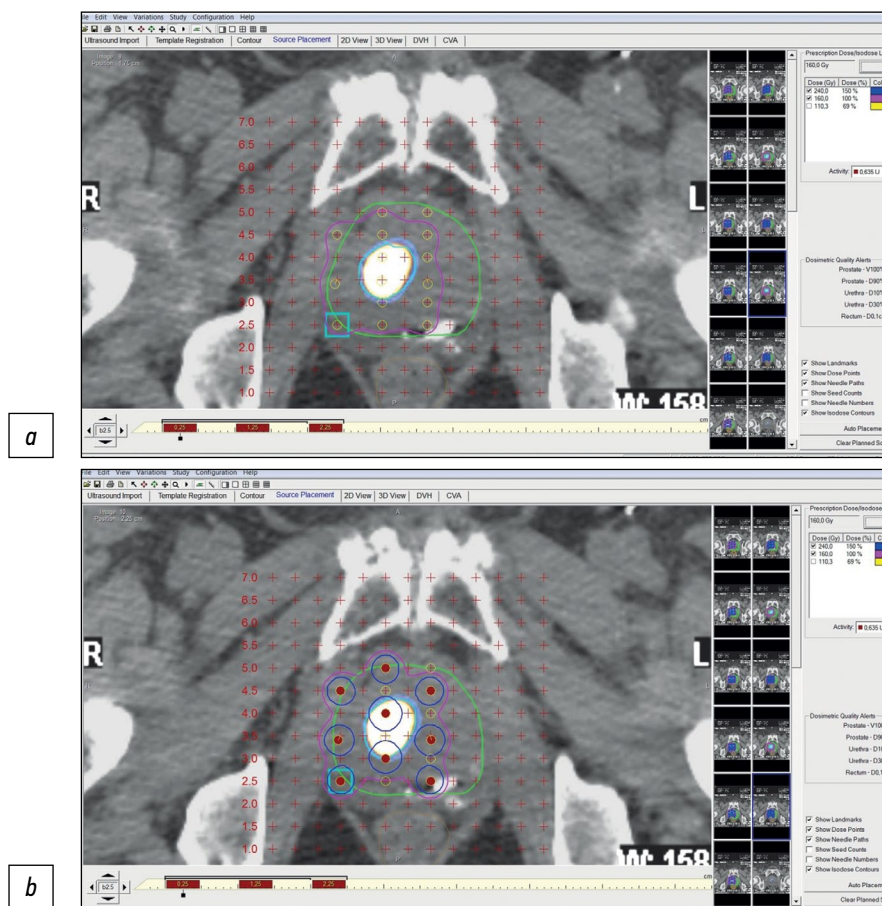


Fig. 1. Stages of dosimetry planning of brachytherapy localized prostate cancer using ^{125}I microspheres considering SPECT/CT with ^{99m}Tc -HYNIC-PSMA: (a) topometric marking and (b) topometric marking and dosimetry planning of brachytherapy.

Table 1. Demographic data and clinical and morphological characteristics of patients

Age ^a , yr	Tumor			Prostate volume/ prostate tumor volume, mL	Localization in pancreas ^d	Planned number of ¹²⁵ I microspheres/length of procedure ^e	Planned number of ¹²⁵ I microspheres/length of procedure ^f
	Stage, TNM ^b	Primary case or relapse ^c	Gleason score				
Patient 1 84 years old	T2N0M0	Primary	7 (4 + 3)	40/40	Right lobe TZa (mid)	60 75 min	60 75 min
Patient 2 79 years old	T2N0M0	Primary	6 (3 + 3)	38/15	Right lobe TZa (apex), Left lobe TZp (mid)	60 75 min	20 25 min
Patient 3 73 years old	T1N0M0	Primary	6 (3 + 3)	36/14	Right lobe TZa (apex), Left lobe PZpl (base) PZpl (mid)	70 87 min	32 45 min
Patient 4 68 years old	T3N0M0	Relapse	7 (4 + 3)	38/15	Right lobe TZp, PZpl (base)	60 75 min	20 25 min
Patient 5 70 years old	T2N0M0	Relapse	6 (3 + 3)	30/15	Right lobe PZpl (mid)	70 87 min	30 40 min
Patient 6 65 years old	T1N0M0	Primary	7 (4 + 3)	60/15	Right lobe TZa (mid)	90 112 min	30 40 min
Patient 7 69 years old	T2N0M0	Primary	6 (3 + 3)	78/78	Right lobe TZa (apex), Left lobe PZpl (base) PZpl (mid)	32 45 min	90 112 min

Note. PSMA, prostate-specific membrane antigen; PZpl (mid/base), posterior zone (middle/basal part); SPECT/CT, single photon emission computed tomography combined with computed tomography; TZa (mid/apex), anterior transition zone (middle/apical part); TZp (mid), posterior transition zone (middle part).

^aAge of patients at the time of treatment.

