“ANALYSIS OF THE QUALITY OF LIFE OF PROSTATE CANCER PATIENTS AFTER LDR BRACHYTHERAPY USING EORTC QLQ-30 AND EORTC QLQ-25 QUESTIONNAIRES”

Kalem, Sophia Katharina

Master's thesis / Diplomski rad

2023

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Rijeka, Faculty of Medicine / Sveučilište u Rijeci, Medicinski fakultet**

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:932258

UNIVERSITY OF RIJEKA

FACULTY OF MEDICINE

INTEGRATED UNDERGRADUATE AND GRADUATE UNIVERSITY STUDY OF MEDICINE IN ENGLISH

Sophia Katharina Kalem

"ANALYSIS OF THE QUALITY OF LIFE OF PROSTATE CANCER PATIENTS AFTER LDR BRACHYTHERAPY USING EORTC QLQ-30 AND EORTC QLQ-25 QUESTIONNAIRES"

GRADUATION THESIS

Rijeka, 2023

UNIVERSITY OF RIJEKA

FACULTY OF MEDICINE

INTEGRATED UNDERGRADUATE AND GRADUATE UNIVERSITY STUDY OF MEDICINE IN ENGLISH

Sophia Katharina Kalem

"ANALYSIS OF THE QUALITY OF LIFE OF PROSTATE CANCER PATIENTS AFTER LDR BRACHYTHERAPY USING EORTC QLQ-30 AND EORTC QLQ-25 QUESTIONNAIRES"

GRADUATION THESIS

Rijeka, 2023

Thesis Mentor: Assoc. Prof. Josip Španjol, MD, PhD

Co Mentor: Assist. Prof. Antun Geršković, MD, PhD

The graduation thesis was graded on _____date_____in ___Rijeka
before the Committee composed of the following members:

1. Assoc. Prof. Romano Oguić, MD, PhD (Committee Chair)
2. Assoc. Prof. Dean Markić, MD, PhD
3. Assist. Prof. Stanislav Sotošek, MD, PhD

The graduation thesis contains 35 pages, 4 figures, 10 tables, 37 references.

Table of Contents

Abbreviations

CT: Computer Tomography

DNA: Deoxyribonucleic Acid

EBRT: External Beam Radiation Therapy

EORTC: European Organization For Research And Treatment Of Cancer

EPIC: European Prospective Investigation into Cancer and Nutrition

HDR: High Dose Rate

ISUP: International Society of Urological Pathology

LDR: Low Dose Rate

MRI: Magnetic resonance imaging

PET: Positron emission tomography

PRO: Patient Reported Outcome

PSA: Prostate-specific antigen

PSMA: Prostate-specific membrane antigen

QLQ: Quality of Life Questionnaire

RPE: Radical Prostatectomy

TNM: Tumor size; (lymph) Nodes; Metastasis

UICC: Union for International Cancer Control

1. Introduction

1.1. Epidemiology

Prostate cancer ranks amongst the most common malignancies worldwide, with 1,414,259 new cases diagnosed in 2020. It made up 7.8% of all cancer cases worldwide that year. In men, prostate cancer is the second most common malignancy, just surpassed by lung cancer, and makes up over 15% of all cancer cases for men (1).

In 2019 the German Center for Cancer register data (Zentrum für Krebsregisterdaten) counted over 68 thousand new cases and over 15 thousand deaths caused by prostate cancer (2).

In Germany in 2017, prostate malignancies were the second most common cause of death caused by malignancies in men and made up 22,7% of all newly diagnosed malignant diseases (3).

The increased number of cases has led to increased interest in the treatment outcomes of this disease. Depending on the socioeconomic status and demographics of a country, the pattern of prostate cancer distribution varies. While in Africa, the incidence is relatively low, with an incidence of 13,9 per 100.000 inhabitants, in Europe, it is almost ten times as high, with 130.9 per 100.000. Similar numbers are obtained when comparing the incidence rate in Asia with the one in Northern America. Asian men have an incidence much closer to African men while north American men have almost the same incidence as European men. The incidence in Latin America ranks between the Western countries and Asia and Africa.

Interesting to note is, that the incidence is not proportional to the mortality rate. While Africa has the highest mortality rate, Northern America and Asia have low numbers, with Europe ranking closely behind them (4).

Similar to other malignant diseases, the risk of developing prostate cancer increases with age. From 1970 to 2002, there was a significant increase in the age-standardized incidence of prostate cancer cases among German men. In Germany, the rate of new diagnoses and the death rate of prostate cancer show an anti-proportional relationship. In 1980 the incidence was below 20.000 cases and 10.000 deaths. The incidence showed a continuous increase over the years and was just below 60.000 in 2005, but the mortality stayed around 10.000 for most of the time, showing a slight decrease after 2000 (5).

In 2016 out of a total of 58.780 patients with prostate cancer, 14.417 deaths were recorded. The death rate is decreasing continuously. While the number of newly diagnosed patients is growing, the death rate has been declining since 2007 and is steady for now.

This decrease in deaths can also be observed in other industrial countries and correlates with the usage of prostate specific antigen (PSA), which is a tool for early diagnostics of prostate diseases. Today, five-year life expectancy after a diagnosis is approximately 89% which is very high compared to other malignancies, and about two-thirds of cases can be diagnosed at an early stage.

The absolute number of deaths caused by prostate cancer today is higher than in the 1980s, but the death rate decreased significantly. This is caused by demographic changes, especially in developed countries where good healthcare allows people to reach older age. Furthermore, black African males are affected more often than European males, while Asian men seem to be affected less often than Europeans (6).

Prostate cancer is a disease that plays an important role today and will most likely continue to do so in the foreseeable future.

1.2. Etiology

The exact etiology of prostate cancer is not known yet, but some risk factors such as older age, smoking, positive family history, chronic inflammation, and obesity have been identified. The most prominent correlation is found for older age, positive family anamnesis, and testosterone (7).

It is evident that prostate cancer positively correlates with the age of the patient since cases usually do not arise before the age of 50. A 35-year-old male is at risk of 0,1% to develop prostate cancer within the next ten years, while this risk lies at around 6% for a man who is 75 years old (2).

A Swedish study supports the role of a positive family history as a risk factor for prostate cancer. The research included over 3.9 million men. It was found that genetics, as well as age, may play an essential role in prostate cancer development. Prostate malignancies in young patients were tested genetically and results showed an increase of specific inheritable genes which are believed to be a predisposing factor to develop prostate cancer.

This study confirmed that the risk of prostate cancer is higher in those patients whose close relatives were also diagnosed with prostate cancer (8,9).

Further evidence that genetic factors play a role in the etiology of prostate cancer is found when comparing Asian, European, and African population groups. Prostate cancer has a significantly higher incidence in African men than in Asian or Caucasian men. In East Asian countries (China and Japan), prostate cancer is a less common problem than in North America and Europe, where it is a prevalent malignancy, as established earlier (10).

But even amongst European countries, there is a significant difference in incidence. Men from northern parts of Europe are more likely to develop the disease than the ones from the Mediterranean area. German men have a medium risk which correlates with the geographic location of the country in the middle of Europe (11).

