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Возрастающая роль функциональной визуализации для навигации радиотерапии и брахитерапии на примере рака предстательной железы

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АННОТАЦИЯ

Брахитерапия успешно применяется в лечении злокачественных новообразований у мужчин и женщин, в редких случаях у детей, как самостоятельный метод (например, при локализованном раке предстательной железы) или адъювантный с дистанционной фокальной лучевой терапией (например, при раке шейки матки, анального канала, головы и шеи, молочной железы и пр.).

Расширение диагностических возможностей (появление компьютерной и магнитно-резонансной томографии) благодаря трёхмерной визуализации дало брахитерапии важное технологическое преимущество перед другими методами. Существует множество вариантов сочетания брахитерапии с дистанционной лучевой или системной противоопухолевой терапией в первой линии, а также в монорежиме при локализованном рецидиве опухоли в ранее облучённой зоне.

Введение интрастатов (полых трубок) для внутритканевой высокодозной брахитерапии осуществляется во время операции, а инкапсулированных (закрытых) радиоактивных микроисточников для низкодозовой брахитерапии — напрямую (чрезкожно).

Отличительной спецификой брахитерапии является резкое падение дозы за пределами опухолевого очага, что минимизирует риск облучения окружающих органов и тканей.

Основным преимуществом брахитерапии в сравнении с дистанционной лучевой терапией является более высокий градиент дозы облучения на границе опухоли (со всех сторон). Более того, нет необходимости уточнения границ неопределённости при облучении мишени: когда опухоль изменяется в процессе лечения, то фиксированные в опухоли источники синхронно меняют своё положение.

Помимо преимуществ в эффективности и безопасности, совокупные финансовые затраты при брахитерапии существенно ниже других вариантов лучевой терапии.

Ключевые слова: молекулярная визуализация, брахитерапия; радиотерапия, рак предстательной железы.

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ЭКО•ВЕКТОР

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The increasing role of functional visualization modalities for navigation of external beam radiation therapy and brachytherapy in prostate cancer

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ABSTRACT

Brachytherapy is successfully used in the treatment of malignant neoplasms in males and females and rare cases in children, as an independent method (with localized prostate cancer) or adjuvant with remote focal radiation therapy (with cancer of the cervix, anal canal, head and neck, breast, etc.).

The expansion of diagnostic capabilities (the advent of computer and magnetic resonance imaging) due to three-dimensional imaging has given brachytherapy an important technological advantage over other methods. Many options are available for combining brachytherapy with remote radiation or systemic antitumor therapy in the first line, as well as in a single mode for localized tumor recurrence in a previously irradiated area.

Intrastates (hollow tubes) for intra-tissue high-dose brachytherapy are administered during surgery and encapsulated (closed) radioactive micro-sources for low-dose brachytherapy are directly administered (percutaneously).

A distinctive feature of brachytherapy is a sharp drop in the dose outside the tumor focus, which minimizes the risk of irradiation of surrounding organs and tissues.

The main advantage of brachytherapy in comparison with remote radiotherapy is a higher radiation dose gradient at the tumor border (from all sides). Moreover, clarifying the boundaries of uncertainty when irradiating the target is unnecessary. When the tumor changes during treatment, the sources fixed in the tumor synchronously change their position.

In addition to the advantages in efficiency and safety, the total financial costs of brachytherapy are significantly lower than other radiotherapy options.

Keywords: brachytherapy; prostate cancer; malignant neoplasms; radiation therapy.

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在前列腺癌病例中，功能成像方法在导航远程放射治疗和近距离放射治疗中的作用越来越大

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简评

近距离放射治疗已成功用于治疗男性和女性的恶性肿瘤，很少用于儿童，无论是单独治疗（如局限性前列腺癌）还是辅助外照射治疗（如宫颈癌、肛管癌、头颈癌、乳腺癌等）。

三维成像带来的诊断能力的扩展（计算机断层扫描和磁共振成像的出现）使近距离放射治疗比其他方法具有重要的技术优势。在第一线，近距离放射治疗与外照射或全身抗癌治疗相结合有许多选择，对于先前照射区域的局部肿瘤复发，也有单一疗法。