^bUICC, 8th ed. (https://oncology.ru/specialist/treatment/tnm/tnm8_summary.pdf).

^cMethod of primary treatment.

^dInternational standard.

^eWithout tumor visualization using SPECT/CT.

^fUnder PSMA/SPECT/CT guide.

reconstruction of the resulting images, the placement of ¹²⁵I microspheres was visually monitored.

Patients were discharged 1 day after brachytherapy and were able to return to normal activities within 3–5 days. None of the patients required bladder catheterization or epicystostomy. Mild difficulty urinating was relieved using alpha-blockers in generally accepted doses. There were no reports of early or late radiation effects.

The duration of the brachytherapy procedure depended on the number of implanted ¹²⁵I microspheres and ranged from 25 to 112 min (mean: 51.7 min), which was 34.8% less than the average estimated time (79.4 min) using a standard procedure (without PSMA-SPECT/CT guide).

No severe complications were observed in the early and long-term post-procedure periods (mean: 24.5 months). Mild dysuric symptoms were reported in two patients for several post-procedure days, but they did not require catheterization or drug therapy and resolved spontaneously.

Case report 1

Patient Zh., 84 years old, was admitted with prostate cancer (PSA of 20 ng/mL; adenocarcinoma, Gleason 7 [4 + 3]). On October 9, 2020, CT-guided interstitial radiation therapy with ¹²⁵I microspheres and pararectal access was performed using SPECT/CT data. PSA levels were 0.16 ng/mL 2 yr later, indicating tumor remission. PSA was 0.1 ng/mL on January 14, 2023.

Figure 2 shows SPECT/CT data with ^{99m}Tc-HYNIC-PSMA.

Case report 2

Patient Z., 79 years old, was admitted with diffuse prostatic hyperplasia. PSA level was 4.5 ng/mL. No abnormal lesions were found in the prostate tissue using ultrasound, TRUS, and contrast-enhanced MRI. SPECT/CT with ^{99m}Tc-HYNIC-PSMA revealed 15-mm³ sites of RP accumulation in the prostate tissue (Figure 3). Because rectal amputation made US-guided prostate biopsy impossible, a targeted CT-guided biopsy

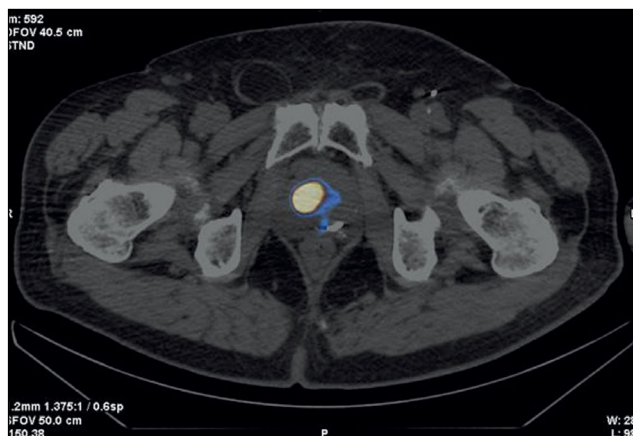


Fig. 2. Patient Zh., 8 years old, SPECT/CT with ^{99m}Tc-HYNIC-PSMA, axial projection: Site of radiopharmaceutical accumulation in the transition zone of the middle part of the right prostate lobe.

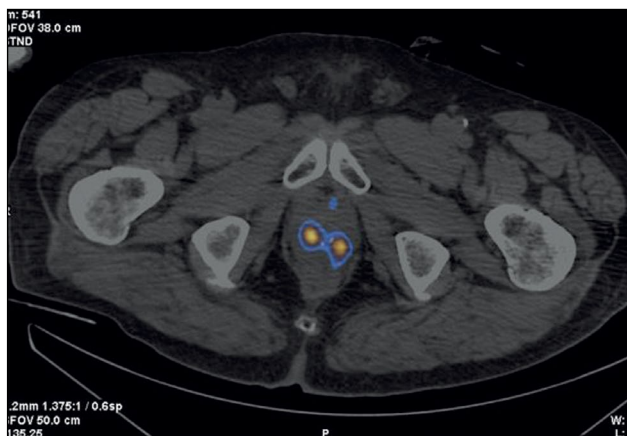


Fig. 3. Patient Z., 7 years old, SPECT/CT with ^{99m}Tc-HYNIC-PSMA: Sites of radiopharmaceutical accumulation in transitory zones of both lobes at the border of the middle third and the apex of the prostate gland.

was performed pararectally. A morphological diagnosis was adenocarcinoma, Gleason 6 (3 + 3).

On January 28, 2021, ¹²⁵I sources were implanted pararectally under a CT guide. In the follow-up examination, PSA levels were 0.2 ng/mL (September 2022) and 0.1 ng/mL (January 14, 2023).