It is not yet established if lifestyle and nutritional habits significantly influence the pathogenesis of prostate malignancies. Some evidence suggests that a diet rich in animal fats and low in fiber favors the development of prostate cancer. In comparison, patients who consume a diet rich in vegetables, soy, and fiber may be at lower risk for prostate cancer. As stated earlier, obesity is a known risk factor for developing prostate malignancies. Therefore, a lack of exercise and poor diet are believed to be contributing factors since they are closely associated with obesity (12).

1.3 Staging

TNM staging is used to determine the stage and therefore therapeutic options for prostate cancer patients. This system is not prostate-specific but used for various malignancies.

It is important to have consistency and standardized values in diagnostics, so a patient can receive adequate care according to guidelines for his specific form of cancer. In the TNM system, each letter is accompanied by a number or additional letter to make staging as precise as possible (7).

TNM explanation

Table 1 (Source 7)

	T: Tumor size

TNM	**N: involved lymph nodes**
	M: metastasis

Table 2 **UICC** (Union for International Cancer Control) staging is often used in addition to TNM classification
Table 2 (Source 7)

I: T1-T2a N0 M0
II: T2b-T2c N0 M0
III: T3 N0 M0
IV: T4 N0 M0; T1-T4 N0 M1

1.4. Gleason Score

The Gleason Score is a prostate-specific staging tool based on histopathological findings of tissue samples obtained by a prostate biopsy. It is named after Pathologist Donald F. Gleason. In addition to TNM classification and PSA value, Gleason score is a prognostic tool for prostate cancer. Values range from 2 (1+1); to 10 (5+5), where two is the lowest possible number, and ten is the highest. In practice the lowest assigned Gleason score is usually 3 because grades 1 and 2 pose virtually no risk. Prostate cancer with a higher Gleason score has less favorable prognosis. The higher the Gleason score, the more malignant the tumor and the chance of recurrence. A score of 7 is considered medium risk, but according to the International Society of Urological Pathology (ISUP), a score of 7 (4+3) yields a higher risk than a score of 7 (3+4). The first number (1-5) is assigned to the predominant cell pattern in the biopsy, and the second number (1-5) is either to the second most predominant cell pattern or the most malignant. In a homogenous tumor, both numbers will have the same value, e.g., 4+4, and any deviation of both numbers indicates tumor heterogeneity, e.g., 5+2.

Gleason score 6 and all numbers below represents slow growing prostate cancer with low malignant potential. High-risk tumors, with a Gleason score of 8-10, are fast-growing tumors with a high potential to grow invasively into surrounding tissues and spread to other organs such as lymph nodes and bones. Depending on the TNM staging, these tumors can cause severe symptoms which can significantly impact a patient's quality of life (13).

1.5. Risk groups

The American doctor d`Amico established a classification of risk groups into low, intermediate, and high-risk patients. This classification consists of TNM status, PSA and Gleason score (14).

EAU risk groups for biochemical recurrence of localized and locally advanced prostate cancer

Table 3 (Source 14)

Risk Group	T category	PSA (ng/ml)	Gleason Score
Low risk	cT1-T2a	< 10	6
Intermediate risk	cT2b	10 – 20	7
High risk localized	cT2c	>20	>7
High risk locally advanced	cT3 – 4 or cN+**	any	

GS = Gleason score
ISUP=International Society of Urological Pathology
*Based on digital rectal examination
**Based on CT/bone scan

1.6. Diagnostics

In several European countries, including Germany, there is a screening program for the early detection of prostate cancer. It is recommended for every man over the age of 45 to visit urologist. This appointment is covered by insurance. The screening appointment involves a digital rectal examination, palpation of inguinal lymph nodes and questions about prostate specific symptoms as well as overall health. This method is quick, easy and cost efficient. If

the digital rectal examination yields a positive result further testing such as PSA Prostate cancer can be detected at an early stage with relatively little expenditure using PSA as a marker. Increased PSA values can be found in the blood in several prostate diseases. A PSA test is not routinely done for screening but after screening yields a positive outcome or prostate cancer is suspected otherwise. While it is a prostate-specific marker, it is not specific to prostate malignancies and can also be elevated in other conditions, such as prostatitis. Nevertheless, it has been used for early diagnostics and as a follow-up parameter for around 40 years in Germany.

PSA alone cannot be used to diagnose prostate cancer definitively, but a European study (ERSPC) which was conducted over 13 years, found a decrease in the death rate of 21% in men that were diagnosed early using PSA. The values are age specific and can differ between individuals, but 4 ng/ml is considered the cutoff point, which is still sensible for diagnosis.

In Germany, digital rectal exams are used as a screening tool for men over the age of 45; this method is highly specific but less sensitive (15).

If the digital rectal examination generates a positive result, transrectal ultrasound can be used as an addition but it is not a primary diagnostic tool. The gold standard for prostate cancer detection is transperineal fusion biopsy. Usually 10 to twelve tissue samples are taken for histopathological examination.Because of the anatomic relation close to the rectum, antibiotic prophylaxis is indicated when taking prostate biopsies. Before samples are taken, it is necessary to do a multiparametric MRI (mpMRI) to get a clear understanding of where the areas with malignant changes are located in the prostate. German guideline does also suggest giving the patient enough time and information so he can make an informed decision if he wants to undergo the procedure to get biopsies.

Further imaging is usually done after the biopsy confirmed prostate cancer diagnosis to evaluate local and or distant spreading to bones, lymph nodes, and other organs (7). Possible choices include CT scanning, MRI, and bone scintigraphy. A relatively new but very efficient imaging method to detect metastasis or local tumor foci is a prostate specific membrane antigen PET CT (PSMA-PET/CT). It can be used to diagnose or exclude tumor recurrence after surgery or radiation as well as planning and follow up for specific treatments. Prostate cancer cells express high numbers of PSMA while on healthy prostate tissue it is

expressed in lower doses or not at all. Therefore PSMA is especially helpful to distinguish between healthy and pathological tissue and is visualized in a PSMA-PET/CT.
Generally imaging techniques are chosen depending on a patient's age, overall health, and potential therapeutic options (16).

1.7. Basics of Mechanism of radiation in Tissue

The cell organelle that radiation therapy aims at is the nucleus because the DNA is located inside. DNA carries genetic information and is the key point for regulating a cell's metabolic functions and division. DNA damage is responsible for any cell damage in healthy tissues, where it is not the desired effect, but also in tumor cells, where damaging DNA is the desired effect that ensures successful treatment. Radiation can cause damage to bases, to a single strand, or can destroy the double helix completely, which is the most severe effect it can have on a cell. Cell death via radiation is achieved in different ways; a cell can either lose its ability to divide when vital mechanisms of the cell cycle are damaged (mitotic cell death), or a cell's natural programmed cell death can be activated (apoptosis). Tumor cells divide uncontrollably, which is one of the main problems for patients. Since then, the tumor can rapidly grow and cause more severe symptoms. But they are also the most sensitive to radiation damage during the process of cell division (mitosis) (17).

