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# CONFORMAL RADIATION THERAPY WITH INDIVIDUAL PLANNING OF TARGET VOLUME FOR LOCALLY ADVANCED NON-METASTATIC PROSTATE CANCER: TRANSFORMATION OF CLINICAL SYMPTOMS AND A CHANGE IN THE QUALITY OF LIFE IN PATIENTS AT THE STAGE OF RADIATION TREATMENT.

**Summary.** The aim of this study was to determine the effect of treatment on the clinical course of the disease and a change in the quality of life in patients who underwent two types of treatment planning: traditional (planning for conventional radiation therapy without monitoring the position of the target volume isocenter) and developed by us, the one which allows the planning for the 3D CRT course followed by monitoring the position of the target volume in the interfractional period. Assessment of quality of life in patients who underwent a course of EBRT with special radiation treatment planning method was carried out using the IPSS scale (International Prostate Symptom Score), which allows the determination the severity of symptoms in patients with urination disorder. Evaluation of a quality of life index was used as an additional method. The incidence rate of the reported disorders in the group of patients with individual treatment planning decreased 2.1 times (from 73% to 34.9%, respectively), while in the control group this rate barely reached 1.3 times (from 68.6% to 51.4%, respectively).

*Keywords. External beam radiation therapy, treatment planning, target volume, prostate cancer.*

Prostate cancer is one of the most common cancers among men around the world: external beam radiation therapy (EBRT) is a standard treatment for localized and locally advanced prostate cancer [1, 2].

The progress made over the past decade in modern radiation therapy has improved treatment tolerance and reduced the risk of complications for organs at risk (OAR) and healthy tissues. It has been made possible by means of strictly conformal methods of irradiation with the introduction of higher doses [3], as well as through the introduction of procedures of the accuracy improvement and reproducibility of radiation therapy by daily checks and correction of the position of the previously reduced target volume [4]. However, there are still no reliable planning models whose goal would be to reduce the genitourinary toxicity due to a change in the filling of the bladder that occurs between the planning computed tomography and the irradiation session. [5]

An estimated 15-year survival rate in patients with prostate cancer after EBRT at T2 and T3 stages is 65–68% and 44–75%, respectively [6], and the most recent results of modern EBRT appear to have been further improved. With such a high life expectancy, tolerance may be an increasingly important criterion for choosing a treatment [7].

In addition to assessing radiation toxicity by the doctor, the subjective assessment of the quality of life by the patient has become an important aspect of tolerance assessment in modern radiotherapy [8]. Specially designed questionnaires, based on a set of questions covering the most important aspects of everyday life and side effects, provide a comprehensive assessment of the patient's quality of life [9]. In most articles devoted to this problem of radiation therapy for prostate cancer, the quality of life appears to remain stable or only slightly decrease after treatment; however, patients experience a number of dysuric disorders, irritative and obstructive symptoms [10].

**Objective:** to evaluate treatment efficacy of patients with locally advanced non-metastatic prostate cancer prepared for the course of conformal radiation therapy using the method of individual planning.

**Materials and methods.** The study involved 63 patients with prostate cancer T2-T3b, stages N0-1NM0. After carrying out a set of necessary diagnostic procedures that confirmed the inoperability of the tumor due to the locally advanced prostate cancer, as well as the absence of distant metastases, these patients became candidates for neoadjuvant radiation therapy. It was performed at the clinic of the State Institution “S. P. Grigoriev Institute for Medical Radiology NAMS of Ukraine” in the period from 2012 to 2016, treatment planning was carried out for each patient (Patents for utility model “Method for radiation treatment planning in patients with prostate cancer” No. 97417 and No. 106050). Radiation treatment planning was done by scanning the patient on a CT scanner with a full bladder and one more time with an empty bladder. CT scans with a full bladder were reference standards. Further, after contouring the target volume and OAR in the planning system, the displacement of the prostate gland was determined and the dependence of its displacement on the filling of the bladder was mathematically proved. Before each irradiation session, using the ultrasound imaging method, the volume of the bladder was determined and using the formulas calculated with mathematical method, the displacement of the target organ in three directions was calculated with the subsequent adjustment of its position in order to match

the reference standard. The treatment was carried out on a Clinac 600C linac with 6 MeV photon energy. The comparison group included patients who underwent planning for conventional EBRT, who were treated on the ROKUS-AM machine with 1.25 MeV.

Assessment of quality of life in patients who underwent a course of EBRT was done according to the IPSS scale (International Prostate Symptom Score), which allows us to determine the severity of symptoms in patients with urination disorder. Assessment of a quality of life index was used as an additional method.

It should be noted that the planning of radiation therapy course was carried out in two ways: traditional (conventional) and personally developed by the author of the study (conformal individualized).

