BACHELOR THESIS

IMPROVING TREATMENT SELECTION FOR LOCALIZED PROSTATE CANCER PATIENTS IN GERMANY

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Improving Treatment Selection for Localized Prostate Cancer Patients in Germany

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Preface

Dear Reader,

This report is about my research project as final part of my bachelor studies in Industrial Engineering and Management at the University of Twente. For the research, I was working together with Elekta, and aim at improving the treatment selection for localized prostate cancer patients in my home country, Germany.

I thank my supervisors at Elekta, Ate Loonstra who was ever very willing to help and answer questions about all kinds of different topics and Dirk Binnekamp for ever giving me a ride to the office and having very interesting discussions during the long drive or at the office. Your expertise and support are very highly appreciated.

A special thanks also to Gréanne Leeftink, who managed to give very to-the-point and valuable feedback throughout the past months on all the changes I made to the topic of my research and research design. Also, the feedback and discussions with my second supervisor at the University of Twente, Amin Asadi, were of great help.

Thank you so much for helping me to conduct that research, which seems so interesting and important to me not only because I am focussing on my home country, but also because it benefits society.

Caleb Trabitzsch

July, 2023

Management Summary

This Research is conducted at Elekta in Veenendaal where Elekta's business line Brachytherapy is located. Elekta is a multinational company that is headquartered in Stockholm. It develops and produces different radiation equipment for cancer care. Brachytherapy, a specific type of radiotherapy, makes use of radioactive isotopes that are temporarily placed inside or close to a lesion by a computer-controlled device called an afterloader. Elekta recently announced that two million treatments have been delivered with its main afterloader "Flexitron".

Problem Description

Prostate cancer is the most common cancer in Germany among men, with around 68,000 new cases annually. The number of cases is projected to rise due to an ageing population in the near future. Various treatment options exist, differing in costs, control rates, and toxicity. Guidelines help determine treatment, but patient and provider preferences can influence treatment selection. These preferences partially explain the up to 50% variation in the use of radiotherapy between Germany and the UK.

Several authors tried to support objectified treatment selection decision-making by developing mathematical models to aid treatment selection by providers and patients. This existing research however does not include salvage treatments and only includes few treatment options, which is why we aim to extend these. Our research focuses on optimizing treatment selection to minimize long-term expected costs, including direct treatment costs, utility management costs, and costs associated with lost utility. This leads us to the following research question:

How can the treatment selection for localized prostate cancer be optimized such that the long-term treatment-associated costs of a patient are minimized?

Method

We develop a Markov model to minimize healthcare payer costs. This includes treatment costs, management costs for treatment-related toxicity, and costs associated with lost utility from prostate cancer and the treatments performed. Considering that there exists a possibility that cancer recurs after a patient's initial treatment and can be treated again, the model takes into account current guidelines on primary and salvage treatment selection. It uses treatment-specific outcomes that include the probability of major toxicities arising as well as cancer recurring. With input data on toxicity and recurrence rates derived from literature, the model compares the different treatments and determines the treatment for which the expected total cost over a ten-year period is the lowest. The model is implemented in Visual Basic for Application for easy use by stakeholders.

Results

A combination of Stereotactic Body Radiation Therapy (SBRT) and Brachytherapy leads to the lowest total cost over ten years for all patient categories. The output shows that the component of costs assigned to the lost utility of a patient contributes as much as 94% to the total expected costs. Based on the literature, the costs assigned to the equivalent of one year of quality-adjusted lifetime lost due to treatment is 36.570€. Given the high influence of lost utility on the total expected costs, we conduct

a sensitivity analysis on this parameter, by stepwise increasing the cost of lost utility. As expected, the fraction that direct treatment costs and toxicity management costs contribute to total costs diminishes, as costs assigned to lost utility increase. Consequently, for low values assigned to lost utility, Brachytherapy or SBRT as monotherapies are the best treatment option, since low treatment costs outweigh the costs assigned to a slightly worse clinical outcome for the monotherapies. However, with increasing costs assigned to lost utility, the combination of the two therapies becomes more attractive even if the treatment is more expensive because it promises slightly better clinical outcomes. Figure 1 shows that the treatment selection is robust for lost utility values of 3200€ or higher. Only with costs assigned to lost utility below 3.200€, which is a 91% reduction, the optimal treatment is changed to SBRT for costs assigned to lost utility between 600€ and 3200€, while Brachytherapy as monotherapy is the optimal treatment option for costs of lost utility below 600€.

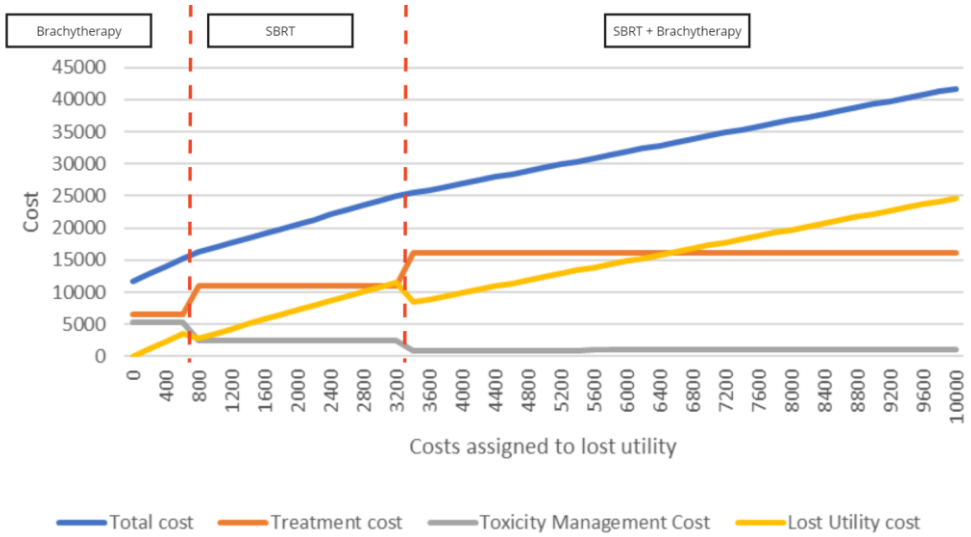

Figure 1: Optimal treatment selection for high-risk patients with changing costs assigned to lost utility

Conclusion

In this research, we developed a mathematical approach to support sequential treatment selection for prostate cancer. This model can be used to determine the primary treatment that is expected to lead to the lowest total costs related to the disease over a ten-year period. We use input parameters based on recently published, peer-reviewed literature. Nevertheless, there is heterogeneity within the populations of the different literature sources used, and some input parameters needed to be estimated since data for these specific situations was not available. Hence, it is essential to critically review all input parameters before our findings can be used in general practice. However, different analyses and experiments have proven that the model reacts to changes in input parameters as expected, and hence can serve as a powerful tool in the future for decision-makers as well as equipment manufacturers to provide potential customers with a reliable comparison of the different treatment options. If input parameters are confirmed by experts, our conclusion to treat patients with a combination of SBRT and Brachy can be used in clinical practice and is expected to significantly reduce the costs of prostate cancer care.

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List of Abbreviations

EBRT	External Beam Radiation Therapy
GS	Gleason Score
HDR	High-dose radiation
MDP	Markov Decision Process
MPSM	Managerial problem-solving method
PSA	Prostate-specific antigen
QALY	Quality adjusted life time years
SBRT	Stereotactic Body Radiation Therapy
SLR	Systematic Literature Review
TNM	Tumour-Node-Metastasis
ICER	Incremental Cost-effectiveness ratio
PCCI	Prostate Cancer Comorbidity Index
BCR	Biochemical Recurrence
RFS	Recurrence free survival
BFFS	Biochemical failure free survival
WTP	Willingness to pay

1. Introduction

As the German health monitoring institution shows, the value of total healthcare expenditure has risen by more than 100% between 2000 and 2020 (Gesundheitsberichterstattung des Bundes 2023). Even with a rising gross domestic product (GDP), the fraction of GDP assigned to healthcare in those 20 years has constantly increased from 10.2% to 13.0%. Together with an aging population, the question of how healthcare will be financed in the future arises (World Health Organization 2020; Worldbank 2023). Prostate cancer being the most common cancer among German men in 2018 with more than 65 thousand new cases that year, is a main contributor to the expected increase in healthcare expenditures (Cancer Tomorrow 2020; Robert Koch Institut 2017). That is the number of yearly prostate cancer cases has risen in the past and is expected to rise to above 120 thousand cases by 2030 (Quante et al. 2016; Stock, Mons, and Brenner 2018).

In the case of localized prostate cancer for low-, intermediate-, and high-risk patients, there are different treatment options namely active surveillance, radiation therapy using stereotactic body radiation therapy (SBRT), brachytherapy, and surgery. Further, there is a possibility to treat a patient with a combination of treatments such as SBRT and brachytherapy. Depending on several factors elaborated on below, each treatment is expected to have different outcomes.

Morgans et al. (2022) found that there are significant differences with regard to treatment selection in different countries. For instance, the percentage of patients with non-metastatic prostate cancer receiving surgery differs by 29,9% when comparing Germany and the US (Morgans 2022), which indicates that the decision-making depends on unknown factors and might not always be objective. In this research, we analyse causes and present decision-support solutions to improve treatment selection for prostate cancer in Germany.

We identify the core problem of this research: *"guidelines on treatment selection are not clear",* and formulate the main research question as follows:

How can the treatment selection for localized prostate cancer be optimized such that the long-term treatment-associated costs of a patient are minimized?

Due to the expected increase in healthcare expenditure overall in Germany and the predicted increase in prostate cancer patients in the near future, as mentioned above, the objective of our research is to provide insight into selecting the best treatment for a patient with localized prostate cancer in Germany such that the total cost per cancer patient is minimized while taking into account the guidance offered by European clinical guidelines. In our research, we take into account the patient's objective to receive the treatment promising the best outcome independent of the cost. We do so, by assigning a reasonable monetary value to a patient's quality-adjusted lifetime years which is already done in practice today and allows making a trade-off between a treatment's cost and its expected outcome. This research uses a Markov Decision Process approach to optimize the treatment selection for a patient with localized prostate cancer based on that patient's individual characteristics such that the long-term treatment-associated costs are minimized.