1.8. History of brachytherapy

After the discovery of radioactivity by Antonie-Henri Becquerel in 1896, the interest in using it for medical purposes grew rapidly. The first use of radioactive material as a treatment was mainly to treat tuberculosis and skin diseases. After the first use of radiation within the uterine cavity in 1902, the idea of implanting radioactive material to treat local tumors soon arose. Alexander Graham Bell proposed to use radium sources encapsulated by the glass and insert them directly into a tumor. This very early form of brachytherapy was predominantly used to treat gynecological cancers with radium.

But in 1911, the first recorded treatment of prostate cancer using radium was recorded. Contrary to the transperineal approach today, in these early stages, a radium source was guided to the prostate via a urethral catheter.

Artificial radiation sources such as iridium-192 were first used in the early 1950s. CT Guided implantation was developed around fifteen years after the first Iodine-125 seeds were used in 1965.

Until the 1980s, Brachytherapy, which was primarily used to treat gynecological cancers, began to gain importance as a therapy for other tumors such as prostate and breast cancer. After this revision of indications for Brachytherapy, the first sonography-guided transperineal seed implantation was performed in 1981 by Bertermann and Brix.

The sonography-guided and CT-controlled seed implantation therapy for prostate cancer, which we today refer to as Brachytherapy, was developed in the early 2000s (17).

1.9. Active Surveillance and watchful waiting

For patients who are at an early stage of their disease, active surveillance may be an alternative to an operation or radiotherapy. Active surveillance includes regular checkups where PSA values are controlled, and digital rectal exams are performed to note any changes in tumor characteristics. Patients may choose to switch from this to a treatment method at any point. This method aims to avoid any side effects from treatment, such as urinary incontinence and erectile dysfunction while being able to note any changes which require treatment immediately. Unfortunately, not every patient is a candidate for active surveillance because age, tumor staging, and comorbidities have to be considered.

Suitable tumor characteristics are a Gleason score of 6 or lower, PSA values of 10ng/ml or lower, and a stage cT1 or cT2a, as well as only two out of twelve tumor-positive biopsies.

During the first two years of active surveillance, digital rectal exams and PSA value control is performed every three months, and if parameters are stable, the time between control exams can be increased to six months. During the first three years, control biopsies are required every twelve to eighteen months; if findings stay consistent, a control biopsy will be done every three years.

Many patients appreciate the advantages of this method because it poses extremely low risks for side effects and is less invasive than traditional therapeutic options. Because of the frequent control appointments, the chance of missing an aggressive course of the disease is also minimal. But not every suitable patient will choose this method over treatment because it can cause a strain on their mental well-being to know they have cancer that is not actively treated. Patient compliance is crucial for a successful outcome since adequate care can only be guaranteed if a patient adheres to the scheduled appointments. To decide on this method, individual consultation and patient education are necessary.

Watchful waiting cannot be used as synonymous with active surveillance because it does not require regular checkups and close monitoring. This method leans into palliative care since the main goal is to treat symptoms of the disease because a cure cannot be achieved. Therefore, the target patient population for this method differs from the one for active surveillance. Patients who will choose watchful waiting usually have life-limiting comorbidities such as cardiovascular disease or a late-stage prostate cancer diagnosis (7).

1.10. Psychological effects of cancer and prostate cancer specifically

Psychological Effects of Cancer, specifically prostate cancer

Being diagnosed with a malignant disease can cause feelings of anxiety and depression in a patient. Patients are usually afraid of a fundamental life changes due to the diagnosis of a malignant disease or the therapy. Fears include not only the fear of dying but also fear of being alone with their disease because it may cause social isolation, being afraid of therapy, side effects, and pain. Waiting for further diagnostics, treatment appointments, and results can be incredibly daunting and may result in psychosomatic symptoms such as insomnia, palpitations, gastrointestinal symptoms, and extreme fatigue.

Besides general anxiety and specific fears, another primary symptom of being diagnosed with a malignancy is depression. Depression can occur at different stages of the disease. The first stage where patients may experience depression is during the initial diagnosis, when a patient realizes that he has cancer. But not only the diagnosis itself can cause depression; surgery can also cause depression, for example, when a scar is left, and the body image is permanently

altered. Another trigger can be the disease or treatment interfering with life plans or a progression of the disease despite adequate treatment.

It is essential to distinguish between transient symptoms, which can overlap with depression and major depression. Temporary symptoms of fatigue, tiredness, despair, and sadness are a normal reaction of any patient who faces their disease and understands the consequences. Major depression is a disease that interferes with a patients day to day life and can be diagnosed using the DSM-5 manual (18).

WHO defines Quality of Life as an ”individual's perception of their position in life in the context of the culture and value systems in which they live and concerning their goals, expectations, standards, and concerns” (19).

Feelings of anxiety and Depression can challenge the above-mentioned perception of a patient's position in life since this position inevitably changes to a more vulnerable one, and the outcome of the situation is uncertain.

Prostate cancer specifically can interfere with a patient's perceived position in life since it comes with challenges concerning their sexuality, specifically erectile dysfunction. Their expectation of being able to achieve a spontaneous erection or an erection at all might not be met after treatment or disease progression. Erectile dysfunction, in return, might lead to depression and problems in their relationship. They may fear losing part of their male identity because they can no longer engage in penetrative intercourse (20).

Another major stressor that can interfere with a patient's quality of life and mental well-being is urinary incontinence. It may be even more distressing to patients than erectile dysfunction (21).

Some men might withdraw from going out in public and having social contacts because they are afraid of leaking urine uncontrollably and feel embarrassed to wear a diaper.

It is important to distinguish this social isolation from social isolation caused by major depression to ensure adequate treatment for the patient (20).

1.11. Therapeutic Options Overview

For any not a candidate for active surveillance or watchful waiting, there are different therapeutic options for any tumor stage. Interventional treatment options include surgery, radiotherapy, hormonal treatment, chemotherapy and immunotherapy.

Treatment will be chosen depending on the tumor stage and the patient's condition. If a patient's life expectancy is ten years or longer, he is a candidate for a therapy with curative intent. Curative prostate cancer therapies include radical prostatectomy, which can be done via retropubic open approach or laparoscopic and robotic-assisted approach, and radiotherapy Radiation therapy is considered a curative approach if there is no evidence of metastasis. Depending on tumor stage either Low Dose Rate Brachytherapy or High Dose Rate Brachytherapy are methods of choice. For later-stage diseases with bone metastasis, radiation is a palliative approach to increase life quality and decrease pain (7).

1.12. Radical prostatectomy

Complete resection of the prostate is a primary form of treatment for prostate cancer without metastases. This treatment aims to have no remaining prostate tissue left after the operation while avoiding urinary incontinence and preserving erectile function. Furthermore, compared to watchful waiting, a radical prostatectomy significantly decreases the risk of progression, metastasis, and mortality of patients who meet the following criteria; local tumor (T1b-T2 N0 M0), PSA 50 ng/ml and a general life expectancy of ten years or more (7).

