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A MULTIMODAL STRATEGY FOR THE TREATMENT OF HIGH-RISK PROSTATE CANCER

ABSTRACT

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ABBREVIATIONS USED IN THE TEXT

5-ARIs	-	5 alpha reductase inhibitors
AR	-	androgen receptor
COX-2	-	cyclooxygenase
CT	-	computed tomography
CYP	-	cytochrome protein
DHT	-	dihydrotestosterone
DNA	-	deoxyribonucleic acid
EAU	-	European Association of Urology
EORTC	-	European Organization for Research and Treatment of Cancer
GSK	-	glucogen synthetase kinase
GS	-	Gleason score
HPV	-	human papillomavirus
HSV	-	herpes simplex virus
IFN	-	interferon
IGF	-	insulin growth factor
IL	-	interlefkin
BMI	-	body mass index
MRI	-	nuclear magnetic resonance
NSAIDs	-	nonsteroidal anti-inflammatory drugs
AO	-	agent orange
ODAC	-	Oncologic Drugs Advisory Committee
PET/CT	-	proton emission tomograph
PG	-	anti-inflammatory prostaglandins
PI-RADS	-	multiparametric index
STD	-	sexualy transmitted diseases
PSA	-	prostate-specific antigen
RNase	-	ribonuclease
SOD	-	superoxide dismutase

SNPs	-	single nucleotide polymorphisms
TCDD	-	tetrachlorodibenzo-p-dioxin
TGF	-	tumor growth factor
TLR	-	toll-like receptor
TNF	-	tumor necrosis factor

INTRODUCTION

1. EPIDEMIOLOGY OF PROSTATE CANCER.

Prostate cancer is the second most common malignancy (after lung cancer) in men worldwide, with 1,276,106 new cases and 358,989 deaths (3.8% of all deaths caused by cancer in men) in 2018. Prostate cancer incidence and mortality worldwide correlate with increasing age, with the average age at diagnosis being 66 years. Of note, African-Americans have a higher incidence rate than white men, with 158.3 new cases diagnosed per 100,000 men, and their death rate is roughly twice that of white men. The reasons for this discrepancy have been hypothesized to be differences in social, environmental, and genetic factors. Although 2,293,818 new cases are predicted by 2040, there will be little change in mortality (a 1.05% increase).

Prostate cancer is most often asymptomatic in the early stages of the disease. The most common complaints are difficulty and frequent urination, nocturia, and these are symptoms that can also occur with prostate hyperplasia. More advanced stage disease may present with urinary retention and low back pain, as bones are the most common site for metastatic disease.

Many prostate cancers are detected on the basis of elevated plasma levels of prostate-specific antigen (PSA > 4 ng/ml), a glycoprotein normally expressed by prostate tissue. However, because men without cancer also have elevated values, biopsy is the standard for confirming prostate cancer. Diet and physical activity play an important role in the development and progression of prostate cancer. Dietary factors are usually associated with the observed worldwide ethnic differences in prostate cancer incidence. Most research is devoted not only to identifying genes involved in the hereditary form of prostate cancer, but also to the mutations occurring in the acquired form. Therefore, detailed analysis of prostate cancer epidemiology and assessment of the risk

factors may help to understand the relationship between genetic mutations and the role of the environment in triggering these mutations and/or influencing tumor progression. Increased understanding of the etiology and the risk factors for prostate cancer will provide ways to identify men at risk and support the development of effective screening and prevention methods.

Based on GLOBOCAN 2018 ratings, Prashanth Rawla et al. estimated worldwide prostate cancer incidence and mortality, and analyzed incidence and mortality, rate trends, and survival rates.

The incidence of prostate cancer varies across regions and populations. In 2018, 1,276,106 new cases of prostate cancer were registered worldwide, which represents 7.1% of all cancers in men. Prostate cancer incidence rates vary widely around the world. The age-standardized rate was highest in Oceania (79.1 per 100,000 people) and North America (73.7), followed by Europe (62.1). Conversely, Africa and Asia have incidence rates lower than those in developed countries (26.6 and 11.5, respectively). Differences in incidence rates were 190-fold between populations with a high rate (France, Guadeloupe, 189.1) and populations with the lowest rate (Bhutan, 1.0).

1.1 Incidence of prostate cancer

The incidence of prostate cancer increases with age. Although only 1 in 350 men under the age of 50 will be diagnosed with prostate cancer, the incidence rises to 1 in 52 men aged 50 to 59. The incidence rate is almost 60% in men over 65 years of age. The reason for the differences between the countries is not entirely clear. Variation in prostate cancer epidemiology worldwide may be related to PSA testing. For example, in Europe, prostate cancer is the most commonly diagnosed cancer among men, accounting for 24% of all new cancers in 2018, with around 450,000 new cases of prostate carcinoma estimated in 2018. While in the US, prostate cancer is the second most common cancer,

accounting for 9.5% of all new cancer cases (164,690 new cases of prostate cancer) recorded in 2018. According to recent research studies, about 20-40% of prostate cancer cases in the US and Europe may be due to overdiagnosis through extensive PSA testing. Research shows that African-Americans have the highest incidence of prostate cancer worldwide and are more likely to develop the disease earlier in life than other racial and ethnic groups. This is reflected in the data not only for African-American men, but also for Caribbean and black Europeans, suggesting that they share a common genetic background that makes them more prone to developing cancer. Of note, Chu et al . reported that the incidence of prostate cancer was about 40 times higher among African-Americans than those in Africa. These differences suggest that environmental factors also play an important role in the etiology of prostate cancer, and variations in incidence may be due to underdiagnosis, differences in screening methods, and differences in access to health care.

1.2 Mortality from prostate cancer

Prostate cancer mortality varies widely worldwide. In 2018, the highest death rates were recorded in Central America (10.7 per 100,000 people), followed by Australia and New Zealand (10.2) and Western Europe (10.1). The lowest percentage was reported in the countries of Asia (South-Central- 3.3; East- 4.7 and South-East 5.4) and North Africa (5.8). One-third of prostate cancer deaths occurred in Asia (33.0%, 118,417 deaths), followed by Europe (29.9%, 107,315 deaths). Prostate cancer mortality increases with age, and almost 55% of all deaths occur after age 65. African-Americans have the highest incidence and mortality from prostate cancer. This suggests not only that these men may have some specific genes that are more susceptible to prostate cancer mutations, but also that these mutations are associated with a more aggressive type of cancer. However, a study conducted by Oliver

et al. in 2007, reported that African-Americans were less likely to identify early symptoms correctly than Caucasian men.

Temporal trends in prostate cancer incidence and mortality vary widely internationally and appear to be closely related to the use of PSA tests for early detection of the disease, particularly in Western countries. Incidence rates in the US, Canada and Australia increased between the 1980s and 1990s, but are now declining due to the rapid spread of PSA testing. Interestingly, a trend is calculated to increase the incidence of prostate cancer worldwide with 1,017,712 new cases (+79.7 overall change) by 2040. The highest incidence of prostate cancer will be recorded in Africa (+120.6%), followed by Latin America and the Caribbean (+101.1%) and Asia (100.9%). On the contrary, the lowest frequency will be registered in Europe (+30.1%). This increase in incidence appears to be related to longer life expectancy. Increasing incidence trends in developing countries are likely due to improved access to medical care as well as increased documentation and reporting of cases. Finally, the fact that the incidence increases in regions where PSA testing is not routinely used suggests that this phenomenon reflects a more westernized lifestyle, including obesity, physical inactivity, and dietary factors.

Prostate cancer mortality in most Western countries, including North America, as well as Western and Northern Europe, has been steadily declining. Although the reasons are not clear, this may reflect both early detection and improved treatment. However, in the US, a recent randomized controlled trial failed to demonstrate the benefits of PSA testing in reducing prostate cancer deaths, although another study in Europe showed such benefits. When trends related to ethnicity were analyzed, the decline in mortality among African-American men was greater than that among white men between 2001 and 2015. Negoita et al. document that improved and newer conditions for detection and treatment and improved treatment of resistant and metastatic prostate

carcinoma may justify these trends. From 2018 to 2040, it is estimated that the death rate will double with 379,005 deaths worldwide. It is estimated that the highest mortality rate will be in Africa (+124.4%), followed by Asia (116.7%), while the lowest incidence will be recorded in Europe (+58.3%). The above finding is not surprising, due to the limited resources for screening and detection of prostate cancer, which increases the chances of its detection in late stages. Furthermore, given that medical care and assistance are not widely available in developing countries, this may provide a possible explanation for the high mortality rate despite the lower incidence.

Although the incidence of prostate carcinoma is high, most cases are found when the cancer is confined to the prostate. The 5-year survival rate in the US for men diagnosed with prostate cancer is about 98%. Data from the Eurocare project (Eurocare-5) of patients with such a diagnosis from 2003 to 2007 show that the 5-year survival rate is 83%. Survival varies from 76% in eastern countries to 88% in southern and central European countries. In addition, survival increased over time across Europe, with the greatest improvement seen in Eastern European countries. Although science has made so much progress in recent decades in uncovering the molecular mechanisms and risk factors involved in prostate cancer, it is still the second leading cause of cancer death in men in the United States. Finally, the general idea for all cancers is that the earlier they are detected, the earlier they can be successfully treated. However, because most prostate cancers have a slow and often indolent course (defined as low-risk tumors), men can avoid immediate treatment (and potential side effects) while safely undergoing active surveillance or watchful waiting.

2. FUTURE PERSPECTIVES

The high incidence of prostate cancer worldwide calls for strengthening the existing tools available to identify trends and prevention strategies to reduce the public health impact of this disease in the future. Prostate cancer registries play an important role in the development of prostate cancer research and care. Indeed, they represent a major source for collecting information on incidence and mortality, disease characteristics, trends and risk factors, quality of care, disparities in access to treatment, long-term data related to oncology and quality of life outcomes, and costs related to disease management. Therefore, improvements in data quality, collection of tissue samples, and availability of feedback to health care providers will increase the relevance of epidemiological studies, especially as regards the evaluation of data collected from underdeveloped countries. Chemopreventive strategies have been studied in several preclinical and small clinical trials to mitigate the global burden of prostate cancer and overtreatment of indolent disease, which is associated with the widespread use of PSA testing. However, a challenge for the future will be to translate preclinical data into clinically useful strategies, which will require very large trials with thousands of participants, such as those of the SELECT trials. Additionally, studies are needed that can fill the knowledge gap regarding the higher incidence and mortality of prostate cancer in African-American men compared to white men. *Research on Prostate Cancer in Men of African Ancestry: Defining the Roles of Genetics, Tumor Markers, and Social Stress* (RESPOND study), funded by the Prostate Cancer Research Institute, was recently conducted. The main goals of this study were to understand how social and genetic variants contribute to the development of aggressive prostate cancer and how these factors interact with each other. Hopefully, the increased knowledge gained within this study will provide new insights into the development of positive screening and chemo-preventive strategies.