Research design

To structurally approach the main research question, we define 7 sub-research questions as further detailed in the research design in Appendix 1.4.

1. *What different treatment options exist for treating localized prostate cancer?*

Since our research aims at improving treatment selection for localized prostate cancer, we first examine what treatments exist and what their characteristics are. Therefore, we conduct a literature search and interview experts in the field of cancer care. We present the findings in a concise summary in Section 2.1, in which we explain how the different treatments work. In this section, we further explain the role of the company supporting us in our research, being one of the market leaders in cancer treatment equipment, Elekta.

2. *What are the guidelines for selecting a treatment for a patient with localized prostate cancer?*

There are guidelines on how to select a treatment for an individual patient in Germany. We investigate how the treatment selection today is performed by conducting a literature search and presenting the main findings in Section 2.2.

3. *What knowledge exists on improving treatment selection?*

Not only to show the importance of our research and the value it adds but also to gain insight into possible approaches for the improvement of treatment selection, we examine what research has already been done on the topic in the past ten years. We assess to what extent we can base our research on existing publications. As can be seen in Section 3, we extend the research performed on optimizing treatment selection for localized prostate cancer patients.

4. *How can the treatment selection process be formulated in a mathematical model?*

Based on existing research found, we formulate a Markov model that can be used to minimize the total cost related to prostate cancer of a specific risk group. In Section 4, we define the variables needed as well as the stage and state variables before formulating the objective function.

5. *What values can be used as input parameters for the mathematical model?*

For the Markov model defined, we require several input variables. In Section 5, we first, discuss the treatment outcomes and the corresponding probabilities, as well as the cost values used as input for the model, as derived from the literature. There, we differentiate between direct treatment costs and costs of managing treatment-related toxicity, as well as review how the clinical outcomes can be taken into account. In essence, we define the following sub-questions:

5.1 *What are possible clinical outcomes of treatments and what are the corresponding probabilities?*

The different outcomes of specific treatments are of high relevance for our research because they influence decision-making substantially. We perform a systematic literature search on different treatment outcomes and discuss the findings in Section 7.1.

5.2 What are the costs related to treating a prostate cancer patient?

Wanting to improve prostate cancer treatment selection from a financial point of view, it is essential to understand the costs related to treating a patient. As mentioned, we distinguish different costs, which are addressed in the following questions.

5.2.1 What are the direct treatment costs for each treatment option?

One contributor to the total costs related to treating prostate cancer are the direct costs related to treatment. They are researched in existing literature as well as semi-structured interviews with experts in Germany.

5.2.2 What are the costs of managing treatment-related toxicity?

In addition to the direct costs related to treatment, the costs related to managing the toxicity of a treatment need to be taken into account.

5.2.3 How to value a patient's life?

Even if our research aims at minimizing the costs related to treating prostate cancer and managing arising toxicity levels thereafter, we need to take into account the expected clinical outcome. Hence, we research in the literature how trade-offs between treatment costs and clinical outcome are done today and search for threshold values used in that trade-off today.

6. What are the results of the optimized treatment selection?

In Section 6, we display and describe the output obtained from the model. Then, we discuss the output and explain the results as well as why some of it deviates from expectations before conducting a sensitivity analysis on one of the input parameters.

7. How can the optimized treatment selection be implemented?

In Section 7, we conclude by critically evaluating the quality of our research by discussing limitations and reliability as well as providing insight on how it can be improved in future research. Moreover, we elaborate on how our research can be used in clinical practice.

Scope

One of the world's largest producers of radiation equipment is Elekta, a global company headquartered in Sweden. The company provides equipment for cancer care such as radiation therapy including brachytherapy, image-guided radiation therapy and radiosurgery. Following the vision to create a world where ¨everyone has access to the best cancer care¨, they are present in over 120 countries with offices in 40 countries (Elekta 2023). We as researchers are part of the organization of Elekta during our research and are thus able to use their network of experts and connections to hospitals around the world.

An implication of our research on improving cancer treatment selection is that treatment selection will be done more objectively and independently of doctors' individual preferences. Interviewing experts at Elekta, we found that for instance brachytherapy is sometimes not chosen as a treatment even if it promises better results, because it requires highly skilled and experienced staff to perform the treatment. Our research is expected to be of help in improving decision-making and is expected to increase the number of brachytherapy treatments performed in the future. Elekta not only produces new products for brachytherapy, but also maintains them, and is hence expected to benefit from the research.

We decide to limit the scope of our research to prostate cancer in Germany because prostate cancer is the most common cancer among German men and according to experts, the utilization of brachytherapy in prostate cancer treatments is relatively low, even if the clinical outcome is said to be better. That indicates that treatment selection for prostate cancer patients could be improved from that point of view. Additionally, current discussions about changes in healthcare and reimbursement systems in Germany and for instance the health minister Karl Lauterbach predicting that every fourth hospital is facing bankruptcy given the current reimbursements they receive and the resulting profits, stress the importance of reducing avoidable costs in healthcare in Germany.

2. Treatments for localized prostate cancer

This section provides an overview of treatments for localized prostate cancer in Section 2.1 and discusses patient characteristics and treatment selection in Section 2.2.

2.1 Overview of treatments

This section briefly elaborates on the most frequently applied treatment options for localized prostate cancer, which are active surveillance, radiotherapy, and prostatectomy (Mottet et al. 2021).

Active surveillance

Active surveillance refers to avoiding an intervention with careful follow-up monitoring. Actively monitoring the tumour has the desired advantage of avoiding the comorbidies created by intervention and is mainly used for patients whose cancer is diagnosed at an early stage and is expected to grow slowly (Prostate Cancer Free Foundation 2021).

Radiotherapy

In radiotherapy, we distinguish between External Beam Radiation Therapy with modern modalities like Stereotactic Body Radiation Therapy and High-Dose Rate Brachytherapy monotherapies as well as a combination of the two.

Stereotactic Body Radiation Therapy

Stereotactic Body Radiation Therapy (SBRT) is a type of external beam radiation therapy (EBRT), in which radiation is delivered to the tumour coming from a source outside of the patient's body. Using the latest equipment including modern type accelerators, this can be done with high precision.

HDR Brachytherapy

High-dose-rate (HDR) Brachytherapy is a radiation treatment, where a radioactive source is brought into or close to the tumour to deliver high-dose levels of radiation. Due to a rapid decrease of radiation further away from the radioactive source, this allows radiating and thereby damaging the tumourous cells as much as possible while keeping the dose delivered to organs at risk (OARs) surrounding the tumour relatively low. Brachytherapy's main advantage over (EBRT) is that by being able to radiate from a closer distance to the tumour, and thereby deliver minimal dose levels to surrounding tissue enabling escalated dose levels far beyond which can be delivered by EBRT modalities. This is of critical importance for improved local control probability of the initial tumour. This additionally implies further minimizing the risk of tumour regrowth over time.

Combining SBRT with an HDR Boost tumour-targeted dose escalation

In case a patient's lymph nodes near the prostate might be affected, a combination of SBRT and HDR brachytherapy is commonly used. This includes SBRT, which radiates the tumour as well as lymph nodes and HDR brachytherapy delivered to the tumour specifically, boosting the sterilization of the tumour very locally.

Prostatectomy

A surgical intervention to treat prostate cancer is called Prostatectomy and is the traditional approach in prostate cancer management. The main type of prostatectomy is the so-called radical prostatectomy, in which the entire prostate and some additional tissue around it are removed (American Cancer Society 2022).

Depending on the risk classification of a patient, following recommendations of guidelines, staff and patient together decide on what treatment to perform.

2.2 Patient characteristics

Which treatment a prostate cancer patient receives is highly dependent on patient characteristics. In Europe this is mainly based on the TNM score, the Gleason Score and blood-based PSA levels of a patient (Mottet et al. 2021). They are elaborated upon below.

TNM Classification

One part of classifying patients today is done using the TNM classification, which includes the size of the tumour (T), the spread of the tumour to nearby lymph nodes (N), and information about whether the tumour has spread to other parts of the body (M). An overview of the classifications is given in Appendix 2.1.

Gleason Score

The Gleason Score is a measure to indicate how abnormal cancerous cells in the prostate look and is given based on a biopsy. A higher Gleason score means the cells are faster growing and more aggressive. Appendix 2.2 provides an overview of how the Gleason scoring is utilized.

PSA level

Prostate-Specific antigen (PSA) is a protein produced by cells of the prostate gland. In a PSA test, the PSA level in a patient's blood is measured. Low PSA levels of around 4ng/ml are said to be normal for a man (National Cancer Institute 2023), while higher PSA levels can be an indicator of cancerous cells in the prostate, which is why the test is often performed in screening programs.

Risk Stratification

In Germany, as well as other European countries, the guidelines of the European Association of Urology (EAU) are used to assign a patient to a specific risk group (Mottet et al. 2021).

Risk classification distinguishes between low-, intermediate-, and high-risk patients, which are dependent on the TNM classification, the Gleason score, and the level of prostate-specific (PSA) antigen detected in the blood. The different risk groups according to EAU and their characteristics are shown in Table 1. Note that there are also other guidelines for prostate cancer treatment, for instance in the United States, where doctors are expected to follow the guidelines of the National Comprehensive Cancer Network (NCCN). There are some differences between the available guidelines with respect to risk classification but since our research is mainly focusing on the German healthcare system, guidelines of the EAU are provided.