The three different surgical techniques that are commonly used today are robotic-assisted prostatectomy, laparoscopic prostatecomy, and retropubic opet prostatectomy.

An approach is chosen depending on the surgeon`s specific skill set and the availability of instruments and assistants. An open approach has been the method of choice over decades, but today the laparoscopic and robotic-assisted approach is most widely used. Trends show that the robot-assisted technique may become standard practice in the near future in Germany.

Post-operative complications after radical prostatectomy are generally low, with 21,6% independent of the technique that has been used. Common early post-operative complications are urinary tract infections and thrombotic events, which are non-surgical complications,

whereas late complications such as urinary incontinence, erectile dysfunction, and vesico-urethral anastomosis are direct complications of surgery (22).

Compared to an open approach, laparoscopic and robot-assisted prstatectomy decrease the trauma caused by accessing the prostate, blood loss and post-operative pain. The minimally invasive approaches also offer a less visible scar. Compared to laparoscopic procedures, the upsides of the robot-assisted approach are 3D visualization of the operating field and automatic compensation of any tremors. Advantages for the surgeon include a less straining position while operating and a relatively steep learning curve. In the US, this approach dominates with 80%, while 20% of cases are approached open, and laparoscopic radical prostatectomies are at less than 1% (23).

1.13. Basics of Brachytherapy

To perform a Brachytherapy (seed implantation) according to German and international standards, the institution where it is performed must have a certificate enabling them to work with radioactive materials. Seed implantation requires a multidisciplinary team consisting of a urologist, radiooncologist, radiophysisist and anesthesiologist. Equipment includes a transrectal ultrasound with a template, enough radioactive seeds with either iodine-125 or palladium-103, and software to calculate the exact position of each seed, as seen in the figure below.

Preoperative preparation includes measuring the individual prostate volume with a transrectal ultrasound which can be done ambulatory or via a CT scan. With the help of nomograms, the correct quantity of seeds is calculated. The Seeds are 4mm long and 1mm wide cylinders covered with titanium and will permanently stay in the prostate tissue. Before the procedure, each patient receives oral antibiotic prophylaxis and an enema to reduce the risk of infection with coliform bacteria and reduce post-operative complications. The procedure can be performed with general or regional anesthesia (24). The procedure is performed in general or regional anesthesia with patient in lithotomy position with hips flexed about 30 degrees and knees at 90 degrees. His feet are fixated on movable footrests with calf support and padding (17). After the patient is in a good position, a urinary catheter is placed to visualize the urethra. An ultrasound probe is placed in the rectum, and prostate is scanned from the base to

the apex in 5 mm intervals. It is important to have a good visualization of the prostate, urethra, and rectum. All data collected by ultrasound is used by the seed implantation software to calculate the exact number and location of seeds. Seed implantation is done by continuous control with ultrasound or X-ray (24). The dosage for iodine-125 seeds and for pallidum seeds is 125 Gy. The exact Seed position can be controlled intraoperatively via a computer program that calculates the dosage. If any correction of seed placement is necessary or the computer program recommends an additional seed to get the correct dosage, it can be done immediately. The transrectal ultrasound is used to aid the urologist in seed implantation the previously calculated position. To minimize the risk of seed migration, they are enveloped in a vicryl net and are deposited in chains, but single enveloped seeds can also be deposited individually. If at least 90% of the prostate tissue receives a radiation dose of 100% according to German guidelines, it is considered an excellent implantation.

After the procedure is completed, a patient must wait 2-3 hours to have his catheter removed. If the patient can urinate after the catheter is removed, he can be released from the hospital on the same day. Before leaving, each patient will receive instructions on post-procedure behavior and instructions on when to come to a control appointment. Follow up is as follows - every three months for first two years, then two times a year for the next two years and then once a year for the six years (7).

The first control CT is done 4-6 weeks after implantation. The goal of this CT is to have a three-dimensional control of the seed location. With this control, the radiation physicist can calculate the final dose distribution and see the final position of the seeds in relation to surrounding tissues to ensure that there was no migration. Healthy tissue preservation with adequate radiation dose for tumor cells can be assured (24).

2. Aims and Objectives

This study aims to record the quality of life after low dose rate brachytherapy (LDR brachytherapy) and to compare it with other literature and references.

Quality of life plays a crucial role after tumor therapy. In additionn to curative therapy, quality of life is the most important treatment goal. In the meantime, assessment of the health and psychosocial related quality of life in the field of oncology have become standard. They are becoming increasingly important, especially with the current demographic changes. The goal of maintaining or improving quality of life accompanies the entire course of the disease and treatment, starting with the diagnosis.

The questionnaires QLQ-C30 and QLQ-PR25 in Europe serve to record the general condition objectively. This QLQ-C30 questionnaire contains 30 questions and assesses the quality of life of oncological patients multidimensionally using ten subscales.

The QLQ-30 questionnaires can be used for patients with any malignancy and can be extended by a tumor specific questionnaire like the PR-25 which is specific for prostate cancer. Other suitable modules were developed for QLQ-C30 as PRO (Patient Reported Outcome) instruments depending on the tumor disease. The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnairs (QLQ-C30) with a prostate-specific module was used, which is currently the currently available assessment criterion for patients with prostate cancer to examine the quality of life in oncology for this disease.

3. Materials And Methods

The following study was performed for 12 years (Mai 2010-Mai 2021) with 338 participants. All patients had histologically verified low risk and locally confined prostate cancer and underwent Brachytherapy. From this patient cohort data from 317 patients about the quality of life and side effects after therapy could be obtained and for 287 patients a PSA is recorded between 1st and 2nd year as well. All patients signed informed consent papers and agreed with the data collection of their anonymized data and that it is used for scientific research. This study was approved by the ethics committee of the Landesärztekammer Hessen. The research was approved by the ethics committee of the Landesärztekammer Hessen. The retrospective study was performed during the working routine in the hospital Eichhofkrankenhaus Lauterbach. Before collecting the data, a thorough revision of brachytherapy indications was done for each patient. Each participant underwent a pre-procedure discussion where an urologist explained treatment modalities, indications, side effects, risks, and complications. The patient and the doctor signed an informed consent document. The discussion took place in the urological praxis in Lauterbach via the standard formula Fa. Diomed. All collected data were verified and analyzed with a standard protocol (electronic patient chart, program TOMEDO) in practice.

3.1. Patient selection

Between 2010 and 2021, 338 male patients with prostate cancer were treated with Brachytherapy. 317 patients were evaluated using questionnaires about post-therapeutic effects and quality of life.

For this retrospective study, patients who fulfilled the following criteria were selected.

Histologically verified prostate cancer, IPSS>/= 10, Flow >15ml/s, residual urine < 50ml, the possibility for dorsal lithotomy position, at least 3 months since a transrectal prostate resection, Prostate volume </= 60ml

3.2. Statistical methods

The official EORTC QLQ-30 scoring manual can be found on the official EORTC QLQ-30 scoring manual website. Via linear transformation, Raw scores which are the direct results from the questionnaires are transformed into point values that range from 1-100. For function scales and life, and quality scales high values correspond to a favorable result because they indicate a high level of functionality and a high level of quality of life. Whereas for single items and symptom scales high values correspond to more negative results because they indicate more severe symptoms (25).