Finally, classical prognostic factors such as PSA testing, Gleason score, and clinical stage of cancer have shown not to be always sufficient to lead to the diagnosis of clinically significant cancer. Given that different genomic aberrations contribute to variation in prostate cancer risk and outcomes, as well as drug response and progression among patients, the identification of novel genetic biomarkers is much needed. This will undoubtedly improve cancer diagnosis, subtype identification and risk stratification. Most importantly, as we move toward personalized medicine, oncogenetic testing and biomarker profiling will facilitate optimal therapeutic intervention based on changes observed in individual patients. Clinical trials have already shown a high success rate of drugs that have been developed using biomarkers in patients with non-small cell lung cancer, therefore it is desirable to achieve the same results for the treatment of prostate cancer.

3. CONCLUSION

Prostate cancer is the most common malignancy in men, second only to lung cancer. The identification of biomarkers such as PSA that are positively associated with the diagnosis of prostate cancer has revolutionized the diagnosis of this disease. In fact, since the introduction of PSA testing and subsequent biopsies, the US has seen the incidence of prostate cancer double since the late 1980s. A similar increase has been reported in other countries, especially in the West. Unfortunately, although it proved effective in reducing prostate cancer-specific mortality, the associated overdiagnosis and severe side effects of treatment recommended against the introduction of PSA as a screening program. Perhaps the most dramatic statistic when it comes to prostate cancer incidence and mortality is how prevalence varies among different racial groups, with the highest prevalence among African-American men. Both biological and socioeconomic factors may explain this discrepancy, but which genes may be involved and

how they may interact with the environment is still unknown and under investigation. In 2018, the RESPOND study conducted to answer these questions. In recent years, the development of new genetic technologies has allowed for the first comprehensive analysis of genetic and epigenetic changes in human prostate cancer. This information, combined with targeted functional studies, helped identify critical signaling pathways involved in prostate cancer initiation and progression. This information will enable the development of new targeted approaches for therapeutic interventions. Research continues to identify genes associated with an increased risk of prostate cancer, and researchers are gathering more insight into the impact that specific genetic changes have on the development of prostate cancer. Although there are no studies that can sufficiently prove a direct link between diet and nutrition and the risk or prevention of developing prostate cancer, many preclinical studies that look at the links between certain diets and cancer suggest that there may be a link. Furthermore, these studies have allowed the identification of the underlying biological mechanisms that may explain this relationship. Therefore, well-designed studies that replicate preclinical findings are warranted to validate the effects of nutritional agents in prostate carcinoma. Finally, future chemoprevention studies should not only include early intervention, but should also emphasize personalized molecularly targeted approaches to select and treat prostate cancer patients that lead to a positive outcome and effective therapy.

LITERATURE REVIEW

1. OVERVIEW OF THE MAIN THERAPEUTIC METHODS USED IN HIGH-RISK AND/OR LOCALLY-ADVANCED PROSTATE CANCER

The main stages in the development of the multimodal approach for the treatment of high-risk and/or locally advanced prostate cancer were as follows - initially radiotherapy was mainly used, then it was combined with hormonal therapy, finally radical prostatectomy combined with extended lymphatic dissection was included.

1.1 Radical prostatectomy

In patients with high-risk and/or locally advanced prostate carncer, surgery is a reasonable choice—as long as there is no urethral sphincter involvement and the tumor is not fixed to the pelvic wall. In all cases, in addition to removing the prostate, an extended lymph node dissection is performed. At the same time, intraoperatively a lymph node graft is not sent, because even if there are metastases in them, their removal improves survival. Also, the patient should be warned pre-operatively that it is possible to include radiotherapy after the operation as part of a multimodal treatment with all possible side effects.

1 .2 Radiotherapy

It is an established approach in patients with high-risk and/or locally advanced prostate cancer. Intensity-modulated radiotherapy combined with hormonal therapy for at least 2 to 3 years has been used—shorter hormonal therapy (although more sparing in patients with comorbidities) has been shown not to improve overall survival. Another

option for multimodal treatment is the addition of brachytherapy to the radiotherapy and hormonal therapy described above.

The question which method (radical prostatectomy or radiotherapy) is preferable in patients with high-risk and/or locally advanced prostate cancer is also interesting. In May 2020, European Urology published the review article *Benefits and Risks of Primary Treatments for High-risk Localized and Locally Advanced Prostate Cancer: An International Multidisciplinary Systematic Review.* Both surgery and radiotherapy should be considered as part of a multimodal treatment plan - the addition of radiotherapy (post-operative) is possible. No definitive dose for radiotherapy can be offered, but higher doses lead to improved biochemical control. In conclusion, the authors state that patients should at all times be fully informed about all available options and the possible application of a multimodal approach – and also about the potential side effects of both local and systemic treatments.

1.3 Hormonal therapy

In article from European Urology (from 2011) hormonal therapy was shown to benefit men with long life expectancy, high ISUP-grade, and short PSA-doubling time (less than 6 months) as part of multimodal treatment for high-risk cancer.

In the recent past (10-15 years ago), this group of patients was treated only with hormonal therapy. There was even recommendation, at the beginning of radical prostatectomy, frozen section from lymph nodes to be examined and, in the presence of metastases, the operation to be terminated. It is now believed that long-term hormonal therapy should be combined with local therapy to improve survival. So, radiotherapy combined with long-term hormonal therapy is currently recommended for the treatment of such patients.

1.4 Adjuvant therapy after radical prostatectomy

Adjuvant therapy usually includes radiotherapy (with or without hormonal therapy) - attempts to use only hormone therapy (even combined with docetaxel) have not shown particular effectiveness.

A special group of patients are those with proven lymph node metastases during the radical prostatectomy. We have the following therapeutic options for them **:**

- **Early adjuvant hormonal therapy** achieves 80% 10-year cancer-specific survival.
- **Adjuvant radiotherapy and hormonal therapy** is associated with improved survival in men with locally advanced disease and a greater number of positive nodes.

Retrospective data from a multicenter study (1,491 patients with lymph node metastases after radical prostatectomy) with a mean follow-up of 8.2 years showed a significantly lower risk of death from all causes with adjuvant radiotherapy compared with early salvage radiotherapy.

The addition of hormonal therapy may improve progression-free survival along with immediate radiotherapy to the prostatic bed in patients with pT3 stage and/or positive surgical margins after radical prostatectomy.

1.5 Patients with biochemical progression after radical prostatectomy

Multimodal therapy in patients with high-risk and/or locally advanced prostate cancer can generally be performed in two ways: either adjuvantly (immediately after radical prostatectomy), or after a period of observation in the event of PSA progression.

1.6 Salvage radiotherapy without hormonal therapy

Early salvage radiotherapy enables the cure of patients with PSA-progression after radical prostatectomy. After PSA progression, cancer-specific survival was 3-fold greater in patients who received radiotherapy. It is particularly effective in patients with a short PSA doubling time.

1.7 Salvage radiotherapy combined with hormonal therapy

In 2020 in JAMA Oncol. *Dess et al*. published an article attempting to clarify which patients benefit from the addition of hormonal therapy to radiotherapy. According to their data, men at high risk of progression (that is, with PSA $\geq$ 0.7 ng/ml and Gleason score $\geq$8) probably need 2 years of hormonal therapy. For those at moderate risk (PSA < 0.7 ng/ml and Gleason score = 8), 6 months of hormonal therapy are sufficient, and an improvement in overall survival is observed when combining radiation and hormonal therapy.

Salvage radiotherapy is of unspecified dose – it should probably be at least 64 Gray for the prostatic bed.

1.8 Treatment of pelvic lymph node metastases

Even after radical prostatectomy, some urologists continue to look for a place for surgical treatment of patients with PSA recurrence. Retrospective series have been published in which pelvic lymph node metastases were detected with PET/CT at mean PSA levels of 2.5 ng/mL. After salvage pelvic lymphadenectomy, 5-year biochemical progression-free survival rates of 6 to 31% have been reported. The 5-year overall survival rate was 84%.

1.9 Observation

This approach makes sense because observation of the natural course of the disease in untreated patients shows that the average time for

metastases to appear is 8 years after the onset of PSA progression. The median time from the appearance of metastases to the death of patients was another 5 years. Thus, active follow-up is possible in patients unwilling to undergo salvage treatment, those with a life expectancy < 10 years, and low-risk patients for relapse (according to the EAU classification).

MATERIAL AND METHODS

The present study is retrospective, single-center. Anonymized data of 1,275 patients were used. They were operated in the Clinic of Urology in "St. Anna" Hospital, Varna for the period 1996-2022. The patients were followed up at the "Marko Markov" Oncology Centre, in compliance with generally accepted ethical requirements.

Criteria for inclusion in the study: patients with performed radical prostatectomy, radiotherapy and/or hormonal therapy.

Exclusion criteria for patients in the study:

- Only radical prostatectomy was performed.
- Patients with missing data from the follow up.

On this basis 404 patients were excluded.

Analysis was performed on a sample of 871 patients.

1. AIM OF THE STUDY

Analysis of the multimodal treatment in high-risk prostate cancer.

2. RESEARCH TASKS

1) Statistical analysis of survival in the risk group and the control group. The risk group contains patients with high-risk prostate cancer- $T_3N_0M_0$, $T_3N_1M_0$, $T_3N_1M_1$, $T_3N_2M_0$, $T_4N_0M_O$, $T_4N_1M_O$, PSA > 20 and GS >7;

The control group contains all other patients – with low- and intermediate-risk prostate cancer in stage $T_2N_0M_0$, PSA < 20 and GS≤7

2) In the high-risk group, patients should be assessed according to the treatment method:

- I group - treated bimodally-operatively and with hormonal therapy; according to survival at 5 and 10 years;

- II group - treated trimodally-operatively, with hormonal and radiotherapy ; again by survival at 5 and 10 years;

3) To analyze the clinical progression in both groups;
4) To analyze the biochemical progression in both groups;
5) To evaluate which of the factors that define the high-risk group-TNM stage, PSA, Gleason score-has the greatest weight in terms of survival, biochemical progression and clinical progression (development of metastases);
6) To determine prognostic criteria for cancer-specific survival according to the severity of the factors- clinical progression, PSA progression, TNM stage, Gleason score, PSA values;

STATISTICAL METHODS

Data were analyzed with IBM SPSS, version 26. The normality of the distribution of continuous variables was tested with Shapiro-Wilk and Kolmogorov-Smirnov tests for one sample.

