ANNOTATION

Dissertation work of Umurzakov Khussan Talipbaevich on the theme 'Improvement of radical treatment of prostate cancer by extroperitoneal endoscopic method' submitted for the degree of Doctor of Philosophy (PhD). on speciality 8D10102 'Medicine'.

Relevance of the research topic:

Prostate cancer (PCa) is one of the most common forms of malignant tumours in men, occupying the 3rd place in the structure of morbidity and the 5th place in the structure of mortality among men in the Republic of Kazakhstan.

Radical prostatectomy (RPE) is the most effective method of treatment of cancer. In the last twenty years the main preference is given to endoscopic methods of treatment, minimally invasive operations of radical prostatectomy historically developed from laparoscopic radical prostatectomy described by Schüssler et al. in 1992 to robot-assisted radical prostatectomy (RARPE) described by Binder et al. in 2003.

The introduction of extraperitoneal endoscopic treatment in RPP allows us to significantly reduce the degree of damage to the tissue surrounding the tumour and thus achieve better healing, adequate cosmetic effect and reduced complication rates.

For the choice of treatment method, we modernised and developed an approach of extraperitoneal laparoscopic radical treatment in cancer, which has not yet been used in RK.

Purpose of the study:

Optimize the extraperitoneal endoscopic method for radical treatment of prostate cancer

Aim of the study:

To optimise the extraperitoneal endoscopic technique for radical treatment of prostate cancer

Objectives of the study:

1. To study the epidemiological situation of prostate cancer and its dynamics in the population of Kazakhstan for 2012-2021 (10 years) .
2. To develop ways and methods of preparation of the surgical field for performance of laparoscopic extraperitoneal method of RPZ treatment
3. To carry out a comparative analysis of clinical efficacy of modified laparoscopic extraperitoneal prostatectomy and traditional laparoscopic intraperitoneal prostatectomy.
4. To evaluate the quality of life of patients who underwent laparoscopic extraperitoneal prostatectomy.

Methods of research

At the first stage of the study we analysed the data on morbidity and mortality from RPW in Kazakhstan for the period 2012-2021. The materials for this stage of the study were Form № 35 'Report on patients with malignant neoplasms' and 'Indicators of Oncological Service of the Republic of Kazakhstan' for the period 2012-2021. The following were studied: morbidity, mortality from RPW, as well

as the proportion of cases of early detection of RPW (I-II stages). All cases of RPW morbidity and mortality registered during this period were taken into account. Intensive epidemiological indicators were calculated per 100,000 men in the population. To assess the dynamics of the studied indicators, the method of determining trends was used - ascending (increase in the values of the studied epidemiological indicators) or descending (decrease in the values). The method of single-factor linear regression was used to quantitatively analyse and assess the statistical significance of the trends obtained.

Subject of the study:

Patients who underwent modified laparoscopic extraperitoneal radical prostatectomy (MLERPE) and conventional laparoscopic intraperitoneal radical prostatectomy (TLIRPE).

The main group included the data of 45 patients who underwent modified laparoscopic extraperitoneal radical prostatectomy (MLERPE), in conditions of VKO ICRC in Ust-Kamenogorsk city. The control group included case histories of 53 people who underwent traditional laparoscopic intraperitoneal radical prostatectomy (TLERPE), according to the data of VKO IARC, CNAM&O in Semey and KazNIIOIR in Almaty for the period 2017-2021.

The sample size was calculated using the online calculator Socioline.ru [https://socioline.ru/rv.php]. The required sample size was 92 people.

We compared clinical outcomes such as blood counts, duration of surgery and hospital stay after MLERPE and TLIRPE. All patient treatment information was obtained from the Comprehensive Medical Information System (CMIS) information system. Preoperative, perioperative, and postoperative data were scanned and recorded retrospectively using our data collection system. Preoperative clinical data included age, body mass index (BMI), serum prostate-specific antigen (PSA), and Gleason score. Perioperative parameters included operative time, blood loss, intraoperative complications, and whether bilateral pelvic lymph node dissection (BPLD) was performed and/ or whether the neurovascular bundle (NVB) was preserved. Postoperative parameters included changes in haemoglobin level, discharge time, catheter removal time, extracapsular, lymphovascular, perineural invasion of seminal vesicles and lymph node metastasis. We used D'Amico risk stratification to determine preoperative risk and patients were categorised as low, intermediate and high risk groups.