在手术期间引入用于间质高剂量近距离放射治疗的intrastats（空心管），并直接（经皮）封装（封闭）用于低剂量近距离放射治疗的放射性微源。

近距离放射治疗的一个显著特点是肿瘤病灶外的剂量急剧下降，从而将周围器官和组织的辐射风险降至最低。

与外束放射治疗相比，近距离放射治疗的主要优点是在肿瘤边缘（从四面八方）有更高的辐射剂量梯度。此外，无需澄清靶向照射过程中的不确定性限制：当肿瘤在治疗过程中发生变化时，固定在肿瘤中的放射源同步改变其位置。

除了疗效和安全效益外，近距离放射治疗的总财务成本大大低于其他放射治疗方案。

关键词：近距离放射治疗；前列腺癌；恶性肿瘤；放射治疗。

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INTRODUCTION

Historically, dosimetric planning for prostate cancer brachytherapy was based on 2D orthogonal computed tomography (CT) pelvic views obtained during implantation. Although radiographic images allowed for accurate visualization of the applicators, they did not provide an accurate estimate of the volume of the target lesion or healthy tissues/organs near the tumor, which could be damaged by irradiation (organs at risk). In the 1990s, with the advancement of diagnostic capabilities, namely, the advent of CT and magnetic resonance imaging (MRI), brachytherapy benefited greatly due to the technological advantages of three-dimensional imaging, so the question of further improving the accuracy of brachytherapy under MRI navigation naturally arises. Moreover, in addition to the efficiency and safety benefits, brachytherapy has significantly lower total financial costs than other radiotherapy options [1].

COMBINED FUNCTIONAL AND ANATOMICAL IMAGING METHODS

The use of brachytherapy in conjunction with external beam radiation or systemic antitumor therapy is becoming increasingly popular in oncology, adding a new dimension to patient management. The functional visualization of organs during physiological processes is complementary to the anatomical image, which contains complete information about the structure of the organs.

At present, many complementary biological processes, such as metabolic activity, cell proliferation, perfusion, hypoxia, etc. can be visualized. Diagnostic functional images in oncology are used to assess the distribution of tumor cells and detect intratumoral heterogeneity, as well as to establish phenotypic characteristics and the nature of the microenvironment in solid tumors, which affect the clinical course and therapeutic response. The largest number of studies has been conducted to determine the mass of the tumor and its clonogenic density, hypoxia, or proliferation.

The combination of functional and anatomical imaging provides structural and metabolic information about the tumor, allowing different subtypes and radioresistant zones in tumor foci to be identified.

Magnetic resonance imaging

Due to the high resolution and high contrast of soft tissues, MRI has become the standard method of anatomical imaging for determining the stage and prevalence of primary tumors. MRI offers numerous technological options for detecting the mechanisms of functional organization of a tumor, such as angiogenesis (perfusion MRI), metabolism (MR spectrometry), and even its cellular composition (diffusion-weighted imaging, DWI). In MRI, the dynamic contrast enhancement (DCE) mode is a technique for flexible analysis of changes in tissue signal intensity following injection of a standard paramagnetic contrast agent (based on gadolinium). The difference in tissue perfusion after injection of a gadolinium-based contrast agent can be evaluated using MRI in DCE mode. Using at least two different b-values in DWI mode, the apparent diffusion coefficient (ADC) can be calculated during postprocessing. Most malignant tumors have increased cell density, which is displayed as increased signal intensity on DWI or a decrease in ADC in quantitative analysis.

Positron emission tomography

Positron emission tomography combined with CT (PET/CT) or MRI (PET/MRI) has significantly improved the diagnostics and staging of malignant neoplasms (lungs, prostate, hematopoietic system, etc.). Despite having a lower spatial resolution than modern CT and MRI, PET allows for the detection of metastases that other methods do not reveal and allows for the initial optimization of the treatment approach. In addition, PET can provide unique functional information about a tumor, such as zones of hypoxia, proliferation, radioresistance, etc. At the current stage, a wide range of "metabolic" radiotracers (radiopharmaceuticals) are available in nuclear medicine (Table 1).