In this case, two problems were revealed: an unknown cause of increased PSA over time and the inability to perform a targeted prostate carcinoma biopsy under US guide. Both problems were successfully resolved using hybrid SPECT/CT with ^{99m}Tc-HYNIC-PSMA followed by CT-guided RP accumulation site biopsy, and precision brachytherapy was performed with a smaller number of ¹²⁵I microspheres due to the SPECT/CT pattern.

Case report 3

Patient K., 73 years old, was admitted with diffuse prostatic hyperplasia, urinary retention, an epicycstostomy, and a 12.7-ng/mL PSA. A multisite biopsy performed under

US guide revealed no evidence of malignant development. SPECT/CT data with ^{99m}Tc-HYNIC-PSMA are shown in Figure 4. SPECT/CT revealed a 14-mm³ site of RP accumulation in the prostate tissue. A CT-guided targeted biopsy was performed using pararectal access. A morphological diagnosis was adenocarcinoma, Gleason 6 (3 + 3).

On November 28, 2020, CT-guided focal implantation of ¹²⁵I sources was performed pararectally. Transurethral resection of the intravesical component was performed, and the epicycstostomy was removed. The follow-up examination (November 28, 2022) showed a PSA level of 0.13 ng/mL, spontaneous urination, and 15-cm³ residual urine.

In this case, problems were as follows: inability to identify the cause of elevated PSA, a “large” volume of the prostate gland, and epicycstostomy. Considering data on RP accumulation patterns and biopsy results, we were unable to successfully solve these problems and perform successful focal brachytherapy using a hybrid diagnostic use of RP CT-guided biopsy.



Fig. 4. Patient K., 73 years old, SPECT /CT with ^{99m}Tc-HYNIC-PSMA, (a) frontal and (b) axial sections: Sites of radiopharmaceutical accumulation in the anterior part of the transition zone in the apex of the right lobe, posterolateral part of the peripheral zone at the level of the base of the left lobe, and posterolateral part of the peripheral zones at the level of the base and middle third of the left lobe of the prostate gland; physiological accumulation of radiopharmaceuticals in the bladder.

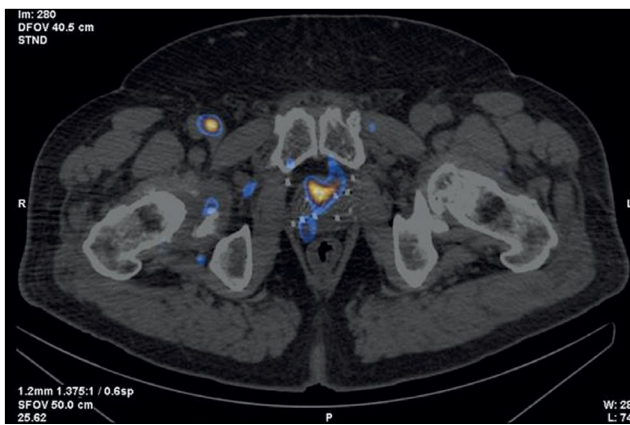


Fig. 5. Patient F., 68 years old, SPECT/CT with ^{99m}Tc -HYNIC-PSMA: Sites of radiopharmaceutical accumulation at the border of the central zone and the posterolateral part of the peripheral zone on the right side at the level of the base of the right prostate lobe. The scan visualizes multiple rods in the prostate gland, implanted during previous brachytherapy.

Case report 4

Patient F., 68 years old, was admitted with prostate cancer, T3a, which had spread to the prostate gland capsule. In 2013, ^{125}I sources were implanted into the prostate tissue and the extracapsular area. PSA has increased since the end of 2020. SPECT/CT was performed using ^{99m}Tc -HYNIC-PSMA due to an increased PSA level of 0.95–2.8 ng/mL after the previous treatment (Figure 5). SPECT/CT revealed a 15-mm³ site of tumor tropic RP accumulation, which was biopsied under the CT guide. A histological diagnosis was prostate adenocarcinoma, Gleason 6 (3 + 3). Dosimetry planning for low-dose brachytherapy was performed using SPECT/CT. On November 03, 2021, ^{125}I microspheres were re-implanted according to topometric markings to implement the dosimetry plan. The PSA level was 0.05 ng/mL during the follow-up examination (January 23, 2023).

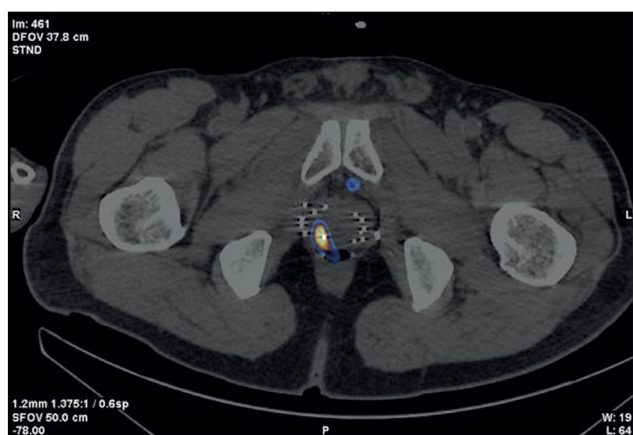


Fig. 6. Patient G., 70 years old, SPECT/CT with ^{99m}Tc -HYNIC-PSMA: Site of radiopharmaceutical accumulation in the posterolateral part of the peripheral zone of the middle part of the right prostate lobe. Multiple rods in the prostate gland were implanted during previous brachytherapy.

