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A B S T R A C T

of the dissertation for the degree of Doctor of Science

**IMPROVING COMPLEX THERAPY TACTICS
FOR LOCAL ADVANCED PROSTATE CANCER**

Speciality: 3224.01 – "oncology"
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INTRODUCTION

The relevance of the research. Prostate cancer is one of the most common diseases and holds a leading position in the overall cancer statistics on mortality among middle-aged and elderly men.In most cases, the disease develops in a part of males who are able to work, and it indicates the relevance of the issue of timely diagnosis and the selection of optimal treatment tactics.[1]

The results of epidemiological studies of prostate cancer show that the incidence varies significantly from country to country. In Europe, in 2008, 382,000 new cases (22.2% of the total) of prostate cancer were diagnosed. The mortality rate from prostate cancer, in turn, was 89,000 (9.3%) and ranked third, behind only lung cancer 255,000 (26.6%) and colorectal cancer 110,000 (11.5%).[2] Based on the results of the European Cancer Observatory (EUREG database), which included data from 26 countries, it was demonstrated that there is a positive movement in the rates of detection of this disease in the countries of Eastern and Southern Europe.[3]

There is a steady increase in the incidence of PC in the Republic of Azerbaijan. For instance, in 2009, the incidence rate was 2.9 per 100,000 male population, while in 2011, 2012 and 2013, this figure was 3.9, 3.9 and 4.3, respectively. The growth of this indicator is primarily associated with the ongoing educational work among the population and the increase in the life expectancy of the male population in the country over the past 10 years.[4]

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[1] Larsen S.B. Socioeconomic position and mortality among patients with prostate cancer: influence of mediating factors / S.B.Larsen, K.Brasso, J.Christensen [et al.] // Acta Oncol, -2017. №56(4). -p. 563-568

[2] Wong, M.C. Global Incidence and Mortality for Prostate Cancer: Analysis of Temporal Patterns and Trends in 36 Countries / Martin C. S. Wong, William B. Goggins, Harry H. X. Wang [et al.] //European Urology, - 2016. Nov; 70, 5, - p. 862-874

[3] Zhou, C.K. Prostate cancer incidence in 43 populations worldwide: An analysis of time trends overall and by age group / Cindy Ke Zhou, David P. Check, Joannie Lortet-Tieulent [et al.] //International Journal of Cancer, -2016. Mar; 138, 6 - p. 1388-1400.

[4] Алиев, Д.А. Эпидемиологические аспекты злокачественных новообразований в Азербайджанской Республике за 2008-2013 гг. / Д.А. Алиев, Ф.А. Гулиев, Ф.А. Марданлы [и др.] // Azərbaycan onkologiya və hematologiya jurnalı, - Bakı: - 2014. №2, - s. 32-38.

Locally advanced prostate cancer is characterized by aggressive tumor biology, the high probability of local and distant metastases, and the presence of an unfavorable prognosis of the disease.[5] Despite the achievements of experimental and clinical oncology, the improvement of diagnostic methods (ultrasound, CT, MRI, etc.), the widespread use of the prostatic specific antigen (PSA) and its derivatives, the prediction of preoperative stage of the disease, in particular, determining the "border" between localized and locally advanced prostate cancer remains unresolved.[6]

To date, in the field of oncourology, issues regarding the treatment of locally advanced prostate cancer (PCA) remain controversial. The reason for the ongoing debate is the inaccuracies in clinical staging and lack of information about the benefits and treatment feasibility of the used methods .In accordance with the guidelines of the European Association of Urology (EAU), the main methods of treatment for prostate cancer are RPE, RT and HT. The presence of concomitant disease, the patient's age, life expectancy, the clinical stage of the disease, and the possibility of progression play an important role in choosing the optimal treatment tactics.[7]

Identification of risk factors contributing to the prediction of extracapsular tumor growth will primarily improve the overall and relapse-free survival rates of competing treatments, such as radical prostatectomy (RPE) and radiation therapy (RT).[8] It is noteworthy that along with a growing interest in the surgical method of treatment, in recent years, the oncourologistshave increasingly begun to point out the feasibility of performing RT in combination with hormone therapy (HT). The combination of radiation and hormone therapies led to an

[5] Choyke P.L. The state of prostate MRI in 2013: into the breach. / P.L.Choyke, B.Turkbey // Oncology (Williston Park), - 2013. №27(4). - p. 274-276

[6] Dell'atti L. Role of transrectal ultrasound in the diagnosis of extracapsular prostate cancer. // Journal Ultrasound, - 2014. №17(1). -p. 47-51

[7] Heidenreich A. EAU guidelines on prostate cancer. / A.Heidenreich, P.J.Bastian, J.Bellmunt [et al.] // Eur Urol, -2014. №65(2), p. 467-479

[8] Bekelman J.E. Effectiveness of androgen-deprivation therapy and radiotherapy for older men with locally advanced prostate cancer / J.E.Bekelma, N.Mitra, E.A.Handorf [et al.] // Journal Clin. Oncol, -2015. №33(7). p. 716-722

improvement in cancer-specific and overall survival.[9]

Surgical treatment of prostate cancer has two main goals: complete cure and local disease control. The problem of the feasibility of performing an RPE in patients with locally advanced prostate cancer remains debatable, and the reason for this is the low relapse-free survival without adjuvant therapy and the high rate of surgical complications. For a long time, the attitude to performing RPE in a locally advanced process or in patients with a high risk of progression was rather skeptical, it was considered unjustified and inappropriate.[10] From a surgical point of view, the prediction of extracapsular tumor growth is necessary to determine the volume of surgical intervention and to inform the patient about possible postoperative complications.[11]

To date, in order to determine the optimal volume of surgical intervention and predict the likelihood of progression, D'Amico classification and Partin nomogram are used. These prognostic models are based on a combination of such parameters as the clinical stage, preoperative PSA level and the degree of tumor malignancy according to the Gleason index on biopsy specimens.[12] Partin and colleagues were the first to propose a mathematical model based on preoperative parameters that could predict the postoperative stage of the disease. In subsequent years, the proposed mathematical model was subjected to a number of changes, improvements, and external validations.[13] Nevertheless, some of the studies failed to demonstrate

[9] Drouin S.J. Combined hormonotherapy with external beam radiotherapy in locally advanced prostate cancer: do side effects overlap the advantages? / S.J.Drouin, M.Rouprêt, A Bossi [et al.] // Prog Urol, - 2010. №20. -p.186-191

[10] Ischia J. Radical prostatectomy in high-risk prostate cancer. / J.Ischia, M.Gleave // Int Journal Urol,- 2013. №20(3). - p. 290-300

[11] Ristau B.T., Cahn D ., Uzzo R.G. et al. The role of radical prostatectomy in high-risk localized, node-positive and metastatic prostate cancer. / B.T.Ristau, D.Cahn, R.G.Uzzo [et al.] // Future Oncol, -2016. №12(5). - p. 687-699

[12] Bhojani N. Partin tables cannot accurately predict the pathological stage at radical prostatectomy. / N. Bhojani, S.Ahyai, M.Graefen [et al.] // Eur Journal Surg Oncol, -2009. №35.- p. 123-128

[13] D'Amico A.V. Predicting prostate specific antigen outcome preoperatively in the prostate specific antigen era./ A.V.D'Amico, R.Whittington, S.B. Malkowicz [et al.] // Journal Urol, -2001. №166.- p. 2185

and confirm the high accuracy and ability of Partin's nomograms in predicting the extracapsular extension of prostate cancer. In addition to predicting the extracapsular extension of the tumor process, an important task facing clinicians is to determine the rate of developing biochemical recurrence after treatment.[14]

However, the widespread use of these predictive models in clinical practice has identified certain deficiencies and demonstrated the need for their improvement and revision. Thus, despite some progress made in studying the range of issues related to patient management, the lack of generally accepted clinical guidelines for the treatment of locally advanced prostate cancer or high-risk patients, induced us to focus on this problem and encouraged us to conduct this study.

Aim of work.

To develop methods to improve tactics and improve treatment results for patients with locally advanced prostate cancer.

Research objectives

1. To evaluate the information content of preoperative clinical and laboratory parameters in predicting the stage of the pathological process.

2. To develop a model for determining extracapsular extension and conduct a comparative assessment with Partin nomogram.

3. To conduct a comparative analysis of the surgical results and combined treatment methods depending on the specificity of patient groups.

4. Using the methods of multifactorial regression analysis, assess the nature of the influence and the data taken into account on the prognosis of the disease.

5. Determine the rational treatment tactics and optimize the volume of lymphatic dissection in patients with prostate cancer in different observation groups.

6. Recommendations for preventive measures to reduce complications and preserve the quality of life, conduct a multivariate

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[14] Blute ML, Bergstralh EJ, Partin AW, et al. Validation of Partin tables for predicting pathological stage of clinically localized prostate cancer. / M.L.Blute, E.J.Bergstralh, A.W.Partin [et al.] // Journal Urol, -2000. №164. p.1591-1595

analysis of complications and provide appropriate ones.

Research methods

The research material includes data on 438 patients diagnosed with prostate cancer who received treatment at the Oncourological Department of the National Center of Oncology of the Ministry of Health of the Republic of Azerbaijan and the Departments of Urology and Radiation Therapy of the University of Hacetepe (Turkey) in 2001-2015. All patients were divided into two groups according to the treatment. The first (surgical) group included 296 patients who underwent radical prostatectomy (RPE). RPE was performed laparoscopically in 30 patients in this group. All patients were assessed for their general condition in the preoperative period and underwent a general clinical examination to develop an optimal treatment plan. The second (combined) group included 142 patients receiving hormone therapy (HT) in combination with radiation therapy (RT). All patients in this group were irradiated under 3D planning conditions using a Clinac 2300/CD linear electron accelerator (Varian Medical Systems, USA) with a photon beam energy of 6-15 MeV.

In all patients, including group II patients, the diagnosis of prostate cancer (acinar type) was verified at the initial stages of treatment by histological examination of biopsies. Prostate biopsy samples were taken in accordance with the EAU recommendations by transrectal ultrasound guided biopsy (TRUS). The grade of differentiation of the tumor on the histological examination was determined according to the Gleason scale.

The subject of the study was the immediate and long-term results of surgical and combined methods of treatment. The nature and frequency of complications, relapse-free and cancer-specific survival, predictive risk factors for biochemical recurrence and clinical progression after radical prostatectomy were studied. Based on the results obtained from the use of statistically significant preoperative and postoperative parameters, mathematical models were developed for predicting the locally advanced prostate cancer and the progression of biochemical recurrence. Based on the results, according to cancer-specific and biochemical relapse-free survival

rates, a comparative evaluation of the treatment results of patients who underwent radical prostatectomy and received hormone therapy in combination with radiation therapy was performed.

Additional evaluation criteria: The QLQ-PR25 module contained three additional symptom scales – urinary (UR), intestinal (BW), and sexual (SX), and treatment-related complications (TR). The health-related quality of life was assessed using the EORTCQLQ-C30 and EORTCQLQ-PR25 questionnaires.