In the fourth stage, quality of life was assessed in patients undergoing MLERPE and TLIRPE. The assessment tool was the EORTC QLQ-C30 Questionnaire, which is available in online format: https://qol.eortc.org/. Eighty-five respondents took part in the survey, including 41 participants who had undergone MLERPE at the Ust-Kamenogorsk IARTC VKO and 44 respondents who had undergone TLIRPE. Ethical Committee approval was obtained from the Ethical Committee of Semey Medical University before starting the study (Protocol No. 2, 18 October 2019). The survey was conducted from July 2021 to December 2021. All study participants gave informed consent after being familiarised with the purpose of the study. Inclusion criteria: voluntary consent to participate in the study, confirmed evidence of undergone MLERPE or TLIRPE

from ERSB. Exclusion criteria: refusal to participate in the study, other type of cancer, other type of surgery.

Consisting of 30 questions, the EORTC QLQ-C30 questionnaire includes a global quality of life scale, five functional scales (physical, role, emotional, social, cognitive functioning), three symptom scales (pain, nausea/vomiting, fatigue) and six individual items (loss of appetite, constipation, diarrhoea, dyspnoea, insomnia). Each item is scored on a scale from 0 to 100, where a higher value corresponds to a better quality of life and/or level of functioning.

The EORTC QLQ-C30 - Awell Score online calculator https://score.awellhealth.com/calculations/eortc_qlq_c30 was used to convert the scores . The converted scores were used for statistical analyses in all domains and the level of significance was set at $p < 0.05$ for all analyses.

Subject of the study: Modified laparoscopic extraperitoneal radical prostatectomy

The surgical intervention is performed using 'Video endoscopic complex with Full HD or 3D image resolution for laparoscopic surgeries'. Manufacturer: Olympus Medical System Corp. Japan.

Figure 1-4 shows the explanations of the proposed technique. Figure 1 shows the trocar placement when performing modified extraperitoneal laparoscopic prostatectomy where trocars №1 and №5 are 10 mm and №2, №3 and №4 are 5 mm. Figure 2 demonstrates how trocars 2, 3, 4 and 5 are inserted under finger control. Figure 3 shows how to palpate the inferior parietal vessels internally.

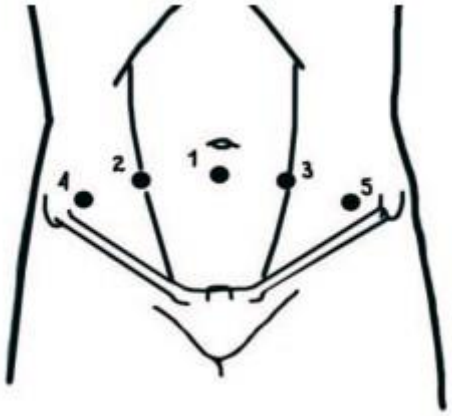

Figure 1. Location of trocars

Figure 2. Installation of working trocars under the control of the index finger. [From your own photo archive]

Figure 3. Palpation of the lower celiac vessels from the inside. [From your own photo archive]

The method of performing the procedure provides for the patient's position on the back with an angle of inclination of the trunk 30-45 degrees. Next, a 2 cm long incision is made along the midline at a distance of 1 cm below the navel (Figure 3, 4).

Figure 4. View of the operational field. [From your own photo archive]

Then the anterior aponeurosis sheet is opened and the rectus abdominis muscle is withdrawn, after which a finger dissection is performed to access the Retzius space. Further, a balloon dissector is performed in the direction of the bosom, in which up to 800 ml of gas is insufflated under visual control.

Once the workspace is completed, the balloon dissector is removed. Using the index finger, the peritoneum is peeled off and moved to the sides of the operative field. Then, under index finger control, four working trocars are inserted (as shown in Figure 2) while the lower suprailiac vessels are palpated internally. The optical trocar is then inserted, and the bladder is peeled from the anterior abdominal wall and the brow bone in a blunt and sharp manner. The bladder is not enlarged. The prostate is visualised without signs of tumour sprouting into adjacent organs.

The pubic-prostatic ligaments located between the superficial branches of the dorsal penile vein (dorsal venous complex) are cut in sequence with the LigaSure device until they reach the urethra. After grasping the apex of the prostate gland, a Foley #16 catheter is inserted through it and the cuff is inflated in the bladder. The posterior surface of the prostate gland is then gradually peeled away from the rectum while the catheter is moved upwards. The lateral neurovascular bundle of the prostate on both sides is crossed with the LigaSure device. During mobilisation of the posterior surface of the prostate gland and seminal vesicles, the vessels feeding the lateral walls of the prostate gland and seminal vesicles are ligated. The seminal ducts are crossed, and then the bladder neck is crossed to remove the prostate and seminal vesicles in a single unit. The bladder neck is partially preserved and the ureteral orifices are controlled. The Foley catheter is passed

through the urethra into the bladder and the cuff is inflated. Next, the lateral surface of the bladder is mobilised to the bifurcation of the iliac vessels on the right and left. Lymphatic dissection is performed along the external and internal iliac vessels and obturator fossa. Under control of the ureter and obturator nerve. The bladder is pulled up to the urethra, a single-row suture is applied to the urethro-vesical anastomosis. Haemostasis is performed. If no bleeding is detected, a drainage tube is left postoperatively, passing extraperitoneally into the small pelvis and exiting externally through the skin. The trocars are removed under endovideoscope guidance. Layer-by-layer suturing of the wound is performed. An aseptic dressing is applied to the wound.

