Брахитерапия рака предстательной железы. Опыт работы филиалов Национального медицинского исследовательского центра радиологии

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Брахитерапия является одним из методов лучевой терапии, позволяющим с помощью малоинвазивного вмешательства подводить к опухолевому очагу высокоэффективную дозу облучения. В зависимости от используемого источника различают низко- и высокомощностную брахитерапию. В статье отражены основные этапы развития и становления брахитерапии рака предстательной железы как за рубежом, так и в России. Описываются основные методики брахитерапии, используемые в современной медицине. Приводятся ссылки на рекомендации ведущих радиотерапевтических организаций по низкомощностной брахитерапии. Описываются основные показания и противопоказания к выполнению брахитерапии источниками низкой мощности дозы при раке предстательной железы. Представлены обобщенные данные по эффективности метода в зависимости от прогноза течения рака предстательной железы. Публикуются результаты работы по низкомощностной брахитерапии филиалов ФГБУ «НМИЦ радиологии» Минздрава России.

***Ключевые слова:** рак предстательной железы, внутритканевая лучевая терапия, брахитерапия, показание, противопоказание, группа прогноза, объединенные результаты*

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Prostate cancer brachytherapy. Experience of the branches of the National Medical Research Center of Radiology

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Brachytherapy is one of the methods of radiotherapy allowing to deliver a highly effective radiation dose to a tumor through a minimally invasive intervention. Depending on the source, brachytherapy can be low- and high-energy. The article describes the main stages of development of prostate cancer brachytherapy both in Russia and abroad. The main methods of brachytherapy used in modern medicine are described. References to recommendations of the leading radiological organizations on low-energy brachytherapy are provided. The main indications and counterindications for brachytherapy for treatment of prostate cancer using low-energy sources are described. Summary data on the ef-

fectiveness of the method depending on prostate cancer prognosis are presented. The results of using low-energy brachytherapy at the branches of the National Medical Research Center of Radiology of the Ministry of Health of Russia are described.

Key words: *prostate cancer, intratissue radiotherapy, brachytherapy, indication, counterindication, prognosis group, summary results*

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Background

According to the Russian Center of Information Technologies and Epidemiological Researches in Oncology (National Medical Research Radiology Center, Ministry of Health of Russia), prostate cancer (PC) is the second most common cancer in Russian men behind tracheal, bronchial, and lung cancer. The proportion of patients with stage 1–2 PC reaches 52.5% [1].

There are two main treatment options for localized PC: surgery (different variants of radical prostatectomy) and radiotherapy (external beam radiotherapy (EBRT) and brachytherapy). Brachytherapy (derived from the Greek word βραχύς, meaning brief or short) is a form of radiotherapy where a radiation source is placed inside the affected organ.

Brachytherapy dates back to 1901, when Henri-Alexandre Danlos, a French dermatologist, first used radioactive radium to treat skin cancer. First use of brachytherapy for the treatment of PC was reported by Pasteau and Degrais in 1914, then by Barringer in 1917. In the 1980s, the method of contact radiotherapy under transrectal ultrasonographic guidance was developed and implemented into clinical practice.

In Russia, prostate brachytherapy with 125I particles was first used in the N.A. Lopatkin Research Institute of Urology and Interventional Radiology in 2000. In 2004, specialists from the A.F. Tsyb Medical Radiological Research Center first performed computed tomography-guided brachytherapy using a three-dimensional stereotactic system. Currently, internal radiotherapy is widely used for PC treatment in all branches of the National Medical Research Radiology Center.

Internal radiotherapy for PC

There are two main prostate brachytherapy techniques: low-dose rate (LDR) brachytherapy (using permanent seed implants containing 125I, 103Pd, or 131Cs) and high-dose rate (HDR) brachytherapy (with temporary placement of highly radioactive isotopes 192Ir, 60Co, or 137Cs inside the prostate)

Brachytherapy has a number advantages over surgery and EBRT, including reduced length of stay in hospital and lower incidence of genitourinary and gastrointestinal complications, which improves the quality of life.

Treatment technique

The main method of LDR for PC is ultrasound-guided transperineal implantation of radioactive seeds. The process of implantation can also be computed tomography-guided and magnetic resonance-guided. Two methods of brachytherapy are officially registered in the Russian Federation: ultrasound-guided and computed tomography-guided [2, 3].