In this case, SPECT/CT with ^{99m}Tc -HYNIC-PSMA allowed for a precision biopsy, which confirmed the local recurrence of prostate cancer and subsequently enabled brachytherapy to be repeated (salvage) under the CT guide.

Case report 5

Patient G., 70 years old, was admitted with prostate cancer (diagnosed in 2005), T2a, adenocarcinoma, Gleason 6 (3 + 3). CT-guided brachytherapy was successfully performed in 2005. The PSA level has increased (1.94–2.31 ng/mL) since 2017. Because of this growth, ultrasound, TRUS, CT, and contrast-enhanced MRI were performed; no data for a local recurrence or another cause of PSA growth were obtained. When the PSA level reached 2.63 ng/mL, SPECT/CT with ^{99m}Tc -HYNIC-PSMA was performed (Figure 6). Results showed a 15-mm³ site of RP accumulation, and a targeted biopsy of a recurrent prostate carcinoma lesion was performed based on its SPECT/CT location. Adenocarcinoma was confirmed histologically, Gleason 6 (3 + 3). On March 10, 2020, a brachytherapy with reimplantation of ^{125}I microspheres was performed. The follow-up examination (December 2022) showed a PSA level of 0.21 ng/mL.

In this case, SPECT/CT with ^{99m}Tc -HYNIC-PSMA enabled prostate carcinoma-targeted biopsy and precision brachytherapy.

Case report 6

Patient M., 65 years old, was diagnosed with benign prostatic hyperplasia. Due to an increased PSA level of 4.5 ng/mL, a US-guided multifocal biopsy was performed with no histological evidence of cancer. A repeat biopsy was performed 3 months later and revealed no malignant tumor. SPECT/CT with ^{99m}Tc -HYNIC-PSMA revealed a site of RP accumulation in the prostate tissue (Figure 7). A CT-guided targeted biopsy was performed, and the following diagnosis was morphologically confirmed: adenocarcinoma,

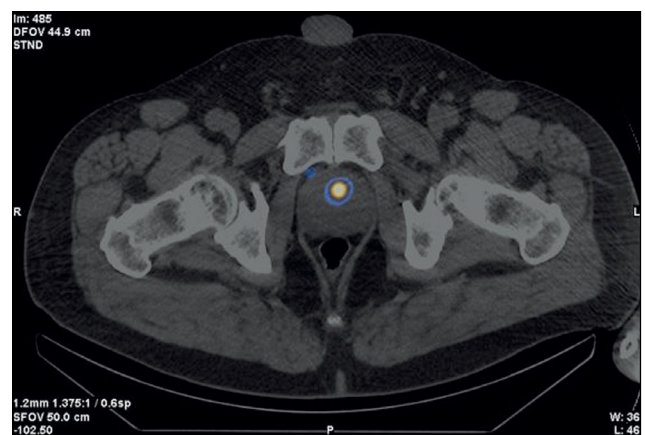


Fig. 7. Patient M., 65 years old, SPECT/CT with ^{99m}Tc -HYNIC-PSMA: Site of radiopharmaceutical accumulation in the transition zone (at the border of the middle third and the base) of the left prostate lobe.

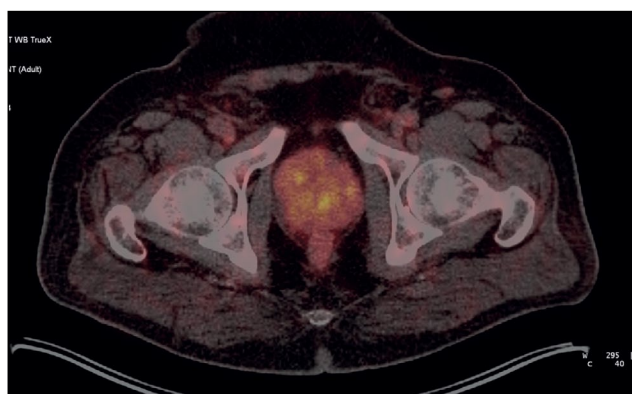


Fig. 8. Patient M., 69 years old, PET/CT with 68Ga-PSMA-11: Sites of radiopharmaceutical accumulation in the prostate gland, multifocal tumor.