Normally distributed continuous variables are presented by mean and standard deviation (SD). Variables that do not follow a normal distribution and/or include very remote and extreme values are presented by median and interquartile range (IQR).

As no normally distributed continuous variables were found in the analyses, non-parametric tests were applied.

The frequencies of the categorical variables were compared using Pearson's X^2 / Fisher's exact test. Within the test (Crosstabs option, IBM SPSS) risks / odds ratios (Odds ratios) are calculated.

Non-parametric Mann-Whitney U and Kruskal-Wallis H tests were used to compare, respectively, two and more than two independent variables that did not follow a normal distribution and/or were category/rank variables. For dependent (correlated) variables, Wikoxon Sign Rank Test (for two variables) and Friedman's test (for more than two variables) were used.

Correlation analysis was applied to determine the strength and direction of dependencies (Phi correlation coefficient for nominal variables and Spearman's Rho correlation coefficient for rank variables). Goodman and Kruskal's Gamma correlation coefficient was used to determine the strength and direction of the relationship between two ordinal variables with more than two attribute levels.

To study survival of the patients, survival analysis was used - Kaplan-Meier method, including Log Rank, Breslow test, and Tarone-Ware test to establish statistical significance and survival curves.

The presence of clinical and biochemical progression, $T_3 - {}_3+$ disease stage, GS ≥ 7, and PSA > 20 were used as predictors of dying from cancer, which were considered both as independent predictors and included in two models of predictors of dying from cancer.

For a single assessment of the considered predictors, standardized β-coefficients (Odds ratios) calculated using the Crosstabs (SPSS) option for risk calculation and logistic regression were used and the calculated standardized β-coefficients were compared.

One model included the presence of clinical and biochemical progression, and the other model of predictors of dying from cancer that was tested included stage T_3–T_3+ disease, GS > 7, and PSA > 20.

Models of predictors of dying from cancer were tested with logistic regression. To confirm the accuracy of the models, an analysis of ROC curves was used - a graphical method for presenting the results of binary classification and evaluating the efficiency of the classification. In addition to the ROC curves, graphs of the overall quality assessment of the models are also presented.

T- tests were performed at a significance level of $\alpha = 0.05$ or $p < 0.05$.

The graphics are designed with IBM SPSS and MS Excel .

1. GENERAL CHARACTERISTICS OF THE SAMPLE

The sample includes 871 patients registered and treated in the period 1996 - 2022 in the "St. Anna" Hospital, Varna. Their age ranged from 48 to 81 years, median 66 (62 – 71). Gleason score of patients ranged from 2 to 10, median 7 (6 – 7); PSA ranged from 2 to 164, median 12 (8–19), and prostate volume ranged from 16 to 120, median 50 (50–60). 532 (61.1%) of the patients were in T-stage 2, and the remaining 339 (38.9%) were in T-stage 3 – 4 (including 2 patients in stage 4). Overall survival ranged from 0 to 25 years, median 6.0 (3–9). 251 (28.8%) of the patients died, of which 105 (12.1%) died from prostate cancer.

1.1 The risk group included 491 (56.4%) patients. Their age ranged from 48 to 81 years, median 67 (63 – 71) years. The Gleason score of the patients in the group ranged from 4 to 10, median 7 (7 – 8); PSA ranged from 2 to 164, median 17 (10–26), and prostate volume ranged from 16 to 120, median 50 (50–60). In this group, 152 (30.9%) of the patients were in T-stage 2, and the remaining 339 (69.1%) were in T-stage 3. Overall survival ranged from 0 to 19 years, median 4.0 (2–7). 143 (29.1%) of the patients died, of which 82 (16.7%) died from prostate cancer.

1.2 ***The control group*** included 380 (43.6%) patients. Their age ranged from 49 to 79 years, median 66 (62 – 70) years. The Gleason score of patients in the group ranged from 2 to 7, median 7 (6 – 7); PSA ranged from 2 to 19, median 10 (7 -12), and prostate volume ranged from 35 to 120, median 50 (50 – 60). In this group, all 380 (100.0%) of the patients had T-stage 2. Overall survival ranged from 0 to 25 years, median 8.0 (3 – 12). 108 (28.4%) of the patients died, of which 23 (6.1%) died from prostate cancer.

The patients in the risk group had higher GS values ($z = -13.305$, $p < .001$, Mann-Whitney U Test), higher PSA values ($z = -13.759$, $p < .001$, Mann-Whitney U Test), higher disease stage ($z = -20.714$, $p < .001$, Mann-Whitney U Test), larger prostate volume ($z = -2.263$, $p = .024$,

Mann-Whitney U Test) and shorter overall survival (z = -3.839, p = .024, Mann-Whitney U Test).

No statistically significant difference was found in the age of the patients in the two groups (z = -1.467, p = .142, Mann-Whitney U Test).

2. SURVIVAL

2.1 Overall survival - risk and control group

Survival data were available for 251 (28.8%) of all patients included in the study, of which 143 (57.0%) were in the risk group and 108 in the control group. The survival of patients in the risk group ranged from 0 to 19 years, median 4.0 (2 - 7) years, and that of patients in the control group - from 0 to 25 years, median 8.0 (3 - 12) years. Figure 1 presents the descriptive statistics of overall survival in the risk and control groups.

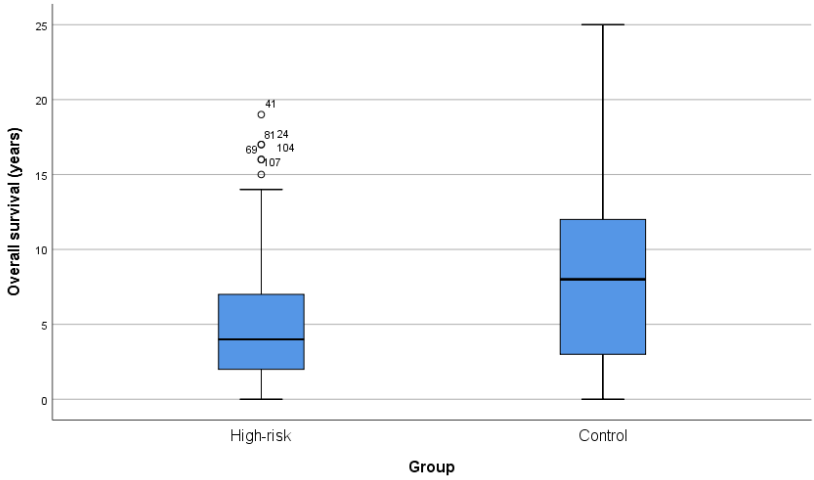

Figure 1. Descriptive statistics of overall survival in the risk and the control group (6 values ≥ 15.0)

Survival of patients in the risk group was lower than that of patients in the control group (z = 3.839, p < .001, Mann-Whitney U Test). This is

also confirmed by the Kaplan-Meier survival analysis and the resulting survival curves. Statistical significance between curves was confirmed by the three significance tests (Log Rank, p = .000; Breslow, p = .000 and Tarone-Ware, p = .000), (Figure 2).

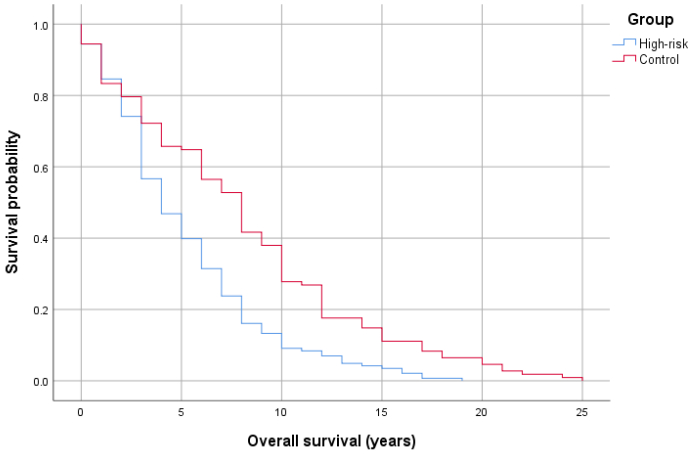

Figure 2. Overall survival in the risk and the control group.

2.2 Overall survival up to 5 years and over 5 years

For the purposes of the analysis, we looked at patient survival in two periods - up to 5 years and over 5 years. 251 (28.8%) patients fell into these periods, of which 124 (49.4%) survived less than 5 years, and 127 (50.6%) survived more than 5 years.

Survival in the ≤ 5-years group ranged from 0 to 5 years, median 3 (1–4) years, and in the > 5-years group, survival ranged from 6 to 25 years, median 9 (7–12) years.

In the risk group, 86 (34.3%) survived up to 5 years, and 57 (22.7%) of the patients over 5 years. In this group, the survival of patients under

5 years ranged from 0 to 5 years, median 3.0 (1 – 4), and the survival of patients over 5 years ranged from 6 to 19 years, median 8.0 (7 – 10).

In the control group, 38 (15.1%) survived up to 5 years, and 70 (27.9%) of the patients survived over 5 years. In this group, the survival of patients under 5 years ranged from 0 to 5 years, median 2.0 (1 – 3), and the survival of patients over 5 years ranged from 6 to 25 years, median 10.0 (8 – 14).

No statistically significant difference was found in the survival under 5 years of patients from the risk and control groups (z = -1.946, p = .052, Mann-Whitney U Test). A statistically significant difference was found in survival over 5 years - the survival of patients in the risk group was lower than that of patients in the control group (z = -2.951, p = .003, Mann-Whitney U Test).

A statistically significant relationship was found between belonging to a risk or control group and the survival period (z = -3.907, p < .001, Mann-Whitney U Test). Patients in the risk group had a higher chance of not surviving more than 5 years (OR = 2.779, 95%CI = 1.656 – 4.664). The risk of a patient in this group not to survive more than 5 years was 1.5 times higher than that of a patient in the control group (RR = 1.545, 95%CI = 1.233 – 1.936).