Table 1: risk stratification by EAU

Low Risk	**Intermediate Risk**	**High risk**	
PSA < 10 ng/mL	PSA 10-20 ng/mL	PSA > 20 ng/mL	any PSA
and GS < 7	or GS 7	or GS > 7	any GS
and cT1-2a	or cT2b	or cT2c	cT3-4 or cN+
Localised			Locally advanced

Treatment selection

For patients belonging to a specific risk group, in Europe, there are guidelines about what treatments are recommended to be used, as shown in Appendix 2.1. It can be seen that for intermediate-risk prostate cancer patients, the main treatments recommended are watchful waiting, active surveillance, radical prostatectomy, and radiation therapy. When examining which of the treatments is actually performed for an intermediate-risk prostate cancer patient, Morgans et al (2022) found that there are significant differences in treatment selections across countries. In Figure 2, non-metastatic, intermediate-risk patients' treatment selection is shown in the upper half, indicated by "M-". It shows that treating a non-metastatic patient with prostatectomy in Germany is substantially more common than in the US or UK. Concurrently, the fraction of patients being treated with radiotherapy is more than 50% higher in the UK as compared to Germany. This indicates that there are differences in decisions made on how to treat prostate cancer patients.

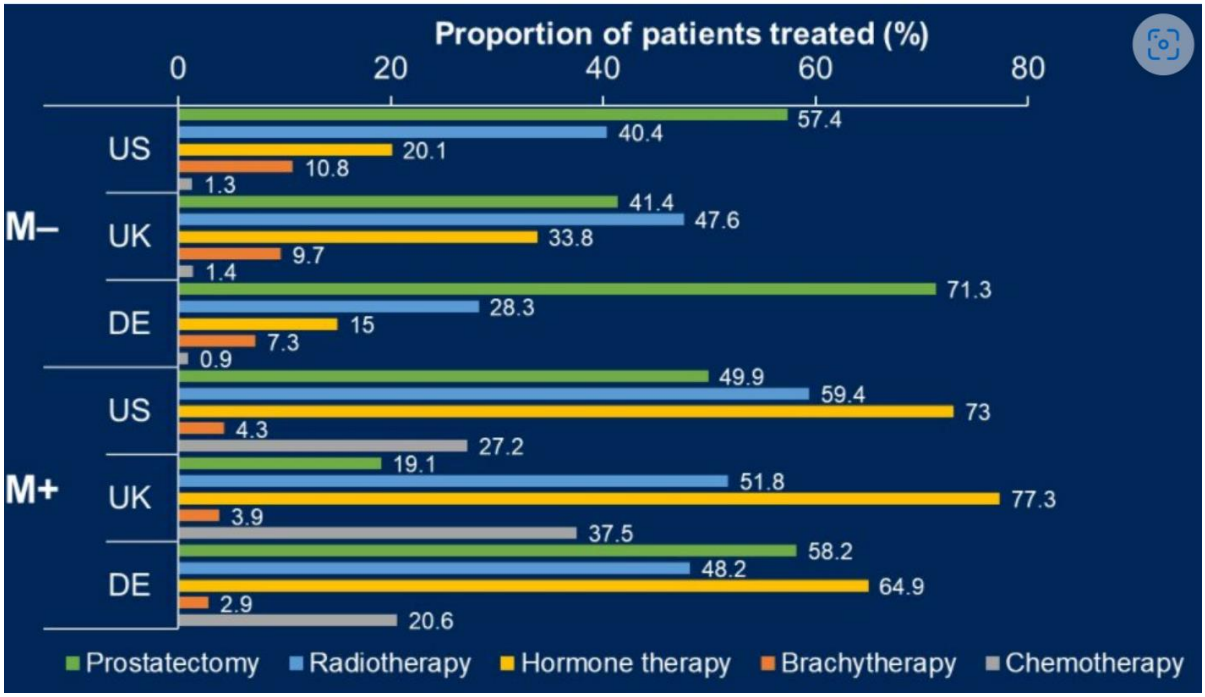

Figure 2: Treatment selection of intermediate-risk prostate cancer patients in Germany, the US and the UK (Morgans 2022)

Aiming to not only understand but improve the treatment-selection process for intermediate-risk prostate cancer patients in Germany, we investigate which individual characteristics of a patient are of importance when selecting a treatment.

Conclusion

Active Surveillance, radical prostatectomy and radiation therapy are the most commonly used approaches for prostate cancer management according to EAU guidelines. Within radiation therapy, we distinguish between SBRT or HDR brachytherapy as monotherapies or a combination of the two. Depending on patient characteristics like PSA level, Gleason score or TNM classification, patients are classified into specific risk categories. Even if guidelines of the EAU exist that recommend specific treatments per risk category there exist significant differences between treatment selection across the European countries.

3. Existing Research

As mentioned above, the treatment selection for patients with localized prostate cancer seems to not always be consistent, which indicates the high relevance of our research. Nevertheless, in order to examine to what extent our research is of value-added, it is essential to explore what research has already been conducted in this field. We therefore conduct a literature search to find relevant publications on the topic. The literature search strategy can be found in Appendix 3.

Literature on Cancer Treatment Selection

As shown in Appendix 3, searching for literature on the topic of cancer treatment selection in general, we find a large number of publications. For instance, Davies et al (2022) discuss recent developments in cancer care and stress the importance of "predictive and prognostic biomarkers" (Davies et al. 2022), referring to individual patients' tumour tissue characteristics that influence the treatment outcome for metastasized prostate cancer. It provides an overview of developments in cancer care and emphasizes the importance of research on the topic of cancer treatment selection. Nevertheless, being about metastasized cancer, it is to be seen as only partially relevant for our research.

Additional recent research on treatment selection for cancer patients is published by Jongeneel et al. (2021). They compare different chemotherapy treatment strategies for stage II colon cancer from a financial standpoint for which they develop a Markov model that compares the total cost of three different treatment strategies (Jongeneel et al. 2021). Even if there are major differences between their research and ours, such as the cancer type or compared treatment strategies, their approach to using a Markov model to compare the costs of different treatments seems of interest to us. We therefore research whether a Markov Model could be used in our research.

Markov Model

There is a possibility that localized prostate cancer recurs after initial treatment and a second decision on second treatment, so called salvage treatment, must be made. That is why the decision process for selecting a treatment for localized prostate cancer can be seen as sequential. Schaefer et al. (2005) argue in their book "*Operations Research and Health Care"*, Markov decision processes (MDPs) are an "*appropriate technique for model[l]ing and solving"* stochastic and dynamic decisions, since *"[m]edical treatment decisions are often sequential and uncertain"* (Schaefer et al. 2005). The idea to use an MDP for research in treatment selection is further approved by Imani et al. (2020), arguing that MDPs are an *"effective way to determine policies for sequential stochastic decision problems according to patients' specific conditions"* (Imani, Qiu, and Yang 2020).

Knowing that a Markov model can be used for our research, we further investigate whether there exist recent publications about treatment selection for localized prostate cancer patients that use a Markov model, as shown in the search log in Appendix 3.1.

Relevant publications

We identify two publications of relevance to our research, which we elaborate upon below. Weng et al. (2022) as well as Naser-Tavakolian et al. (2023) compare different options for treating localized prostate cancer from a financial point of view using a Markov model. Weng et al. (2022) compare different treatment options per risk category of a patient over an 8-year period. The model used can be seen in Figure 3.

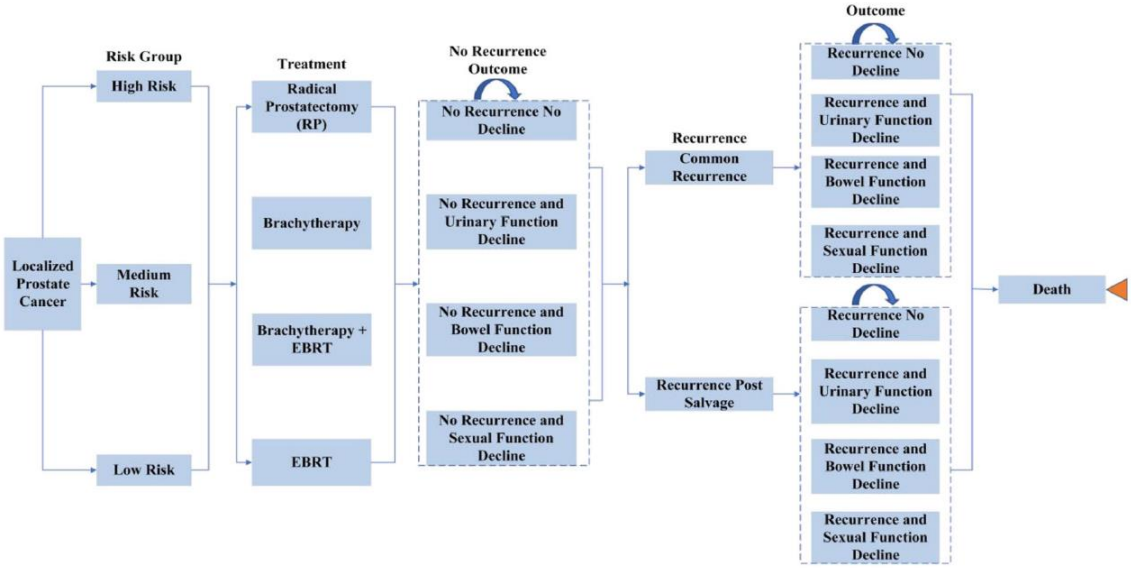

Figure 3: Markov Model Weng et al. (2022)

Similar to Weng et al. (2022), Naser-Tavakolian (2023) developed a Markov model to determine the optimal primary treatment for a specific patient with their individual characteristics, as can be seen in Appendix 4. They include age-adjusted prostate cancer comorbidity (PCCI) values, that influence treatment outcomes.

As mentioned, according to the guidelines for treating localized prostate cancer in Germany, prostatectomy, active surveillance as well as SBRT and brachytherapy as monotherapy and a combination of the two are the most relevant treatment options. Weng et al. (2022) compare the different radiation therapies mentioned to prostatectomy for low-, medium- and high-risk localized prostate cancer patients. They do not allow the decision actively surveil the tumour, even if especially for low-risk prostate cancer patients, active surveillance is found to be a cost-effective treatment option (Naser-Tavakolian et al. 2023; Noble et al. 2020). The selection of treatments compared is limited even further in the research by Naser-Tavakolian et al. (2023), who only compare active surveillance, prostatectomy and radiotherapy. Within the latter, they do not distinguish between the different treatment options there are, despite clinical proof of significant differences between EBRT, brachytherapy, and a combination of the two (Weng et al. 2022).

