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Research Article

CT Perfusion as New Modality in the Arsenal of Diagnostics for Advanced Prostate Cancer

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Abstract

Prostate cancer (PC) is one of the most common malignancies in men. Every year, 34,540 (5.5%) new cases of prostate cancer are diagnosed in India, making it the 7th most common malignancy in the male population, with annual mortality rate 16.783 (5.4%) patients. Tumour neoangiogenesis is the cause of delayed diagnosis and choice of treatment and rehabilitation according to various studies. Monitoring changes in tumour vascular pattern is currently a fundamental problem in oncology, and microvascular density is considered to be the «gold standard» in assessing neoangiogenesis and the aggressiveness of many cancers. Perfusion computed tomography is a relatively recently developed technique that allows quantitative and qualitative assessment of haemodynamic changes in tumour neoangiogenesis.

During the study, 45 patients with morphologically verified PCa were included in the final sample. The mean age of patients was 63 ± 13 years, serum PSA level was 15.41 ± 7.32 ng/ml, final PiRADS score >4, Gleason score >8. Taking into account data from world literature and their own experience, the authors proposed a modified evaluation algorithm. Statistical analysis of sensitivity, specificity and accuracy of CT-perfusion method was performed in the study.

Blood volume (BV) and blood flow (BF) were found to be statistically significant parameters for PCa diagnosis, while mean time to flow (MTT) and permeability (PS) showed no statistically significant differences between healthy tissue and "hot spots". A statistical analysis of the sensitivity, specificity, and accuracy of the CT perfusion method has been carried out. The prospects for using the method in choosing treatment and rehabilitation tactics among patients with localized PCa were noted.

CT perfusion demonstrates high indices of sensitivity and specificity in PCa diagnostics (86.96% and 62.50% respectively) and may be used as an instrumental PCa diagnostic method in future. However, it has drawbacks such as high radiation exposure and limited capabilities in soft tissue assessment. The prospects of using this method as a multimodal approach in the planning of treatment and rehabilitation tactics for patients with prostate cancer are noted.

Keywords: Blood Volume; Blood Flow; Mean Transit Time; Permeability; Localised Prostate Cancer; CT Perfusion

Prostate cancer (PC) is the one of most common malignant men neoplasms. Around 1,6 million cases of PC are diagnosed annually in the world, and 366 thousand of men dies from PC every year. Recent years appears to be with exceptionally fast growth of PC morbidity, indicate doubling number of reported cases by 2030. In Russia, prostate cancer ranks second in the morbidity structure of malignant neoplasms in men (14.9%). Every year, 34,540 (5.5 %) new cases of prostate cancer are diagnosed in India, making it the 7th most common malignancy in the male population, with annual mortality rate 16.783 (5.4%) patients [3].

The problem of screening, early diagnosis and local staging of PC cannot be overestimated due to the associating this pathology with many economic, social and biological factors. At this moment the main diagnostic methods are digital rectal examination and measuring the level of prostate-specific antigen (PSA) in blood for screening, magnetic resonance imaging (MRI) with using different sequences, and prostate biopsy under control of transrectal ultrasound (TRUS) [4]. At the same time each of these methods has limitations to their use. For example, the determination of the PSA level does not allow assessing the level of metastatic activity and the "aggressiveness" of the tumor.

According to various studies data, 30-40% of patients develop a recurrence of the disease or a metastatic lesion after radical prostatectomy and radiation therapy. In other patients, as well, localized tumors have a low potential for metastasis and local spread [5].

MRI still remains the "gold standard" as an instrumental study in the diagnosis of prostate cancer, however, this research method has a number of significant methodological imperfections, such as: analysis of temporal signals, pharmacokinetics of the contrast media, the dependence of the intensity of the MR signal on the concentration of the contrast media, especially in large vessels [7]. Furthermore, the presence of metal structures in the body, claustrophobia, etc. may be limiting factors [8]. Interpretation of prostate MRI requires work experience with functional imaging forms such as diffuse-weighted MRI, dynamic contrast-enhanced MR perfusion, and magnetic resonance spectroscopy [9].

Core needle biopsy for the purpose of morphological verification and tumor gradation according to the Gleason scale is also not without flaws, the leading among which is a limited number of biopsies, as a result of which it is possible to miss a small tumor node. A research by Heidehher., *et al*. (2015) demonstrated that tumor gradation according to preoperative biopsy results was significantly different from that after radical prostatectomy [6,10].