Digital biomarkers: radiomics

Clinical aspects and anatomical imaging techniques provide important prognostic information regarding the clinical course of a tumor, but they cannot predict the response of a tumor to treatment. The development of reliable prognostic biomarkers could improve the choice of the optimal treatment approach and individualize the therapeutic approach. Radiomics, as a method of extracting and analyzing large amounts of quantitative radiological data from medical images using high-performance methods, can be used to develop digital biomarkers that can be used in choosing the most effective and safe treatment approach. Digital biomarkers perfectly complement the qualitative and quantitative characteristics of the tumor process, such as clinical manifestations, morphological pattern, and metabolomic (in particular, tumor markers) and molecular genetic studies. Comprehensive consideration of all significant parameters enables the development of reliable predictive models that improve patient treatment outcomes and the development of medical decision support systems based on evidence-based clinical experience and creative international multidisciplinary communication.

RELIABLE PROGNOSTIC MODELS AS A DECISION SUPPORT SYSTEM

Brachytherapy allows for the delivery of heterogeneous doses within the volume of the irradiated target; however, there is a risk of local recurrence, which is associated with radioresistance of the remaining tumor foci in particular. Functional imaging provides a presentation of tumor biology, allowing for more adaptable dosage distribution to the actual

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Table 1. Range of radiotracers for molecular imaging in oncology and endocrinology

Metabolic pathway	Scope of application	Molecular imaging method	
		SPECT/CT	PET/CT
Energy glycolysis	Oncology	-	^{18}F-FDG
Synthesis of thyroid hormones	Endocrinology, oncology (thyroid diseases)	$^{99m}TcO_4$ (pertechnetate) ^{123}I ^{131}I	^{124}I
Hypoxia	Oncology	-	^{18}F-FAZA (nitroimidazole) ^{18}F-FISO ^{64}Cu-ATSM
Proliferation	Oncology	-	^{18}F-FLT
Cell membrane	Oncology	-	^{18}F/^{11}C-choline
Somatostatin receptors (STR 2.5)	Endocrinology, oncology (neuroendocrine tumors)	^{99m}Tc-HYNIC-TOC (tectrotide)	^{68}Ga/^{64}Cu-DOTA-TATE/NOC/TOC
Norepinephrine synthesis	Endocrinology, oncology (pheochromocytoma, paraganglioma, neuroblastoma)	^{123}I/^{131}I-MIBG	^{124}I-MIBG
Glucagon-like peptide type 1 receptors (GLP-1)	Endocrinology, oncology (insulinoma)	^{99m}Tc-HYNIC-exendin-4 (tectrotide)	^{68}Ga/^{64}Cu-DOTA-exendin-4
Estrogen receptors	Endocrinology, oncology	-	^{18}F-FES
Androgen receptors	Endocrinology, oncology	-	^{18}F-FDHT
her2neu receptors	Oncology	-	^{89}Zr-DFO-trastuzumab
PSMA receptors	Oncology	^{99m}Tc-HYNIC-PSMA	^{68}Ga/^{18}F-PSMA
Activity of tumor-associated fibroblasts	Endocrinology, oncology	-	^{68}Ga/^{18}F-FAPI
Bone metabolism	Endocrinology, oncology	^{99m}Tc-MDP (technefor, pyrfotech etc.)	^{18}F-NaF (Sodium fluoride)

Note. FDG, fluorodeoxyglucose; FAZA, fluoroazomycin arabinoside; ATSM, diacetyl-bis-N4-methylthiosemicarbazone; MIBG, metaiodobenzylguanidine; FES, fluoroestradiol; FDHT, fluorodihydrotestosterone; PSMA, prostate-specific membrane antigen

tumor site. The planned total focal dose of radiation either can be individualized, with dose levels set for the full volume of the target, or can have different sublevels of radiation doses, such as the dominant tumor focus or, for example, more radioresistant hypoxic foci (biological target volume).

The potential role of functional imaging in radiation oncology is important at all stages of the management of patients with prostate cancer, namely, at stage 1 for primary tumor staging; stage 2 for planning radiotherapy in order to determine more accurately the target volumes or escalate the radiation dose; and stage 3 for case follow-up of patients in order to control the achievement of a complete response as well as detection of tumor recurrence.

For cancers of the prostate, surgical treatment, external beam radiation therapy, and brachytherapy are the preferred treatment options. The American Society of Clinical Oncology recently validated the role of brachytherapy. For low-risk carcinomas not suitable for active follow-up, brachytherapy with microsources of iodine-125 remains the treatment method that provides the best balance of biochemical control with optimal preservation of sexual function [2]. Brachytherapy should be offered as a supplementary treatment option to patients who have an unfavorable (moderate or high) risk of biochemical recurrence. Thus, based on the results of three randomized clinical trials involving a combination of external beam radiation therapy and brachytherapy, it was concluded that additional brachytherapy significantly improved survival without signs of biochemical recurrence [3]. When compared to treatment outcomes after only external beam radiation therapy or radical prostatectomy (propensity-scored pairwise test) for prostate cancer with a very high risk of biochemical recurrence (Gleason 9–10), the addition of brachytherapy improved not only survival without biochemical recurrence and without metastases but also overall 7-year survival rate [4].