Weng et al (2022) conclude by providing insight into the most cost-effective treatment option based on a patient's risk classification. For patients in the medium-risk group, they argue that brachytherapy is the treatment associated with the lowest cost, while it also offers the lowest effect on quality-adjusted lifetime years (QALYs). Combining it with EBRT increases the costs significantly (from 52,723$ to 85,380$) while increasing the effect on QALY by 1,5. Naser-Tavakolian et al. (2023) find the

dominant treatment approach that is found to be the most cost-effective for each PCCI value of a patient diagnosed with localized prostate cancer.

Apart from the treatment options included in the research, it is also important to discuss the nature of the Markov models proposed in the two publications mentioned. As can be seen in Appendix 4, there is only a single decision made about treatment after a patient is diagnosed with cancer in the model created by Naser-Tavakolian et al. (2023). The flow of arrows going into one direction shows that the possibility that a patient can be treated again if the tumour is recurring, is excluded in their research. Similarly, it is not clear to what extent and how salvage treatments are taken into account by Weng et al. (2022). Based on their proposed model and the fact that they do not explicitly discuss it in their publication, we assume that they do not allow salvage treatments either. Not considering salvage treatment options is a major limitation, since we found that depending on the treatment and risk category of a patient, the probability of biochemical recurrence within five years after treatment is above 40% (Fuller et al. 2022a) while on average, 52,1% of the recurrences are again of localized prostate cancer (Price et al. 2016). Hence, not considering the possibility to treat recurring localized prostate cancer is an assumption that is too limiting and prohibits generalizing the results in clinical practice.

Conclusion

Markov Modelling is a suitable technique for modelling medical treatment decisions, as current literature uses it for optimizing cancer treatment selection for localized prostate cancer patients. However, in existing research, simplifying assumptions are made that significantly limit the use of results in clinical practice. We will develop a Markov Model for our research that includes the most relevant treatments for localized prostate cancer as well as secondary treatment selection. Thereby, we overcome the major limitations of existing research and provide a framework for optimal treatment selection in Germany in practice.

4. Mathematical Model

Having concluded that a Markov model is suitable for our research in Section 3, in this section, we elaborate on how we structure the Markov model in Section 4.1, before formulating the mathematical model in Section 4.2.

Model Structure

As explained, in our model we relax the assumption that a patient can only be treated once. Using a Markov decision process (MDP) to optimize decision-making will allow sequential decision-making. Thereby, we are able to include the possibility that patients can be diagnosed with localized prostate cancer more than once and therefore, a decision about what treatment to perform can be made twice for a single patient, which will increase the realism of the models presented in the existing publications. However, the EUA guidelines do not include any information on treatment selection or constraints for treating cancer that recurs twice, so selecting a tertiary treatment. That is why for our research, we limit the treatment options for secondary treatments based on what primary treatment a patient has received. For that, we use the EUA guidelines about treating recurring cancer, which are discussed in Section 4.2 – *decision variables*.

Figure 4 displays the structure of the Markov Model created in our research. The upper part represents the model structure as it was done by Naser-Tavakolian et al. (2023). As all input values of Naser-Tavakolian et al. (2023) are published, we use their research as a baseline and extend it by adding the secondary treatment selection, which is presented in the red part of Figure 4.

As Figure 4 shows, after a patient is diagnosed with localized prostate cancer, a decision is made on the primary treatment for that patient. Based on the treatment selected, the patient enters different states with specific probabilities after treatment. First, if Active Surveillance is selected, the patient's cancer is not fought directly. Instead, the patient is kept under Active Surveillance, while the localized prostate cancer remains unchanged. However, the patient might develop side effects, or the cancer begins to spread which results in the patient entering the stage "metastasis". Additionally, a patient under active surveillance might change their opinion on receiving primary treatment, which is indicated by the arrow going back from "Localized PCa under AS" to "Patient with localized prostate cancer".

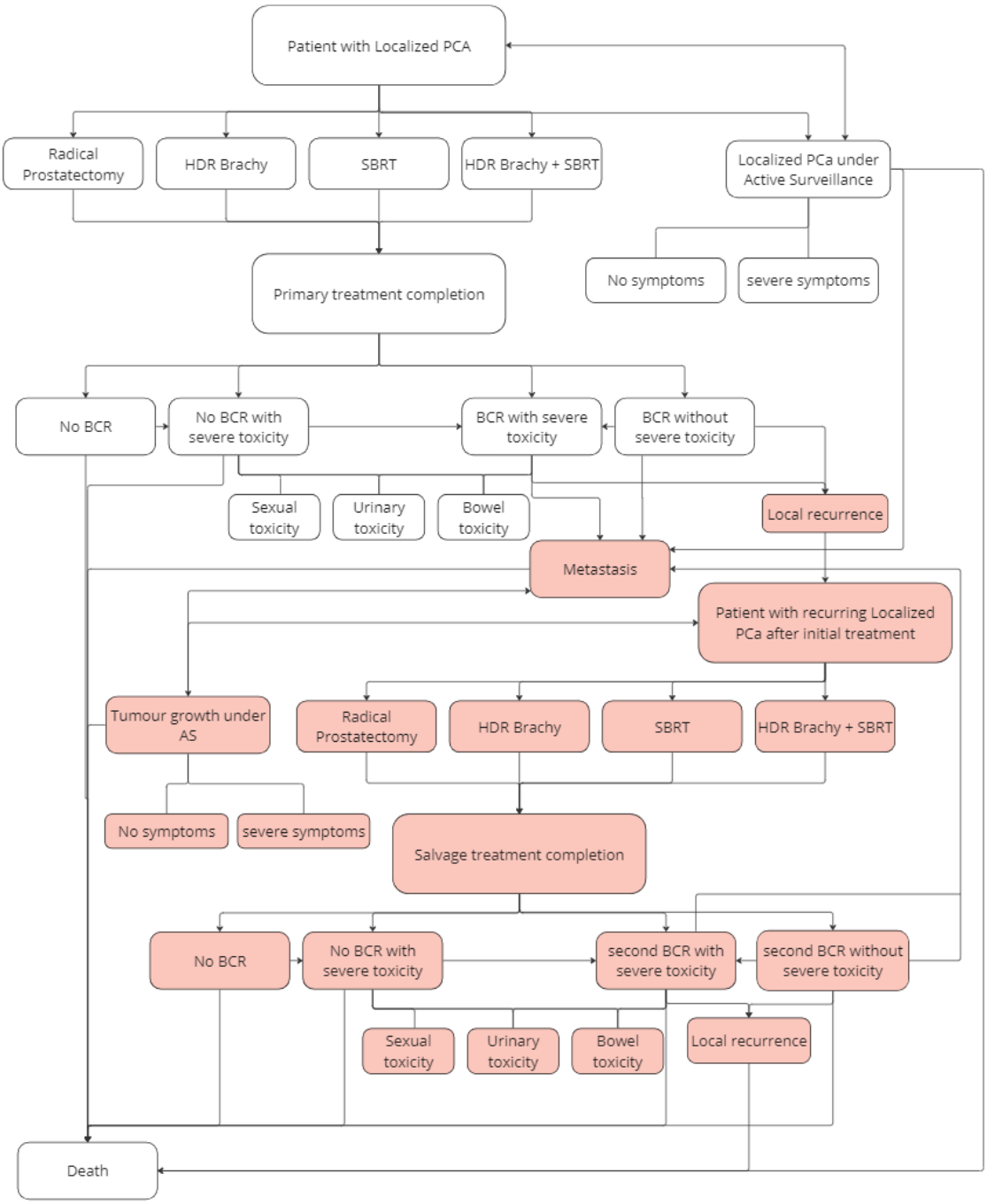

Figure 4: Markov Model for optimal treatment selection

If a patient receives any of the other treatments, namely Radical Prostatectomy (RP), HDR Brachytherapy, SBRT or a combination of SBRT and Brachytherapy, different treatment outcomes can occur. After treatment, the patient can be cancer free for some time, but there is a possibility that there is biochemical recurrence (BCR). Indifferent from the presence of cancer, a treated patient might develop toxicities, as discussed above. In the case of BCR, the cancer might be metastasized and cannot be treated by the treatments compared in our research. In that case, the patient can remain with metastasized cancer for some time before eventually dying. However, as explained above, some patients with BCR develop local recurrence and can receive one of the treatments included in our

research again. Guidelines on salvage treatment selection are taken into account, but there exists a possibility that patients undergo one of the treatments again, and similar to after the primary treatment selection, enter one of the treatment outcome situations with or without severe toxicity as well as with or without BCR.

We should acknowledge the limitation of not including any treatments for patients with metastasized cancer following primary treatment. Both cases would significantly increase the complexity of the model and we think, this is a reasonable simplification to make, given that even more simplifications are made in existing research. The possibility to include treatments for metastasized cancer and the related treatments with costs assigned and different outcomes is left for future research.

The guidelines of EAU only cover secondary treatments such that we do not consider the rare case in which recurring localized PCa can be treated more than twice. Additionally, the follow-up period for cancer treatments is often around five years, which is why the probabilities of some specific outcomes are given for five years. This is elaborated more upon in the section "Input parameters". Since we found that a number of specific treatment outcomes are not researched for more than five years, and we allow at most two treatments, we decide to limit the Markov model to ten years. That trade-off must be made between long-term toxicity management costs being underrepresented in our research if we decide on a shorter time period in the model and treatment outcomes such as toxicities and biochemical recurrences becoming less reliable on a very long time horizon.

Model formulation

To formulate the problem as a Markov Model, we define stages, state variables, decision variables, transition function, and immediate cost function. Then, we introduce the objective function and provide the recursive formulation.