Highlights of the thesis

1. The developed mathematical model in comparison with Partin nomogram, has statistically reliable indicators of calculating the probability of local-prevalence of (APC), which allows to determine the optimal amount of surgery.

2. The developed mathematical model for predicting biochemical relapse (BCR) after RPE allows to identify a group of patients with the highest probability of PSA growth in the postoperative period.

3. The choice of the most rational treatment tactics depending on the risk group of prostate cancer progression.

4. Enlarged pelvic lymphadenectomy (LAE) significantly increases the detection of regional metastases compared to obturator (closed) lymphadenectomy and increases relapse-free survival, in particular, in patients with intermediate risk of prostate cancer.

Scientific novelty of the research.

The novelty of the results is predetermined by the created methodology, which allowed to optimize the tactics of complex therapy of locally advanced prostate cancer. The methodology is based on a comprehensive analysis of heterogeneous indicators (clinical, laboratory and instrumental data) and a generalization of the results. This approach will optimize the existing algorithm for the treatment of patients with locally advanced prostate cancer, improve surgical tactics and determine the volume of operations to achieve optimal oncological results. The collected data will help to determine the effectiveness of the treatment with subsequent prediction of overall and progression-free survival by identifying the pathological and histological features of the tumor and factors directly affecting the results of treatment of patients with locally

advanced prostate cancer.

Practical significance of the research

The mathematical model developed as a result of the study for predicting extracapsular extension allows us to determine the stage of prostate cancer based on preoperative clinical and pathomorphological data, that directly affects the determination of the volume of surgical intervention and increases the percentage of resectability. Predictive significant analysis of the of various factors allows us to provide recommendations for determining the basic principles of a comprehensive approach to the selection of patients of locally-common prostate cancer, for each of the treatments with a subsequent assessment cancer risk degree. Implementation of the study results in the practical work of oncologists, urologists and radiation therapists will limit cases of hypo- and hyperdiagnosis of (APC), therefore, will provide an increase in the resection of (APC) and reduce the frequency of postoperative complications. Based on study results, it is possible to conduct a comparative assessment of life quality and analyze ways to improve it with different treatment methods.

The study results are used in the formation of study guides, in the training process in the departments of oncology, urology, radiation diagnostics and therapy.

Approbation of the work

The main provisions and results of scientific research were discussed at the scientific and practical conference dedicated to the 80th anniversary of Professor E. I. Ibragimov (Baku, 2010), at the IV Congress of the Russian Society of Oncourologists (Moscow, 2010), at the VI Congress of Oncologists and Radiologists of the CIS countries (Dushanbe, 2010), at the VI Congress of the Russian Society of Oncourologists (Moscow, October 5-7, 2011), at the scientific and practical conference dedicated to the birthday of national leader G. A. Aliyev (Baku, 2012), at the VIII Congress of oncologists and radiologists Evraazii (Kazan, 2014), at the 11th Congress of the Russian Society of Oncourologists (Moscow, 2016), Scientific seminar of ED 2.06 Dissertation Council operating under Azerbaijan Medical University (March 18, 2021, protocol N 1) at the

interdepartmental conference of National Center of Oncology (Baku, May 29, 2018, protocol №1).

Publication of research materials and implementation to practice

Based on the research, 43 publications were published. Scientific works were published in Azerbaijan (19 articles and 4 abstracts, as well as in foreign journals (13 articles and 7 abstracts).

Application of the dissertation

Scientific conclusions and practical recommendations have been implemented into the clinical practice of urology therapy department at Hajettepe University (Turkey) and Oncourology and Radiation therapy departments of the National Center of Oncologyof the Ministry of Health of Azerbaijan Republic, and are also used in the educational process of the Azerbaijan State Institute of Advanced Medical Studies named after A.Aliyev.

Scope and structure of the dissertation: The dissertation is presented on 354 pages of the text (614286 characters) and consists of an introduction (16599 characters), a literature review (109527 characters), 7 chapters containing research materials and methods (341900 characters), conclusions (51890 characters), findings and practical recommendations (4530 characters), a list of references (84315 characters). The work is illustrated by 66 figures and 50 tables. The list of references contains 350 bibliographic sources, 41 of which are works of local authors and 309 are foreign.

Materials and research methods

The study material was based on the data of 438 patients diagnosed with prostate cancer who received treatment on the basis of the oncourological department of the National Center of Oncology of the Ministry of Health of Azerbaijan Republic and the departments of Urology and Radiotherapy of the University of Hajettepe (Turkey) from July 2001 to November 2015.

All patients were divided into two groups according to the treatment. The patient's consent was the main factor in the choice of treatment method and was based on the provision of complete

information about the diagnosis, therapeutic and side effects of the treatment. The exclusion criterion was the patient's history of previous radiation or hormonal therapy, surgery performed on the prostate, metastasis of the lymph nodes andthe bones.

The first (surgical) group consisted of 296 patients who underwent RPE. Surgery was performed on 100 (33.8%) patients aged 50-59, 154 (52%) aged 60-69 years. Eleven (3.7%) patients were not older than 50 years (44-49). In 31 (10.5%) cases, the age of the patients exceeded 70 years.Thirty patients in this RPE group were performed a laparoscopy method. In the preoperative period, all patients underwent general clinical examinations to assess the general condition of the patient and develop an optimal treatment plan. Patients with a follow-up period of less than 12 months and with no follow-up data were excluded from the study.

In order to predict the clinical stage of the disease, to determine the resectability of the malignant process and to exclude metastatic lesions, CT or MRI were performed along with a package of laboratory tests before all patients undergoing surgical intervention. The indications for osteoscintigraphy were preoperative PSA ≥ 20 ng / ml or a low degree of tumor differentiation.

According to the classification of D'Amico, in the surgical group, 96 (32.4%) patients were at low risk, 114 (38.5%) patients were in the intermediate group, and 86 (29.1%) patients were at high risk.

The second (combined) group consisted of 142 patients who received RT in combination with HT. In this group of 16 (11.3%) patients were aged 50-59 years. At the age of 60-69 and older than 70 years, at the beginning of treatment, there were 62 (43.7%) and 64 (45.1%) patients, respectively.

According to the D'Amico classification, in the combined group of 27 (19.0%) patients entered the low risk group, 114 45 (31.7%) patients in the intermediate group, and 70 (49.3%) patients in the high risk group.

For patients with intermediate and high risk, HT was performed 3 months before RT in the amount of maximum androgen blockade. The planned duration of HT was 24 months.

All patients in this group were irradiated under 3 D conditions – planning on a linear electron accelerator Clinac 2300 / CD (Varian Medical Systems, USA) with photon beam energy of 6-15 MeV.

In all patients, including patients of II group, the diagnosis of prostate cancer (acinar type) was verified at the treatment stages by histological examination of biopsy specimens. RV biopsy samples were collected in accordance with EAU recommendations using transrectal biopsy and ultrasound navigation. The grading of the degree of tumor differentiation on histological examination was carried out according to the Gleason score.

The subject of the study was the immediate and long-term results of surgical and combined treatment methods. The nature and frequency of complications, relapse-free and cancer-specific survival, prognostic risk factors for biochemical recurrence and clinical progression after RPE were studied.

Follow-up after surgical treatment included PSA determination every 3 months for 2 years, every 6 months for the next 2 years, and then once a year.

Survival before biochemical recurrence was defined as the time from surgery to an increase in PSA levels above 0.2 ng / ml, confirmed by at least two consecutive analyzes. In patients in the combined treatment group, the diagnosis of biochemical progression was set on the basis of an increase in PSA levels of 2 ng / ml or higher after reaching the minimum tumor marker after treatment.

Patients with suspected development of biochemical recurrence or clinical progression in order to identify regional and distant metastases underwent CT or MRI of the pelvis and retroperitoneal space. Another method of choosing a radiological study to determine the prevalence of the process was osteoscintigraphy and PET-CT. Patients in the surgical group, in the presence of suspicious sites with digital or radiological examinations, underwent biopsy of the UVA zone under the control of TRUS.

In the combined treatment group, 43 (30.3%) patients underwent a prostate biopsy after 18 months of treatment.

Cancer-specific survival was the primary endpoint of the study,

and the fact of death from a cause associated with PCA was taken as an event. Observation was considered complete if the patient died before the observation end date. Observation was considered censored if, the patient was alive by the time the observation was completed, dropped out of the observation, or if reliable information about his future fate was not possible. The start date of observation was taken as the start of treatment, the date of completion of the study was considered November 1, 2015.

Complications of the early postoperative period (30 days from the date of surgery) were evaluated according to the Clavien-Dindo classification.

In our study, in accordance with the classification of Clavien-Dindo, all patients were divided into five groups. The 1st group included patients with any postoperative complications that do not require surgical or medical correction. Group 2 - patients who required medical correction, blood transfusion, and parenteral nutrition. The 3rd group included patients who underwent radiological, surgical or endoscopic intervention under local (IIIa) or general (IIIb) anesthesia. The fourth group consisted of patients with life-threatening complications requiring emergency care or intensive therapy with multiorganic(IVa) or polyorganic (IVb) insufficiency. The fifth group includes patients in whom there was death from complications.

We also studied the incidence of catheter-associated urinary tract infections (CAUTI). A catheter- associated bacteriuria is diagnosed if one or more microorganisms in an amount exceeding 10^5 cfu/ mlexist in patients with no symptoms of urinary infection.

Patients in the surgical group, depending on the diagnosis of local or systemic relapse, underwent HT or RT of the postoperative field. In the combination treatment group, patients with disease progression were given courses of systemic chemotherapy with docetaxel. All patients with bone metastases in both groups were treated with zoledronic acid every 28 days.

The evaluation of toxicity resulting from radiation therapy was assessed according to RTOG / EORTC (Radiation Therapy Oncology Group/ European Organization for Research and Treatment of

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Cancer) and CTCAEv. 4.0 (Common Terminology Criteria for Adverse Events) standards.

Health-related quality of life was assessed using the EORTC QLQ - C 30 and EORTC QLQ - PR 25 questionnaires. The data were processed in accordance with the recommendations of the European Organization for Research and Treatment of Cancer (EORTC).

Evaluation on all scales was carried out in points from 0 to 100 and was calculated according to the formulas: for functional scales, for symptomatic scales, for general health scales.

The QLQ - PR 25 module contained three additional symptomatic scales - urinary (UR), intestinal (BW) and sexual (SX) and treatment-related complications (TR). Urinary retention was assessed using a brief questionnaire from the International Urinary Incontinence Consultation (ICIQ - SF). The survey of patients was conducted on the 1st, 3rd and 12th postoperative month.

The analysis of the results and the construction of diagrams were carried out using the statistical software package SPSS 18.0 for Windows. The duration of observation was estimated from the first day of treatment of prostate cancer to the last day of observation or death. The analysis without recurrence and cancer-specific survival after the treatment was evaluated by using the Kaplan-Meier method, the differences in survival were determined using a log - rank test. To identify predictably significant factors for survival, one of the multivariate Cox's regression analysis was used.