Gleason 7 (4 + 3). When planning low-dose brachytherapy using ¹²⁵I microspheres, SPECT/CT data were entered into the dosimetry planning system. On October 4, 2020, the focal implantation of ¹²⁵I microspheres was performed under a CT guide using pararectal access based on data on local isotope accumulation in the prostate tissue. The follow-up examination (January 2023) showed a 0.11-ng/mL PSA level.

Case report 7

Patient M., 6 years old, had an increased PSA level of 6.8 ng/mL and underwent a multifocal prostate biopsy at a local clinic. The diagnosis was confirmed morphologically as adenocarcinoma, Gleason 6 (3 + 3), based on data from the transitory zone of the right prostate lobe. Adenocarcinoma elements were not found in other prostate biopsy specimens. Considering MRI evidence of changes in the same zone, implantation with 30 ¹²⁵I sources with a 32-cm³ volume was proposed.

SPECT/CT with ^{99m}Tc-HYNIC-PSMA revealed diffuse focal RP accumulation under the base of the bladder. PET/CT with 68Ga-PSMA-11 was additionally performed to more accurately visualize prostate lesions. PET/CT revealed multiple sites of RP accumulation in the prostate gland, indicating that the tumor was multifocal (Figure 8). Implantation planning was adjusted to include the total volume of the prostate gland (78 cm³) using 90 ¹²⁵I microspheres (instead of preliminary 30 microspheres).

On February 25, 2022, implantation was performed for the total volume of the prostate gland. The initial prostate volume for brachytherapy was 32 cm³. PET/CT revealed a volume of 72 cm³ for implantation. The PSA level decreased to 0.31 ng/mL within a year after brachytherapy.

Changes in PSA levels in all patients included are shown in Figure 9.

All patients are under clinical supervision and have regular follow-up examinations.

DISCUSSION

A biopsy of prostate lesions is required to confirm the diagnosis and select a management strategy. This procedure is often performed under a US or MRI guide [14–15]. Because radiological structural diagnostics methods (ultrasound, CT, and MRI) do not always visualize lesions of the primary tumor, traumatic multifocal biopsies are often required [15]. False-negative biopsy results are reported in up to 49% of cases. If blood PSA levels increase, a biopsy is repeated [16]. A repeat biopsy is typically performed within 3 months after the initial [16]. Conventional diagnostic methods (ultrasound, CT, and MRI), particularly multiparametric MRI, visualize structural abnormalities but do not differentiate between benign and malignant tumors or assess the borders of a malignant tumor and its multifocal nature [15–17].

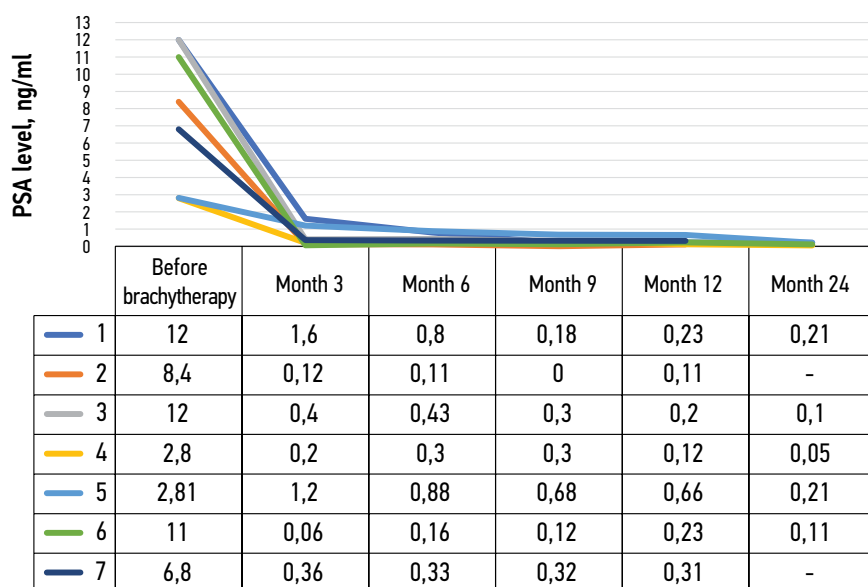


Fig. 9. Changes in prostate-specific antigen levels in individual patients.

The morbidity and false-negative results of conventional prostate biopsy can be reduced with PSMA-receptor imaging guidance using SPECT/CT and/or PET/CT [18–21].

For prostate carcinomas with a low and moderate risk of recurrence (Gleason ≤ 7), no growth beyond the organ capsule, and evidence of metastases, brachytherapy with ^{125}I microspheres is the least traumatic of all recommended treatment options, demonstrating not only high effectiveness but also high quality of life [22].

Molecular imaging methods (SPECT and PET) combined with cross-sectional imaging (CT and MRI) differentiates between lesions of malignant prostate tumors with high expression of PSMA receptors and benign structural lesions. As a result, it is possible to perform a US-guided targeted biopsy of positive lesions (considering molecular imaging data) and accurately plan and provide CT-guided brachytherapy.