Multiparametric MRI (mpMRI) and PET/CT have emerged as promising modalities for staging primary and recurrent prostate cancer. New PET/CT tracers have improved the detection of small, early-stage metastatic tumors. Moreover, cross-validation is required to determine the nature and clinical significance of these latent and PET/CT-detectable lesions. Based on the clinical status of the patient at the time of the visit, the following strategies can be suggested [5]:

- Suspected localized prostate cancer: mpMRI
- Suspected advanced prostate cancer: PET/CT with ^{68}Ga-PSMA-11, osteoscintigraphy
- Biochemical recurrence after treatment: PET/CT with ^{68}Ga-PSMA-11, as well as mpMRI for local control or MRI to evaluate lymph nodes and bone structures

Despite its high prognostic value, the Gleason score often underestimates the additional contribution of radiomics in clarifying the true clinical stage at the time of biopsy [6].

In real clinical practice, a previously unknown metastatic lesion of regional lymph nodes or distant metastases can be detected. PET/CT-detected lesions with high expression of prostate-specific membrane antigen (PSMA) receptors have a high risk of tumor aggressiveness [7]. In particular, these data help to improve understanding of the prognosis of aggressiveness and the risk of tumor recurrence, as well as the optimal selection of patients for brachytherapy and other treatment options.

Planning of brachytherapy for prostate cancer involves the entire volume of the prostate as a target for irradiation. The radiation dose of the gland is heterogeneous, and an ablative dose of radiation must be applied to all intraglandular tumor foci. According to recent findings, combining mpMRI and ^{68}Ga-PSMA PET/CT improves diagnostic accuracy in identifying these intraglandular tumors. PET/MRI with ^{68}Ga-PSMA outperforms mpMRI in accuracy (area under ROC curve 0.88 vs. 0.73; $p < 0.001$) and PET/CT (0.88 vs. 0.83; $p = 0.002$) for localized prostate cancer. PET/CT with ^{68}Ga-PSMA was more accurate than mpMRI (0.83 vs. 0.73; $p = 0.003$) [8]. Similar results were obtained by P. Donato et al. [9], as PET/CT with ^{68}Ga-PSMA detected tumor foci more frequently (78%; ROC 0.817) than mpMRI (69%; ROC 0.729).

Recently, there has been an increased interest in methods of focal therapy for prostate cancer, in patients with tumors of low (in an independent version) and high (in addition to other methods of focal therapy) risk. There is mounting evidence that dominant carcinoma foci within the prostate gland have the highest predictive value for the development of metastases and tumor recurrence after primary therapy. This highlights the need for improved visualization of carcinoma foci in terms of their dominance in size and prediction of biological aggressiveness. S. Rylander et al. [10] published the results of a dosimetric study of three mpMRI-guided low-dose brachytherapy models: (1) a "risk-adaptive" plan with prostate radiation dose de-escalation of at least 125 Gy (clinical target volume, CTV), (2) plan determined by mpMRI with dose escalation to 145–250 Gy (gross tumor volume, GTV) and a 5-mm exposure limit for all tumor foci, and (3) reference plan with a standard clinical prostate radiation dose of 145 Gy. With a significant dose reduction to the urethra and bladder neck, the risk-adaptive planning concept and dose escalation model for macroscopically defined tumor foci were technically feasible [10]. Recent studies have examined the effect of a local boost of high-dose brachytherapy on dominant intraprostatic lesions using mpMRI- or PET/CT-guided functional imaging. These two studies demonstrated excellent tolerability and low toxicity of treatment, as well as considerable structural and biochemical response rates. C.C. Hsu et al. [11] reported the results of low-dose brachytherapy with mpMRI-guided planning in patients who had previously received low-dose brachytherapy. This technology is quite feasible in clinical practice alongside others (surgery, external beam radiation therapy) and has a much lower toxicity [11].