Indications

The existing brachytherapy guidelines are based on a number of factors used to determine disease prognosis, including the level of prostate-specific antigen (PSA), Gleason score (World Health Organization, 2016), and T stage (extent of the tumor). The European Association of Urology (EAU) recommends using brachytherapy in patients with favorable prognosis: T1–T2aN0M0 stage, total Gleason score ≤ 6 or 7 (3 + 4) in < 33% biopsy samples, and PSA ≤ 10 ng/mL [4]. The Guidelines developed by the American Brachytherapy Society (ABS) have an expanded list of indications for brachytherapy and allow its use in patients with grade 3 PC, total Gleason score < 10, and PSA < 50 ng/mL [5]. For patients with unfavorable and intermediate prognosis, ABS recommends the combination of brachytherapy plus EBRT/hormone therapy or multimodal treatment using all three methods (Table 1).

Absolute contraindications to LDR brachytherapy include metastases and life expectancy of < 5 years. Relative contraindication include acute prostatitis, large prostate volume (more than 50-60 cm^3), rectal diseases, (ulcerative colitis, proctitis, etc.), and pronounced dysuric disorders (high IPSS score, residual urine).

Currently available implantation techniques enable brachytherapy in patients with a history of transurethral resection of the prostate and large prostate volume [6, 7]. Hughes et al. demonstrated that the presence of prostatitis does not affect urination after brachytherapy [8]. Grann et al. reported no statistically significant increase in gastrointestinal toxicity among patients with inflammatory diseases of the rectum [9]. The experience and statistical data suggest that the patient's age is not a limitation for brachytherapy, because the procedure is well tolerated regardless of age. Promising relapse-free survival among young patients expands the capability of this technique [10].

Таблица 1. *Показания для применения брахитерапии*

Table 1. *Indications for brachytherapy*

Рекомендации Европейской ассоциации урологов и радиоонкологов (ESTRO/EAU/EORTC) Recommendations of the European Society for Radiotherapy and Oncology (ESTRO/EAU/EORTC)	Рекомендации Американской ассоциации брахитерапии (ABS) Recommendation of the American Brachytherapy Society (ABS)
Уровень ПСА ≤10 нг/мл PSA level ≤10 ng/ml	Уровень ПСА ≤50 нг/мл PSA level ≤50 ng/ml
Сумма балов по шкале Глисона 6 (3 + 3) или 7 (3 + 4) в <33 % биоптатов Total Gleeson score 6 (3 + 3) or 7 (3 + 4) in <33 % of biopsies	Сумма балов по шкале Глисона ≤10 Total Gleeson score ≤10
Клиническая стадия T1c–T2aN0M0 Clinical stage T1c–T2aN0M0	Клиническая стадия T1–T2c, выборочно T3N0M0 Clinical stage T1–T2c, selectively T3N0M0
Объем предстательной железы ≤50 см^3 Prostate volume ≤50 cm^3	Объем предстательной железы <60 см^3 Prostate volume <60 cm^3
≤50 % положительных биоптатов ≤50 % of positive biopsies	При промежуточном и неблагоприятном прогнозе – комбинированное лечение: брахитерапия + дистанционная лучевая терапия/гормонотерапия For intermediate and poor prognosis – combined treatment: brachytherapy + external-beam radiotherapy/hormonal therapy
≤12 баллов по Международной шкале оценки простатических симптомов ≤12 on the International Prostate Symptom Score	

Примечание. *Здесь и в табл. 2: ПСА – простатический специфический антиген.*
Note. *Here and in Table 2: PSA – prostate-specific antigen.*

Brachytherapy for PC in patients with favorable and intermediate prognosis

According to the recommendations of the leading international organizations (ESTRO/EAU/EORTC/ABS), brachytherapy as monotherapy is indicated for individuals with favorable prognosis: PSA < 10 ng/mL, Gleason score of 6 or 7 (3 + 4) in < 33% biopsy samples, and stage T1c–T2a PC. The most common isotope used in prostate brachytherapy is 125I. There is no evidence that 103Pd seeds have any advantages over 125I seeds. The minimum therapeutic dose for PC is 145 Gy.