Provisions for defence

Epidemiological indicators of RPJ in Kazakhstan for the period from 2012 to 2021 years had a stable character, without dynamic changes in the direction of sharp increase or decrease of indicators. In some regions of Kazakhstan there were statistically significant trends in 5-year survival rates and early detection of cancer.

Modified laparoscopic extraperitoneal radical prostatectomy prevents early postoperative complications as well as complications in the late postoperative period.

The general state of health of the patients who underwent LPE corresponded to the average level according to the scale of QOL assessment. Physical function had the lowest index among the functional scales in patients who underwent LRE. In the group of respondents who had undergone LERPE the indicators on functional scales were better. But in the pain scale, the average rank in the TLIRPE group was statistically higher than in the MLERPE group.

Results:

Statistically significant upward and downward trends were found for both the incidence of RPW ($p=0.702$) and mortality from the disease ($p=0.150$) over the period 2012-2021. The trend in 5-year survival in RC from 2012 to 2021 showed a downward trend. The detection rate of stage I-II RPV had almost the same rates, the detection rate of stage III RPV decreased and that of stage IV increased.

MLERPE helps to avoid peritoneal injury, prevents gas penetration into the abdominal cavity and reduces the risk of pelvic vascular injury. There was a statistically significant decrease in haemoglobin level, in the TLIRPE group compared to the MLERPE group. There was also a statistically significant decrease in the red blood cell count in the TLIRPE group compared to the MLERPE group. TLIRPE required longer time than MLERPE, the difference in the duration of the operation was statistically significant. At the same time, the hospital stay was longer in patients who underwent TLIRPE than in patients who underwent MLERPE.

The mean value of general health status was higher in the respondents who underwent the modified method of intervention than in the respondents who underwent the traditional method of intervention. The scores on physical, role emotional functioning were higher in the MLERPE group than in the TLIRPE group. Cognitive function, social functioning was at a fairly high level in respondents of both groups. Patients who underwent traditional method of

intervention had more pronounced health problems than patients who underwent modified method of intervention.

Scientific novelty:

1. The analysis of epidemiological indicators of prostate cancer in the Republic of Kazakhstan was carried out.
2. The method of modification of extraperitoneal laparoscopic extended radical prostatectomy has been developed
3. The assessment of the quality of life of patients with prostate cancer after laparoscopic radical prostatectomy has been carried outPractical significance of the obtained results

The introduction of extraperitoneal endoscopic treatment in RPJ allows to significantly reduce the degree of damage to the tissues surrounding the tumour and, thus, to achieve better healing, adequate cosmetic effect and reduced complication rate.

This technique avoids blood loss in the patient, avoids pneumoperitoneum and reduces the risk of CO2 saturation. In the early stages of the postoperative period, it prevents the development of peritonitis, and in the later period it excludes the formation of adhesions

The main points put forward for defence.

Epidemiological indicators of RPW in Kazakhstan for the period from 2012 to 2021 had a stable character, without dynamic changes towards a sharp increase or decrease in the indicators. In some regions of the Republic of Kazakhstan there were statistically significant trends in 5-year survival rates and early detection rates of RPW

Modified laparoscopic extraperitoneal radical prostatectomy prevents early and late postoperative complications.

Assessment of the quality of life of those who underwent LRPE, accordingly to the level on the QOL assessment scale. Physical function had the lowest score among the functional scales in patients who underwent LRPE. In the group of patients who underwent LLERPE, 86 6 per cent had better scores on the functional scales physical, also on the pain scale, the mean rank was statistically higher in the LLERPE group than in the LLERPE group.

Doctoral student's personal contribution.

During the 3 years of conducting clinical research. A selection of case histories of patients with RPV in whom radical prostatectomy was performed was carried out. The dissertant under the guidance of scientific advisors carried out the main part of the research, developed a method of preparation of the operating field for the performance of the extended laparoscopic extraperitoneal method of treatment of RPH, obtained a patent for invention. Also in the process of the study, the doctoral student conducted a thorough analysis, statistical processing and interpretation of the results of the obtained data, reasonable conclusions were made.