Stages

Since we assume we can make decisions every 6 months, we define the stage as the start of month t where $\in \{1,7,13,\dots,121\}$.

State

Knowing that a characteristic of a Markov model is that a decision can be made by only considering the current state without looking at past states, it is important to create states that include history (Siebert et al. 2012).

We define state variables {i,j,k,l} such that they provide enough information to allow decision-making without looking at the past states of a patient:

- i: initial risk category of a patient
- j: health status of a patient {Patient with localized PCa, localized PCa under AS, no cancer after primary treatment, BCR after primary treatment, primary local recurrence, Patient with recurring PCa after initial treatment, recurring PCa under AS past initial treatment, No cancer past salvage treatment past initial treatment, BCR post salvage treatment past initial treatment, metastasis, death}.
  Note that
  $\{primary\ treatment, salvage\ treatment\} \in \{AS, RP, Brachy, SBRT, Brachy + SBRT\}$.
- k: main toxicity of a patient {none, GU, GI, sexual}
- l: number of time periods in that state {0,1,…12}

Decision variable

Every six months, a decision D is made about what treatment is performed for a patient.

$$D \in \{AS, RP, Brachy, SBRT, Brachy + SBRT\}$$

We consider that not all decisions can be done at all times. As shown in Table 2, the set of feasible decisions depends on the current health status of a patient.

Table 2: feasible decisions per health status

Health status	**Feasible decisions**
Patient with Localized PCa	$\{AS, RP, Brachy, SBRT, Brachy + SBRT\}$
Primary PCa under AS	$\{\}$
No cancer after primary treatment	$\{\}$
BCR post-radiation therapy (Brachy / SBRT / Brachy & SBRT)	$\{\}$
BCR post radical prostatectomy	$\{\}$
Local PCa recurrence after primary treatment	$\{AS, (RP), Brachy, SBRT, Brachy + SBRT\}$
Recurring PCa after radiation therapy (Brachy / SBRT / Brachy & SBRT) under AS	$\{\}$
Recurring PCa after RP under AS	$\{\}$
No cancer post salvage treatment	$\{\}$
Second BCR	$\{\}$
Metastasis	$\{\}$
Death	$\{\}$

The EUA guidelines on secondary treatment selection do not exclude the possibility to radiate a patient again after having received any type of radiation therapy as primary treatment. The treatment outcomes can of course be expected to differ, which we take into account with specific input parameters for primary and salvage treatment outcomes. As a consequence of the fact that radiation therapies can be performed more than once, the only strict limitation of salvage treatment selection is therefore that a patient who has received primary radical prostatectomy cannot be treated with surgery again, since most of, or the entire prostate has already been removed.

Transition function

Taking decision d at stage t and state (i, j, k, l) results in an update in the stage to $t + 1$ and state to (i',j',k',l'). This transition function depends on the decision made as well as the risk classification of a patient and transition probabilities.

Since we do not differentiate between different risk categories for salvage treatment selection but use average values, the risk category of a patient is only relevant for the treatment outcome after their initial treatment. Using the initial risk category of a patient is hence sufficient throughout the model. Consequently, there is no need to update the risk classification of a patient. Therefore, we define the following constraint:

$$i = i'.$$

The health status of a patient, j, might change based on stochastic values found in literature and decision d. Due to the nature of the process, there are limitations to health status that can be transitioned to, as shown in Table 3.

Table 3: possible health status transitions

Health status in period t	**Possible health status in period t+1**
Primary treatment selection	{No cancer after primary treatment, primary PCa under AS, BCR after primary treatment, death}
Primary PCa under AS	{Primary PCa under AS, primary treatment selection, metastasis, death }
No cancer after primary treatment	{No cancer after primary treatment, BCR, metastasis, death}
BCR after primary treatment	{Patient with recurred localized PCa, metastasis, death}
Patient with recurred localized PCa past initial treatment,	{Patient with recurred localized PCa past initial treatment, no cancer post salvage treatment past initial treatment, metastasis, death}
recurring PCa after primary treatment under AS	{recurring PCa after primary treatment under AS, Patient with recurred localized PCa past initial treatment, metastasis, death}
No cancer past salvage treatment past initial treatment	{No cancer past salvage treatment past initial treatment, BCR, metastasis, death}
BCR	{BCR, Metastasis, death}
Metastasis	{Metastasis, death}
Death	{death}

A visual overview of possible state transitions is given in Figure 5. A patient does not transition health status every time period. In grey, health statuses are highlighted that the patient can stay in for more than one time period.

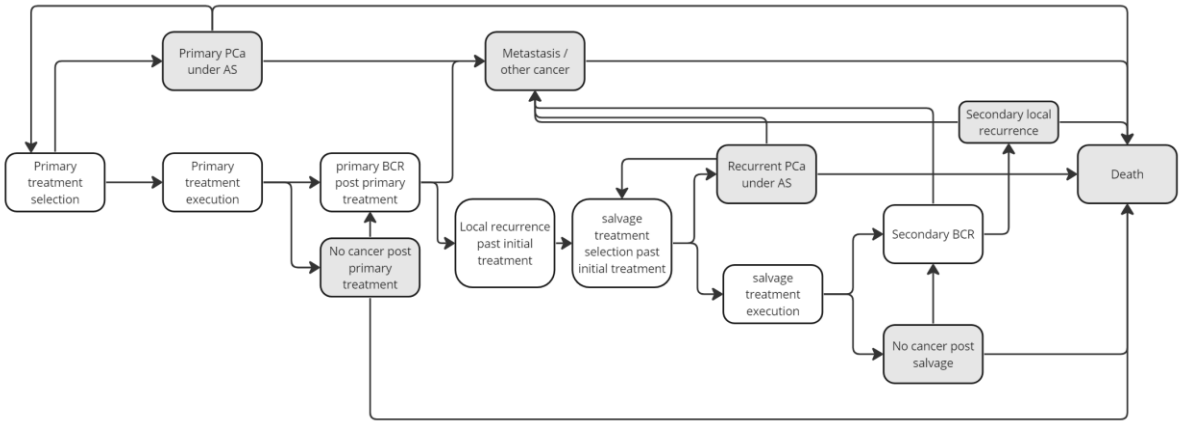

Figure 5: health status transition overview

In case the patient's health status does not change, the time, l', they have spent in that status increases by one. Otherwise, they are new in a new health status. Then, the time they are in the health status is 0.

$$l' = l + 1 \;\; \forall \, j = 0$$

$$l' = 0 \ \forall j \neq 0$$

Further, as discussed with experts in the field of cancer care, we assume that potential toxicity of a patient does not change after 3 years after treatment, since we believe in this case, patient with toxicity have developed treatment-related toxicity that cannot be cured. Hence, the following constraint is formulated.

$$k' = k \ \forall \ l' > 6.$$

Value function

The value function $f_t(i,j,k,l)$ represents the minimal total costs of treating a patient, managing the long-term toxicity and costs associated to lost utility of a patient's life from period t until the end of the observation period. It consists of direct costs related to a patient being in state (i,j,k,l), $Dr(j,k,l,d)$, and the indirect costs of the future states.

$$f_t(i,j,k,l) = \min_{d \in D} \left[Dr(j,k,l,d) \ + \sum_{i',j',k',l' \in I',J',K',L'} f_{t+1}(i',j',k',l') * P(i',j',k',l'|i,j,k,l,d) \right]$$

The direct cost related to a patient being in state (i,j,k,l), and decision d is made, $Dr(j,k,l,d)$, consists of treatment costs, toxicity management costs and costs associated to lost utility. Hence, the health status (j), the main toxicity (k), and the decision made (d) impact the direct costs.

We introduce the following notation:

- $TC(d) : Treatment\ cost\ of\ treatment\ d$
- $MC(k) : Cost\ per\ 6\ months\ of\ managing\ toxicity\ k\ of\ a\ patient$
- $LU(j) : Cost\ of\ lost\ quality\ of\ life\ of\ a\ patient\ being\ in\ health\ state\ j\ for\ 6\ months$

$$Dr(j,k,l,d) = TC(d) + MC(j,k,l) + LU(j)$$

Where,

$$LU(j) = \big(1 - Utility(j)\big) * \ QALY\ threshold.$$

And,

$$TC(d) : treatment\ cost\ of\ treatment\ d$$

And,

$$MC(j,k,l) : Cost\ of\ managing\ toxicity\ of\ a\ patient\ in\ state\ (j,k,l)\ for\ 6\ months.$$

Treatment costs, toxicity management costs, QALY threshold and utility values are researched in the literature and kept as adjustable input values in our model.

Since we decide to include a 10-year period in the model, we do not include any costs that incur after that period. Hence, the following terminal condition can be defined for month 121:

$$f_{121}(i,j,k,l) = 0 \ \forall \ i,j,k,l$$

Using the described constraints about possible decision and health status transitions together with the terminal condition, we are able to compute total expected costs per treatment for every time period and every state a patient can find themselves in. The outcomes of the formulated model additionally depend on the probabilities of treatment outcomes and treatment-related toxicity. In the next two sections, we elaborate on the input parameters and outcomes of the model, respectively.

Conclusion

In this section, we defined the mathematical model and discussed its structure. Using an MDP, we are able to allow sequential decision-making and take into account the EAU guidelines for treatment selection. We formulate the mathematical with 6-month periods as stages and states being the current health status of a patient. The decision on treatment selection can only be done if a patient finds themselves in some specific state. Hence, we define possible decisions per health state as well as feasible health state transitions. The value function consists of a direct cost, including treatment costs, toxicity management costs as well as costs assigned to lost utility, and costs starting from the next 6-month period until the end of the observed period.

5. Instance parameter description

In this section, we describe the relevant input data, consisting of the different cost parameters as well as treatment outcomes. Considering the cost values, we discuss direct costs related to treatment as well as the costs of managing treatment-related toxicity and the costs associated with the lost utility of a patient. Treatment outcomes are mainly about the probabilities of treatment-related toxicities and different probabilities of cancer recurring after a specific treatment.