Foreign authors report 10-year PSA-free survival rates of 87–98% in patients with favorable prognosis that underwent brachytherapy as monotherapy [11–14]. In a large study by Zelefsky et al. that involved 2693 patients with T1-T2 PC treated with brachytherapy monotherapy (without hormone therapy), the 8-year relapse-free survival rate was 74% and 61% in individuals with favorable and intermediate prognosis respectively [15].

Blasko et al. reported a 82% 9-year relapse-free survival rate among patients with intermediate prognosis (PSA > 10 ng/mL, Gleason score > 7, stage T2b PC) treated with brachytherapy monotherapy [16]. The addition of EBRT did not increase survival (84% vs 85%) [11]. Potters et al. reported a 12-year progression-free survival rate of 80% in patients receiving both monotherapy and combined treatment [12]. Stone et al. demonstrated high efficacy of brachytherapy monotherapy: the 12-year relapse-free survival was 79.2% [13]. Therefore, the combination of brachytherapy with EBRT appears to have no significant benefits compared to brachytherapy alone in patients with intermediate prognosis.

Our own experience with LDR brachytherapy

A total of 1187 ultrasound-guided and computed tomography-guided implantations of 125I seeds were performed in the three branches of the National Medical Research Radiology Center between 2000 and 2016.

The mean age of patients that underwent brachytherapy was 60.5 years (range: 47–77 years). The Gleason score varied between 6 and 8. The mean PSA level was 8.3 ng/mL. The mean prostate volume before implantation was 35.8 cm^3 (range: 13.0–91.4 cm^3). The mean maximum urine flow rate was 17.8 mL/s.

The cohort comprised 806 patients (67.9%) with favorable prognosis (D'Amico classification), 275 patients with intermediate prognosis (23.2%), and 106 patients (8.9%) with unfavorable prognosis. We used 125I seeds (produced by Amersham or Bebig) with an activity of 0.2–0.65 mCi. Seeds were implanted using the VarySeed 7.1, 8.1 and PSID software.

The biochemical relapse-free survival (PSA-free survival) at 60 months was 96.0% (98.5% in patients with favorable prognosis, 90.0% in patients with intermediate prognosis, and 98.1% in patients with unfavorable prognosis) (Table 2). Of note, patients with intermediate and unfavorable prognosis additionally received adjuvant hormonal therapy for 6–24 months.

Urinary retention was the most common complication observed in 13 patients (1.1%). Five patients (0.4%) required epicystostomy in the post-implantation period. Grade 3

Таблица 2. *Пятилетняя безрецидивная выживаемость пациентов, которым была проведена брахитерапия в филиалах ФГБУ «НМИЦ радиологии» Минздрава России*

Table 2. *Results of 5-year relapse-free survival among patients who underwent brachytherapy at the branches of the National Medical Research Radiological Center of the Ministry of Health of Russia*

Показатель Characteristic	**Число пациентов, *n* (%)** Number of patients, *n* (%)	**Результат, %** Result, %
ПСА-безрецидивная выживаемость на срок 60 мес в группе благоприятного прогноза PSA relapse-free survival in 60 months in the favorable prognosis group	806 (67,9)	98,5
ПСА-безрецидивная выживаемость на срок 60 мес в группе промежуточного прогноза PSA relapse-free survival in 60 months in the intermediate prognosis group	275 (23,2)	90,0
ПСА-безрецидивная выживаемость на срок 60 мес в группе неблагоприятного прогноза PSA relapse-free survival in 60 months in the poor prognosis group	106 (8,9)	98,1
Общая безрецидивная выживаемость на срок 60 мес (5-летняя безрецидивная выживаемость) Total relapse-free survival in 60 months (5-year relapse-free survival)	1187 (100)	96,0

radiation urethritis (according to RTOG classification) was registered in 4 patients (0.34%), urethral stricture–in 3 patients (0.25%), grade 2 radiation rectitis–in 1 patient (0.1%), and grade 3 radiation rectitis–in 1 patient (0.1%).

Thus, our results of brachytherapy are comparable with those reported by foreign authors. The number of complications after brachytherapy was relatively low; most of them were expectable.

In conclusion, we believe that brachytherapy performed by highly-professional physicians and medical physicists plays an important role in the management of PC. The Center of Brachytherapy at the National Medical Research Radiology Center is planning to expand the use of brachytherapy for various types of cancer and to continue the research activity to improve patients' quality of life and survival.

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