**Results and its discussion.** One of the main components of the study was to determine the effect of treatment on the clinical course of the disease and change in the quality of life in patients who underwent two types of preradiation planning: traditional (planning of the conventional radiation therapy without monitoring the position of the target volume isocenter) and developed by us, the one which allows planning for the 3D CRT course followed by monitoring the position of the target volume in the interfractional period.

All clinical symptoms were divided into irritative and obstructive.

The first group includes symptoms such as:

- frequent urination;
- feeling of not completely empty bladder;
- discomfort in the perineum (most often spastic or painful).

Obstructive symptoms include:

- difficulty in the process of urination;
- atypical nature of the urine stream (too thin or intermittent);
- urinary retention;
- prolongation of the urination process;
- tension of the abdominal muscles for the sensation of complete emptying of the bladder.

Table 1 presents information that allows you to track the dynamics of the main symptoms of the disease in accordance with the selected method of radiation therapy planning — conformal individualized or conventional.

Table 1

**THE INFLUENCE OF THE METHOD OF PRERADIATION PREPARATION FOR RADIATION TREATMENT OF LOCALLY ADVANCED PROSTATE CANCER ON THE DYNAMICS OF DISEASE SYMPTOMS.**

| Treatment protocol/symptoms | Irritative symptoms | | Obstructive symptoms | |
|---|---|---|---|---|
| Individualized 3D CRT (main group, n=63) | n | % | n | % |
| baseline | 25 | 39,7 | 14 | 22,2 |
| complete improvement | 7 | 11,1 | 4 | 6,3 |
| partial improvement | 15 | 23,8 | 10 | 15,9 |
| need for continuous catheterization | — | — | 6 | 9,5 |
| Conventional RT (control group, n=35) | | | | |
| baseline | 15 | 40,4 | 9 | 25,7 |
| complete improvement | 4 | 11,4 | 1 | 2,9 |
| partial improvement | 6 | 17,1 | 2 | 5,7* |
| need for continuous catheterization | — | — | 6 | 17,1* |

Note: * - significant differences ($p < 0.05$, CCU).

The first group of symptoms (irritative) was found in approximately 40% of the investigated cases. The dominance of such symptoms can be explained by the fact that they develop at an early stage of the disease, as a rule, being the first clinically detected sign of locally advanced prostate cancer.

Approximately 10% of patients showed a positive trend regarding the reduction or disappearance of irritative symptoms during the radiation treatment. It is symptomatic that these data were identified both in the main and in the control groups.

As for the partial improvement of the declared symptoms, it is 3D CRT that gives the greater effect (the difference with the control group reaches 6.7%: 23.8% of cases of partial improvement in the main group, while in the control this figure is kept at 17,1%). The obtained results give reasons to consider 3D CRT as a very promising way to control the symptoms of prostate cancer.

Obstructive symptoms characteristic of later stages of the disease were much less common in the studied groups than irritative ones (on average, 2 times). And although the incidence rate of these events is not very high, infravesical obstruction is extremely burdensome for patients and requires the earliest possible improvement of symptoms.

The data presented in table 1, clearly demonstrates that the effectiveness of removing organic barriers to

the normal outflow of urine was much higher when using 3D CRT. In 2.9% of cases, a complete improvement of obstructive symptoms was achieved in the control group of patients (where traditional radiation planning was carried out). While the conformal individualized method gave 6.3% of cases of complete improvement of obstructive disorders, which is 2.2 times more than in the control group.

Statistical significance is especially evident when analyzing cases of partial improvement of obstructive symptoms. As a result of applying a conformal individualized method of radiation therapy planning in 15.9% of patients, a weakening of the symptoms of infravesical obstruction was noted. While among the control group of such patients there were only 5.7% of cases, i.e., 2.8 times less.

No less conclusive are the results associated with the need for constant catheterization of the bladder in the late stages of the disease. In the main group, where treatment was planned in an individual conformal way, the possibility of extracting a urinary catheter was 1.8 times higher: the need for catheterization of the bladder in the case of 3D CRT was 9.5% of cases, and in the control group it reached 17.1%. It is also significant that, according to the Kruskal-Wallis test ($p < 0.05$), the demonstrated difference can be considered statistically significant.

This is another convincing argument that allows us to assess the prospects of the proposed method for planning of EBRT. It is the improvement of the methodology for conducting radiation therapy that allows us to talk about obvious advantages, the main of which is achieving control over the symptoms of the disease under study. Recall that it is individual conformal planning, during which the position of the target volume is strictly and regularly monitored, that allows the minimum displacement of PTV and OAR from session to session.