The calculations in the model that allow finding the treatment with the lowest overall cancer treatment-related cost are based on cost values and treatment outcomes identified in the literature. Of course, we try to find reliable data, but we are aware that there are limitations to the accuracy of values used today, and even more importantly, we know that treatment costs and probabilities of outcomes will change over time for instance due to improvements in cancer care. With data currently available in the literature, we show the working of the model and conduct a sensitivity analysis on some input parameters. If new evidence is available, for instance, because of technological progress, the input parameters can be adapted, and the model can be run with these new values.

For simplicity, we display the actual values used in Appendix 6. Nevertheless, we elaborate on them, and if relevant, the assumptions we made, in this section.

Treatment outcomes

To gain insight into the outcomes of different treatments, we conduct a literature search to answer the following question:

What are possible clinical outcomes of treatments and what are the corresponding probabilities?

We found a large number of comorbidities that can occur after different cancer treatments. After discussions with experts in the field of cancer care at Elekta, we decided to restrict comorbidities included in our research to urinary, bowel and sexual comorbidities of grade 3 and higher, because those seem to be the most relevant comorbidities after prostate cancer treatments and starting at grade 3, significant costs related to managing the toxicity occur.

Since for several treatment outcomes, the probabilities of occurring are not given in six-month periods, but are needed for our model, we assume that the probabilities remain constant between given periods. Hence, we use the following formula to convert given cumulative probabilities in six-month period rates:

$$r = \frac{\ln\left(\frac{1 + A_t}{1 + A_0}\right)}{\Delta t}$$

Where

$$r = \textit{6-month probability}$$

$$A_0 = probability\ until\ beginning\ of\ observed\ period$$

$$A_t = probability\ at\ end\ of\ observed\ period$$

$$\Delta t = \textit{time difference between } t_0 \textit{ and } t_1 \textit{ in number of 6-month periods}$$

This for instance, allows us to translate a 6% probability of cancer recurring in one year to a 2,91% probability of cancer recurring in the first half of a year, assuming that the continuous rate of cancer recurrence remains constant over that year. An example of values used as input for the model is provided in Table 4:

Table 4: Toxicity rates after initial treatment

Toxicity after initial treatment					
Symptoms	**Active Surveillance**	**Radical Prostatectomy**	**Brachy**	**SBRT**	**Brachy + SBRT**
Sexual					
1 year	*2,20%*	*43,10%*	*27,50%*	*22,40%*	*7,38%*
2 years	*8,09%*	*40,27%*	*34,27%*	*27,93%*	*9,01%*
3 years	*14,70%*	*37,60%*	*42,00%*	*34,09%*	*10,70%*
Urinary					
1 year	*0,00%*	*18,50%*	*6,44%*	*0,22%*	*0,78%*
2 years	*1,82%*	*17,85%*	*13,06%*	*0,43%*	*1,57%*
3 years	*3,70%*	*17,20%*	*20,60%*	*0,65%*	*2,37%*
Bowel					
1 year	*0,00%*	*0,00%*	*0,00%*	*0,00%*	*0,00%*
2 years	*0,25%*	*0,00%*	*0,00%*	*0,00%*	*0,00%*
3 years	*0,50%*	*0,00%*	*0,00%*	*0,00%*	*0,00%*

The references to the values used can be found in Appendix 5. Additional values used in the model are given in Appendix 6.

Treatment costs

Wanting to reduce healthcare expenditure overall, we investigate the costs from a payer's perspective. Therefore, we examine the costs health insurances in Germany pay for specific treatments, which are shown in Appendix 6. The accurate reimbursements paid by the insurers, according to experts in the field, seem to differ between each hospital. Since there are no predefined and transparent prices insurance companies pay, the actual costs per treatment seem to depend on the negotiation skills of a hospital to some extent and are seldom published. We hence use average values found in the literature that do not distinguish between privately and publicly insured patients, which can be adapted in the future. Especially, considering the current discussion on a reformed payment system for German hospitals, where hospitals receive a lump-sum reimbursement for specific treatments and thereby economic pressure is reduced (Bundesministerium für Gesundheit 2023), we expect that treatment costs can be estimated better within the near future.

Costs of managing toxicity

Apart from the costs that arise from the treatment itself, different patients' toxicity profiles and related costs should be considered when selecting the optimal treatment. As mentioned above, we limit treatment-related toxicities included in our research to urinary, sexual and bowel comorbidities of grade 3 and higher. Similar to the direct treatment costs, we use average values found in the literature that can be adapted easily. These are shown in Appendix 6.

Valuing a patient's life

Making a trade-off between a treatment's cost and the expected outcome is challenging and raises ethical questions. Can a doctor reject a patient receiving the treatment that would promise the best clinical outcome to that patient, if the treatment costs are too high? Undoubtedly, every patient should receive the treatment best suitable for them. However, already today, the mentioned trade-off is made using so-called "willingness to pay" (WTP) values per QALY gained (Iino, Hashiguchi, and Hori 2022).

Together with the challenges concerning financing healthcare expenditure in the future, as mentioned in the introduction, this economic evaluation of different treatments gains importance. If treating a patient with treatment A costs a multiple as compared to if they had been treated with treatment B, but the difference in clinical outcome is minimal, the latter one might be the treatment to select in order to avert redundantly high healthcare expenditure.

As indicated, today, to make decisions about whether the expected clinical outcome justifies the costs of treatment, insurance companies define a threshold value that is acceptable to spend per QALY gained. In the literature, we found that reimbursement companies in Germany on average seem to take 30 000€ in 2012 as a threshold for acceptable treatment costs if the expected quality-adjusted lifetime increases by one year (Gandjour 2012). With total inflation of 21,9% between 2012 and 2022 (THE WORLD BANK 2023), we computed that the WTP value per QALY gained in Germany today is approximately 36 570€.

Implementation

Based on the mathematical model defined and the structure of the model, we solve the Markov decision process with stochastic dynamic programming. Therefore, we compute the total expected cost from a given time until the end of the period, given that a patient finds themselves in a specific state at a specific time. We solve it recursively, meaning that we start from the last time period, and find the optimal decision and related total costs to every health state computing the total expected costs from the second to last period until the end, given a specific health state. After, we are able to compute the costs from the time before until the end, including the previously computed costs for the final stage as described in the mathematical model. This is repeated until the total expected future costs of the first time period are computed.

We decide to implement the mathematical model in the pre-installed program in Excel, Visual Basic for Applications (VBA). That is because it can be seen as a program commonly understood and allows one to easily adjust the input values used in the model on an Excel spreadsheet and by clicking on a button, updating the solution.

We implement the mathematical model and test it by computing the costs in different parts of the code and evaluating whether there are differences. Additionally, we test for every state, that the probabilities to any other state sum up to one. For instance, a patient with no cancer after treatment can either remain in this state, develop BCR, or die, as can be seen in Figure 5. The probability that a patient without cancer after treatment transitions to either of the three states mentioned must be one since there are no other options.

Furthermore, we comment on the code in many parts to explain what each part is doing. This allows us to not only go through it and critically assess it today, but also enables the model to be adjusted in the future when guidelines change or additional aspects are taken into account in future research.

Despite the complexity of the problem at hand, we are able to efficiently implement the mathematical model in VBA such that using a button on the sheet, the results can be updated in a fraction of a second. The run time currently is found to be between 0,4 and 0,5 seconds on our devices.

Conclusion

We found input values that we can use for solving the mathematical model. Since there is such a great amount of input data points, for simplicity and readability, we display most actual values used in the

appendix. As explained in this section, we are able to transform cumulative data points over longer time periods than 6 months into 6-month rates and find treatment outcomes that depend on a patient's risk category and the treatment performed, as shown in Appendix 6. Direct costs of treatments as well as costs associated with managing toxicity are provided in Appendix 6. Further, we found the costs assigned to the utility of a patient to be around 36 570€ per year.

Having defined the mathematical model in Section 4 and found input values in this section, we are able to implement the model in VBA. To solve it, we use dynamic programming and proceed recursively. Running for around half a second, the code finds the optimal treatment per risk category, as discussed in Section 6.

6 Results

In this section, we first display the results of the model with the input parameters as explained above and discuss the results thereafter. Additionally, we analyse how the output would change in case the WTP value is changed.

Outcomes of the Model

Solving the mathematical model with the input parameters as discussed yields different expected total costs. Figure 6 displays the total costs per primary treatment selected and risk group.

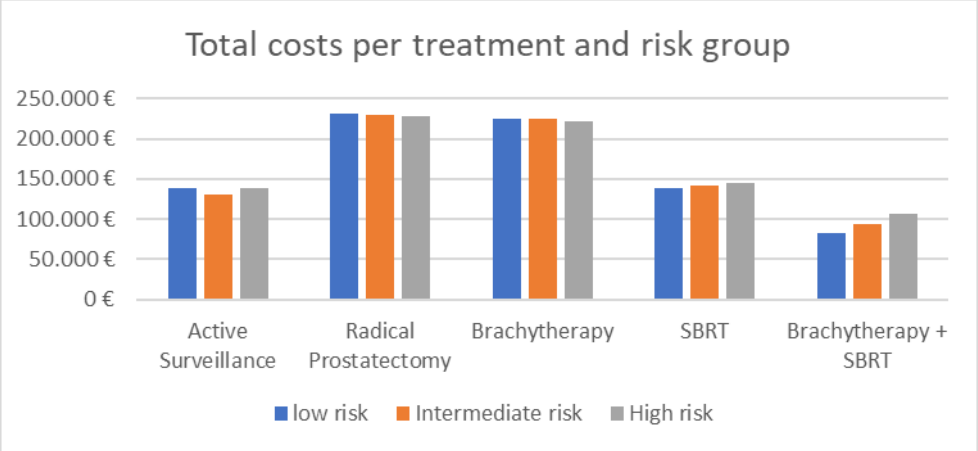

Figure 6: total costs per treatment and risk group

There are major differences with regard to total expected costs among the different primary treatments selected. The SBRT treatment with a Brachytherapy boost (called "Brachytherapy + SBRT in Figure 6) has the lowest costs associated and can hence be seen as the most attractive primary treatment selected for all risk groups. Further, the higher the risk group, the higher the expected total cost for men treated with SBRT + Brachytherapy. The same pattern can be seen for SBRT treatments, while for the other alternatives, there is not a clear correlation between a risk group and the expected total costs.