In order to identify significant differences in the observed quantitative indicators in the compared groups of patients, the nonparametric method - Wilcoxon-Mann-Whitney test was applied for independent samples. To assess the relationship of qualitative features, the Pearson χ^2 method was used.

In order to analyze the practical value of the prognosis, the ROC-curve (Receiver Operator Characteristic) was used. Differences with a significance level of 95% ($p < 0.05$) were considered statistically significant.

Research results

Radical prostatectomy was performed in 296 patients. Based on the results of pathomorphological studies of the retrieved margin, the stage of pT2a was detected in 39 (13.2%) patients, while in 13 (4.4%) and 156 (52.7%) patients respectively the tumor process was at the pT2 b stage and pT2c. The presence of extracapsular extension was diagnosed in 56 (18.9%) patients, with stage p T3 b being exposed to 32 (10.8%) patients.

In order to predict the probability of the prevalence of the tumor process, we calculated the areas under the operational ROC- curves for preoperative parameters. The statistical analysis for the PSA level was 0.658 ± 0.033 ($p < 0.001$, 95% CI 0.593-0.723). The obtained result emphasized the reliable value of this marker in predicting the local prevalence of the tumor process. In the study group, with a threshold of preoperative PSA corresponding to 9.4 ng / ml, the sensitivity and specificity of the tumor marker were respectively 51.1% and 70.7%.

In the study, derivatives of PSA also showed reliable values. So, the areas under the operating ROC- curves for PSA density, free form and the ratio of the level of free to total PSA were 0.742 ± 0.038 ($p < 0.001$; 95% CI 0.667-0.816), 0.595 ± 0.044 ($p = 0.034$; 95% CI 0.508-0.682) and 0.404 ± 0.043 ($p = 0.032$; 95% CI 0.319-0.488), respectively.

Based on the analysis of the obtained results, we came to the conclusion that digital rectal examination (DRE) does not fully reflect, and in some cases underestimates, the prevalence of the tumor process. Nevertheless, despite a certain diagnostic limitation, the implementation of this research method is necessary during the initial examination of the patient. In the studied cohort of patients, the discrepancy between clinical and pathomorphological staging was 28.9%.

Another important preoperative prognostic parameter is the degree of tumor differentiation by biopsy. In order to study the prognostic value of this parameter in predicting the pathological stage of the disease, we calculated the area under the operating ROC curve. The result was 0.663 ± 0.036 ($p < 0, 001$; 95% CI 0.592-

0.734), which indicated the significant value of the Gleason index in predicting the stage of the disease.

In addition to generally accepted prognostic factors, we studied the prognostic value in determining the local prevalence of the process of such as preoperative parameters, the number of positive columns, tumor lesion expressed in percentage and the number of columns with> 50% lesion in the biopsy material of the prostate gland.

In order to identify the relationship of these parameters with the postoperative stage, we conducted an appropriate correlation analysis. The one-way analysis of variance showed reliable values for the number of positive columns, the maximum damage to the columns, expressed as a percentage and the number of columns with a lesion > 50%. The area under the operating ROC curve for maximum damage to the column was 0.774 ± 0.044 (p< 0.001; 95% CI 0.689-0.859). Similar indicators for the number of positive columns and columns with a lesion > 50% were 0.724 ± 0.049 (p< 0.001; 95% CI 0.629-0.819) and 0.771 ± 0.045 (p <0.001, 95% CI 0.682-0.860), respectively.

In order to improve the diagnostic accuracy and informational content of MRI, we conducted a comparative analysis of the prognostic significance (informational content) of various identifiable signs characterizing the extraorganized spread of prostate cancer. The accuracy of all the analyzed signs turned out to be approximately comparable, however, the differences in the indicators of diagnostic sensitivity, specificity and value of prognostic values attract attention. In particular, the most sensitive MRI sign of a locally advanced process was the degree of visualization of the gland capsule, which was 80.1%, but its specificity was only 59.1%. The remaining MRI criteria for extraorganized extension of the malignant process possessed a rather high specificity (>80%) with low sensitivity. The facts mentioned above indicate the need for the integrated use of these features.

We studied the prognostic value of the main MRI criteria for locally advanced prostate cancer and clinical data based on the results of univariate and multivariate analysis. The multivariate model included 4 indicators that statistically significantly influenced

the risk of locally advanced prostate cancer: the presence / absence of a clear visualization of the prostate gland in a T2-weighted image *(p = 0.007)*, detection of formation in prostate gland > 1.3 cm in the largest dimension *(p = 0.001)*, multifocal tumor *(p = 0, 036)* and the ratio of the visualized tumor to seminal vesicles *(p = 0.03)*.

Based on the obtained results, a mathematical model was developed for predicting the local prevalence of the tumor process using statistically significant preoperative indicators. The complete set of predictors, which allows to increase the accuracy of predicting the local prevalence of the tumor process, was: total PSA, PSA density, MRI score, Gleason index, number of positive columns, maximum percentage of tumor in the column, number of columns with lesions of more than 50%.

A comparative assessment of the diagnostic properties of Partin nomogram was carried out and the mathematical model by constructing ROC- curves with determining the areas under them was developed by us. The statistical significance of the discriminatory possibilities of the mathematical model that we developed is 0.857 ± 0.042 *(p< 0.001*; 95% CI 0.774–0.940*)* that exceeds Partin nomogram's similar indicators 0.606 ± 0.068 *(p = 0.091*; 95% CI 0.474–0.739*)* (Fig.1).
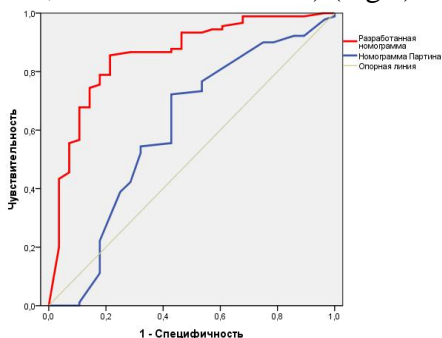

Figure 1. ROC curves of predictive capabilities of nomograms.

It should also be noted that while calculating the probability of tumor spread process out of the capsules, was indicated followings: a mark corresponding to 52%, has the highest sensitivity and specificity and account for 78.9% and 82.1% respectively.

In the study, the average follow-up time in the surgical group was 52.3 ± 2.2 (12-166) months, and in the combined treatment group 54.7 ± 3.0 (12-144) months. Statistical analysis did not show a significant difference *(p = 0.522)* between the groups.

In our study, a PSA level > 0.2 ng / ml was taken with a BCR threshold in two consecutive measurements. In the surgical group, BCR was diagnosed in 52 (17.6%) of 295 patients, and 41 (28.9%) of 142 patients in the combined treatment group. The mean time to development of BCR in the surgical group was 24.8 ± 2.8 months (95% CI: 19.296-30.281), and in the combination treatment group this indicator was 25.5 ± 2.3 months (95% CI: 20.942- 30,033). Statistical analysis did not show a significant difference *(p=0,772)* between the groups.

Based on the obtained results, we conducted a comparative assessment of the treatment outcomes of patients undergoing RPE and RT in combination with GT, according to the criteria of cancer-specific and disease-free biochemical survival.

During the observation period, 10 (19, 2%) of 52 patients with BCR who underwent RPE had a mortality rate due to the progression of prostate cancer. In turn, mortality from prostate cancer in the RT group was observed in 17 (41.5%) of 41 patients. In order to determine the effect of the treatment method on cancer- specific survival, we used the Kaplan-Meier method with a log rank test (LogRanktest). According to our data, the treatment method turned out to be an independent factor affecting cancer-specific survival *(p < 0.001)*.

Five and 10-year cancer-specific survival in the surgical group was 98% and 84%, respectively. The corresponding indicators for the combined treatment group, in turn, were 85% and 72%, respectively.

The dependence of the disease-free biochemical and carcinogenic specific survival on the treatment method was assessed in accordance with the risk groups for D' Amico classification.

In the low-risk group, BCR was diagnosed in 8 (8.3%) of 96 patients who underwent RPE, and 4 (1 4.8%) of 27 patients who received combined treatment. The mean time to development of BCR in the surgical group was 43.5 ± 7.2 months (95% CI: 29.313-

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57.687), and in the combination treatment group this indicator was 35.0 ± 11.0 months (95% CI: 13, 3 81-56.619). Statistical analysis did not show a significant difference *(p = 0.671)* between groups.

In the surgical group, 5- and 10-year-old cancer-specific survival rates were 99% and 86%, respectively, while the corresponding rates for patients in the combined treatment group were 98% and 86%, respectively. Thus, our data did not demonstrate the significant value of the treatment for cancer-specific survival in the low-risk group of patients *(p = 581)*.

A similar analysis was also performed for patients with intermediate risk according to D' Amico classification.

According to the obtained data in the surgical group, the 5- and 10-year cancer-specific survival rates were 98% and 82%, respectively, while the for patients in the combined treatment group were 94% and 78%, respectively. The data obtained for patients at intermediate risk did not demonstrate the reliable significance of the treatment on the indicators of relapse-free biochemical and cancer-specific survival *(p = 0.834 and p = 0.417)*.

An analysis was also carried out aimed at determining the effect of the treatment method on relapse-free biochemical and cancer-specific survival in patients with a high risk of progression by using the Kaplan-Meier method with a logarithmic rank test (LogRanktest). According to the results obtained, a statistically significant difference was observed between the groups according to the criterion of disease-free biochemical survival *(p = 0.012)* (Fig.2).

Based on the data obtained in the surgical and combined groups, the 5-year cancer-specific survival was 97% and 66%, respectively *(p< 0.001)* (Fig. 3)

This fact, in turn, determines the advantage of the surgical treatment over RT.

The risk functiongraph of the mortalityrate from prostate cancer demonstrates the absence of differences in the first 12 months after treatment. With further observation, a sharp rise in mortality cases in the LT group is noted. Further, relative stabilization is observed during 60 months of observation in this group .In turn, the risk of mortality

increases after 72 months of follow-up in the surgical group. Thus, our observations on the advantage of RPE over RT in treating patients with a high risk of progression found full confirmation when studying the indicators of cancer-specific survival in this group of patients. The results showed statistically significant differences (LogRanktest, $\chi^2 = 14.581$; $p < 0.001$).
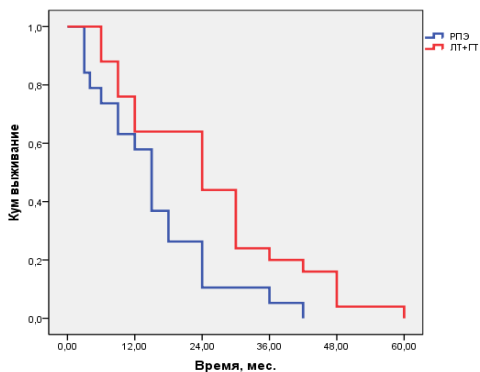

Figure 2. Relapse-free biochemical survival in the high-risk group depending on the method of treatment
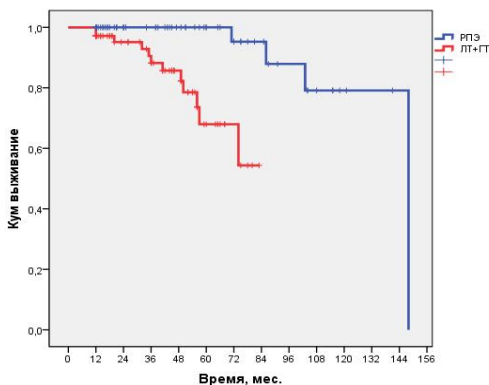

Figure 3. Cancer-specific survival in the high-risk group, depending on the method of treatment.