The paper presents original clinical experience proving the feasibility of precision biopsy and brachytherapy of localized nonmetastatic prostate cancer (pT1–3N0M0) guided by PSMA-receptor molecular imaging (SPECT/CT with $^{99\text{m}}\text{Tc}$ -HYNIC-PSMA and PET/CT with ^{68}Ga -PSMA-11). Topometric marking and dosimetry planning of brachytherapy of tumor lesions using ^{125}I microspheres was also based on the above hybrid molecular imaging data. As a result, topometric imaging of prostate carcinoma lesions enabled us to accurately plan and perform brachytherapy while reducing radiation exposure to healthy tissue and surrounding adjacent organs at risk, hence improving the patient's quality of life after treatment.

Due to the selective overexpression in prostate cancer tumor cells, PSMA-receptor molecular imaging using positron emission tomography (PET) has been used effectively in clinical practice. If PET/CT with ^{68}Ga -PSMA-11, ^{18}F -DCFPyL (piflufolostat F-18), and ^{18}F -PSMA-1007 is not achievable, SPECT/CT with $^{99\text{m}}\text{Tc}$ -HYNIC-PSMA may be performed. There are no significant differences in the specificity of PSMA-receptor imaging using PET/CT and SPECT/CT, but the sensitivity of PET/CT is significantly higher; therefore, this method is recommended when results of PSMA-receptor SPECT/CT are negative or questionable [23–25]. However, a valuable advantage of SPECT/CT with $^{99\text{m}}\text{Tc}$ -HYNIC-PSMA is the ability to improve molecular imaging of tumor lesions in the second phase (delayed, ≥ 15 h after RP administration) [26].

At the current stage of personalized and precision oncology development, molecular imaging (SPECT and PET), particularly when combined with structural cross-sectional pictures (CT and MRI), enables the detection of tumor lesions based on receptor characteristics or intracellular metabolism. This is especially true for increased precision of external beam radiation therapy, which includes brachytherapy [27].

In our patients, the average implantation time was reduced by one-third (34.8%), proportionally to decreased implanted microspheres. Approximately 15–20 min was spent positioning the patient on the tomograph table

after spinal anesthesia and installing and positioning the stereotactic attachment to the CT scanner. The length of this process is determined by the patient's weight and general condition rather than the number of implanted sources. On average, it takes about one and a half minutes to install one needle, position it under CT control, remove styles, load sources, and remove the needles with a control scan. Decreased implantation time is also associated with greater preparedness of the implantation plan due to more accurate visualization of the affected area and its configuration. Therefore, in most cases, there was a significant decrease in the number of microspheres, procedure time, personnel radiation exposure, CT scanner occupancy, and rate of injury and subsequent prostate gland swelling (six out of seven). In another case, there were indications for increasing the number of implanted microspheres based on PET/CT data using ^{68}Ga -PSMA-11, which was considered when planning and performing the procedure.

Brachytherapy can provide high doses of radiation at tumor sites (average: 160 Gray) and is associated with minimal irradiation of surrounding healthy prostate tissue, including the urethra. It does not irradiate adjacent organs at risk (bladder and rectum).

When SPECT/CT with $^{99\text{m}}\text{Tc}$ -HYNIC-PSMA and PET/CT with ^{68}Ga -PSMA-11 were used in a clinical population of seven patients with primary ($n = 5$) and recurrent ($n = 2$) prostate carcinomas of low and moderate risk, a total number ^{125}I microspheres implanted were less (by 36%; 404/282) than the potential number of microspheres implanted using standard technique without PSMA-receptor hybrid molecular imaging methods. Simultaneously, as previously reported, molecular imaging reduced the number of sources in six cases while increasing the number of microspheres in one case (multifocal tumor). We are not discussing the willingness to "save" microspheres; instead, we are talking about the priority of precise diagnostic and treatment processes and personalized increases in the effectiveness and safety of treatment.

A positive biochemical response was achieved in all clinical cases, with PSA levels decreasing to low values and a tendency to decrease further.

ALGORITHM FOR PSMA-PRECISION BRACHYTHERAPY FOR LOCALIZED PROSTATE CANCER

In our cases, the use of hybrid molecular PSMA-receptor imaging (SPECT/CT and PET/CT) methods enabled us to:

- personalize and increase the precision of diagnostic (biopsy) and therapeutic (brachytherapy) procedures in patients with prostate cancer;
- reduce time, increase accuracy, and reduce injury rate associated with morphological verification of the primary tumor: in three of seven cases, a biopsy (previously unsuccessful and traumatic multifocal one)

of the tumor was performed using SPECT/CT from the site of accumulation of ^{99m}Tc-HYNIC-PSMA, and in all three cases, the presence the tumor was confirmed by histological examination;