Conclusions.

Thus, the analysis of the dynamics of epidemiological indicators did not reveal the presence of statistically significant upward and downward trends both for the incidence of RPW (B=-0.167 (95% CI: -1.140;0.805), p=0.702) and mortality from

RPW (B=-4.387 (95% CI: -10.7;1.97), p=0.150). In East Kazakhstan oblast the epidemiological situation with RPW morbidity was the most unfavourable. A statistically significant trend of decreasing incidence of RPW in Almaty city (B=-0.289 (95% CI: -0.289; 0.023), p=0.036), and in Zhambyl oblast (B=-1.733 (95% CI: 0.500; 2.966), p=0.012) and North Kazakhstan oblast (B=-0.190 (95% CI: 0.000; 0.381) p=0.050) there is a statistically significant increase in incidence rates. Mortality rate from RPW was the highest in North-Kazakhstan region. No statistically significant trends of decrease and increase in mortality rates from RPW in the regions of the Republic of Kazakhstan were revealed. Over the period 2012-2021, the epidemiological situation with cancer in Kazakhstan has a steady trend towards improvement, but at the same time, the regions of the country differ significantly both in the initial values of epidemiological indicators and in the observed trends in their change.

During modified laparoscopic extraperitoneal radical prostatectomy (MLERPE) it is recommended to install four working trocars under the control of the index finger, palpating the lower suprailiac vessels from inside, which helps to prevent damage to vessels and peritoneum, which improves the quality of the operation. MLERPE excludes the occurrence of peritonitis in the early postoperative period, as well as the formation of adhesions in the late postoperative period.

The risk of complications according to D'Amico in the groups of patients with MLERPE and TLIRPE was estimated as low. TLIRPE required longer time than MLERPE, the difference was statistically significant (p=0.000). There was a statistically significant decrease in mean postoperative haemoglobin (p=0.000) and red blood cell count (p=0.000) in the post-TLIRPE group compared to patients in the MLERPE group. The mean hospital stay was longer in the TLIRPE group than in the MLERPE group, the difference was statistically significant (p=0.000). The analysis of outcomes after MLERPE and TLIRPE revealed the occurrence of complications in ten patients (19.0%) in the TLIRPE group and in three patients (6.6%) in the MLERPE group.

The general state of health of the respondents of both groups corresponded to the average level according to the scale of QOL assessment. Of the symptoms, fatigue, pain and insomnia were the most bothersome. Complaints of nausea/vomiting were expressed insignificantly in both groups. There were statistically significant differences in physical, role, social functioning between the respondents of both groups. These indicators were better in the group of respondents who underwent MLERPE. The average rank on the pain scale in the TLIRPE group was statistically higher than in the MLERPE group.

Approbation of the results of the dissertation.

The main provisions of the dissertation work were reported at:

1. VII Congress of oncologists and radiologists of Kazakhstan with international participation on 17-18 October 2019, Nur-Sultan city
2. I Central Asian Congress of Urologists CACU. 25-26 October 2019, Almaty city.
3. International online conference ‘Oncology of Kazakhstan. Yesterday, today, tomorrow’ 10-11 December 2020, Almaty city.

4. VIII Congress of oncologists and radiologists of Kazakhstan with international participation. 14-16 October 2021, Turkestan city.
5. Scientific-practical conference with international participation: 'New strategies of diagnostics and treatment in oncology'. 25-26 April 2022, Almaty.
6. XIII Congress of oncologists and radiologists of CIS and Eurasia, 27-29 April 2022. Astana.

Implementation of the results of the study in practice.

1. Patent for invention №35437 from 31.12.2021. Method of preparation of the operating field for extraperitoneal endoscopic treatment of prostate tumours.
2. Act of introduction into practice of the department of JSC 'Kazakh Research Institute of Oncology and Radiology'**.**

Publications.

According to the results of the research 5 scientific papers have been published: 3 - in the journals recommended by the Committee for Quality Assurance in the sphere of education and science of the Ministry of Education and Science of the Republic of Kazakhstan; 1 - in the journal included in the international database Scopus and Web of Science Core Collection (Clarivate Analytics) - Q3; 1 thesis in the material of the international scientific-practical conference; 1 RK patent for invention was received.

Scope and structure of the thesis

The thesis is set out on 108 pages and consists of an introduction, literature review, materials and methods of research, 3 sections of own research, conclusion, list of used sources and appendix. The dissertation contains 13 tables, 26 figures. The list of used literature includes 125 sources, of which 12 in Russian and 113 in a foreign language