The reason for such difficulties in diagnosis is that PC is a biologically heterogeneous disease. Many patients with localized, slow-growing cancers live for a long time without treatment, while others develop metastases, despite the apparent limitation of the process [11].

Various researches links to the tumor neoangiogenesis, as the most possible reason for this [12]. Monitoring changes in the vascular pattern of a tumor is currently a fundamental problem in oncology, and the density of the microvascular bed is considered the "gold standard" in assessing neoangiogenesis and the aggressiveness of many types of cancer [13]. Monitoring changes in the vascular pattern of a tumor is currently a fundamental problem in oncology, and the density of the microvascular bed is considered the "gold standard" in assessing neoangiogenesis and the aggressiveness of many types of cancer [13]. Unfortunately, systematic histological evaluation of these parameters in routine clinical practice is not possible [14]. This factor led to a growing interest in the development of new functional imaging techniques for non-invasive quantification of tumor microcirculation.

Perfusion computed tomography (PCT) is a quite recently developed method that allows quantitative and qualitative estimation of hemodynamic changes during tumor neoangiogenesis [12]. The CT perfusion study is based on calculating the change in tissue density over time after an intravenous bolus injection of a contrast agent using a series of dynamic CT images [16]. During the analysis of literature data, a high efficiency in the diagnosis of prostate cancer was noted, for example, according to Cullu., *et al*. in 2014 sensitivity, specificity, positive predictive value, negative predictive value and accuracy of detection of prostate cancer were determined in 76%, 82%, 77%, 82% and 80%, while these indicators were slightly inferior to MRI [8] (Table 1).

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
T2W1	77	64	62	78	70
DWI	81	66	64	81	73
T2W1+DWI	81	74	71	83	77
PCT	76	82	77	82	80
T2W1+DWI+PCT	91	87	84	92	89

Table 1: Diagnostic efficiency of single and combined methods of PC imaging [8].

Note: PPV - positive predictive value; NPV - negative predictive value; PCT – perfusion computed tomography; PC – prostate cancer; DWI - Diffusion-weighted imaging.

The study main goal is to evaluate the diagnostic significance of CT perfusion as a method of a multimodal approach in the diagnosis and planning of rehabilitation of localized forms of prostate cancer.

The goals of study:

- Determine the perfusion parameters of the normal prostate parenchyma and histologically verified tumor nodes.
- Make a statistical analysis of the sensitivity, specificity and accuracy of the CT perfusion method to the diagnosis of prostate cancer.
- Evaluate the prospects for the introduction of CT perfusion as one of the stages in the formation of an effective rehabilitation program for patients with prostate cancer.

Data and Methods

All procedures performed in the research involving human subjects conform to the ethical standards of the institutional and/or national research ethics committee and the 1964 Declaration of Helsinki and its subsequent revisions or comparable ethical standards. Informed voluntary consent was obtained from each of the patients included in the study.

Clinical data

The study retrospectively analyzed the results of examinations of 51 patients with histologically verified prostate cancer, who were examined on the basis of St. Luke's Clinical Interdisciplinary Centre from 03.25.2021 to 08.30.2023. The following data were used: age, the level of prostate-specific antigen in serum, the results of the study of MRI and CT perfusion of the prostate. The excluding factors were: the presence of metal foreign bodies that give pronounced artifacts in the study area (total hip replacement, etc.), motor artifacts, and a history of allergic reactions to the administration of non-ionic contrast agents. The final sample included 45 patients with histologically verified by FUSION-biopsy prostate cancer, among whom the mean age was 63 ± 13 years, serum PSA level 15.41 ± 7.32 ng/ml, final PiRADS scores of > 4, and Gleason > 8.