The obtained results demonstrated that for patients of low and intermediate risk, surgical and combined treatment methods have comparable results according to the criteria of disease-free biochemical and carcinogenic specific survival. Due to these data, it seems possible to conduct an individual approach with the obligatory informing each patient. In turn, in patients with a high risk of progression, surgical treatment showed a statistically significant advantage, highlighting this treatment method to the forefront, in particular for patients who do not have serious contraindications for radical surgery.

In the cohort study, 90 (93.7%) patients in the low-risk group, had RPE without LAE. Removal of lymph nodes (LN), limited by the obstructive fossa, was performed in 6 (6.3%) patients. The average number of removed LNs was 12.2 ± 1.4 (9-17). In none of the cases did histological examination determine the presence of metastatic damage. Biochemical relapse in this group was diagnosed in 8 (8.3%) of 96 patients.

In the intermediate-risk group, obstructive and extended LAE were performed in 53 (46.5%) and 61 (53.5%) patients, respectively. The average number of removed LNs at the indicated volumes was 11.4 ± 0.4 (8-18) and 25.3 ± 0.7 (20-51), respectively. In 2 (3.8%) of 53 patients undergoing RPE with obstructive LAE, histological examination revealed metastatic LN. It should be noted that metastatic lesion in the group of patients with advanced LAE was also noted in 2 (3.3%) cases.

In order to conduct a comparative assessment of the effect of volumes of performed LAE on relapse-free biochemical survival, the patient's data were subjected to statistical analysis using the Kaplan-Meier method with a logarithmic rank test (LogRanktest). The mean time to development of BCR for patients with obstructive LAE was 16.5 ± 2.6 months (95% CI: 11.389-21.611). This indicator in the group with advanced LAE, in turn, was 37.7 ± 8.1 months (95% CI: 21.786-53.668). A comparative assessment conducted between the two groups showed a significant difference in Wilcoxon (Wilcoxon) (*p = 0.003*) (Fig.4).
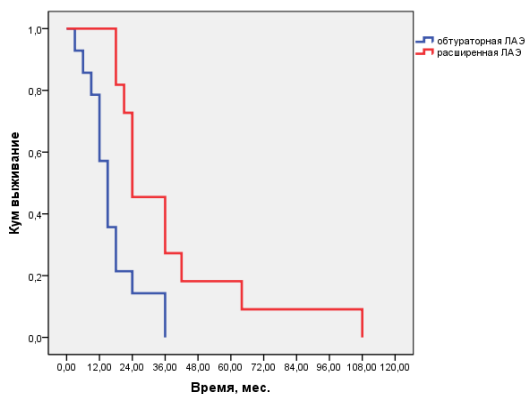
Figure 4. Comparative assessment of relapse-free biochemical survival depending on the volume of LAE performed in the intermediate risk group.

risk group are recommended to have an expanded pelvic LAE, since it significantly prolongs the time before the development of BCR.

In our study, the role of preoperative factors was analyzed and a mathematical model for predicting extracapsular extension was constructed. In order to validate the developed model, we formed an experimental group of 219 patients. All patients were divided into 3 groupsdepending on the likelihood of risk of local prevalence of the process.

The low-risk group consisted of 72 (32.9%) patients with a probability level ranging from 0% to 33%. In turn, the intermediate and high groups consisted of 65 (29.7%) and 82 (37.4%) patients with a probability level varying between 34-66% and 67-100%, respectively.

In the experimental group of patients with low, intermediate and high risk, BCR was diagnosed in 5 (6.9%), 15 (23.1%) and 15 (18.3%) cases, respectively.

In the low- risk group, the average time to develop BCR for patients in the examination cohort was 38.4 ± 6.2 months (95% CI: 26.292-50.508). It should be noted that the corresponding indicators for patients in the surgical and combined groups were 43.5 ± 7.3

months in (95% CI: 29.313-57.687) and 35.0 ± 11.1 months (95% CI: 13.381-56.619) respectively. Statistical analysis did not show a significant difference (*p = 0.882*) between groups.

In the intermediate-risk group, the average time to development of BCR in the experimental group was 40.2 ± 6.0 months (95% CI: 28.446-51.954), while for patients with the surgical and combined groups this indicator was 25.8 ± 4.3 months (95% CI: 17.338-34.342) and 22.7 ± 3.0 months (95% CI: 16.770-28.563), respectively (Fig. 1).

The results of a statistical study showed a significant difference (*p = 0.048*). It is noteworthy that the average values in the combined group turned out to be worse than inpatient group under examination, despite the ongoing GT. This fact, first of all, may be associated with the inclusion in the experimental group of patients who underwent RPE with expanded pelvic LAE.

The mean time to development of BCR in the experimental group of patients with a high risk of progression was 12.9 ± 2.4 months (95% CI: 8.190-17.544). The corresponding indicators for patients in the surgical and combined groups were 15.5 ± 2.5 months (95% CI: 10.623-20.430) and 25.3 ± 3.1 months (95% CI: 19.275-31.365), respectively (Fig. 5).
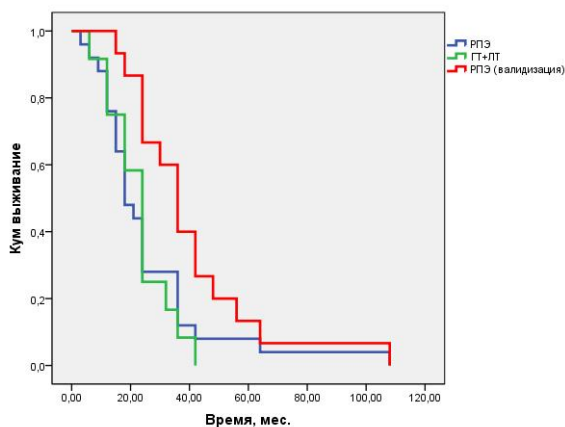

Figure 5. Comparative assessment in intermediate-risk groups according to the criterion of disease-free biochemical survival.

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Statistical analysis aimed at determining the effect of the treatment method on relapse-free biochemical survival in patients with a high risk of progression showed reliable significance (*p = 0.004*). (Fig.6)
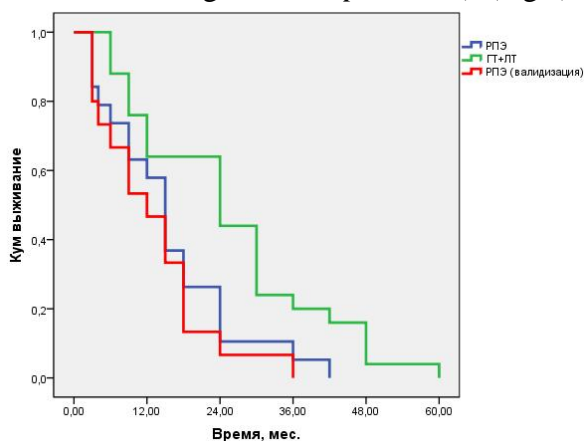

Figure 6. Comparative evaluation in high-risk criterion biochemical progression-free survival.

Summing up the results, it can be noted that in patients with a low risk, even after appropriate stratification and classification revision, there was no significant difference between treatment methods.

In turn, in patients with intermediate risk, the statistical significance of the result once again confirms the feasibility of an extended pelvic LAE.

The statistical significance in the high-risk group demonstrates the advantage of the combined treatment over the surgical method according to the criterion of disease-free biochemical survival.

In the experimental group of patients with a low risk of progression, there were no cases of constant death from prostate cancer. In the intermediate and high-risk groups, in turn, 1 and 4 cases were recorded, respectively. Given the insufficient number of required patients for reliable statistical analysis, we did not perform calculations for cancer-specific survival in the examination group.

In order to study the prognosis factors of BCR after RP, we analyzed the pre- and postoperative parameters of 295 patients who

underwent RPE. A comparative assessment of patients with and without BCR with age factor did not show a significant difference *(p = 0.165)*. We also performed calculations of the area under the operational ROC-curves in order to determine the relationship between age and BCR. The obtained data was 0.550 ± 0.041 (*p = 0.258*, 95% CI: 0.469-0.631). Based on the calculations above, it can be noted that the age of the patient is not a statistically significant factor in predicting the development of BCR in the postoperative period.

The preoperative parameters, on which clinicians decide to carry out a particular treatment method or to predict the development of BCR, are the level of preoperative PSA, the clinical stage and the Gleason index.

The area under the operating ROC- curves for the total PSA was a 0.619 ± 0.043 *(p = 0.007*, 95% CI: 0.535-0.703*)*. The result demonstrated the clinical value of this test in predicting BCR.

A comparative analysis in groups with a PSA level of up to and more than 10 ng / ml of data in patients with BCR after RPE showed a significant difference by the Pearson χ^2 criterion. In a group of patients with a PSA level of up to 10 ng / ml, BCR development was observed in 28 (13.0%) of 201 patients, and in a group with a PSA of more than 10 ng / ml in 24 (25.5%) of 94 ($\chi^2 = 5.94$; *p = 0.015*). Thus, a reliable relationship was found between PSA levels and the risk of developing BCR.

The obtained data on patients with BCR after RP in both groups were also subjected to statistical analysis according to the Kaplan-Meier method with a logarithmic rank test (LogRanktest). The period before the development of BCR in the group of patients with a PSA level of up to 10 ng / ml was 29.6 ± 4.5 months (95% CI: 20.753-38.489). These indicators in the group with PSA> 10 ng / ml *,* in turn, amounted to 18.7 ± 2.3 months (95% CI: 14.194-23.197). Comparative evaluation conducted between two groups demonstrated reliable difference of Wilcoxon (Wilcoxon) *(p = 0.042)*.

Clinical staging is the main parameter in a number of prognostic models aimed at calculating the risk of developing BCR after surgical treatment by using data from preoperative examinations. In the group we studied, based on clinical results, stage CT1c was diagnosed in 116

(39.2%), while stages T2a, T2 b and T2c were detected in 41 (13.9%), 62 (21%) and 32 (10.8%) patients, respectively. The spread of the tumor process beyond the capsule of the prostate gland and the involvement of seminal vesicles were observed in 45 (15.3%) patients.