3. CANCER-SPECIFIC SURVIVAL

Of all 251 patients who died, 105 (41.8%) died of cancer and 146 of other diseases as the cause of death. Survival for those who died from cancer ranged from 0 to 12 years, median 3 (2–4) years, and for those from other causes from 0 to 25 years, median 8 (6–12) years. Survival of those who died of cancer was lower than that of those who died of other causes (z = 9.423, p < .001, Mann-Whitney U Test). This is also confirmed by the Kaplan-Meier survival analysis and the resulting survival curves. Statistical significance between the curves was

confirmed by the three significance tests (Log Rank, p = .000; Breslow, p = .000 and Tarone-Ware, p = .000).

3.1 Survival under 5 years

91 (36.3%) patients have a cancer-specific survival of less than 5 years, and 14 (5.6%) patients have a survival of more than 5 years. 33 (13.1%) patients had survival from another cause under 5 years, over 5 years – 113 (45.0%) patients.

A statistically significant relationship was found between cause of death and survival period (z = -9.994, p < .001, Mann-Whitney U Test). The probability of a patient dying from cancer within 5 years was higher than that of dying from cancer after more than 5 years (OR = 22.258, 95%CI = 11.238 – 44.082). The risk of a patient dying from cancer in the first 5 years was 6.6 times higher than dying from another cause (RR = 6.657, 95%CI = 4.016 – 11.035). The Kaplan-Meier survival curves of patients who died of cancer at a period of less than and over 5 years confirm these results. Statistical significance between the curves was confirmed by the three significance tests (Log Rank, p = .000; Breslow, p = .000 and Tarone-Ware, p = .000).

3.2 Cancer-specific survival – risk and control group

In the risk group, 143 (57.0%) patients died, 82 (57.3%) died of cancer, and 61 patients died of other causes. Survival of those who died from cancer in the risk group ranged from 0 to 12 years, median 3 (2–4), and that of those who died from another ranged from 0 to 19 years, median 7 (6–10).

In the control group, 108 patients died, of which 23 (21.7%) died of cancer, and 85 died of other causes. Survival of those who died from cancer in the control group ranged from 0 to 8 years, median 2 (1–3), and that of those who died from other varied from 0 to 25 years, median 9 (6–12).

A statistically significant association was found between belonging to a risk or control group and dying from cancer (z = -5.721, p < .001, Mann-Whitney U Test *).* ***The chance of a patient in the risk group to die from cancer was higher (OR = 4.968, 95%CI = 2.817 – 8.763). The risk of a patient in the risk group to die from cancer was 1.8 times higher than that of a patient in the control group (RR = 1.869, 95%CI = 1.505 – 2.321).*** This is also confirmed by the Kaplan-Meier survival analysis and the resulting survival curves. Statistical significance between the curves was confirmed by the three significance tests (Log Rank, p = .000; Breslow, p = .000 and Tarone-Ware, p = .000), (Figure 3*).* A similar relationship for dying from another cause was not found (Log Rank, p = .194; Breslow, p = .890 and Tarone-Ware, p = .525)

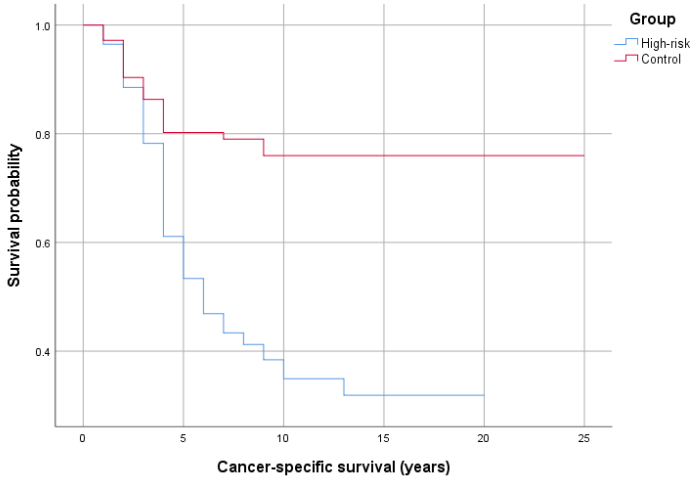

Figure 3. Survival of cancer patients in the risk and control groups

Table 1. Patient survival

Deceased patients:		Time to death		Total
		≤ 5 years	> 5 years	
Risk group	Died of prostate cancer	71	11	82
	Other cause of death	15	46	61
	Total	86	57	143
Control group	Died of prostate cancer	20	3	23
	Other cause of death	18	67	85
	Total	38	70	108
Total	Died of prostate cancer	91	14	105
	Other cause of death	33	113	146
	Total	124	127	251

In the risk group, the survival of 86 (60.1%) patients was less than 5 years, and 57 (39.9%) – more than 5 years . ***Of them, 71 (82.6%) patients died of cancer in the period up to 5 years, and 11 (13.4%) – in the period over 5 years.*** 15 (24.6%) patients in the period up to 5 years and 46 (75.4%) patients in the period over 5 years died from another disease as the cause of death (Table 1).

A statistically significant relationship was found between the survival period up to and over 5 years and the cause of death ($z = -7.463$, $p < .001$, Mann-Whitney U Test). The probability of a patient in the risk group to die of cancer within 5 years was higher than that of dying after more than 5 years (OR = 19.794, 95%CI = 8.360 – 46.867). The risk of a patient in this group to die from cancer in the first 5 years was 4.2 times higher than dying from another cause (RR = 4.278, 95%CI =

2.494 – 7.339). The correlation is high and statistically significant (Phi = .626, p < .001)

In the control group, the survival from cancer of 38 (35.2%) patients was less than 5 years, and 70 (64.8%) – more than 5 years. Of them, 20 (87.0%) died of cancer in the period up to 5 years, and 3 (13.0%) – in the period over 5 years. 18 (21.2%) patients in the period up to 5 years and 67 (78.8%) patients in the period over 5 years died of other causes.

A statistically significant relationship was found between the survival period in the control group and the cause of death (z = -5.833, p < .001, Mann-Whitney U Test). The probability of a control patient to die of cancer within 5 years was higher than that of dying after more than 5 years (OR = 24.815, 95%CI = 6.627 – 92.924). The risk of a patient to die from cancer in the first 5 years was 12 times higher than dying from another cause (RR = 12.281, 95%CI = 3.899 – 38.685). The correlation is moderate and statistically significant (Phi = .564, p < .001)

A statistically significant relationship was found between the cause of death within 5 years and whether the patients belonged to a risk or control group (z = -3.362, p < .001, Mann-Whitney U Test). The probability of a risk patient to die from cancer within 5 years was higher (OR = 4.260, 95%CI = 1.828 – 9.927). The risk of a patient in the risk group to die from cancer in the first 5 years was 1.7 times higher than that of a patient in the control group (RR = 1.716, 95%CI = 1.163 – 2.534).

The probability of risk patient dying of cancer after more than 5 years was higher (OR = 5.341, 95%CI = 1.412 – 20.206). The risk of a patient in the risk group dying from cancer after more than 5 years was 1.9 times higher than that of a patient in the control group (RR = 1.930, 95%CI = 1.357 – 2.746).

4. TIME TO OCCURANCE OF METASTASES (CLINICAL PROGRESSION)

Data on the occurrence of metastases are available for 46 (5.3%) of the patients - 39 (84.8%) are in the risk group and 7 (15.2%) are in the control group. A statistically significant relationship was found between belonging to a group and the occurrence of metastases ($z = -3.990$, $p < .001$, Mann-Whitney U Test), The chance of a patient from the risk group to get metastases is higher (OR = 4.598, 95% CI = 2.033 – 10.399 **).** ***Patients in the risk group had a 1.5 times higher risk of clinical progression than patients in the control group (RR = 1.547, 95%CI = 1.349 – 1.775).***

Time to occurrence of metastasis for the risk group ranged from 0 to 7 years, median 3 (1–4) years, and time to occurrence of metastasis for the control group ranged from 1 to 7 years, median 2 (1–5) years.

No statistically significant difference was found in the time to occurrence of metastasis for patients in the two groups ($z = -.499$, $p = .618$, Mann-Whitney U Test). This is confirmed by the three reliability tests (Log Rank, $p = .872$; Breslow, $p = .610$ and Tarone-Ware, $p = .784$) from the Kaplan-Meier survival analysis and the resulting survival curves.

42 (4.8%) patients had a survival of less than 5 years until the onset of clinical progression. Of them, 36 (85.7%) were from the risk group, and 6 (14.3%) from the control group.

No statistically significant difference was found in the time to occurrence of metastasis in the first 5 years for patients in the two groups ($z = -.958$, $p = .338$, Mann-Whitney U Test). This is confirmed by the three significance tests (Log Rank, $p = .474$; Breslow, $p = .322$ and Tarone-Ware, $p = .361$) from the Kaplan-Meier survival analysis and the resulting survival curves.

Of all 143 deaths in the risk group, 38 (30.9.2%) patients died with clinical progression. A statistically significant association was found between the occurrence of clinical progression and death ($z = -9.776$, $p < .001$, Mann-Whitney U Test). The probability of a patient with clinical progression to die was higher (OR = 125.581, 95%CI = 17.037 – 925.654). Patients with clinical progression had a 92-fold higher risk of dying than patients without clinical progression (RR = 92.476, 95%CI = 12.819 – 667.115). The correlation is moderate and statistically significant (Phi = .442, $p < .001$).

Of all 82 (57.3%) patients who died of cancer in the risk group, 37 (45.1%) patients had clinical progression. A statistically significant association was found between the occurrence of clinical progression and dying from cancer ($z = -5.573$, $p < .001$, Mann-Whitney U Test). The probability of a patient with clinical progression to die from cancer was higher (OR = 167.322, 95%CI = 39.022 – 717.464). ***Patients with clinical progression had a 92-fold higher risk of dying from cancer than patients without clinical progression (RR = 92.274, 95%CI = 22.687 – 375.303). The correlation is high and statistically significant (Phi = .616, p < .001).***

Of all 23 (21.3%) patients who died of cancer in the control group, all 7 patients with clinical progression died of cancer. The correlation was moderate and statistically significant (Phi = .540, $p < .001$. Patients without clinical progression had a lower chance of dying from cancer (OR = .696, 95%CI = .531 - .912).