CT scans were performed on a 128-slice spiral CT (Revolution EVO, General Electric Medical Systems). Processing, analysis, and measurements were performed on a GE AW VS7 workstation using the CT Perfusion 4D Multi-Organ software. Due to lack of a standardized protocol for CT perfusion of the prostate gland, taking into account the data of world scientific works and writings and experience of our own, we used an independently developed algorithm. Before the start of the study, the patient was prescribed to drink 1 liter of water in order to moderately fill the bladder. Scanning was performed in the supine position. As a beginning, native scan of the pelvic organs was performed from the level of the superior anterior iliac spine to apparent line that lies 1 cm caudally to the level of the ischial tuberosities. Study area for CT perfusion of the prostate was within structures 1-2 cm cranial and caudal to the base and apex of the prostate. The patient had injection of a contrast media with a concentration of 350 mg iodine/ml into the cubital vein, with an injection rate of 4 ml/sec. through a 18G peripheral venous catheter. The study was performed in a volumetric mode with 28 series on the 10^{th}, 13^{th}, 16^{th}, 19^{th}, 22^{nd}, 25^{th}, 28^{th}, 31^{st}, 34^{th}, 37^{th}, 40^{th}, 43^{rd}, 46^{th}, 49^{th}, 52^{nd}, 55^{th}, 72^{nd}, 75^{th}, 92^{nd}, 95^{th}, 112^{th}, 115^{th}, 132^{nd}, 135^{th}, 152^{nd}, 155^{th}, 172^{nd}, 175^{th} seconds after the injection of a contrast agent with a slice thickness of 5 mm.

Using the CT Perfusion 4D Multi-Organ application, prostate perfusion maps were created automatically by taking into account the densitometric voxel density of the prostate relative to the left external iliac artery, which varied during the study. The following perfusion parameters were assessed: blood flow (BF) (ml/min/100g), permeability surface (PS) (ml/min/100g), mean transit time (MTT) (sec), blood volume (BV) (ml/100g).

Statistical analysis

Conducted with the software package for statistical analysis Statistica, Excel application. Parametric criterion was used during the study: Student's t-criterion.

Results

The study analyzed perfusion maps of the prostate gland in patients before FUSION-biopsy and obtained numerical perfusion values of healthy parenchyma and "hot spots" or foci of malignant prostate neoplasms that were later verified histologically. The data we got are comparable with the results obtained in studies around the world (Table 2).

	BV (ml/100 g)	BF (ml/min/100g)	MTT (sec)	PS (ml/min/100g)
Normal PG tissue	4.53 ± 1.41	19.22 ± 4.53	16.30 ± 4.10	26.15 ± 7.12
Malignant lesions	11.12 ± 2.55	46.36 ± 11.80	18.85 ± 4.42	37.37 ± 11.68

Table 2: Perfusion parameters of healthy prostate parenchyma and malignant neoplasms.

Note: the figures are given in the format: mean ± standard deviation; BV - blood volume; BF - blood flow; MTT - mean transit time; PS - permeability surface.

Using parametric criterion we determined statistical significance between mean perfusion scores of healthy prostate tissue and malignant neoplasm for the main four perfusion indicators: BV (Blood volume), BF (Blood flow), MTT (Mean transit time) and PS (Permeability surface) (Table 3).

Perfusion parameter	Student's t-criterion	p-criterion
BV	2.15	0.04168
BF	2.06	0.04819
MTT	0.43	0.06710
PS	0.6	0.55026

Table 3: Results of statistical analysis of the main parameters of CT perfusion as an indicator of prostate cancer.

Note: BV - blood volume; BF - blood flow; MTT - mean transit time; PS - Permeability surface.

The obtained data show statistical significance of BV, BF parameters, while MTT and PS show statistically insignificant differences between the tumor lesion and the healthy prostate tissue. The main perfusion maps used to identify tumor nodes are shown below (Illustration 1).