In our study, while stratifying patients into risk groups in accordance with D' Amico classification, it was found that the number of patients in the low, intermediate and high risk groups was 96 (32.4%), 114 (38.5%) and 86 (29.1%), respectively. Meanwhile, 8 (8.3%) of 96 patients in the low-risk group were subsequently diagnosed with BCR. In the intermediate and high-risk groups, BCR was observed in 25 and 19 patients, respectively.

The time to development of BCR in patients at high risk according to the D' Amico classification was 15.5 ± 2.5 months (95% CI: 10.623-20.430). In turn, the corresponding indicators for low-risk groups were 43.5 ± 7.2 months (95% CI 29.3 13-57.687), and for patients in the intermediate-risk group they were 25.8 ± 4.6 months (95 % CI: 17.338-34.342). As a result of the analysis, a statistically significant difference was found between the risk groups according to the D' Amico classification (LogRank $p = 0,004$).

Speaking about risk groups, it should be noted that one of the important preoperative factors used in the classification of D' Amico is the Gleason index. In order to determine the role of the Gleason index in predicting the development of BCR, we calculated the area under the operating ROC curve. The area under the operating ROC -curve Gleason amounted to index for a 0.656 ± 0.044 ($p< 0.001$, 95% CI: 0,570-0,743). Conducting a statistical analysis of the relationship between the Gleason index on biopsy specimens and the development of BCR, we obtained a reliable significant correlation according to Pearson and Spearman ($p< 0.001$). The obtained data indicate the significant role of the Gleason index, both a single factor and a combination with other preoperative parameters, in particular, used in the classification of D' Amico, in conducting BCR prediction.

Another issue to be studied is determining the significance of the role in the number of positive columns on the development of BCR.

When conducting a statistical analysis of the histopathological

results of biopsy, it was determined that the average number of positive columns for groups with the absence and presence of BCR is 3.61 ± 0.19 (1-10) and 4.36 ± 0.50 (1-12), respectively. In order to determine the nature of the relationship between the positive columns and BCR, we performed a correlation analysis with the calculation of the Pearson correlation coefficient. The obtained indicator of consistency between the two values also did not demonstrate a statistically regular relationship *(p = 0.122)*.

In the study group, along with determining the number of positive biopsy columns, we assessed the significance of the tumor percentage on the biopsy specimens.

The area under the operating ROC curve for the percentage tumor lesion of the column was 0.739 ± 0.058 *(p = 0.002*, 95% CI: 0.626-0.852*)*. The indicators of sensitivity and specificity with a percentage lesion of 55% were 81.3% and 65%, respectively. Based on the obtained result, we established a conditional threshold corresponding to 50% and calculated the number of tumorpercentage on the biopsy specimens with a content exceeding this threshold.

The conducted Pearson correlation coefficient analysis with the calculation, determined a statistically regular relationship between the number of biopsies with a tumor percentage of more than 50 % *(p < 0.01)*.

A comparative analysis of BCRdata after RPE in groups with a tumor percentage of more than 50% by the Pearson χ^2 criterion also showed a significant difference. So, in the group of patients with the development of BCR, the tumor content was more than 50% in 13 (81.3%) of 16 patients, and in the group without BCR, in 62 (45.3%) patients of 137 ($\chi^2 = 6.06$; *p < 0.02)*.

Thus, based on the obtained results, the high statistical significance of the following preoperative indicators was determined: total PSA, free PSA, ratio of free PSA to total PSA, PSA density, Gleason index, maximum percentage of tumors in the column.

A pathomorphological study of the prostate gland after RPE allows you to fully determine the histological type of tumor, differentiation, pathological stage, as well as the condition of the surgical edges of the slice.

After the surgical treatment, the Gleason index on the retrieved margin corresponded to 6 in 167 (56.6%) cases. The Gleason index 3 + 4 and 4 + 3 was detected in 80 (27.1%) and 23 (7.8%) patients, respectively. In turn, a Gleason index of ≥ 8 was diagnosed in 25 (8.5%) patients.

To determine the statistically significant relationship between the Gleason index on a retrieved margin and the likelihood of developing BCR in the postoperative period, we calculated the area under the operating ROC curve. The area under the operating ROC curve for the Gleason index was 0.650 ± 0.046 ($p = 0.001$; 95% CI: 0.560-0.739).

To determine the effect of the differentiation degree on the time before the development of BCR after RPE, the Kaplan-Meier method with the LogRank test were used. Despite the obtained statistically significant results while performing calculations by using the ROC-curve ($p = 0.001$), which determine the relationship between the degree of differentiation and BCR, we did not determine a significant difference according to Kaplan-Meyer between groups, according to the time criterion until BCR development (according to LogRank $p = 0.251$). The statistical analysis by Breslow (Generalized Wilcoxon) also did not determine a significant difference ($p = 0.247$).

To determine survival before BCR in both groups, we performed a statistical analysis using the Kaplan-Meier method with a logarithmic rank test. The mean time to development of BCR in patients with a Gleason index of 3 + 4 was 26.5 ± 7.3 months in (95% CI: 12.332-40.668). In turn, the corresponding indicator for patients with a differentiation degree of 4 + 3 was 27.1 ± 6.3 months (95% CI: 14.799-39.451).

The statistical analysis did not determine the reliable significance between the subgroups and, according to LogRank, amounted to $p = 0.844$, and according to Breslow (Generalized Wilcoxon) this indicator corresponded to $p = 0.929$. Based on the obtained result, it can be concluded that the time to the development of BCR in both groups from a statistical point of view does not show significant differences.

In our study, we examined the frequency and prognostic value

of the tertiary Gleason index in predicting the risk of developing BCR after RPE.

In the study group, a tertiary Gleason index ≥ 4 was fixed in 32 (10.8%) patients and held <5 tumor volumes in the removed gland. In the remaining 263 (89.2%) patients, the presence of a tertiary Gleason index was not observed. BCR development was noted in 15 (46.9%) cases. The mean time to BCR development in the group with no tertiary Gleason index was 27.9 ± 3.5 months (95% CI: 21.047-34.899). This indicator in the group with the presence of the tertiary Gleason index, in turn, was 16.9 ± 3.7 months (95% CI: 9.664-24.203) (Fig .7).
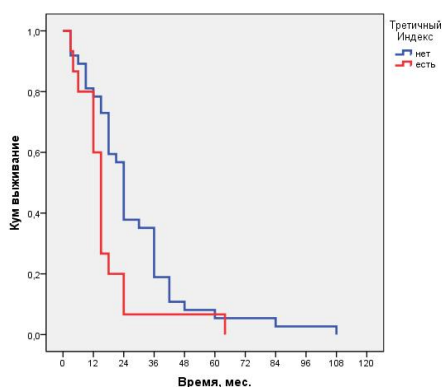

Figure 7. Comparative assessment before BxR in patients with tertiary Gleason index.

A comparative assessment conducted between the two groups determined a significant difference in LogRank *(p = 0.021).*

In order to determine the nature of the relationship between the tertiary Gleason index and the risk of developing BCR, we conducted an analysis with the calculation of the χ^2 criterion according to Pearson. The obtained indicator of consistency between the two values showed a statistically regular relationship ($\chi^2 = 21.147$; *p < 0.001).*

From a theoretical point of view, it is known that the positive surgical margin may be a prognostic factor that closely correlates with BCR. In the study group, in 67 (22.7%) patients, a pathomorphological study revealed the presence of a tumor in the section. A biochemical

relapse was diagnosed in 30 (13.2%) of 228 patients with a negative surgical margin, while an increase in PSA level in the postoperative period was observed in 22 (32.8%) of 67 patients with a positive surgical margin. The analysis of the relationship between the two variables determined reliable significance according to Pearson ($\chi^2 = 13.810$; $p < 0.001$). A similar analysis conducted in groups showed a statistically significant correlation in the groups of low ($\chi^2 = 7.392$; $p = 0.007$) and intermediate ($\chi^2 = 6.545$; $p = 0.011$) risks. In the high-risk group, in turn, the correlation index was ($\chi^2 = 0.655$; $p = 0.418$).

Other factors that can play a significant role in the development of BCR include extracapsular extension and invasion of the seminal vesicles. In the study, morphologically verified spread of the tumor beyond the gland capsule is associated with an increased risk of biochemical progression of the disease ($\chi^2 = 30.321$; $p < 0.001$). In the study group, 13 (23.2%) of 56 patients with extracapsular extension in the postoperative period showed the development of BCR. Seminal vesicle invasion was diagnosed in 32 patients with a pathomorphological study. In the period of postoperative observation, the development of BCR was diagnosed in 19 (59.4%) patients. Based on the obtained data, it can be noted with confidence that tumor ingrowth into the seminal vesicles in patients included in the study is associated with an unfavorable risk of developing BCR.

In order to determine a statistically significant relationship between tumor volume (expressed as a percentage) and the probability of developing BCR in the postoperative period, we calculated the area under the operating ROC curve, which amounted to 0.687 ± 0.039 ($p < 0.001$, 95% CI: 0.611-0.764) The obtained result demonstrated the clinical significance of this parameter in predicting BCR. Tumor volume in patients with and without BCR was 28.5 ± 2.9 (1-90) and 17.7 ± 1.2 (1-85), respectively. A Wilcoxon statistical analysis showed reliable significance between the two variables *(p< 0.001).*

Another parameter often identified during pathomorphological examination is the presence of perineural invasion in a retrieved specimen.

In our study, the presence of perineural invasion was diagnosed in

88 (29.8%) patients. Biochemical relapse was diagnosed in 32 of 207 (15.5%) patients in the group with no perineural invasion, and 20 (26.8%) of 88 in the group with perineural invasion. A comparative assessment conducted between the two groups did not determine a significant difference in LogRank *(p = 0.782).*

We also performed a correlation analysis with the calculation of the Pearson correlation coefficient in order to determine the nature of the relationship between perineural invasion and BCR. The obtained indicator of consistency between the two values did not demonstrate a statistically regular relationship ($\chi^2 = 2.247$; *p = 0.134*).

In order to conduct a statistical assessment of the relationship between damage to the Lymph nodes and the risk of developing BCR, we analyzed data from 147 patients who underwent RPE with expanded Lymphadenectomy.

During the observation period, BCR was diagnosed in 10 (83.3%) of 12 patients. Statistical analysis aimed at determining the correlation between the presence of metastatic LN and BCR showed a statistically significant Pearson result ($\chi^2 = 31.852$; *p < 0.001*).

The mean time to BCR development in the group with no metastatic LN was 25.5 ± 4.8 months (95% CI: 16.043-34.957). This indicator in the group with the presence of affected LN, in turn, amounted to 20.0 ± 6.5 months (95% CI: 7.261-32.739). A comparative assessment conducted between the two groups did not determine a significant difference in Log Rank (*p = 0.424*).

Thus, based on the obtained results, such postoperative indicators as the Gleason index, tertiary Gleason index, the state of the surgical margin, the postoperative stage and tumor volume showed statistically significant values in predicting BCR.