As a result of using such a technique, the improvement of irritative and obstructive disorders was faster and more pronounced. This was achieved due to the bi-directional process: tumor regression and elimination of parathumor inflammation led to an improvement in urine outflow; the volume of normal tissue adjacent to the tumor and subject to post-radiation changes in organs (urethra and bladder) decreased. Accordingly, the analysis clearly demonstrates the advantages of the innovative method of EBRT planning.

The American Urological Association questionnaire, used to standardize patient symptoms and known as the International Prostate Symptom Score (IPSS), was selected to comprehensively review patients 'quality of life as urinary disorder. This questionnaire allows you to evaluate how subjectively severe urination disorders appear to each patient. According to the methodology of the study, patients are asked 7 questions about the various manifestations of dysuria. The severity of symptoms is evaluated by each patient, based on a 6-point scale. The degree of violations on average is:

- 0-8 points - mild disorders;
- 9-19 points - moderate;
- 20 or more points are heavy.

The results of a study of a subjective assessment by patients of the degree of their own disorders during urination are presented in table 2.

Table 2

**SUBJECTIVE ASSESSMENT OF PATIENTS WITH PROSTATE DISEASES ACCORDING TO THE IPSS METHODOLOGY (INTERNATIONAL PROSTATE SYMPTOM SCORE) DEPENDING ON THE CHOSEN METHOD OF PRERADIATION TREATMENT PREPARATION FOR RT OF LOCALLY ADVANCED PROSTATE CANCER.**

| Treatment protocol/IPSS score | Before treatment | | After treatment | |
|---|---|---|---|---|
| Individualized 3D CRT (main group, n=63) | n | % | n | % |
| 0-8 | 17 | 26,9 | 8 | 12,7 |
| 9-19 | 15 | 23,8 | 7 | 11,1 |
| ≥20 | 14 | 22,2 | 7 | 11,1 |
| Total | 46 | 73 | 22 | 34,9 |
| Conventional RT (control group, n=35) | | | | |
| 0-8 | 8 | 22,9 | 7 | 20 |
| 9-19 | 9 | 25,7 | 6 | 17,1 |
| ≥20 | 7 | 20 | 5 | 14,3 |
| Total | 24 | 68,6 | 18 | 51,4* |

Note: * - significant differences ($p < 0.05$, CCU).

Analyzing obtained data, it is necessary to emphasize fairly equal conditions in which the patients of the main and control groups were. Almost similar were:

- the frequency of dysuric disorders assessed subjectively (73% in the main and 68.6% in the control group);

- the severity of symptoms of urination disorders (maximum - ¼ cases of disorders of varying severity).

Consequently, all patients participating in the study experienced approximately the same degree of subjective discomfort. Such homogeneous initial data allow us to reasonably assume that the main factor that caused the transformation of clinical symptoms during and after treatment can be considered the method of preradiation preparation.

After the end of the radical RT treatment course, a second control assessment was carried out according to the chosen technique. Its results demonstrate the convincing advantages of the irradiation planning methodology developed by us even more. In this case, the most burdensome symptoms of prostate cancer are controlled much more effectively compared to the traditional method of radiation.

Especially evident (and statistically significant, according to the Kraspel-Wallis criterion) are the results associated with the overall frequency of subjectively assessed urination disorders. So, in the main group, as a result of treatment, the frequency of reported disorders decreased by 2.1 times (from 73% to 34.9%, respectively). While in the control group this frequency barely reached 1.3 times (from 68.6% to 51.4%, respectively).

It should be noted that after the end of treatment in the control group, 3-8% of various dysuric disorders were observed more than in the main group.

However, it is worth paying attention to the severity of dysuria before and after treatment in each of the studied groups. So, in the main group, the proportion was more beneficial for the main group:

- for mild disorders - 1.6 / 1;
- for medium violations - 1.5 / 1;
- for severe violations - 1.3 / 1.

Patients with localized prostate cancer usually have several radical treatment options, such as radical prostatectomy, brachytherapy, and 3D CRT. The results of our study provide useful data for understanding the function of urination specifically after the course of 3D CRT. According to the data obtained, it is obvious that radiation therapy, planned on the basis of an individual conformal method that controls the position of the target volume, guarantees much more reliable control over the symptoms of the disease in the study, manifested at different stages of prostate cancer. In the group of patients who underwent preradiation training using the individualized method, the frequency of reported disorders decreased 2.1 times (from 73% to 34.9%, respectively), while in the control group this frequency barely reached 1.3 times (from 68.6% to 51.4%, respectively).

This is explained by a more uniform dose distribution in reduced PTV, while irradiation of surrounding intact organs and tissues (primarily the bladder) is significantly minimized. It is recommended to continue monitoring both groups, including more patients for further results.

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