5. BIOCHEMICAL PROGRESSION-FREE SURVIVAL

Data on the occurrence of biochemical progression is available for 44 (5.1%) of the patients - 37 (84.1%) are from the risk group and 7 (15.9%) are from the control group. A statistically significant relationship was found between belonging to a group and the occurrence of biochemical progression ($z = -3.803$, $p < .001$, Mann-Whitney U Test). The probability of risk-group patient to have

biochemical progression was higher (OR = 4.343, 95%CI = 1.914 – 9.854). ***Patients in the risk group had a 1.5-fold higher risk of biochemical progression than patients in the control group (RR = 1.532, 95%CI = 1.328 – 1.767).***

Time to biochemical progression for the risk group ranged from 0 to 6 years, median 2 (1–2) years, and time to biochemical progression for the control group ranged from 0 to 6 years, median 2 (0–5) years.

No statistically significant difference was found in the time to biochemical progression for the patients in the two groups (z = -.372, p = .710, Mann-Whitney U Test), This was confirmed by the three tests of reliability (Log Rank, p = .435; Breslow, p = .867 and Tarone-Ware, p = .672) from the Kaplan-Meier survival analysis and the resulting survival curves.

42 (4.8%) patients had a survival of less than 5 years until the occurrence of biochemical progression. Of them, 36 (83.8%) are from the risk group, and 6 (14%) - from the control group.

No statistically significant difference was found in the time to biochemical progression in the first 5 years for patients in the two groups (z = -.372, p = .710, Mann-Whitney U Test). This is confirmed by the three significance tests (Log Rank, p = .981; Breslow, p = .701 and Tarone-Ware, p = .815) from the Kaplan-Meier survival analysis and the resulting survival curves**.**

Of all 143 deaths in the risk group, 36 (25.2%) patients died with biochemical progression. A statistically significant association was found between the occurrence of biochemical progression and death (z = -9.482, p < .001, Mann-Whitney U Test). Patients with biochemical progression had a higher probability of dying (OR = 116.748, 95%CI = 15.819 – 861.607). Patients with biochemical progression had an 87-fold higher risk of dying than patients without biochemical progression

(RR = 87.608, 95%CI = 12.127 – 632.902). The correlation is moderate and statistically significant (Phi = .596, p < .001).

Died of prostate cancer

Of all 82 (57.3%) patients who died of cancer in the risk group, 35 (42.7%) patients had biochemical progression. A statistically significant association was found between the occurrence of biochemical progression and dying from cancer (z = -5.573, p < .001, Mann-Whitney U Test). The probability of a patient with biochemical progression to die from cancer was higher (OR = 151.543, 95%CI = 35.314 – 650.315). ***Patients with biochemical progression had an 87 times higher risk of dying from cancer than patients without biochemical progression (RR = 87.287, 95%CI = 21.416 – 355.767).*** The correlation is moderate and statistically significant (Phi = .596, p < .001).

Of all 23 (21.3%) patients who died of cancer in the control group, all 7 patients with biochemical progression died of cancer. The correlation was moderate and statistically significant (Phi = .540, p < .001. Patients without biochemical progression had a lower chance of dying from cancer (OR = .696, 95%CI = .531 - .912).

6. TREATMENT OF THE RISK GROUP-OVERALL AND CANCER-SPECIFIC SURVIVAL

All treated patients were 485 (55.7%), of which 140 (28.9%) were treated with double therapy (surgery and hormonal therapy) and 345 (71.1%) were treated with triple therapy (surgery, hormonal and radiotherapy). Of all 485 treated patients, a total of 151 (31.1%) died, of which 38 (25.1%) received double therapy, and 113 (74.9%) received triple therapy. No statistically significant association was found between the type of therapy and the patients' overall survival (z = -1.208, p = .227, Mann-Whitney U Test).

Of all 485 treated patients, 89 (18.4%) died of cancer. Of the 140 patients treated with double therapy, 15 (10.7%) died of cancer, and of the 345 patients treated with triple therapy – 74 (21.4%) died of cancer. A statistically significant relationship was found between type of therapy and dying from cancer (z = -2.765, p = .006, Mann-Whitney U Test). The probability of a patient on dual therapy to die from cancer was higher than the probability to die from something else (OR = 2.276, 95%CI = 1.256 – 4.122). Even higher was the chance of a patient on triple therapy to die from cancer than the probability to die from something else (OR = 6.315, 95%CI = 3.597 – 11.084).

Treatment of the risk group

Of all 491 patients in the risk group, patients treated with dual therapy were 119 (24.2%) and 342 (69.7%) were treated with triple therapy. The remaining 30 (6.1%) were only operated but not treated after that with hormonal and/or radiotherapy-they were excluded from the analysis.

Of all 380 patients in the control group, 21 (5.5%) were treated with dual therapy, 3 (0.8%) were treated with triple therapy, and 357 (93.7%) patients were only operated.

A total of 24 patients died in the control group, of which 14 died of prostate cancer-13 were treated with dual therapy and 1 was treated with triple therapy. 10 patients died of other causes, of which 8 were treated with double and 2 with triple therapy. No statistically significant association was found between treatment and dying (z = -.919, p = .358, Mann-Whitney U Test). As the number of treated patients in the control group was insufficient to compare the therapies, we analyze further only the risk group.

Of all 491 patients in the risk group, patients treated with dual therapy were 119 (24.2%). Their ages ranged from 50 to 81 years, median 67 (63 – 71). The GS of the patients in the group ranged from 4 to 10,

median 8 (7 – 8). PSA ranged from 4 to 75, median 20 (10–26), and prostate volume ranged from 40 to 100, median 50 (50–60).

Of all 491 patients in the risk group, patients treated with triple therapy were 342 (69.7%). Their ages ranged from 48 to 79 years, median 66 (63 – 71). The GS of the patients in the group ranged from 4 to 10, median 7 (7 – 8). PSA ranged from 2 to 164, median 15 (10–25), and prostate volume ranged from 16 to 100, median 50 (50–60).

A statistically significant relationship was found between the type of treatment and GS. Patients treated with dual therapy had a higher GS ($z = -2.411$, $p = .016$, Mann-Whitney U Test) than those treated with triple therapy.

A statistically significant relationship was also found between the type of treatment and the T-stage of the disease. Patients treated with dual therapy had a lower T-stage ($z = -15.272$, $p < .001$, Mann-Whitney U Test).

No statistically significant difference was found in PSA values ($z = -1.156$, $p = .248$, Mann-Whitney U Test), prostate volume ($z = -.831$, $p = .406$, Mann-Whitney U Test) and age ($z = -.356$, $p = .722$, Mann-Whitney U Test) of those treated with dual and triple therapy.

Overall survival of the risk group

Data on overall survival in this group were available for 137 (29.7%) patients, with 25 (18.2%) treated with dual and 112 (81.8%) treated with triple therapy. Overall survival for patients treated with dual therapy ranged from 0 to 17 years, median 6 (3–8) years, and for those treated with triple therapy ranged from 0 to 19 years, median 4 (2–7) years. Despite the difference in median survival, overall survival was not statistically significantly different for the two types of therapy ($z = -1.535$ $p = .125$, Mann-Whitney U Test). This is confirmed by all three tests of significance (Log Rank, $p = .140$; Breslow, $p = .132$ and Tarone-

Ware, p = .105) from the Kaplan-Meier survival analysis and the resulting survival curves (Figure 4).

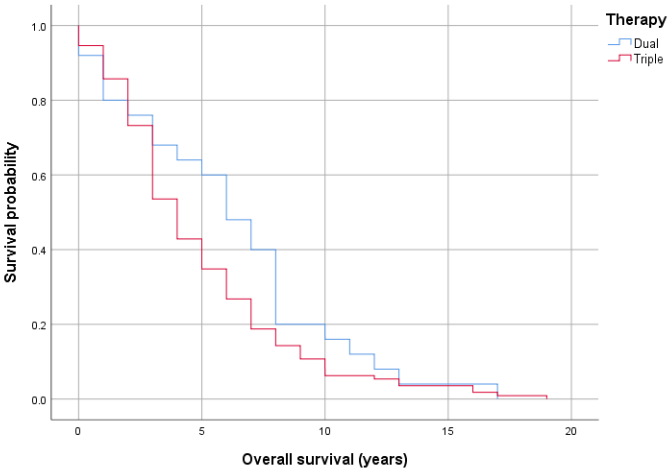

Figure 4. Overall survival of those treated with dual and triple therapy.

Cancer-specific survival of the risk group

Data on cancer survival in this group were available for 81 (17.6%) patients, with 8 (9.9%) treated with dual and 73 (90.1%) treated with triple therapy. ***Cancer survival for patients treated with dual therapy ranged from 1 to 8 years, median 4 (1.50 - 7.50) years, and for those treated with triple therapy ranged from 0 to 12 years, median 3 (2 - 4) years.*** Regardless of the difference in median cancer survival, it was not statistically significantly different for the two types of therapy (z = -.900 p = .368, Mann-Whitney U Test). This is confirmed by all three tests of significance (Log Rank, p = .247; Breslow, p = .375 and Tarone-Ware, p = .256) from the Kaplan-Meier survival analysis and the resulting survival curves (Figure 5).

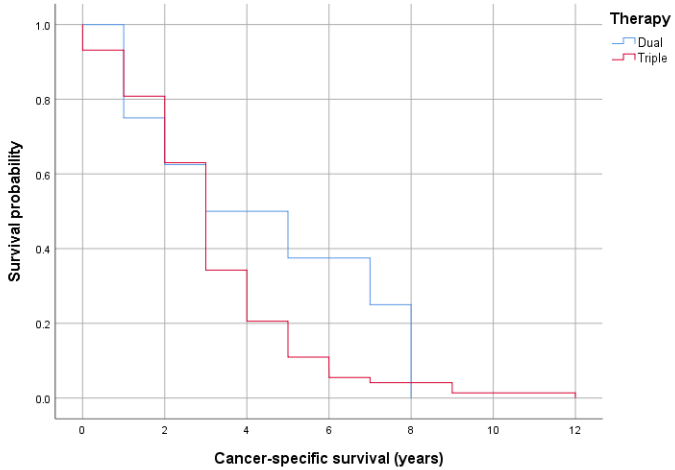

Figure 5. Cancer-specific survival of those treated with dual and triple therapy

Overall survival up to and more than 5 years

When overall survival was divided into groups up to and over 5 years, 83 (60.6%) survived ≤ 5 years, and 54 (39.4%) – > 5 years. Of all patients with survival data, 10 (7.3%) dual therapy patients and 73 (53.3%) triple therapy patients survived ≤ 5 years, and 15 (10.9%) dual therapy patients and 39 (28.5%) the patient with triple therapy survived > 5 years***. In this grouping, a statistically significant difference was found in the overall survival of those treated with double and triple therapy (z = - 2.321 p = .020, Mann-Whitney U Test). Patients with dual therapy had a lower probability of 5-year survival (OR = .356, 95%CI = .146 - .867). The probability of triple therapy patients to survive 5 years were 1.2 times that of dual therapy patients (RR = 1.218, 95%CI = 1.014 – 1.463).***

In the group with survival ≤ 5 years, the overall survival of patients with dual therapy ranged from 0 to 5 years, median 1.5 (1 – 3), and that of

patients with triple therapy from 0 to 5 years, median 3 (2 – 4) (Figure 6).