In order to predict BCR, a mathematical model was constructed according to the Bayes formula for a complex of independent features. The main factors used for these purposes are preoperative total PSA, Gleason index on biopsy, maximum percentage of tumor in the column, Gleason index after surgery, tertiary Gleason index, condition of the surgical margin, postoperative stage and tumor volume.

In order to comparatively evaluate the diagnostic properties of

the developed model (nomogram), we used the method of constructing ROC- curves with determining the area under them.

The discriminatory potential of the developed nomogram turned out to be statistically significantly higher than 0.829 ± 0.029 *(p< 0.001*; 95% CI 0.772–0.886*)* in comparison with the Stephenson nomogram 0.610 ± 0.043 *(p = 0.013*; 95% CI 0.526–0.694*)* (Fig. 8).
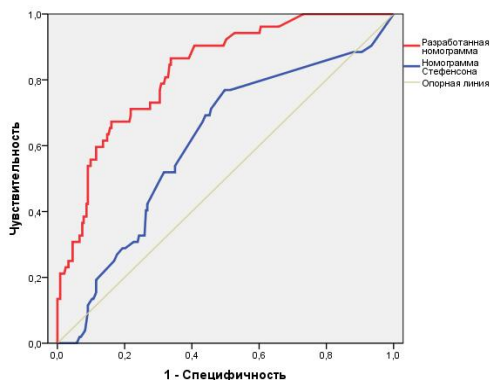

Figure 8. ROC curves of predictive capabilities of nomograms.

Despite the statistically reliable indicators of the Stephenson model in predicting BCR, the area under the curve characterizing the nomogram developed by us presented good results, which emphasizes the feasibility of its use in clinical practice.

The work assessed the frequency and nature of complications after RP and RT. When conducting a correlation analysis determining the relationship between the stage of the disease and the frequency and nature of complications, we did not demonstrate a statistically significant difference (*p> 0.05*).

In the early postoperative period, 97 complications were recorded in 51 (17.2%) of 296 patients. The presence of one complication was noted in 18 (35.3%) patients, two complications - in 24 (47.1%) patients. In 9 (17.6%) patients three complications were observed. The most common complication observed in the early postoperative period in 21 (7.1%) patients hadurethrovesical anastomosis leakage. In this study, 8 (2.71%) cases of wound infections were recorded. In our opinion,

the main reasons for the development of this complication are a relatively high body mass index and associated type 2 diabetes mellitus.

Hemorrhagic complications were observed in 11 (3.72%) patients, which in 8 (2.71%) cases were shown by hematuria and in 3 (1.01%) cases by extravesical bleeding and the formation of paravesical hematoma. In our study, control of this complication was conservative in all cases.

In 1 (0.34%) patient, a rather rare complication was diagnosed - distal ureteral obstruction due to ureteral orifice edema. The manifestation of clinical signs of this complication was noted on the 3rd day after surgery. Despite intensive anti-inflammatory therapy, taking into account a creatinine increase in blood and an increase in ureterohydronephrosis, bilateral percutaneous nephrostomy was performed. On the 14th postoperative day, the patient underwent 2-sided antegrade pyelography and noted full restoration of the natural passage of urine. Nephrostomy drainages were alternately removed.

In the early postoperative period, pneumonia was diagnosed in 2 (0.68%) patients.

In 3 (1.01%) patients of the total number, after surgery developed acute coronary insufficiency. This complication, according to the Clavien-Dindo classification, corresponded to grade IV a. 2 (0.68%) patients had a history of angina pectoris; these patients were operated on after assessing the risk of cardiac complications and appropriate therapy.

In 8 (2.7%) patients, gastrointestinal complications were observed.

Due to central nervous system complications in 2 (0.68%) patients in the postoperative period, the hemorrhagic stroke development was noted and confirmed radiologically.

Another complication, requiring in some cases an increase in the length of hospitalization, is lymphorrhea. The lymphocele diagnosis was made on the basis of secreted lymphatic fluid presence through the drainage tubes for 7 days after surgery in a volume of ≥ 50 ml / day. In the study group, this complication was observed in 1 (1.7%) of 59 patients who underwent obstructive and in 16 (10.9%) of 147 patients who underwent extended lymphadenectomy.

The main complications in the late postoperative period include

ED, urinary incontinence, and stricture of UA. All of the above complications uniquely negatively affect the quality of patients' life and require adequate intervention and correction.

In the study, 47 (15.9%) patients complained of difficulty urinating or weakening the pressure of the urine stream after RPE. In 21 (7.1%) cases, the problem was solved by mechanical expansion of the urethrovesical anastomosis site with metal dilators (bougie).

It should be noted that in 17 (65.4%) of 26 patients, regardless of the surgical intervention method after complete removal of the urethral catheter, a complete restoration of urination function was observed. However, anastomotic strictures tend to recur and require repeated intervention. Three patients subsequently underwent repeated optical urethrotomy. In 4 cases, this problem was solved by postoperative urethral bougienage of the anastomotic zone. This procedure was performed once a week for two months before reaching adequate urination.

After the intervention, in 8 (30.7%) patients, mild urinary incontinence associated with physical activity was observed. In turn, in 1 (3.9%) case after removal of the catheter, the patient noted complete incontinence.

In 1 patient, the presence of suture material in the anastomosis zone was revealed during transurethral resection of the UVA zone, in the mode of minimal thermal coagulation

Another serious complication after RPE is urinary incontinence. In order to study this problem, we carried out a comparative assessment between our proposed technique for the reconstruction of the bladder neck and reconstruction according to the generally accepted classical technique. The main group consisted of 26 (38.8%) patients, while the control group consisted of 41 (61.2%) patients. The mean time of observation in the study and control groups was 26.8 ± 4.1 and 48.4 ± 5.6 months, respectively.

The obtained data on patients in both groups were subjected to statistical analysis according to the Kaplan-Meier method with a logarithmic rank test. The mean time to recovery of urine retention function in the study group was 4.38 ± 0.7 (95% CI: 3.090-5.710)

months compared to 6.52 ± 0.5 (95% CI: 5.447-7.500) months for patients in the control group. A comparative assessment conducted between the two groups showed a significant difference in Wilcoxon (Wilcoxon) *(p = 0,042) (Fig.9)*
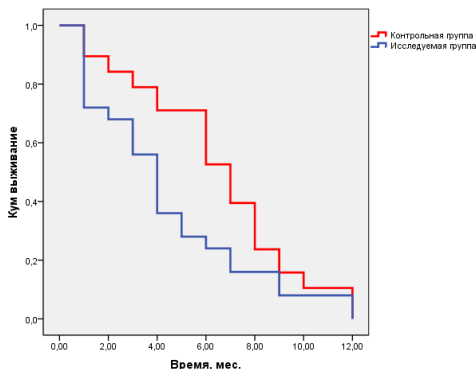

Figure 9. Comparative assessment of bladder neck reconstruction methods.

A statistically significant result emphasizes the effectiveness of our reconstruction method. It should be noted that in the control group, 90.2% of patients 30 days after surgery had a lack of complete control on urinary retention function. In the next 3, 6 and 12 months of follow-up, this indicator was 80.5%, 56.1% and 7.3%, respectively. In turn, in the study group, urinary incontinence in the above time intervals was noted in 73.1%, 57.7%, 26.9% and 3.8%, respectively. In 1 patient in the main group and in 3 patients in the control group, after 12 months there was no restoration of the urinary retention function.

The average time between RPE and male sling implantation surgery was 18.4 ± 1.3 months. The average number of used urological pads per day is 3.7 ± 1.2. In the preoperative period, uroflowmetry and urodynamic studies determined the average detrusor pressure at maximum flow (speed) as 32.3 ± 4.2 cm H_2O, and the average leakage point pressure as 21.6 ± 8.2 cm H_2O.

In none of the cases did postoperative radiological studies determine the presence of a significant volume of residual urine. Despite the relatively small number of patients who underwent surgery

to implant a male sling, we confirm the possibility of regulating urethral compression by introducing the solution into a silicone dilator. Short surgery times and minimal hospital stay are other benefits of this intervention. In our opinion, this surgical intervention with moderate urinary incontinence allows us to achieve encouraging results and improve the quality of patients' life.

In order to select the optimal treatment method, we performed a comparative analysis of early and current toxicity in the group of patients who received radiation therapy. In this case, both local and general reactions and complications were evaluated.

The average concentration of hemoglobin at the time of admission to the hospital was 12.3 ± 1.8 mg / dl. In total, anemia of one degree or another was observed in the treatment period in 88 (61.9%) patients. Moreover, 62 (43.7%) patients developed grade I anemia according to RTOGAcuteToxicity Criteria, 24 (16.9%) - grade II anemia, and only two patients developed grade III anemia, which was more associated with renal failure.

The average number of leukocytes before treatment was $6.2 \cdot 10^9 \pm 2.8 \cdot 10^9$ / L. As a result of leukopenia treatment I level was observed in 31 (21.8%) patients, II degree – in 12 (8.5%) cases, II I extent - in 3 (2.1%) patients. Leukopenia of the IV degree was not observed. In 96 (67.6%) patients, the content of leukocytes in peripheral blood did not fall below normal indicators.

In order to determine acute hematologic toxicity, we also examined the platelet content in peripheral blood. The average platelet count before treatment was $297.6 \cdot 10^9 \pm 32.8 \cdot 10^9$ / L. A total of 38 (26.7%) patients had some degree of thrombocytopenia. As a result of treatment, thrombocytopenia of the first degree was observed in 29 (20.4%) patients, of the second degree - in 9 (6.3%) cases. Thrombocytopenia of the III - IV degree was not observed. In 104 (72.3%) patients, the platelet count in the peripheral blood did not fall below normal indicators.

One of the most common reactions was nausea / vomiting, which in some cases significantly reduced the life quality of patients, contributed to weight loss, and decline of the general condition. Acute gastrointestinal toxicity of I and II degrees was observed in 42

(29.6%) and 19 (13.4%) cases, respectively. Not a single case of severity IIIIV was recorded.

Acute radiation rectitis of I, II, and III degree was observed in 95 (66.9%), 32 (22.5%), and 8 (5.6%) patients, respectively. Reactions of IV severity were not met. All radiation reactions from the rectum quickly stopped and did not cause interruptions in treatment.

The treatment of acute radiation cystitis was the most difficult problem among all the complications. Long courses of steroidal and non-steroidal anti-inflammatory drugs, painkillers, uroseptics were used. Radiation dermatitis was observed much less frequently, mainly in patients with obesity and was always localized in the "fat apron" area. Dermatitis I and II degree were observed in 19 (13.4%) and 7 (4.9%) cases, respectively.

In order to assess the late toxicity of treatment, radiation complications from rectum and bladder mucosa were studied, occurrence of which in all groups did not differ much and averaged 1.5 (0.75 - 2.5) years. It should be noted that in the study group, 1 patient (0.7%) after 3 years of observation was diagnosed with bladder cancer stage T1 NxM 0 G 1. After transurethral resection, the patient was given a course of intravesical chemotherapy in accordance with the existing guidelines.