To put the collected data into relation, reference values from the EORTC were used (26).

Except for the quality of life scales, all questions have four possible answers ranging from 1 to 4

Table 4 (Source 27).

1.	Not at all
2.	A little
3.	Quite a bit
4.	Very much

Function Scales

High scores indicate a high functioning of a patient. Five questions were recorded.

Table 5 (Source 27)

1.	Physical functioning: Questions 1-5
2.	Role function: Questions 6 and 7
3.	Cognitive function: Questions 20 and 25
4.	Emotional functioning: Questions 21-24
5.	Social functioning: Questions 26 and 27

Symptom scales

Contrary to the Function scales, for the symptom scales a higher value shows more suffering or symptoms. Ideally, scores would be as low as possible.

1. Pain: Questions 9 and 19
2. Fatigue: Questions 10,12,18
3. Nausea and vomiting: Questions 14 and 15

Single items

1. Dyspnea: Question 8
2. Loss of appetite: Question 13
3. Insomnia: Question 11
4. Constipation: Question 16
5. Diarrhoea: Question 17
6. Financial difficulties: Question 28

For Questions 29-30 answering possibilities rank from 1 to 7 where 1 is very bad and 7 is excellent.

Quality of life scales

1. Global Health

For the assessment of Quality of Life, there is an additional questionnaire that is cancer-specific. The prostate-specific questionnaire PR-25 was developed for patients with different stages of the disease but in this study, they were only used for patients with a locally confined tumor. The prostate-specific questionnaire is used in combination with the QLQ-C30 questionnaire.

For the interpretation of this part, it is important to note that higher values indicate a lower quality of life. For questions about the future, high values indicate the level of positivity a patient sees toward the future. Answering possibilities for patients rank from 1 (not at all) to 4 (very much) like in the majority of questions from the EORTC QLQ-C30 questionnaire (28).

3.3. Quality of Life Questionnaires and the EORTC

In our Study, Quality of Life Questionnaires by the EORTC were used. Currently, 15 European countries, as well as Australia, Canada, and the US.

In 1987 the first version of the QLQ was developed by the EORTC. The original intent was for them to be used only in clinical trials. Still, today, these questionnaires are used in several types of study, such as cross-sectional and longitudinal surveys. The goal of this questionnaire is to be accessible and usable regardless of cultural characteristics, to be suitable for independent use and to be expandable with other cancer-specific questionnaires. They were designed to aid the standardization of assessment and make data more comparable. Questionnaires consist of 30 questions which are meant to give a short overview of a patient's general health-associated quality of life. The supplementation questionnaires, which include questions that are targeted at a specific type of cancer, e.g., Urinary symptoms in prostate cancer or speaking and feeding difficulties in head and neck cancer, give a more detailed view of a patient's symptoms, side effects, and quality of life (29).

The questionnaire can be interpreted using the official scoring manual.

The questionnaire can be subdivided into subscales and single items. There are five functional scales, three symptom scales, a global health scale, and six single items. After interpretation with the scoring manual, each scale and the single item have a point score that ranges from 1-100 (25).

3.4. Reference values

The QLQ-30 is the most common questionnaire which is used to evaluate the Quality of life after therapy, but its use is limited if there are no standardized values with which the results of the questionnaire can be compared to. The EORTC has collected Quality of life scores from the general population concerning functioning scales and global Quality of life. These values give an idea of how the general population sees their life quality and aid as a landmark for all other research results generated in this field of study. Data from 11 countries from the European Union, as well as Russia, Turkey, Canada, and the US, were collected and sorted by gender and age. It was converted into comparable point values on the same scale as our point

values. These reference values are called EORTC QLQ-C30 Norm. Specific reference values also exist for the non-European countries on the list (30).

Furthermore, the EORTC collected data on the life quality of cancer patients suffering from a specific type of cancer from clinical trials and epidemiological studies to create baseline values to which all newly completed QLQ-30 questionnaire results can be compared. The reference values listed in Table 1,2,3,4 can be accessed freely via the EORTC web page (26).

At this point, only reference data for the QLQ-30 questionnaire is available, but not for the prostate-specific module.

3.5. Questionnaires

(Source 27)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

(Source 28)

ENGLISH

EORTC QLQ - PR25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
31. Have you had to urinate frequently **during the day**?	1	2	3	4
32. Have you had to urinate frequently **at night**?	1	2	3	4
33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35. Have you had difficulty going out of the house because you needed to be close to a toilet?	1	2	3	4
36. Have you had any unintentional release (leakage) of urine?	1	2	3	4
37. Did you have pain when you urinated?	1	2	3	4
38. Answer this question only if you wear an incontinence aid: Has wearing an incontinence aid been a problem for you?	1	2	3	4
39. Have your daily activities been limited by your urinary problems?	1	2	3	4
40. Have your daily activities been limited by your bowel problems?	1	2	3	4
41. Have you had any unintentional release (leakage) of stools?	1	2	3	4
42. Have you had blood in your stools?	1	2	3	4
43. Did you have a bloated feeling in your abdomen?	1	2	3	4
44. Did you have hot flushes?	1	2	3	4
45. Have you had sore or enlarged nipples or breasts?	1	2	3	4
46. Have you had swelling in your legs or ankles?	1	2	3	4

Please go to the next page

During the last 4 weeks:	**Not at all**	**A little**	**Quite a bit**	**Very much**
47. Has weight **loss** been a problem for you?	1	2	3	4
48. Has weight **gain** been a problem for you?	1	2	3	4
49. Have you felt less masculine as a result of your illness or treatment?	1	2	3	4
50. To what extent were you interested in sex?	1	2	3	4
51. To what extent were you sexually active (with or without intercourse)?	1	2	3	4

PLEASE ANSWER THE NEXT FOUR QUESTIONS ONLY IF YOU HAVE BEEN SEXUALLY ACTIVE OVER THE LAST 4 WEEKS:

52. To what extent was sex enjoyable for you?	1	2	3	4
53. Did you have difficulty getting or maintaining an erection?	1	2	3	4
54. Did you have ejaculation problems (eg dry ejaculation)?	1	2	3	4
55. Have you felt uncomfortable about being sexually intimate?	1	2	3	4

4. Results

Tables 1- 4 show point values from this study (results) and reference data from the EORTC. The reference data includes values from the overall population of men in general and values from men with prostate cancer in all stages.

The category of function scales consists of five subscales. High numbers are favorable because they indicate a good function.

Functioning scales

Table 6 (Source 26)

	Reference value: PCA all stages	Own Data	All male population
Physical function	80,2	82,3	86,0
Role function	82,7	84,1	84,5
Cognitive function	83,2	84,8	76,6
Emotional function	76,6	78,3	85,2
Social function	80,2	83,5	86,7

Symptom scales consist of three subscales where low values are favourable because high values indicate a high burden of symptoms.