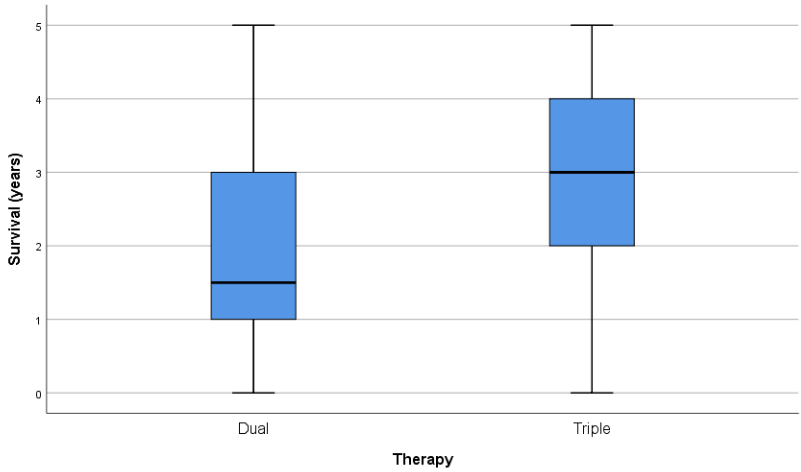

Figure 6. Descriptive statistics of overall survival ≤ 5 years in those treated with dual and triple therapy in the risk group.

Despite the apparent difference in survival in favor of triple therapy, this difference was not statistically significant (z = -1.349, p = .177, Mann-Whitney U Test). This is confirmed by all three tests of significance (Log Rank, p = .261; Breslow, p = .145 and Tarone-Ware, p = .187) from the Kaplan-Meier survival analysis and the resulting survival curves.

In the group with a survival of more than 5 years, there are 54 patients, of which 15 are with double and 39 with triple therapy. Overall survival of patients with dual therapy ranged from 6 to 17 years, median 8 (7 – 11), and that of patients with triple therapy ranged from 6 to 19 years, median 8 (7 – 8) (Figure 7).

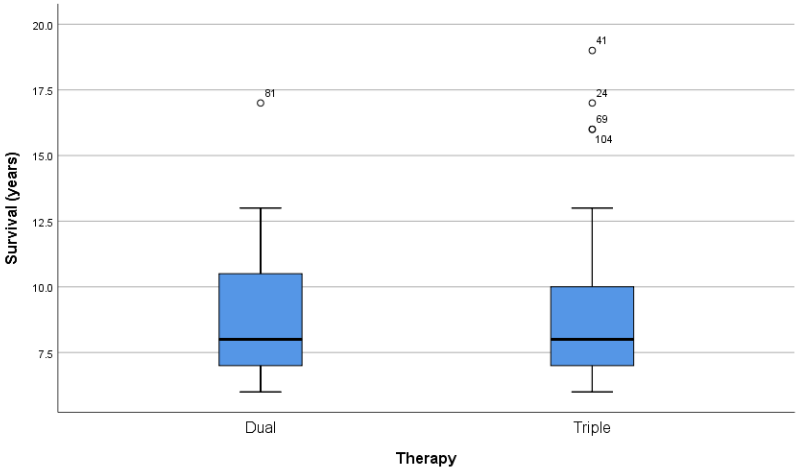

Figure 7. Descriptive statistics of overall survival > 5 years in those treated with dual and triple therapy in the risk group.

No statistically significant difference was found in the overall survival of patients treated with dual and triple therapy in the group with survival greater than 5 years (z = -.313, p = .754, Mann-Whitney U Test). This is confirmed by all three tests of reliability (Log Rank, p = .944; Breslow, p = .756 and Tarone-Ware, p = .817) from the Kaplan-Meier survival analysis and the resulting survival curves.

Cancer-specific survival up to and more than 5 years

In the group with cancer-specific survival up to 5 years inclusive, there are 70 patients, of which 5 patients had double and 65 - triple therapy. Cancer-specific survival of patients with dual therapy ranged from 0 to 5 years, median 2 (1–3), and that of patients with triple therapy from 0 to 5 years, median 3 (2–4) (Figure *8*).

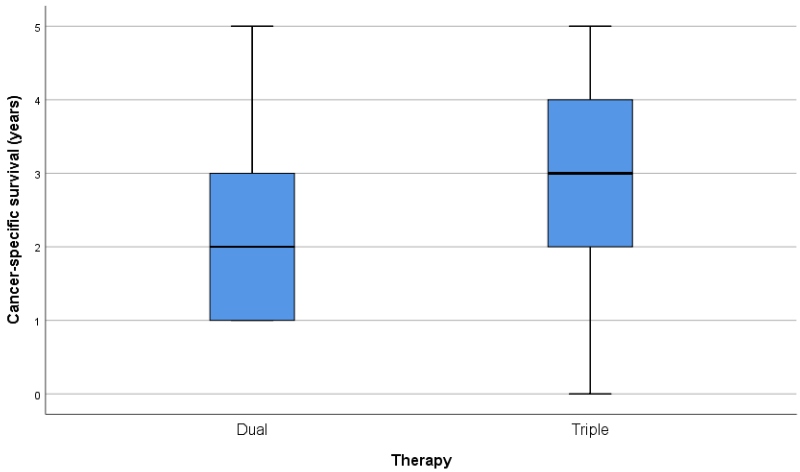

Figure 8. Descriptive statistics of cancer-specific survival ≤ 5 years in those treated with double and triple therapy in the risk group.

Despite the apparent difference in survival in favor of triple therapy, this difference was not statistically significant (z = -.561, p = .575, Mann-Whitney U Test). This is confirmed by all three tests of significance (Log Rank, p = .809; Breslow, p = .560 and Tarone-Ware, p = .649) from the Kaplan-Meier survival analysis and the resulting survival curves.

In the group with cancer survival of more than 5 years, there are 11 patients, of which 3 patients had double and 8 - triple therapy. Cancer survival of patients with dual therapy ranged from 7 to 8 years, median 8 (7–8), and that of patients with triple therapy from 6 to 9 years, median 6.5 (6–9) years.

No statistically significant difference in cancer survival over 5 years was found between those treated with dual and triple therapy (z = -.526, p = .599, Mann-Whitney U Test). This is confirmed by all three tests of reliability (Log Rank, p = .827; Breslow, p = .610 and Tarone-Ware, p

= .865) from the Kaplan-Meier survival analysis and the resulting survival curves.

Of all 137 patients who died with treatment, a total of 25 (137) patients treated with dual therapy and 112 (137) patients treated with triple therapy died from the risk group. A statistically significant relationship was found between treatment type and deaths (z = -2.411, p = .016, Mann-Whitney U Test). Dual therapy patients had a lower chance of dying (OR = .546, 95%CI = .333 – .896).

Of all 137 patients who died with treatment in the risk group, 81 (59.1%) died of cancer, of which 8 (9.9%) with dual therapy and 73 (90.1%) with triple therapy. A statistically significant association was found between treatment and dying from cancer (z = -3.606, p < .001, Mann-Whitney U Test). The probability of a patient treated with dual therapy to die from cancer was lower (OR = .266, 95%CI = .124 - .569).

7. CLINICAL PROGRESSION

Clinical progression (that is the occurrence of methastases) occurred in 46 (from 485) of the patients, with 11 (from 46) treated with double and 35 (from 46)- with triple therapy. The period without clinical progression in patients treated with dual therapy ranged from 0 to 7 years, median 2 (1 – 6) years, and in patients treated with triple therapy ranged from 0 to 6 years, median 3 (1 – 3). No statistically significant association was found between the occurrence of clinical progression and the time to occurrence of clinical progression in years (z =-.551, p = .582, Mann-Whitney U Test). This is confirmed by all three tests of significance (Log Rank, p = .089; Breslow, p = .577 and Tarone-Ware, p = .290) from the Kaplan-Meier survival analysis and the resulting survival curves.

42 (46) patients had a clinical progression-free period of less than 5 years - 8 (46) patients with double therapy and 34 (46) with triple

therapy. 4 (46) patients had a clinical progression-free period of more than 5 years - 3 (46) patients with double therapy and 1 (46) patient with triple therapy.

A statistically significant association was found between the occurrence of clinical progression and the survival period until the occurrence of clinical progression, considered in an interval below and above 5 years (z = -2.479, p = .013, Mann-Whitney U Test) . A triple therapy patient's probability of clinical progression within 5 years were higher (OR = 12.750, (95%CI = 1.168 – 139.235).

8. BIOCHEMICAL PROGRESSION

Biochemical progression occurred in 44 (485) patients, of whom 12 (44) were treated with double and 32 (44) with triple therapy. The period without biochemical progression in patients treated with dual therapy ranged from 0 to 6 years, median 1.5 (.5 – 5) years, and in patients treated with triple therapy this period ranged from 0 to 5 years, median 2 (1 – 2).

No statistically significant relationship was found between the occurrence of biochemical progression and the period without biochemical progression in years (z = -.557, p = .578, Mann-Whitney U Test). This is confirmed by all three tests of significance (Log Rank, p = .117; Breslow, p = .574 and Tarone-Ware, p = .311) from the Kaplan-Meier survival analysis and the resulting survival curves.

42 patients had a biochemical progression-free period of less than 5 years - 10 patients with double therapy and 32 patients with triple therapy. 2 (from 2) patients with double therapy and none with triple therapy had a biochemical progression-free period of more than 5 years.

A statistically significant association was found between the occurrence of biochemical progression and the survival period until the occurrence

of biochemical progression, considered at an interval below and above 5 years (z =-2.337, p = .019, Mann-Whitney U Test). The risk of a dual therapy patient experiencing biochemical progression within 5 years was lower (RR = .238, (95%CI = .139 – .409)) than that of a triple therapy patient.