There are drawbacks to all imaging methods, such as the effect of artifacts during PET/CT data reconstruction on the correction of attenuation caused by the contrast agent, metal implants, and patient movement. The PET/CT presentation should be reconstructed with or without attenuation correction, as attenuation artifacts can be revealed [12]. A nuclear medicine specialist should always include information about the possible impact of artifacts discovered during the study in the conclusion. With the advancement of PET/CT and MRI resolution, it will be possible to visualize even microscopic tumor foci.

When performing brachytherapy, image registration still has a lot of uncertainty, which can lead to misunderstandings in target localization. Image registration accuracy can be improved by positioning the patient during radiation therapy on MRI and PET/CT. Simulations on MRI and PET/CT require close interaction between radiotherapists and radiologists, which is even more important in brachytherapy since the risk of anatomical deformity increases during the procedure. In order to minimize the consequences, several solutions have been proposed and studied, including the method of elastic repositioning of sources [13] and the use of MRI in the operating room where brachytherapy is performed [14]. The algorithms developed for automatic superposition of various visualizations will become more accurate overtime, increasing the rate of registration and verification.

In cases when brachytherapy is performed after external beam radiation therapy for targeted dose escalation, it is necessary to determine which imaging methods (before or after external beam radiation therapy) provided more reliable information about radioresistant lesions [15].

Functional imaging may be used as an adjunct to CT planning prior to the initiation of external beam radiotherapy, or prior to brachytherapy to adapt to an early response. Pre-therapeutic ^{18}F-FDG PET/CT aids in the identification of lesions with high aggressiveness or radioresistance (markers of hypoxia), as well as the presence of a residual tumor, which may be useful in planning the boosting of such lesions and reducing unwanted radiation exposure to risk organs.

The choice of a functional imaging method to determine the biological aggressiveness of a carcinoma is critical, and at this stage, PET/CT with various tracers-indicators of the biological properties of a tumor (^{18}F-FDG, ^{18}F-FMISO/FAZA, ^{18}F-FLT, ^{68}Ga/^{18}F-PSMA-receptor) is possible. The results of retrospective studies facilitate in the selection of a method for functional imaging of the biological characteristics of tumors, as well as in determining the dose escalation regimen or dose planning strategy. Several studies have found associations between functional imaging and (1) histological findings/(2) localized foci of residual tumor or recurrence. H. Park et al. [16] revealed a good correlation between ^{11}C-choline PET/CT and histological findings in

prostate cancer. T.F. Fassbender et al. [17] emphasized the added value of PET/CT with ^{68}Ga-PSMA-11 and ^{68}Ga-RM2, as well as their strong correlation with histological presentation. Some studies have found that areas of high tracer uptake on pre-therapeutic ^{18}F-FDG PET/CT, labeled as "hotspots," later turned out to be predominant foci of local recurrence [18, 19].

Numerous techniques for segmenting ^{18}F-FDG-positive lesions on PET/CT have been proposed in the literature. There is currently no consensus on more accurate and reliable methods. Given the low (40%) sensitivity threshold of PET/CT, the method should be used with extreme caution in the presence of small tumors that accumulate poorly in contrast, as well as in the presence of heterogeneous tracer capture within the lesion [20].

Nowadays, when planning radiotherapy, molecular imaging methods are most commonly used as auxiliary methods; however, with the expansion of the list of oncometabolic radiopharmaceuticals (tracers), the increase in the resolution of single-photon emission CT and PET, the replenishment of evidence-based experience, and the development of artificial intelligence in radiomics, the improvement of functional imaging methods for navigating radiotherapy (remote radiation therapy and brachytherapy) is expected.

Many medical centers now have ultrasound machines and CT scanners, but MRI and PET/CT are only available at a few select institutions, making it difficult for a patient to undergo a PET/MRI examination [21].

It is also necessary to consider the heterogeneity of the quality of performance and interpretation of the results of functional imaging methods, as well as their cost and study duration. Based on global evidence-based experience, it is critical to improve the indications, namely, the patient and the time it is reasonable to prescribe one or more methods of functional imaging.

CONCLUSION

Thus, functional imaging techniques hold great promise for personal optimization of radiotherapy, especially brachytherapy, in all stages of prostate cancer. The use of cutting-edge technologies and interdisciplinary integration allow us to precisely increase the efficiency and reduce the toxicity of focal therapy in each individual case.

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