Symptome scales

Table 7 (Source 26)

	Reference value: PCA all stages	Own Data	All male population
Fatigue	26,9	24,1	27,1
Pain	23,3	21,3	21,6
Nausea/ Vomiting	5,1	3,4	6,1

Single Items consists of six single items without subscales. Low values are favorable because high values indicate a high burden of symptoms.

Single Items

Table 8 (Source 26)

	Reference value: PCA all stages	Own Data	All male population
Dyspnea	16,8	11,1	15,5
Loss of appetite	10,4	10,1	9,6
Insomnia	24,5	23,3	23,6
Constipation	14,6	14,1	10,9
Diarrhoea	8,4	12,5	10,0
Financial Situation	9,1	8,9	10,4

Quality of life scales

High values indicate a good Quality of life

Table 9 (Source: 26)

	Reference value: PCA all stages	Own Data	All male population
Quality of Life	68,4	70,3	68,8

PCA: Prostate Cancer

PV: Point Values Scale 0-100

PR-25 module

There is no standardized reference data for the PR-25 module.

The table shows results of four studies with different treatments for prostate cancer. High values for all symptom subscales indicate a high symptom burden. For Sexual activity and functioning, high values indicate a good function.

Table 10 (Sources: 31, 32, 33, 34)

Scales	Erikson 2014 HDR+EBRT	Selli 2014 RPE	Korde 2019 HDR+ERBT	Arrasa 2009 ERBT	Own Data 2022 LDRBT (own data)
Patient Number	86	403	33	137	287
Urinary Symptoms	19	19,2	24,4	19,8	18,7
Bowel Symptoms	9	7	3,5	3,5	5,7
Hormone Symptoms	12	12,7	12,4	12,9	10,3
Sexual Activity	30	25,8	31,3	10,6	29,1
Sexual Function	60	52,0	43,9	50,9	51,7

HDR: High Dose Radiation Brachy Therapy, EBRT: External beam Radiation Therapy, RPE: Radical Prostatectomy , LDR: Low Dose Rate Brachy Therapy, PV: Point values on scale 0-100

5. Discussion

This study aimed to collect data about the life quality of low-risk profile prostate cancer patients after LDR brachytherapy and compare it with reference data (26). All patients who participated in this study were treated with a curative intent. There is relatively little data on the Quality of life after LDR Brachytherapy specifically. Reference data can be found in the EORTC manual. In our study, 317 patients filled out the EORTC QLQ-30 as well as the PR-25 questionnaire 12-24 months after they were treated for low-risk profile prostate cancer using LDR Brachytherapy. The results were converted into points from 1-100 for each question using formulas provided by the EORTC scoring manual, and results were compared to the reference data as well as other research studies in the field.

For Functioning scales, Symptoms scales, single items, and the Quality of Life scale, all values from the reference data for the overall male population as well as the prostate cancer population show very little difference from our data. In the functioning scale, our patients rated all subscales of functioning slightly higher than the overall prostate cancer population. Values for the general male population in the subscales of Physical function, Role function, Emotional function, and social function were slightly better except for Cognitive function, which our patients rated 8,2 points higher.

In all subscales of the symptom scale, our patients rated their symptoms slightly lower than the reference data of the overall male population as well as the prostate cancer population. They experienced less pain, fatigue, and nausea/vomiting.

In the single items, the most significant differences can be seen for the category of Dyspnea, Constipation, and Diarrhea. Our patients generally experienced significantly less Dyspnea than both reference groups.

Our patients experienced the same degree of constipation as the overall cancer population and these results were slightly higher than in the general male population. The only category in which our patients had a worse result compared to the other two examined groups was diarrhea. This could be due to the nature of Brachytherapy which puts some stress on the rectum. Insomnia, Loss of appetite, and financial situation scores showed almost no difference between all three groups.

A study by Shin et al. investigated changes in health-related Quality of life after different methods of radical prostatectomy. Between 2014 and 2015, 258 patients answered the QLQ-

30 questionnaires. After 12 months, the biggest differences can be seen in the categories of emotional function, pain, financial situation, urinary symptoms, sexual function, and overall Quality of life. Patients in our study rated their emotional function significantly lower than in the reference data for the overall male population but higher than the overall prostate cancer population. and experienced more pain. Our patients ranked their financial situation as better, experienced fewer urinary symptoms, and rated their sexual functioning after treatment significantly higher. While most other categories in the mentioned study were rated as slightly better, it is interesting to note that the overall Quality of life 12 months after treatment was rated 5,9 points higher in our cohort (35).

A study by Morton et al. explores the question of changes in the health-related Quality of life of intermediate-risk prostate cancer patients who were treated with HDR- Brachytherapy and external beam radiation therapy. One hundred twenty-five patients completed EPIC questionnaires which are the US equivalent to the EORTC questionnaires. After treatment, a significant reduction in urine function, bowel function, and sexual function can be seen. Scores for hormone symptoms stayed constant (36).

A German Dissertation from 2022 investigated the Quality of life of cancer patients treated with HDR Brachytherapy. Fifty-seven patients completed the QLQ-30 questionnaires 12 months after treatment. Our cohort rated all functioning subscales higher than in the mentioned study; the most prominent differences can be seen in role function (13,83 points) and cognitive function (11,5 points). A similar trend can be seen in the symptom scales, where our patients rated all symptoms lower than the mentioned study. In the single items category, our patient ranked all items except the loss of appetite as a lesser burden than the referenced research. The most significant discrepancy was seen in the category of insomnia, which our patients rated significantly lower (16,59 points). Our patients also rated their overall Quality of life better than the mentioned study. Our research is only somewhat comparable to the referenced research because the cohort includes patients with locally advanced prostate cancer. In contrast, our study included only the patients with organ confined prostate carcinoma (37).

For the PR-25 module, there is currently no reference database, but Table four shows studies that used the PR-25 questionnaires. The data is also not strictly comparable since patient groups are of very different sizes and have different stages of disease than our patients.

In a study from Erikson et al., 86 patients from Sweden who were treated for localized prostate cancer answered the PR-25 module (31). In Selli et al., 403 patients from different European countries who were treated for low to intermediate-risk prostate cancer answered the PR-25 module in various stages of treatment, including twelve months after, which are the values used in the table above(32). In a German dissertation by J.C. Korde, 33 patients were treated for different stages of prostate cancer using HDR-Brachytherapy as well as External Beam Radiation Therapy (33). In the previous referenced study, 137 patients with localized prostate cancer were treated with External Beam Radiation therapy (34). All studies show relatively similar results for the PR-25 module. Our patients experienced slightly fewer urinary symptoms but values ranked in between the other studies for bowel symptoms. Our patients experienced the least symptoms related to hormonal changes, while for sexual activity and sexual function, values again lie in between the other studies.

Concerning the results of our study in comparison with reference data and other research, Brachytherapy has very similar outcomes compared to other treatment modalities for prostate cancer. It is superior in a few categories and inferior in others, but overall differences in point values are minor. Since there is relatively little data on the development of life quality of prostate cancer patients treated with LDR-Brachytherapy research where QLQ-30 and PR-25 questionnaires are answered before, during, and after treatment would be very interesting and could give better insight on the actual changes in patients subjective view on their health-related life quality for this specific treatment modality.