9. PREDICTORS OF CANCER MORTALITY

We look at five major predictors of cancer mortality:

- ***clinical progression;***
- ***biochemical progression of PSA ;***
- ***disease stage T 3 – 3+;***
- ***GS values >7;***
- ***PSA values > 20;***

GS and disease T-stage

We consider GS in two groups – ≤7 and > 7. We consider the stages of the disease in three groups: stage T1 - T1N0M0, 145 (16.6%) patients; stage T2 – T2N0M0 and T2N1M0, 387 (44.5%) patients and stage T3-3+ – T3 and T4, 339 (38.9%) patients, of which only 2 with stage T4.

GS values > 7 have 599 (68.8%) of the patients, the remaining 272 (31.2%) patients have GS values less than 7.

Patients in T1 stage with GS > 7 are 68 (46.9%), and with GS < 7 – 77 (53.1%). In T2 stage are 256 (66.1%) patients with GS > 7 and 131 (33.8%) patients with GS < 7. In T3-3+ stage are 275 (81.1%) patients with GS > 7 and 64 (18.9%) patients with GS < 7 (Figure 9).

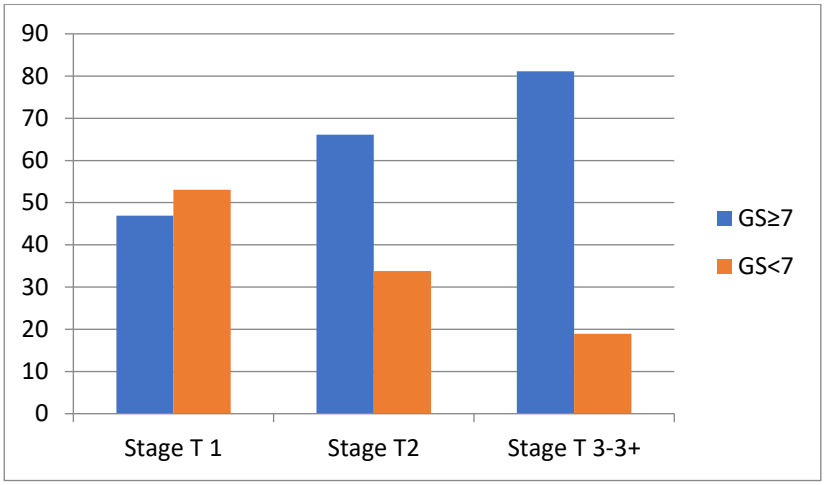

Figure 9. Distribution of patients by T-stage and GS values

The probability of a patient with GS > 7 being in stage T3 was higher than that of being in stage T1 (OR = 4.866, 95%CI = 3.182 – 7.440). The risk of a patient with GS >7 being in T3 stage was 1.7 times greater than that of a patient with GS < 7 (RR = 1.730, 95%CI = 1.444 – 2.072).

The probability of a patient with GS > 7 to be in stage T3 was higher than that of being in stage T2 (OR = 2.199, 95%CI = 1.559 – 3.102). The risk of a patient with GS > 7 being in stage T3 was 1.2 times greater than that of a patient with GS < 7 (RR = 1.226, 95%CI = 1.123 – 1.339).

The probability of a patient with GS > 7 to be in stage T2 was higher than that of being in stage T1 (OR = 2.213, 95%CI = 1.501 – 3.262). The risk of a patient with GS > 7 being in the stage T2 was 1.4 times greater than that of a patient with GS < 7 (RR = 1.411, 95%CI = 1.170 – 1.701).

When considering disease stages below T 3 and T 3 – 3+, the GS of patients in stage T 3 – 3+ ranged from 4 to 10, median value 7 (IQR =

7 - 8), and those in stage T1-2 ranged from 2 to 10, median value 7 (IQR = 6 – 7). A statistically significant association was found. Patients with GS ≥ 7 were in a higher disease stage (z = -7.456, p = .001, Mann-Whitney U Test).

The probability of a patient with GS > 7 to be in T 3 – 3+ stage was higher than that of being in T2 stage (OR = 2.758, 95%CI = 1.997 – 3.810). The risk of a patient with GS > 7 to be stage T 3 – 3+ was 1.3 times greater than that of a patient with GS < 7 (RR = 1.332, 95%CI = 1.223 – 1.451).

GS and biochemical and clinical progression

A statistically significant relationship was found between GS values and the presence of clinical progression (that is metastases) (z = -2.406, p = .016, Mann-Whitney U Test) and biochemical progression (z = -2.583, p = . 010, Mann-Whitney U Test). Patients with GS > 7 had a higher risk of clinical progression than those with GS < 7 (OR = 2.636, 95%CI = 1.164 – 5.972). The risk of a patient with metastases having GS > 7 was 2.5 times that of a patient without metastases (RR = 2.530, 95%CI = 1.146 – 5.584). Patients with GS > 7 had a higher risk of biochemical progression than those with GS < 7 (OR = 3.003, 95%CI = 1.254 – 7.191). The risk of a patient with biochemical progression to have GS > 7 is 2.9 times greater than that of a patient without biochemical progression. (RR = 2.876, 95%CI = 1.230 – 7.191).

GS and PSA

PSA values of the patients with GS > 7 ranged from 2 to 164, median value 13 (IQR = 9 – 20), and those with GS < 7 ranged from 4 to 68, median value 10 (IQR = 8 – 15). Patients with GS > 7 had higher PSA values (z = -4.557, p < .001, Mann-Whitney U Test). The chance of a

patient with PSA >20 to have GS >7 was greater (OR = 1.992, 95%CI = 1.343 – 2.954).

After using logistic regression with available data, patients with clinical and biochemical progression were found to have the highest risk of dying from cancer, followed by T stage 3 – 3+, GS >7 and PSA >20.

Single rating of the major predictors of cancer mortality

For a single assessment of the considered factors, the probability of dying from cancer (odds ratio) was used.

The probability of a patient with clinical progression to die from cancer was higher (OR = 104.590, 95%CI = 14.090 – 776.349). The risk of a patient with metastases to die from cancer was 61 times higher than that of a patient without metastases (RR = 61.181, 95%CI = 8.565 – 437.037). Validity of the model 58.2%.

The probability of a patient with biochemical progression to die from cancer was higher (OR 96.667, 95%CI = 13.016 – 717.921). The risk of a patient with biochemical progression to die from cancer was 58 times higher than that of a patient without PSA progression (RR = 58.400, 95%CI = 8.565 – 437.037). Validity of the model 74.5%.

The probability of a T 3 and 3+ patient to die from cancer was higher (OR = 5.042, 95%CI = 2.930 – 8.678). The risk of a patient in stage T3 – 3+ to die from cancer was 2.4 times higher than that of a patient in a lower stage (RR = 2.424, 95%CI = 1.790 – 3.284). Validity of the model 69.7%.

The probability of a patient with GS >7 to die from cancer was higher (OR = 2.398, 95%CI = 1.412 – 4.071). The risk of a patient with GS >7 to die from cancer was 2 times higher than that of a patient with

GS < 7 (RR = 2.195, 95%CI = 1.349 – 3.571). Validity of the model 87.9%.

The probability of a patient with PSA > 20 to die from cancer was higher (OR = 1.930, 95%CI = 1.231 – 3.025). The risk of a patient with PSA > 20 to die from cancer was 1.6 times higher than that of a patient with PSA ≤ 20 (RR = 1.638, 95%CI = 1.192 – 2.250). Validity of the model 87.9%.

The ORs are plotted on Figure 10.

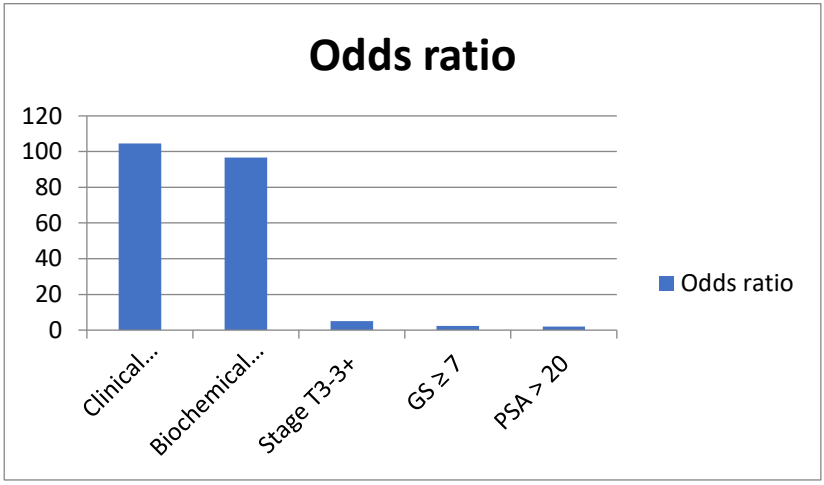

Figure 10. ORs for the various risk factors for dying from cancer presented as unit estimates.

Multiple scoring models

The model includes the presence of clinical and biochemical progression (table 2). The model has an accuracy of 93%.

Table 2. Variables in the Equation

		B	SE	Wald	df	Sig.	Exp(B)	95% CI for EXP(B) Lower	Upper
Step 1 [a]	Clinical progress-ion	3.626	.880	16,970	1	.000	37,570	6.692	210.919
	Biochem. progress-ion	2.861	.940	9.254	1	.002	17.472	2,766	110.351
	Constant	-3.947	.939	17,659	1	.000	.019		

a. Variable(s) entered on step 1: Clinical progression, Biochemical progression.

Although the parameter values are lower, the model confirms the independent estimates. It can be assumed that a higher probability of dying from prostate cancer carries the presence of clinical progression (metastases), (OR = 37.570, 95%CI = 6.692 – 210.919), followed by the presence of biochemical progression (OR = 17.472, 95%CI = 2.766 – 110.351).

To further evaluate the predictors of dying from cancer and to determine which predictor was better, we used ROC curve analysis with categorical predictors. The presence of clinical progression has a higher predictive value. Table 3 presents the area under the curves for each of the considered parameters and the statistical significance of each of them.

Table 3. Area under the ROC curves for each of the considered parameters and the statistical significance of each of them.

Test Result Variable(s)	Area	Std. Error [a]	Asymptotic Sig. [b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Cl. progression	.711	.034	.000	.645	.777
Biochem. progression	.701	.034	.000	.634	.767

a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

The model including stage T 3 – 3+, GS > 7 and PSA >20 as predictors, demonstrated a validity of 87.8% (table 4).

Table 4. Variables in the Equation

		B	SE	Wald	df	Sig.	Exp(B)	95% CI for EXP(B)	
								Lower	Upper
Step 1 [a]	TNM 3 - 3+	1.131	.229	24.372	1	.000	3.098	1.978	4.854
	GS≥7	.609	.280	4.739	1	.029	1.839	1.063	3.181
	PSA > 20	.584	.252	5.379	1	.020	1.792	1.095	2.935
	Constant	.794	.227	12.201	1	.000	2.213		

a. Variable(s) entered on step 1: TNM 3 - 3+, GS > 7, PSA > 20.