- determine the stage of the tumor and exclude regional and distant metastases;
- increase precision of dosimetry and topometric location of ¹²⁵I microsourses to reduce the risk of radiation reactions and improve patient quality of life;
- increase accuracy of microsourse implantation due to tumor-targeted planning of interstitial radiation therapy of the tumor lesions with morphological confirmation;
- distribute radioactive sources using a hybrid molecular imaging guide (SPECT/CT, PET/CT, and PET/MRI) and approve the dosimetry plan;
- reduce the waiting time by targeted biopsy of the tumor lesion, considering PSMA-receptor hybrid scintigraphy (SPECT/CT and PET/CT) data on its location; and
- increase the number and topometric plan of placement of ¹²⁵I microsourses during brachytherapy (in this series of cases, the number of microsourses was 36% lower, and the procedure time was 34.8% less than the standard treatment plan).

Based on the data given, an algorithm for PSMA-precision brachytherapy for localized prostate cancer was developed and used in the clinical practice of our clinic (Figure 10).

The strength of the study is the use of the original, innovative technology of precision brachytherapy under

molecular PSMA-receptor imaging guide using SPECT/CT with ^{99m}Tc-HYNIC-PSMA. The half-life of ^{99m}Tc is 6 h, allowing for delayed (next day) SPECT/CT of areas of interest and more clearly visualize sites of accumulation of ^{99m}Tcwith virtually no background half-lives of ¹⁸F and ⁶⁸Ga are 110 and 68 min, respectively)The limitations of our study are a small clinical sample (seven patients), a short period of follow-up (up to 2 yr), and a lack of MRI disk revision (only conclusions were analyzed, which in all cases were negative regarding tumor lesion localization), as well as the inability to evaluate and compare the diagnostic value of methods. All these aspects should be considered while designing further studies.

We found no reports on the use of such technology in the Russian or foreign literature; therefore, on January 25, 2023, invention patent No. 2788859, “Method of targeted brachytherapy for prostate cancer under hybrid PSMA-receptor scintigraphy guide” was obtained [28].

CONCLUSION

The study suggests that the precision of targeted biopsy and low-dose brachytherapy with ¹²⁵I microsourses for localized prostate carcinomas can be improved using hybrid methods of PSMA-receptor molecular imaging (SPECT/CT and PET/CT). The methods are complementary in terms of diagnostic and therapeutic guides; however, SPECT/CT is more accessible than PET/CT. The availability of cold kits (HYNIC-PSMA) enables one to examine any radioisotope diagnostic laboratory with appropriate equipment.

Possible algorithm for PSMA-precision brachytherapy of prostate cancer using ¹²⁵I microsourses

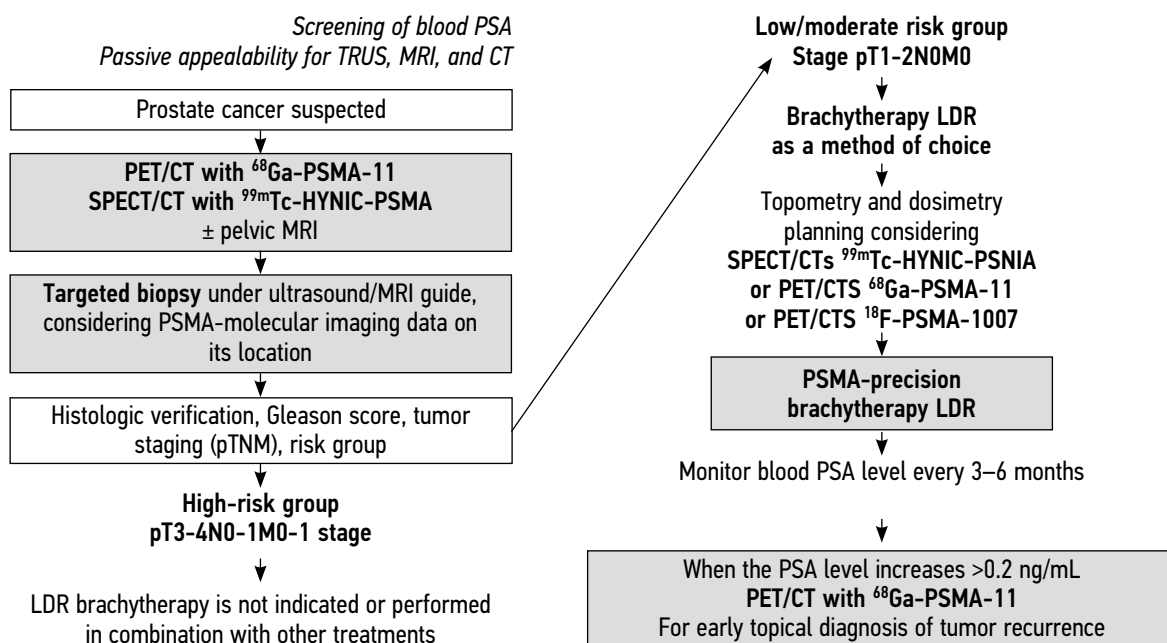


Fig. 10. Algorithm for selecting patients for low-dose brachytherapy, emphasizing increasing precision under PSMA-receptor molecular imaging guide. ku, contrast enhancement; LDR, low-dose rate; PSMA, prostate-specific membrane antigen.