To further investigate the differences in costs per primary treatment selected and the risk group, we display the distribution of the costs, for low, intermediate and high-risk group patients in Figures 7, 8 and 9, respectively.

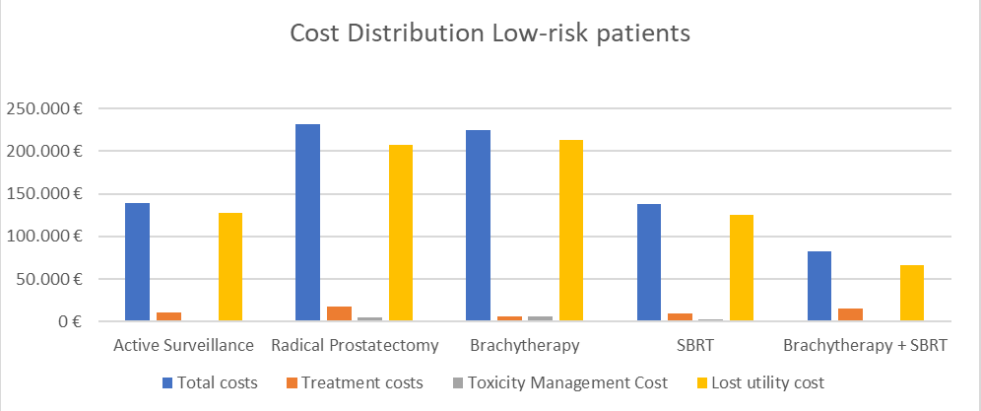

Figure 7: Cost distribution per treatment for low-risk patients

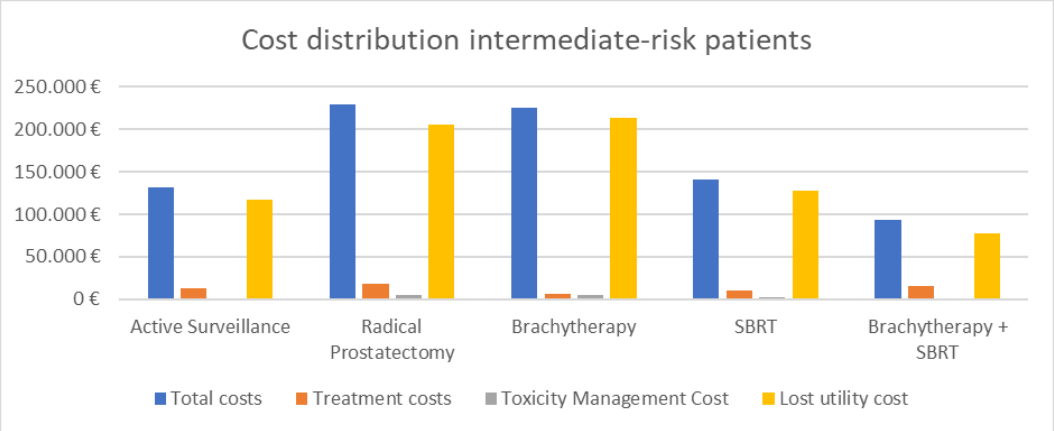

Figure 8: Cost distribution per treatment for intermediate-risk patients

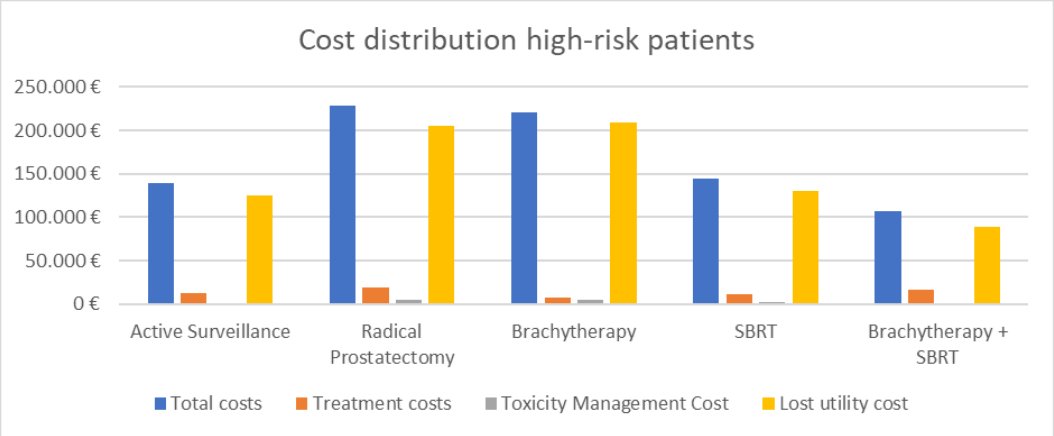

Figure 9: Cost distribution per treatment for high-risk patients

Figures 7-9 allow comparing the direct treatment costs, toxicity management costs and lost utility costs. The lost utility cost is very high compared to toxicity management costs and direct treatment costs. If for instance brachytherapy treatment is chosen to be the primary treatment for a low-risk patient, direct treatment and toxicity management costs each make up two to three per cent, while lost utility costs constitute to more than 94% of the total costs.

As mentioned, for the optimal treatment to select, namely SBRT + Brachytherapy, there exists a positive correlation between the risk classification of a patient and the total expected costs, as expected. Therefore, patients with higher risk classifications, who have higher chances of cancer recurring and eventually dying from the disease, incur higher total expected costs.

The total costs for low-risk patients treated with Brachytherapy being slightly lower than for higher-risk patients is not as expected. However, it can be explained by the input parameters of the model. As explained, the model does not distinguish between different probabilities of toxicities occurring for the different risk groups. The high toxicity rates for primary Brachytherapy lead to high toxicity management and lost utility costs after treatment and therefore make Brachytherapy a less attractive primary treatment. The longer a patient has those high side effects after brachytherapy, the more expensive it is. Since the probability of biochemical recurrence is higher for high-risk patients than for low-risk patients, the expected time between primary and secondary treatment is lower for high-risk patients. If cancer returns in the form of localized prostate cancer, it can be treated again and the

optimal treatment is selected in the model. This treatment is likely to be different from Brachytherapy and has lower side effects, hence lower toxicity management costs and lower lost utility costs. The costs being slightly lower for high-risk patients is a consequence of side effects after primary Brachytherapy treatment and therefore, a sooner selection of optimal salvage treatment with lower toxicity levels yields a lower cost. For further research, the probabilities of treatment-related toxicities should be revised, since we question that probabilities of toxicities arising after a salvage treatment are lower than they had been before the treatment.

Furthermore, as described above, toxicity management costs can be seen to be relatively low compared to the other costs identified. This can be explained by rather low input values assigned to managing toxicity. For instance, if a patient has an erectile dysfunction after treatment, the costs of managing that toxicity is 470,5€ per 6 months. At the same time, the utility being 89% in that case, the costs associated to lost utility are 4022,7€ ((100%-89%) * 36570€).

As Figures 7-9 show, the costs of lost utility, which are partially caused by high toxicity levels, contribute significantly to the total costs which is why indirectly, treatment-related toxicity does have a greater effect on total cost than toxicity management costs only. That can be explained by the high input value of threshold willingness to pay 36 570€ per QALY gained. If a patient's quality of life is mitigated, the costs assigned to the lost utility are consequently very high.

Sensitivity analysis

Since we question the realism of lost utility cost being that high, and it is subjective to the decision maker, what monetary value they would assign to a patient's QALY gained or lost, we change the input value for the QALY threshold and compare the outcomes. We use 51 QALY input values ranging from 0€ to 10 000€ in steps of 200. We chose the upper limit after seeing that SBRT + Brachytherapy treatments are optimal for all risk categories for QALY values above 5000 and hence, extending the experiment to a higher upper boundary is not expected to be insightful but rather decrease the visibility of changes in cost distributions for the low QALY values. Figures 10, 11, and 12 show the distribution of total costs with the changing QALY input value explained for low-, intermediate-, and high-risk patients.

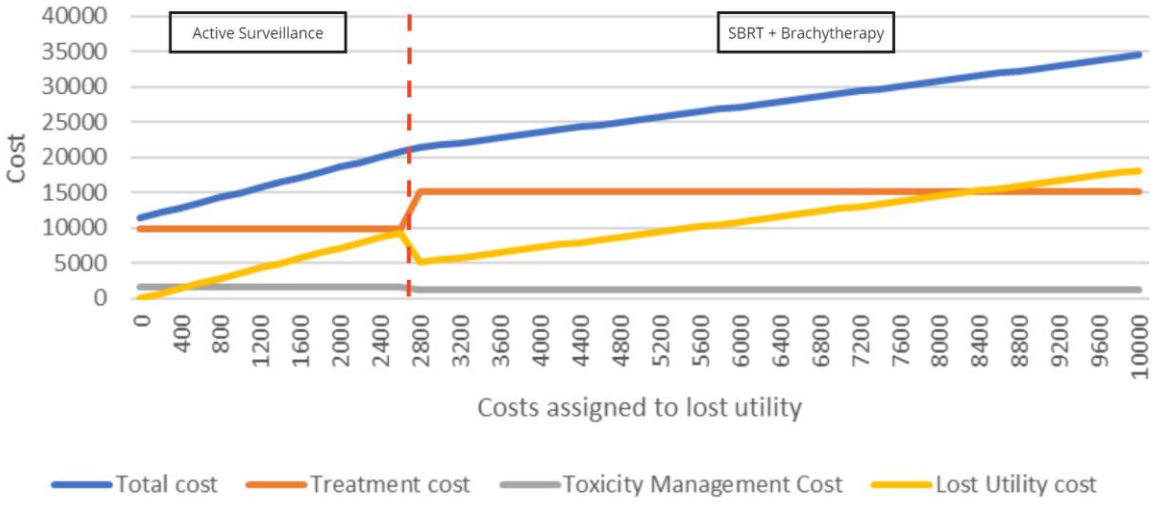

Figure 10: Cost distribution for low-risk patients depending on lost utility cost