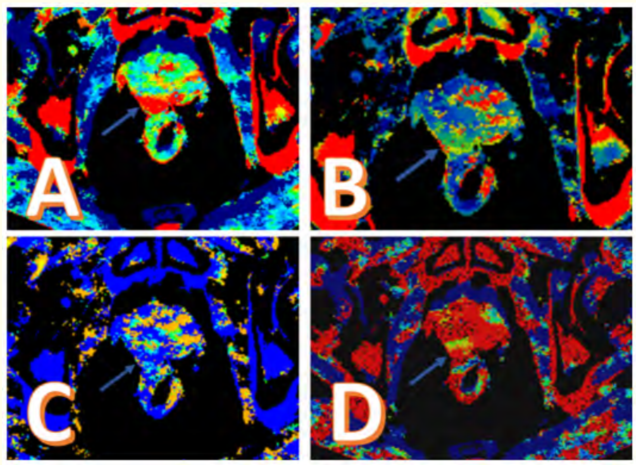

Illustration 1: PCT maps: blood volume BV (A), blood flow BF (B), mean transit time MTT (C), permeability PS (C). A patient 67 y.o. with a PSA level of 14.62/ng/ml. An irregularly shaped area 23x22 mm with altered perfusion characteristics (marked with an arrow) was detected in the middle third of the prostatic transition zone on the right side. Perfusion values were BF - 40; BV - 9; PS - 31; MTT - 23. The obtained parameters correspond to prostatic cancer. The described area was marked as a "zone of interest" and morphological evaluation confirmed a denocarcinoma (Gleason 8).

Considering the main CT-perfusion parameters, conclusions about the presumptive diagnosis of patients were made. Retrospective analysis revealed the following results (Table 4).

Total number of patients:
- 45 patients;

True positive results:
- 27 patients;

False positive results:
- 6 patients;

False negative results:
- 6 patients;

True negative results
- 6 patients.

Table 4: Results of retrospective analysis of the conducted studies.

Based on the results of CT-perfusion and biopsy data, the efficacy of the diagnostic test was noted (Table 5).

Statistical index	Obtained result
Sensitivity	81.82%
Specificity	50.00%
Positive likelihood ratio	1.64
Negative likelihood ratio	0.36
Positive predictive value	73.33%
Negative predictive value	50.00%
Accuracy	80.65%

Table 5: Statistical characteristics of the efficiency of the diagnostic study.

Discussion

Based on the research data obtained in the study, the high diagnostic value of CT-perfusion in the diagnosis of prostate cancer cannot be denied, however the problem of rehabilitation of patients after prostate cancer treatment is still of great importance for the world scientific community and for clinical practitioners. In order to restore the level of erection and control of urination after surgical treatment of prostatic cancer, and in order to prevent organic lesions and psycho-emotional stress, medical rehabilitation should be started as soon as possible after treatment [17]. According to the scientific publications, subjectively, the most difficult-to-tolerate complications of prostate cancer treatment are the urinary incontinence and erectile dysfunction, which occur in 40% and 60% of patients, correspondingly [18,19].

Bellomi M. 2010 suggested that "If CT-perfusion was able to reliably identify foci in the prostate, it would theoretically be possible to apply radiotherapy in a more targeted way, minimizing the radiation dose to the surrounding healthy tissue" [20], which would allow to reduce the radiation load on healthy tissues while preserving the effectiveness of radiation therapy, which would make it easier to rehabilitate this group of patients.

Potential use of CT-perfusion to evaluate the efficacy of radiation therapy is being considered, which would reduce the frequency of TURP and prostatectomy in patients with localized forms of prostate cancer. Since CT-perfusion is suitable for measuring BF, PS, BV the method can be used for evaluation of tumor response to radiation therapy [21,22].

However, CT-perfusion method, as well as others, is not without imperfections. First of all, it is a radial loading, the effective dose in this research is about 15-16 mSv, depending on the constitutional features of a patient. This dose is higher than in conventional multiphase CT investigation of this area, but still acceptable, especially for patients for whom MRI is not suitable or not available. Secondly, the resolution of CT-perfusion in soft tissue assessment is limited. Thirdly, it was found difficult to detect small tumor nodules (less than 10 mm).

The Conclusions

- On the background of the CT-perfusion studies, we identified numerical perfusion parameters for healthy parenchyma and prostate cancer, with the results correlating with the results of other studies in the world literature. BV (Blood volume) and BF (Blood flow) were statistically significant parameters, while MTT (Mean transit time) and PS (Permeability surface) showed no statistically significant differences between healthy tissue and "hot spots".
- A Statistical analysis of the sensitivity, specificity and accuracy of the CT-perfusion method was performed, which was 81.82%, 50.0%, 80.65% respectively, which is slightly inferior to MRI (T2W1 and DWI sequences), which is currently considered the "gold standard" in the diagnosis of prostate cancer.
- A perspective direction of using this diagnostic modality is to include it for evaluation of efficacy of radiation therapy, determination of treatment tactics and planning of rehabilitation procedures.

Conflict of Interest

The authors have no conflict of interests to declare.

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