6. Conclusion

Prostate cancer is among the most common cancers in men. Age has been identified as one of the major risk factors. Increasing numbers can be expected in Western countries because of the demographic changes in society. Quality of life plays an important role, especially for patients with early stages of disease, because they have the most options for different therapy methods. These include active surveillance, hormone therapy, chemotherapy, prostatectomy, or radiation therapy.

For an early-stage disease with a localized tumor, guidelines suggest Brachytherapy with Iod-125 seeds as one curative approach. Brachytherapy is a minimally invasive approach that can be done in an ambulatory setting for most patients and only requires one intervention. Side effects of this method are mainly related to urinary tract and sexual function, which may have an impact on life quality for patients. In the past, evaluation of therapy methods was done primarily by looking at the mortality rate, life expectancy, and clinical symptoms. Still, new trends also focus on the overall quality of life. They are focusing more on a patient's subjective view of their health and functioning in life.

This study aimed to evaluate the quality of life after LDR Brachytherapy for patients with a low-risk profile prostate carcinoma. Three hundred and seventeen patients were asked about their quality of life 12-24 months after therapy. To generate reliable, standardized results, the QLQ-C30 questionnaires from EORTC, which are designed for cancer patients, were used. Additionally, the prostate-specific module QLQ PR 25 was used to evaluate prostate-specific symptoms.

In comparison with the reference data from EORTC, Brachytherapy showed identical to slightly better results concerning the quality of life than other therapeutic options. To ensure good results, it is essential only to treat patients who fulfill all criteria for the indications according to guidelines. The results of this study confirm that Brachytherapy is a valid option for patients with low-risk prostate cancer and a life expectancy of ten or more years.

7. Summary

The aim of this study was to analyze the Quality of Life after LDR Brachytherapy of patients with low risk prostate cancer and to compare it to other literature. The Study was performed using the QLQ-30 and the PR-25 questionnaires to collect data from 287 probands. Since there is very little data on this exact topic, comparisons were made between LDR Brachytherapy and other treatments. In conclusion it can be said that our results showed a similar Quality of life for patients treated with LDR Brachytherapy. This study shows that LDR Brachytherapy is a valid option for patients with low risk prostate cancer. After therapy, a good Quality of Life is expected for these patients.

Key words:
Prostate cancer; LDR Brachytherapy, Quality of Life, EORTC, Low risk prostate cancer, Rijeka, Germany

8. Literature cited

1. Worldwide cancer data: World cancer research fund international [Internet]. WCRF International. 2022 [cited 2023 Apr 22]. Available from: https://www.wcrf.org/cancer-trends/worldwide-cancer-data/
2. Krebs - Prostatakrebs [Internet]. www.krebsdaten.de. Zentrum für Krebsregisterdaten; Robert Koch Institut; 2022 [cited 2022 Apr 2]. Available from: https://www.krebsdaten.de/Krebs/DE/Content/Krebsarten/Prostatakrebs/prostatakrebs_node.html
3. Heuveling J. Prostatakrebs, Krebs der Vorsteherdrüse [Internet]. www.krebsgesellschaft.de. Deutsche Krebsgesellschaft; 2021 [cited 2023 Apr 2]. Available from: https://www.krebsgesellschaft.de/onko-internetportal/basis-informationen-krebs/krebsarten/prostatakrebs/definition-und-haeufigkeit.html
4. Wang L, Lu B, He M, Wang Y, Wang Z, Du L. Prostate Cancer Incidence and Mortality: Global Status and Temporal Trends in 89 Countries From 2000 to 2019. Frontiers in Public Health. 2022 Feb 16;10. https://www.frontiersin.org/articles/10.3389/fpubh.2022.811044/full
5. Bertz J, Giersiepen K, Haberland J, et al. Krebs in Deutschland Häufigkeit und Trends [Internet]. Saarbrücken: Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V.; 2006 [cited 5AD Feb]. Available from: https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/vergangene_ausgaben/downloads/krebs_in_deutschland_5.pdf?__blob=publicationFile
6. Franke M, Schönfeld I, Barnes B, et al. Krebs in Deutschland für 2015/2016 [Internet]. Berlin : Zentrum für Krebsregisterdaten und Gesellschaft der Epidemiologischen Krebsregister Deutschland e.V.; 2020 [cited 2023 Feb 8]. Available from: https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2019/krebs_in_deutschland_2019.pdf?__blob=publicationFile
7. Deutsche Gesellschaft für Urologie e. V. (DGU). S3-Leitlinie Prostatakarzinom [Internet]. 2021 Oct [cited 2023 April 25]. Available from: https://

www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Prostatatkarzinom/Version_6/LL_Prostatakarzinom_Langversion_6.2.pdf

8. Gerhauser C, Favero F, Risch T et al. Molecular Evolution of Early-Onset Prostate Cancer Identifies Molecular Risk Markers and Clinical Trajectories. Cancer Cell 2018;34(6):996-1011.
9. Brandt A, Bermejo JL, Sundquist J, Hemminki K. Age-Specific Risk of Incident Prostate Cancer and Risk of Death from Prostate Cancer Defined by the Number of Affected Family Members. European Urology. 2010 Aug;58(2):275–80.
10. Giona S. The Epidemiology of Prostate Cancer [Internet]. Bott SR, Ng KL, editors. PubMed. Brisbane (AU): Exon Publications; 2021 [cited 2023 Apr 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK571326/
11. ECIS - European Cancer Information System
From https://ecis.jrc.ec.europa.eu, accessed on day/month/year
© European Union, 2023
12. Jacob LM. Der kausale Zusammenhang von Prostata-Hyperplasie, chronischer Prostatitis und Prostatakrebs. Deutsche Zeitschrift für Onkologie [Internet]. 2019 Jun [cited 2019 Nov 18];51(02):74–80. Available from: https://www.thieme-connect.de/products/ejournals/abstract/10.1055/a-0865-8464
13. Montironi R, Santoni M, Mazzucchelli R, Burattini L, Berardi R, Galosi AB, et al. Prostate cancer: from Gleason scoring to prognostic grade grouping. Expert Review of Anticancer Therapy. 2016 Mar 23;16(4):433–40.
14. Santis D, Gillessen S, Grummet J, Henry A, Van Der Kwast T, et al. EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer [Internet]. European Association of Urology ; 2023 [cited 2023 Apr 26]. Available from: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-EANM-ESTRO-ESUR-ISUP-SIOG-Guidelines-on-Prostate-Cancer-2023_2023-03-27-131655_pdvy.pdf
15. Gerharz EW, Köhl U, Engl T. Chancen und Risiken der Prostata-MRT [Internet]. springermedizin.de. 2022 [cited 2023 Mar 15]. Available from: https://www.springermedizin.de/prostatakarzinom/prostatakarzinom/chancen-und-risiken-der-prostata-mrt/20285708