Radiation therapy in combination with HT was performed in 115 (81%) of 142 (100%) patients with intermediate and high risk of prostate cancer progression according to the D'Amico classification.

A decrease in libido was noted in 37 (32.2%) patients. All 37 patients at the beginning of therapy in the QOL questionnaires noted a normal level of libido. It is important to note that this group of patients was composed of patient group at the age of up to 66 years. This factor caused a feeling of anxiety and concerns and had an extremely negative effect on QOL. Unfortunately, it was extremely difficult to carry out targeted drug correction of reducing patients' libido in full. Patients of mostly young age were offered a consultation of psychologists and sexopathologists.

Erectile dysfunction, in turn, was also one of the main points

worsening QOL. For accurate quantitative determination of the erectile reduction degree, the IIEF-5 scale (international index of erectile function) was used. According to the severity of ED, in accordance with this classification, it was divided into 3 degrees of severity: mild, moderate and severe.

In the study, ED associated with the treatment was observed in 78 (67.8%) patients. The remaining 64 (32.2%) patients at the time of initiation of therapy according to questionnaires already had complaints of ED. In the group of patients receiving combined treatment, severe ED was observed in 23 (29.5%) patients, moderate in 37 (47.4%) patients. Mild ED was diagnosed in 18 (23.1%) patients.

Patients of the combined treatment group who had severe ED were corrected by regular intake of tadalafil in a dosage of 5 mg x 1 time per day. Mild and moderate erectile dysfunction was corrected by herbal remedies, which are biologically active additives.

In our study, gynecomastia was observed in 18 (15.6%) patients under 55 years of age. Patients complained only of an enlargement and minor pain in the mammary glands. No medical correction of this complication was carried out. After 2 months from the start of therapy, patients did not complain of discomfort from the enlargement and pain in the mammary glands.

In our study, cardiovascular complications were observed in 21 (18.2%) patients aged 62 years and older. These complications appeared to be pain behind the sternum, increased blood pressure, arrhythmias, and in most cases had a clinical picture of angina pectoris.

Hepatic insufficiency was observed in 41 (35.6%) patients, which was appeared by an increase in the enzymes transaminases, bilirubin, and a decrease in the level of albumin. Referring to biochemical parameters, the degree of its severity was regarded as the first. By means of infusion therapy in combination with hepatoprotectors, on average 1 week after the start of therapy, it was possible to achieve normalization level of the indicators shown above. The course of treatment was supplemented by the introduction of a 20% albumin solution. Further, hepatoprotectors were prescribed for prophylactic purposes.

In our study, in order to analyze the QOL of patients who underwent RPE or distance radiotherapy in combination with GT, a comparative assessment of the questionnaire results was performed.

The presented results did not demonstrate statistically significant differences according to the criteria of preoperative PSA and the clinical stage. There was also no significant difference between the groups when stratifying patients into risk groups in accordance with the classification of D' Amico.

I would like to note that most patients already have a change in QOL indicators associated with emotional and psychological factors since the diagnosis of prostate cancer. To obtain representative and comparable results and their application in clinical practice, we used standard QOL assessment tools based on subjective perception and giving an integrated digital characteristic of physical, psychological and social functioning. The obtained results did not demonstrate a statistically significant difference between the research methods after 1, 3 and 12 months and amounted to $p = 0.349$, $p = 0.067$ and $p = 0.064$, respectively. The use of radical antitumor methods of treatment can leave lasting consequences in the form of impaired organ functions and systems that lead to disability of the patient, disruption of vital processes and adaptation in society, which in turn can cause suffering commensurate with the presence of an untreated malignant neoplasm.

Based on the results, we determined a statistically significant difference after the first month of treatment $(p = 0.036)$. In turn, there was no significant difference between the study groups after 3 and 12 months of treatment $(p = 0.316$ and $p = 0.072)$.

The development of BCR and the progression of the disease can also lead to a deterioration in QOL.

One of the main advantages of the study is a relatively long observation period. Statistical analysis, quality of life questionnaire EORTC QLQ - C 30 results, in particular, according to general health criteria, functional indicators, and symptom based on the QLQ - PR 25 module, showed satisfactory results, and main unfavorable factors that negatively affect QOL were recognized violations as urinary retention function $(p < 0.001)$ and disease progression $(p < 0.05)$.

Conclusions

1. For locally advanced prostate cancer, the level of total PSA, its density, free form and the ratio of free to total levels were 0.658 ± 0.033 *(p < 0.001*, 95% CI 0.593-0.723), 0.742 ± 0.038 *(p <0.001*; 95% CI 0.667-0.816), 0.595 ± 0.044 *(p = 0.034*; 95% CI 0.508-0.682) and 0.404 ± 0.043 *(p = 0.032*; 95% CI 0.319-0.488), respectively. The maximum lesion of the biopsy column, the number of positive columns and columns with a lesion of more than 50% was 0.774 ± 0.044 *(p < 0.001*; 95% CI 0.689-0.859), 0.724 ± 0.049 *(p <0.001*; 95% CI 0.629-0.819*)* and 0.771 ± 0.045 *(p <0.001*, 95% CI 0.682-0.860*)*, and for the Gleason index, 0.663 ± 0.036 *(p <0.001*; 95% CI 0.592-0.734).

It was found that visualization of the prostate gland *(p = 0.007)*, detection of the formation in the largest dimension > 1.3 cm *(p = 0.001)*, multifocal tumor *(p = 0.036)* and its relation to seminal vesicles *(p = 0.03)* are MRI predictors of locally advanced PC *(p < 0.001)* [2, p.17-20], [8, p.18-25], [21, p.55-60]

2. The result of the extracapsular extensionrisk assessment was 0.857 ± 0.042 *(p < 0.001*; 95% CI 0.774–0.940*)*, which compared with the similar result of the Partin nomogram - 0.606 ± 0.068 *(p = 0.091*; 95% CI 0.474–0.739*)* showed an advantage use of the mathematical predicting model developed by us [36, p.65-71].

3. In the general cohort of patients, 5- and 10-year-old cancer specific survival in the surgical group was 98% and 84%, respectively, and in the combined treatment group, 85% and 72%, respectively *(p < 0.001)*. Moreover, the highest significance was revealed for high-risk patients - 97% and 66%, respectively *(p< 0.001)* [33, p.367-372], [42, p.19-25].

4. A statistically significant relationship between BCR and the level of total PSA, free form and its density was determined, which amounted to 0.619 ± 0.043 *(p = 0.007*, 95% CI: 0.535-0.703), 0.636 ± 0.062 *(p = 0.017*, 95% CI: 0.515 -0.758) and 0.677 ± 0.049 *(p = 0.002*, 95% CI: 0.581-0.773), respectively. For the Gleason index and tumor volume in the retrieved specimen, the corresponding rates were 0.650 ± 0.046 *(p = 0.001*; 95% CI: 0.560-0.739)   and

0.687 ± 0.039 *(p < 0.001*, 95% CI: 0.611-0.764).

The discriminatory capabilities of the developed BCR prediction nomograms are statistically significantly higher than 0.829 ± 0.029 *(p< 0.001*; 95% CI 0.772–0.886) compared with the Stephenson nomogram 0.610 ± 0.043 *(p = 0.013*; 95% CI 0.526–0.694) [30, p.39-44], [34, p.49-54].

5. The average time before the development of BCR in the surgical, combined and experimental groups for patients with intermediate risk was 25.8 ± 4.3 (95% CI: 17.338-34.342), 22.7 ± 3.0 (95% CI : 16.770-28.563) and 40.2 ± 6.0 (95% CI: 28.446-51.954) months, respectively *(p = 0.048)*. The factors influencing this situation are careful selection and recommendations for an extended Lymphadenectomy forpatients with prostate cancer in the intermediate group [12, p.44], [38, p.890-894]

6. It was found that the average time to restore the function of urine retention in patients who underwent reconstruction of the bladder neck according to our methodology was 6.52 ± 0.5 (95% CI: 5.447-7.500) compared with 4.38 ± 0.7 (95% CI: 3,090-5,710) months for patients with generally accepted reconstruction according to the classical method *(p = 0.042)*, which is confirmed by the analysis of the results of the EORTC QLQ - C 30 quality of life questionnaire and QLQ - PR 25 module *(p< 0.001)* [39, p.70-73], [40, p.59-62].

Practical recommendations

1. Using the developed mathematical model for predicting extracapsular extension in oncourology will improve the ability of predicting the local incidence of prostate cancer and will contribute to the selection of optimal treatment tactics and the appropriate volume of surgical intervention.

2. Using the developed mathematical model for predicting biochemical relapse will allow us to build an individual prognosis for a specific patient and identify the need for the most careful observation.

3. Comparable results of surgical and combined treatment methods according to the criteria of relapse-free and cancer-specific survival in patients with low and intermediate risk prostate cancer lead to the joint choice of the doctor and the patient for the

optimal treatment tactics.

4. It is necessary to improve cancer-specific survival in patients with an intermediate and high risk of PC progression, and extended pelvic lymphadenectomy.

5. The developed technique for reconstruction of the bladder neck allows you to restore the function of urine retention in a shorter time, which will positively affect the quality of life of this category of patients in the postoperative period.

List of published works

1. Гулиев, Ф.А., Мусаев, Т.Н., Керимов, А.Х., Ализаде, А.М. Прогнозорование отдалённых результатов лечения больных с костными метастазами (КМ) рака предстательной железы (РПЖ.) // Материалы VI съезда онкологов и радиологов стран СНГ, -Душанбе: - 2010 г. - с. 239.
2. Гулиев, Ф.А. Скрининг рака предстательной железы: Современный взгляд и состояние проблемы в Азербайджане / Ф.А.Гулиев, Т.Н.Мусаев, А.М.Ализаде // Azərbaycan onkologiya və hematologiya jurnalı, -Bakı: - 2011. №1. - s.17-20.
3. Гулиев, Ф.А., Мусаев, Т.Н. Первый опыт хирургического лечения местнораспространенного рака предстательной железы // Материалы 6-го конгресса РООУ, - Москва;- 2011. - с. 75-76.
4. Мусаев, Т.Н. Гормонотерапия больных диссеминированным раком предстательной железы / Т.Н.Мусаев, А.Х.Керимов, А.М.Ализаде, Ф.А. Гулиев [və d.] // Azərbaycan onkologiya və hematologiya jurnalı, -Bakı: -2010, №1. - s. 99-104.
5. Мусаев, Т.Н., Керимов, А.Х., Гулиев, Ф.А., Ализаде, А.М., Аджалов, О.В. Оценка качества жизни (КЖ) больных с костными метастазами (КМ) рака предстательной железы (РПЖ) // Professor E.İ. İbrahimovun 80-illik yubileyinə həsr olunmuş elmi-praktik konfransın materialları, - Bakı: -2010, - s. 87-88.
6. Мусаев, Т.Н., Керимов, А.Х., Ализаде, А.М., Гулиев, Ф.А., Аджалов О.В. Лечение болевого синдрома у пациентов с генерализованным раком предстательной железы //

Материалы V конгресса Российского общества онкоурологов, -Москва: -2010 г. - с. 89.