Although the OR values for the parameters included in the model were lower, the model confirmed the independent estimates. The highest probability of dying from prostate cancer carries the presence of disease stage T3 - 3+ (OR = 3.098, 95%CI = 1.978 – 4.854), followed by GS >7 and PSA >20.

These results are also confirmed by the Rock curve analysis. The presence of clinical progression has a higher effect. Table 5 presents the area under the curves for each of the considered parameters and the statistical significance of the analysis for each of them. The ROC curves are presented in Figure 11.

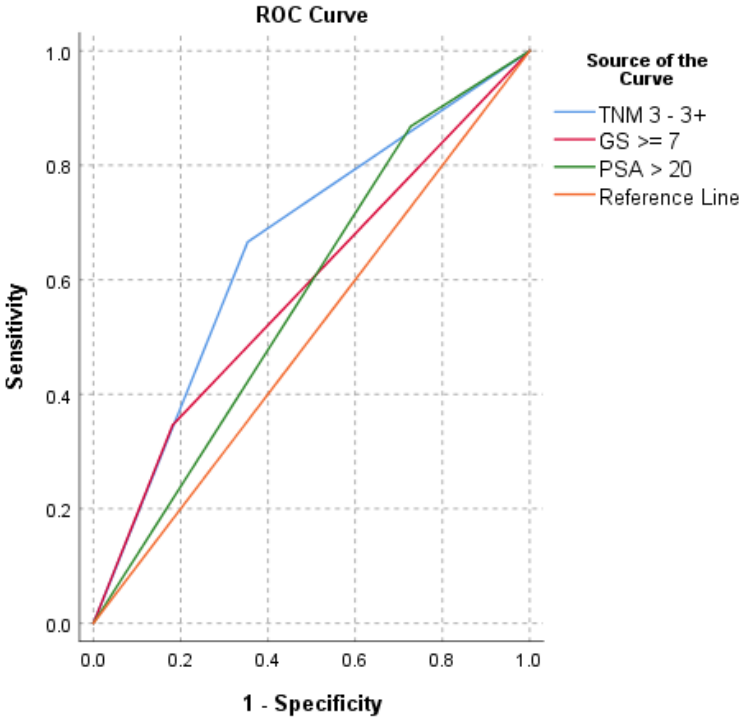

Figure 11. ROC curves of performance of T 3 – 3+, GS > 7 and PSA>20 for dying from prostate cancer

Table 5. Area under the ROC curves for each of the considered parameters and the statistical significance of each of them.

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval Lower Bound	Upper Bound
TNM 3 - 3+	.656	.030	.000	.598	.714
GS > 7	.582	.029	.004	.526	.638
PSA > 20	.570	.033	.031	.507	.634

a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

Figure 12. presents a plot of model quality showing the lower bound of the confidence interval for each of the predictors in the model. All three values are above 0.5, which suggests a good model. In this analysis again, a more serious predictor is disease stage T 3 – 3+, and the weakest – PSA values.

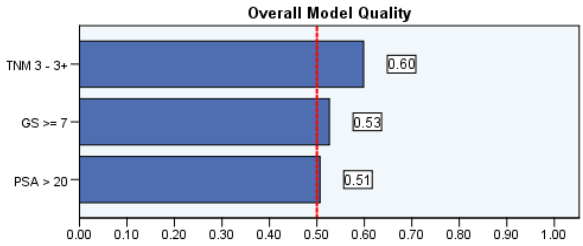

Figure 12. A plot of model quality

10. OVERALL SURVIVAL UNDER 5 YEARS AND OVER 5 YEARS

The probability of a patient to die from cancer up to and including 5 years are higher than not dying from cancer (OR = 22.258, 95%CI = 11.238 – 44.082)

The probability of a patient to die from cancer after more than 5 years were much lower than not dying from cancer (OR = .045, 95%CI = .023 – .089).

The risk of a patient to die from cancer within 5 years inclusive is 3.8 times greater than that of dying after more than 5 years (RR = 3.834, 95%CI = 2.814 – 5.225).

11. MULTIMODAL THERAPY AND ITS RELATIONSHIP TO CANCER - SPECIFIC SURVIVAL

A statistically significant relationship was found between the type of therapy and survival up to 5 years inclusive, (z = -2.815, p = .005, Mann-Whitney U Test). The probability of a patient with triple therapy to die from cancer up to and including 5 years was higher (OR = 5.500, 95%CI = 1.549 – 19.527). This probability for dual therapy patients was lower (OR = .182, 95%CI = .051 – .646)

No statistically significant relationship was found between the type of therapy and survival beyond 5 years (z = -.503, p = .615, Mann-Whitney U Test).

12. CLINICAL PROGRESSION /METASTASES/ UP TO 5 YEARS AND OVER 5 YEARS

A statistically significant association was found between the presence of metastases and the survival less than and more than 5 years (z = -2.880, p = .004, Mann-Whitney U Test). The probability of a patient with metastases to live <5 years was greater than that of a patient without metastases (OR = 2.690, 95%CI = 1.352 – 5.354). Accordingly, the chance of a patient with metastases to live >5 years was lower (OR = .372, 95%CI = .187 – .740). The probability of a patient with metastases to live < 5 years is 1.5 times greater than that of living more than 5 years (RR = 1.526, 95%CI = 1.191 – 1.954).

13. BIOCHEMICAL PROGRESSION UP TO 5 YEARS AND OVER 5 YEARS

A statistically significant association was found between the presence of biochemical progression and the survival period less than and more than 5 years (z = -2.594, p = .009, Mann-Whitney U Test). The probability of a patient with biochemical progression to live <5 years was greater than that of a patient without biochemical progression (OR = 2.464, 95%CI = 1.231 – 4.931). Accordingly, the chance of a patient with biochemical progression to live >5 years was lower (OR = .406, 95%CI = .203 – .812). The risk of a patient with biochemical progression to live < 5 years was 1.7 times higher than that of living more than 5 years (RR – 1.669, 95%CI = 1.066 – 2.611).

14. TNM STAGE AND SURVIVAL UP TO 5 YEARS AND OVER 5 YEARS

A statistically significant relationship was found between disease stage and survival less than and more than 5 years ($z = -4.621$, $p < .001$, Mann-Whitney U Test).

The probability of a patient in stage T 2 to survive >5 years was higher than that of a patient in stage T 3 – 3+ (OR = 3.386, 95%CI = 2.003 – 5.724). The probability of a T2 patient to survive more than 5 years was 1.7 times higher than that of surviving less than 5 years (RR = 1.676, 95%CI = 1.330 – 2.113).

The probability of a T3 – 3+ patient to survive more than 5 years were lower (OR = .295, 95%CI = .175 – .499) than a T 1 - 2 patient. The risk, a stage T 3 – 3+ patient to live <5 years was 1.8 times greater than surviving >5 years (RR = 1.803, 95%CI = 1.400 – 2.322).

15. PSA AND SURVIVAL UP TO 5 YEARS AND ABOVE 5 YEARS

The probability of a patient with PSA > 20 to live <5 years was higher than that of a patient with PSA ≤ 20 (OR = 2.189, 95%CI = 1.183 – 4.049). The risk of a patient with PSA > 20 to live < 5 years was 1.4 times greater than that of surviving more than 5 years (RR = 1.425, 95%CI = 1.110 – 1.828).

The risk of a patient with PSA ≤ 20 to survive more than 5 years was 1.5 times greater than that of surviving less than 5 years (RR = 1.536, 95%CI = 1.057 – 2.233).

CONCLUSIONS:

1. ***The risk of a patient in the risk group to die from cancer is 1.8 times higher than that of a patient in the control group. This is also confirmed by the Kaplan-Meier survival analysis and the resulting survival curves. Statistical significance between curves was confirmed by the three significance tests.***
2. ***The chance of patients with dual therapy to survive 5 years is lower. The chance of triple therapy patients surviving 5 years inclusively is 1.2 times greater than that of double therapy patients.***
3. ***No statistically significant difference was found in the time to biochemical progression in the first 5 years for patients in both groups.***
4. ***Patients in the risk group have a 1.5 times higher risk of clinical progression (occurrence of metastases) than patients in the control group.***
5. ***A statistically significant association was found between the occurrence of biochemical progression and the survival period until the occurrence of biochemical progression, considered in an interval below and above 5 years. The risk of a dual therapy patient experiencing biochemical progression within 5 years was lower than that of a triple therapy patient.***
6. ***A statistically significant association was found between the occurrence of clinical progression and the survival period until the occurrence of clinical progression, considered in an interval below and above 5 years. A patient with triple therapy has a higher chance of clinical progression within 5 years.***
7. ***The following prognostic criteria for survival were established:***

7.1 A patient with clinical progression is 61 times more likely to die from cancer than a patient without metastases

7.2 A patient with biochemical progression is 58 times more likely to die of cancer than a patient without PSA progression.

7.3 The chance that a patient in stage T 3 and 3+ will die from cancer is 2.4 times higher than that of a patient in a lower stage.

7.4 The chance of a patient with GS > 7 to die from cancer is 2 times higher than that of a patient with GS < 7.

7.5 A patient with PSA > 20 is 1.6 times more likely to die of cancer than a patient with PSA ≤ 20.

CONTRIBUTIONS

1. A retrospective study was carried out of 871 patients operated for prostate cancer at the Urological Clinic of the "St. Anna" Hospital.
2. A statistical analysis and processing of the obtained results was performed.
3. The multimodal treatment of high-risk prostate cancer is analyzed.
4. Prognostic criteria for cancer-specific survival of high-risk prostate cancer have been developed.
5. It has been proven that patients with high-risk prostate cancer need to be treated multimodally.
6. It has been proven that patients with high-risk prostate cancer can and should undergo radical prostatectomy, in the framework of multimodal treatment, with very good cancer-specific survival.
7. The new strategy proved that radical prostatectomy for high-risk or locally advanced prostate cancer should be performed with the aim of accurate staging and reduction of tumor burden as the operation is part of multimodal therapy.

PUBLICATIONS RELATED TO THE TOPIC

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4. **Ganev T** , Dulgerov V, Abushev I, Nankova M, Genova M. Primary adenocarcinoma of the urethra in a woman. MD. 2017;14(4):80–1.

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