The innovative technology of PSMA-precision biopsy brachytherapy guided by hybrid molecular imaging can be used for primary and recurrent localized prostate cancer, improving accuracy, reducing invasiveness of procedures, and increasing the medical and economic efficiency of low-dose brachytherapy with ¹²⁵I microspheres.

Further research is required to develop the technology and evaluate long-term treatment outcomes in a larger group of patients.

ADDITIONAL INFORMATION

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of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. P.V. Sviridov — management of patients, brachytherapy procedure conduction, test writing and preparing of images, P.O. Rumiantsev — paper idea, design, coordination, paper writing and edition; M.V. Degtyarev — introduction and interpretation of SPECT/CT and PET/CT, writing of corresponding parts of the paper; S.S. Serzhenko — introduction and interpretation of SPECT/CT, writing of corresponding parts of the paper; D.B. Sanin — dosimetry planning of brachytherapy, writing of corresponding parts of the paper; S.V. Styrov — execution of computed tomography, writing of corresponding parts of the paper; D.Yu. Agibalov — data elaboration, paper edition; S.V. Korenev — assistance in obtaining diagnostic information about treated patients, helping in paper edition.

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AUTHORS' INFO

* **Pavel O. Rumiantsev**, MD, Dr. Sci. (Med.);
address: 8 Malaya Konyushennaya street, 191186 Saints
Peterburg, Russia;
ORCID: 0000-0002-7721-634X;
eLibrary SPIN: 7085-7976;
e-mail: pavelrum@gmail.com

Pavel V. Sviridov;
ORCID: 0009-0008-3362-8255;
eLibrary SPIN: 4702-3067;
e-mail: p_sviridov73@mail.ru

Mikhail V. Degtyarev;
ORCID: 0000-0001-5652-2607;
eLibrary SPIN: 7725-7831;
e-mail: germed@mail.ru

Sergei S. Serzhenko;
ORCID: 0000-0003-2326-1396;
eLibrary SPIN: 4713-8986;
e-mail: vv1ld@yandex.ru

Dmitry B. Sanin, Cand. Sci. (Biol.);
ORCID: 0009-0004-2047-4921;
eLibrary SPIN: 8939-9101;
e-mail: dimitresko82@yandex.ru

Sergey V. Styrov;
ORCID: 0000-0003-4315-8855;
eLibrary SPIN: 9019-8520;
e-mail: rizost@yandex.ru

ОБ АВТОРАХ

* **Румянцев Павел Олегович**, д-р мед. наук;
адрес: Россия, 191186, Санкт-Петербург,
ул. Малая Конюшенная, д. 8;
ORCID: 0000-0002-7721-634X;
eLibrary SPIN: 7085-7976;
e-mail: pavelrum@gmail.com

Свиридов Павел Владимирович;
ORCID: 0009-0008-3362-8255;
eLibrary SPIN: 4702-3067;
e-mail: p_sviridov73@mail.ru

Дегтярев Михаил Владимирович;
ORCID: 0000-0001-5652-2607;
eLibrary SPIN: 7725-7831;
e-mail: germed@mail.ru

Серженко Сергей Сергеевич;
ORCID: 0000-0003-2326-1396;
eLibrary SPIN: 4713-8986;
e-mail: vv1ld@yandex.ru

Санин Дмитрий Борисович, канд. биол. наук;
ORCID: 0009-0004-2047-4921;
eLibrary SPIN: 8939-9101;
e-mail: dimitresko82@yandex.ru

Стыров Сергей Викторович;
ORCID: 0000-0003-4315-8855;
eLibrary SPIN: 9019-8520;
e-mail: rizost@yandex.ru

* Corresponding author / Автор, ответственный за переписку

Dmitry Yu. Agibalov;

ORCID: 0000-0003-2995-7140;

eLibrary SPIN: 6938-5804;

e-mail: agibalovd@bk.ru

Sergey V. Korenev, MD, Dr. Sci. (Med.), Professor;

ORCID: 0000-0003-2310-0576;

eLibrary SPIN: 5257-4476;

e-mail: korenevsv@mail.ru

Агибалов Дмитрий Юрьевич;

ORCID: 0000-0003-2995-7140;

eLibrary SPIN: 6938-5804;

e-mail: agibalovd@bk.ru

Корнев Сергей Владимирович, д-р мед. наук, профессор;

ORCID: 0000-0003-2310-0576;

eLibrary SPIN: 5257-4476;

e-mail: korenevsv@mail.ru