16. Maurer T, Eiber M, Schwaiger M, Gschwend JE. Current use of PSMA–PET in prostate cancer management. Nature Reviews Urology [Internet]. 2016 Feb 23 [cited 2019 May 22];13(4):226–35. Available from: http://www.nature.com/articles/nrurol.2016.26

17. Strnad V, Pötter R, Kovacs G. Praktisches Handbuch der Brachytherapie . 2nd ed. Bremen - London - Boston : UNI-MED Verlag AG; 2010.
18. Hilke Stamatiadis-Smidt, Harald zur Hausen, Otmar D. Wiestler, Hans-Joachim Gebest (Hrsg.): Thema Krebs, Springer Verlag 2006 https://www.krebsgesellschaft.de/onko-internetportal/basis-informationen-krebs/nebenwirkungen-der-therapie/angst-und-depression.html
19. World Health Organization. WHOQOL - measuring quality of life| the world health organization [Internet]. World Health Organization. 2012 [cited 2023 May 31]. Available from: https://www.who.int/tools/whoqo
20. De Sousa, A., Sonavane, S. and Mehta, J. (2012) Psychological aspects of prostate cancer: A clinical review, Prostate cancer, and prostatic diseases. U.S. National Library of Medicine. Available at: https://pubmed.ncbi.nlm.nih.gov/22212706/ (Accessed: April 22, 2023).
21. McCullough AR. Prevention and management of erectile dysfunction following radical prostatectomy. Urologic Clinics of North America. 2001 Aug;28(3):613–27.
22. Haidl F, Al-Monajjed R. Prostatakarzinom – chirurgische Komplikationen. Thieme-connect . 2020 Jun 17;51(0001-7868).
23. Thüroff JW. Laparoskopische vs. robotische Operationen in der Urologie. der Urologe . 2012 Apr 27;51(5):615–6.
24. Interstitielle LDR-Brachytherapie beim lokal begrenzten Prostatakarzinom Abschlussbericht Beratungsverfahren gemäß § 137c SGB V (Krankenhausbehandlung) [Internet]. Gemeinsamer Bundesausschuss . Bundesanzeiger ; 2014 [cited 2023 Apr 28]. Available from: https://www.g-ba.de/downloads/40-268-2617/2013-12-19_KHMe-RL_Brachytherapie_ZD.pdf
25. Fayers P, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: European Organisation for Research and

Treatment of Cancer, 2001. Available from: https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf

26. Scott N, Fayers P, Aaronson N, Bottomley A, De Graeff A, Groenvold M, et al. EORTC QLQ-C30 Reference Values This manual presents reference data for the QLQ-C30 based upon data provided by EORTC Quality of Life Group Members and other users of the QLQ-C30 Sprangers on behalf of the EORTC Quality of Life Group EORTC Quality of Life Group [Internet]. 2008. Available from: https://www.eortc.org/app/uploads/sites/2/2018/02/reference_values_manual2008.pdf
27. Questionnaires - EORTC - Quality of Life : EORTC – Quality of Life [Internet]. qol.eortc.org. Available from: https://qol.eortc.org/questionnaires/
28. Prostate - EORTC - Quality of Life : EORTC – Quality of Life [Internet]. qol.eortc.org. EORTC; [cited 2023 Jun 1]. Available from: https://qol.eortc.org/questionnaire/qlq-pr25/
29. Frayers P, Bottomlay A. Quality of life research within the EORTC—the EORTC QLQ-C30. European Journal of Cancer. 2022 Mar;38. Available from: https://www.ejcancer.com/article/S0959-8049(01)00448-8/fulltext#%20
30. Nolte S, Liegl G, Petersen MA, Aaronson NK, Costantini A, Fayers PM, et al. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. European Journal of Cancer. 2019 Jan;107:153–63. Available from: https://www.ejcancer.com/article/S0959-8049(18)31522-3/fulltext
31. Hjäm-Eriksson M, Lennernäs B, Ullen A, Johansson H, Hugosson J, Nilsson S, et al. Long-term health-related quality of life after curative treatment for prostate cancer: A regional cross-sectional comparison of two standard treatment modalities. International Journal of Oncology. 2014 Oct 29;46(1):381–8.
32. Selli C, Bjartell A, Burgos J, Somerville M, Palacios JM, Benjamin L, et al. Burden of Illness in Prostate Cancer Patients with a Low-to-Moderate Risk of Progression: A One-Year, Pan-European Observational Study. Prostate Cancer. 2014;2014:1–8.
33. Korde JC. Lebensqualität, sexuelle Funktion und Akuttoxizität bei der kombinierten Strahlentherapie des Prostatakarzinoms [Internet] [Dissertation PDF]. [Medizinische Fakultät der Christian-Albrechts-Universität zu Kiel]; 2019 [cited 2023 May 20].

Available from: https://macau.uni-kiel.de/servlets/MCRFileNodeServlet/macau_derivate_00001699/Dissertation_Jan_Korde.pdf

34. Arraras JI, Villafranca E, Arias de la Vega F, Romero P, Rico M, Vila M, et al. The EORTC Quality of Life Questionnaire for patients with prostate cancer: EORTC QLQ-PR25. Validation study for Spanish patients. Clinical and Translational Oncology. 2009 Mar;11(3):160–4.
35. Shin DW, Lee SH, Kim TH, Yun SJ, Nam JK, Jeon SH, et al. Health-Related Quality of Life Changes in Prostate Cancer Patients after Radical Prostatectomy: A Longitudinal Cohort Study. Cancer Research and Treatment. 2019 Apr 15;51(2):556–67.
36. Morton GC, Loblaw DA, Chung H, Tsang G, Sankreacha R, Deabreu A, et al. Health-related quality of life after single-fraction high-dose-rate brachytherapy and hypofractionated external beam radiotherapy for prostate cancer. International Journal of Radiation Oncology, Biology, Physics [Internet]. 2011 Aug 1 [cited 2023 Jun 1];80(5):1299–305. Available from: https://pubmed.ncbi.nlm.nih.gov/20708853/
37. Huang-Tiel H. Lebensqualität und klinische Ergebnisse nach HDR- Brachytherapie beim lokal fortgeschrittenen Prostatakarzinom [Internet] [Dissertation PDF]. [vorgelegt der Medizinischen Fakultät Charité – Universitätsmedizin Berlin]; 2022 [cited 2023 May 20]. Available from: https://refubium.fu-berlin.de/bitstream/handle/fub188/32941/Dissertation_HT_online.pdf;jsessionid=80B0E2E2F1BE4AD895ADF6590CFC1303?sequence=1

9. Curriculum Vitae

Sophia Katharina Kalem was born in Fulda, Germany on April 6th, 1998. She received her high school diploma (Abitur) from Marienschule Fulda, Germany. During her school time she spent one year at an English boarding school. In 2017, she began her integrated undergraduate and graduate studies at the Faculty of Medicine, University of Rijeka in Croatia which she is expected to complete in July 2023. During her studies in Croatia she completed several traineeships in different German hospitals such as Diakonissen-Stiftungskrankenhaus Speyer and Asklepios Südpfalzklinik Kandel. Throughout her studies in Croatia she obtained a proficiency level B1 certificate for Croatian language.