7. Мусаев, Т.Н. Эффективность золендроновой кислоты в профилактике костных метастазов у больных с местнораспространенным раком предстательной железы / Т.Н.Мусаев, Р.С.Зейналов, А.Х.Керимов, Ф.А. Гулиев [и др.] // Онкоурология, -Москва: -2011. №1.- s. 62-66.

8. Гулиев, Ф.А. Простатический специфический антиген и его молекулярные изоформы в диагностике рака предстательной железы // Azərbaycan onkologiya və hematologiya jurnalı, -Bakı: -2012. №1. - s. 18-25

9. Гулиев, Ф.А., Мусаев, Т.Н., Аджалов, О.В. Эффективность и частота осложнений при различных схемах трансректальной биопсии предстательной железы // Ümummilli lider H.Ə.Əliyevin ad gününə həsr olunmuş elmi-təcrubi konfransın materialları, -Bakı:- 2012.- s.65-67.

10. Гулиев, Ф.А., Мусаев, Т.Н. Осложнения гормонотерапии у больных местнораспространенным раком предстательной железы (МРПЖ) // Ümummilli lider H.Ə.Əliyevin ad gününə həsr olunmuş elmi-təcrubi konfransın materialları, -Bakı:- 2012.- s. 61-65.

11. Гулиев, Ф.А. Эпидемиология, этиопатогенез и профилактика рака предстательной железы// Azərbaycan onkologiya və hematologiya jurnalı, - Bakı:- 2013. №1.- s. 17-23.

12. Гулиев, Ф.А., Халилов, Э.Ш. Прогнозирование биохимического рецидива рака предстательной железы после радикальной простатэктомии на основании дооперационных данных // Akademik R.N. Rəhimovun 90 illik yubileyinə həsr olunmuş elmi-praktik konfransın materialları Bakı,- 2013.- s. 44.

13. Алиев, Д.А. Эпидемиологические аспекты злокачественных новообразований в Азербайджанской Республике за 2008-2013 гг. / Д.А.Алиев, Ф.А.Марданлы, Ф.А.Гулиев [и др.] // Azərbaycan onkologiya və hematologiya jurnalı, -Bakı: -2014. №2.- s. 32-38.

14. Алиев, Д.А. Методы лечения местно-распространенного рака предстательной железы / Д.А.Алиев, Ф.А.Гулиев // Sağlamlıq jurnalı, -Bakı: - 2014. №5. -s.180-186.

15.Гулиев, Ф.А. Эндоскопическая хирургия стриктуры уретерове-зикального анастомоза после радикальной простатэктомии // Cərrahiyyə jurnalı, -Bakı: -2015. №4 (44).- s. 22-26.

16.Гулиев, Ф.А. Осложнения комбинированного лечения больных местнораспространенным раком предстательной железы / Ф.А.Гулиев, Т.Н.Мусаев // Евразийский онкологический журнал, Тезисы VIII съезда онкологов и радиологов Евразии, -Казань: - 2014.- с. 690.

17.Гулиев, Ф.А. Радикальная простатэктомия при раке предстательной железы / Ф.А.Гулиев, Х.Озен // Azərbaycan onkologiya jurnalı, -Bakı: -2015. №1. -s. 54-57.

18.Гулиев, Ф.А. Осложнения гормонотерапии у больных местнораспространенным раком предстательной железы и пути их коррекции / Ф.А.Гулиев, Т.Н.Мусаев, О.В.Аджалов, А.Т. Казымов // Azərbaycan təbabətinin müasir nailiyyətləri jurnalı, -Bakı: -2015. №2.- s. 145-149.

19.Гулиев,Ф.А.Лапароскопическая радикальная простатэктомия: реальность и перспективы / Ф.А. Гулиев, Т.Н. Мусаев // Azərbaycan Tibb Jurnalı, -Bakı: -2015. № 3.- s. 121-125.

20.Алиев, Д.А. Прогностическая классификация рисков наличия местно-распространенного рака предстательной железы / Д.А.Алиев, А.Р.Алиев, А.Т.Казымов, Ф.А.Гулиев // Sağlamlıq jurnalı, -Bakı: -2015. №3. - s. 21-29.

21.Казымов, А.Т. Оценка степени местной распространенности рака предстательной железы по данным магнитно-резонансной томографии и клинических прогностических факторов / А.Т.Казымов, И.Г.Исаев, А.М.Ализаде, Ф.А.Гулиев [и др.] // Онкоурология, -Москва: -2015. №2.- с. 55-60.

22.Гулиев, Ф.А. Сравнительная характеристика основных классификаций риска прогрессирования заболевания после радикального лечения рака предстательной железы / Ф.А.Гулиев, А.Т.Казымов, А.Р. Алиев // Georgian Medical News, -Тбилиси: -2015. № 5 (242). - с. 13-17.

23.Гулиев, Ф.А. Прогностическое значение периневральной инвазии в развитии биохимического рецидива после

радикальной простатэктомии // Онкология и радиология Казахстана, -Астана: - 2015. №4.- s. 48-51

24. Guliyev, F.A. Urethral stricture is an unpleasant complication after prostate surgery: A critical review of current literature. / F.A.Guliyev, E.Sogutdelen, H.Haberal, B. Akdogan // Journal of Urological Surgery, - Ankara: - 2016. № 1. - p. 1-6

25. Гулиев, Ф.А. Сравнительная оценка ранних осложнений после радикальной простатэктомии у пациентов с локализованным и местно-распространненым раком предстательной железы // Azərbaycan onkologiya jurnalı, -Bakı: -2016.- №2.- s. 21-26.

26. Гулиев, Ф.А. Частота и характер осложнений у больных, перенесших радикальную простатэктомию / Ф.А.Гулиев, З.Ш.Везирова, Т.Н.Мусаев, Э.Ш. Халилов // Белорусский Онкологический журнал, - Минск: - 2016.- №3.- с. 14-20.

27. Везирова, З.Ш. Антибактериальная терапия катетер-ассоциированной инфекции мочевых путей после радикальной простатэктомии / З.Ш.Везирова, Ф.А.Гулиев // Анестезиология и реаниматология, - Москва: - 2016. № 61. - с. 304-307.

28. Guliyev, F.A. Radical prostatectomy for locally advanced (cT4) prostate cancer // Clinical Oncology, -Tbilisi: - 2016. №4.- с. 54-57

29. Quliyev, F.Ə. Radikal prostatektomiyada genişləndirilmiş çanaq limfadenektomiyanın ağırlaşmaları // Cərrahiyyə, -Bakı:- 2016. № 4.- с. 36-40

30. Гулиев, Ф.А. Прогностическое значение третичного индекса Глиссона в развитии биохимического рецидива после радикальной простатэктомии // Azərbaycan Tibb Jurnalı, - Bakı: -2016. № 3.- s. 39-44

31. Гулиев, Ф.А., Мусаев, Т.Н. Факторы прогноза положительного края хирургического среза после радикальной простатэктомии // Материалы 11-го конгресса РООУ, - Москва: - 2016.- с.38.

32. Гулиев, Ф.А., Мусаев, Т.Н .Роль третичного показателя Глисона в прогнозировании биохимического рецидива после радикальной простатэктомиит // Материалы 11-го конгресса

РООУ, -Москва: - 2016. - с.39.

33. Исаев, И.Г. Отдаленные результаты гормонолучевой терапии рака предстательной железы промежуточного и высокого риска / И.Г.Исаев, Ф.А. Гулиев, К.С.Акперов, З.Ш.Везирова // Евразийский онкологический журнал, -Минск: - 2017. №5. - с. 367-372

34. Гулиев, Ф.А. Прогностическое значение объема опухоли на развитие биохимического рецидива у пациентов со стадией pT2 / Ф.А.Гулиев, Б.Акдоган // Sağlamlıq jurnalı, - Bakı: - 2017. № 4. - s. 49-54.

35. Гулиев, Ф.А. Методы диагностики локального рецидива у пациентов с биохимическим рецидивом после радикальной простатэктомии / Ф.А.Гулиев, Э.Ш.Халилов, Ф.А.Новрузов // Sağlamlıq, -Bakı: - 2017. № 5. - s. 7-16.

36. Гулиев, Ф.А. Математическая модель прогнозирования экстракапсулярной экстензии у больных раком предстательной железы / Ф.А.Гулиев, Г.Д.Эфендиев, А.Т.Казымов [и др.] // Белорусский Онкологический журнал, - Минск: - 2017. № 4 (44). - с. 65-71.

37. Исаев, И.Г. Анализ частоты осложнений лучевой терапии у пациентов раком предстательной железы / И.Г.Исаев, Ф.А.Гулиев, К.С.Акперов, Н.Р.Алиева // Казанский медицинский журнал, - Казань: - 2017. № 5. - с. 680-688.

38. Гулиев,Ф.А. Предикторы биохимического прогрессирования рака предстательной железы // Казанский медицинский журнал, - Казань: - 2017. № 6. - с. 890-894

39. Гулиев, Ф.А. Оценка качества жизни, больных раком предстательной железы после радикальной простаэктомии / Ф.А.Гулиев, Э.Ш.Халилов, З.Ш. Везирова // Клиническая хирургия, -Киев: - 2017. № 8.- с. 70-73.

40. Гулиев, Ф.А. Модифицированная пластика шейки мочевого пузыря после радикальной простатэктомии у пациентов с местно-распространенным раком предстательной железы // Cərrahiyyə, -Bakı: - 2017. № 3.- s. 59-62

41. Гулиев, Ф.А. Использование ПЭТ/КТ с 18-фторэтилхолином

в диагностике биохимического рецидива рака предстательной железы / Ф.А.Гулиев, Ф.Новрузов, Е.Мехти // Биомедицина, -Баку: - 2017. №4. -с.8-10.

42. Гулиев, Ф.А. Сравнительная оценка отдаленных результатов радикальной простатэктомии и дистанционной лучевой терапии при раке предстательной железы // Azərbaycan Tibb jurnalı, - Bakı: - 2018. №2.- s.19-25

43. Guliyev, F.A. 225c-PSMA-617 treatment and follow up in advanced stage metastatic castration resistant prostate cancer First clinical experience from Azerbaijan / F.A.Guliyev, J.Aliyev, F.Novruzov, et al. // European journal of nuclear medicine and molecular imaging,- 2019. 46. - p. s650-s651

List of Accepted Abbreviations

BCR – biochemical relapse
HT – hormone therapy
EAU – European Association of Urology
QOL – the life quality
CT – computed tomography
LAE – lymphadenectomy
RT – radiation therapy
LN – lymph nodes
IIEF – international index of erectile function
MRI – magnetic resonance imaging
LAPC – locally advanced prostate cancer
PG – prostate gland
DRE – digital rectal examination
PSA – prostatic specific antigen
PCA – prostate cancer
RPE – radical prostatectomy
UVA – urethrovesical anastomosis
ED – erectile disfunction

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