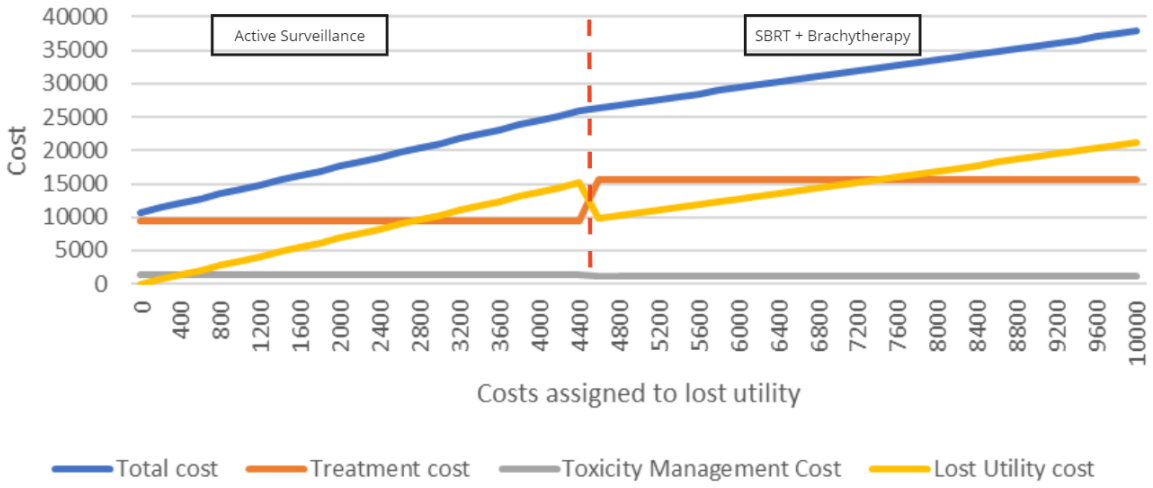

Figure 11: Cost distribution for intermediate-risk patients depending on lost utility cost

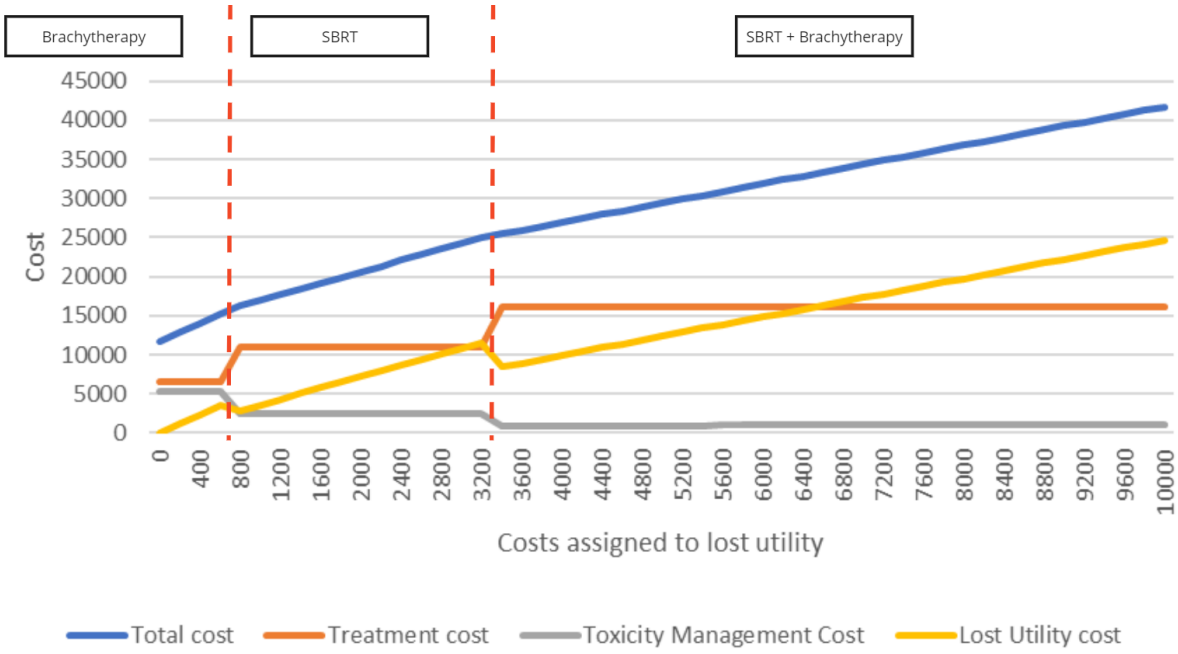

Figure 12: Cost distribution for high-risk patients depending on lost utility cost

As expected, the figures all show that there is an increase in total costs with higher QALY values used as input. The total curve presented in blue, for all risk groups seems to not be a linear function. Instead, they appear to be linear on the right halves of Figures 10-12. For low- and intermediate-risk patients, one bend can be seen, while for high-risk patients, there are two. At a closer look, it can be seen that those bends in total costs are at the same QALY values, where the curves for the individual cost contributors change. Apart from the QALY value, all other input parameters remain the same, if the treatment selected does not change, the treatment as well as toxicity management cost does not change. This is shown by the grey and orange graphs being horizontal apart from single points of QALY. Those points are the ones, at which the optimal treatment changes. It can be seen that with an increasing QALY value, treatments for all risk groups change. The numerical output shows that for low-risk patients for instance, the most attractive treatment is Active Surveillance for QALY values below

2800€, while for higher values, SBRT + Brachy is the optimal treatment to select. That explains the change of the orange and grey lines in Figure 10. Similarly, Figures 11 and 12 can be used to find threshold values of QALY input values at which the optimal treatment selection is changed. Similar to low-risk patients, the optimal treatment to select for intermediate-risk patients changes from Active Surveillance for low QALY values to SBRT + Brachytherapy for higher values. For high-risk patients, two changes in optimal treatment to select can be seen. For them, based on the input data and EAU guidelines included in the model, Brachytherapy is the treatment to choose for QALY values below 600€, while SBRT is optimal for QALY values between 800€ and 3200€, and the combination of SBRT and Brachytherapy yields the lowest expected total costs for any QALY input value above 3200€. Brachytherapy being the optimal treatment for high-risk patients if a low QALY value is used in the model is a possible consequence of input parameters about treatment costs and outcomes, but might also be different to the other risk categories, since Active Surveillance, as discussed in Section 2, is not a treatment option for high-risk patients according to the current EUA guidelines.

The threshold at which Active Surveillance becomes less attractive than alternative treatments being at higher QALY costs for low-risk than for intermediate-risk patients indicates that Active Surveillance is a more attractive treatment for intermediate-risk patients than for low-risk patients. Again, this deviates from our expectations, since we would expect patients with a higher-risk category to benefit more from a definitive primary treatment than low-risk patients. Nevertheless, this is not an unrealistic result based on the input parameters used in the model, such as in this case, the probabilities of developing symptoms under Active Surveillance or the probabilities of patients asking for definitive treatment after Active Surveillance.

Analysing the effect of changing QALY input values to the output of the model shows the effect a single value can have on the entire solution. Depending on what value is used, not only the total costs but also the optimal treatment to select change. That emphasizes the importance to review input values used in the model and verify that input values are updated with new data published in the future.

In addition to the sensitivity analysis on the effect that a change of costs assigned to utility has on the model's outcome, we investigate how changes in toxicity levels affect the treatment. Discussing the current input variables with experts from the field, they indicate that the toxicity levels of Brachytherapy might be too high. That is why we decide to conduct another sensitivity analysis on the optimal treatment selection depending on the toxicity levels after initial brachytherapy. Therefore, we conduct an experiment that, starting with initially used values, decreases those in steps of 5% and evaluates how the optimal treatment selection changes. The results are shown in Table 5.

Table 5: Optimal treatment selection per risk-group and toxicity levels for brachytherapy.

Multiplier for Initial Brachytherapy Toxicity	Optimal Treatment		
	Low-Risk Patients	Intermediate-Risk Patients	High-Risk Patients
1	Brachytherapy + SBRT	Brachytherapy + SBRT	Brachytherapy + SBRT
0,95	Brachytherapy + SBRT	Brachytherapy + SBRT	Brachytherapy + SBRT
0,9	Brachytherapy + SBRT	Brachytherapy + SBRT	Brachytherapy + SBRT
0,85	Brachytherapy + SBRT	Brachytherapy + SBRT	Brachytherapy + SBRT
0,8	Brachytherapy + SBRT	Brachytherapy + SBRT	Brachytherapy + SBRT
0,75	Brachytherapy + SBRT	Brachytherapy + SBRT	Brachytherapy + SBRT
0,7	Brachytherapy + SBRT	Brachytherapy + SBRT	Brachytherapy + SBRT
0,65	Brachytherapy + SBRT	Brachytherapy + SBRT	Brachytherapy + SBRT
0,6	Brachytherapy + SBRT	Brachytherapy + SBRT	Brachytherapy + SBRT
0,55	Brachytherapy + SBRT	Brachytherapy + SBRT	Brachytherapy + SBRT
0,5	Brachytherapy + SBRT	Brachytherapy + SBRT	Brachytherapy + SBRT
0,45	Brachytherapy + SBRT	Brachytherapy + SBRT	Brachytherapy + SBRT
0,4	Brachytherapy + SBRT	Brachytherapy + SBRT	Brachytherapy
0,35	Brachytherapy + SBRT	Brachytherapy	Brachytherapy
0,3	Brachytherapy	Brachytherapy	Brachytherapy
0,25	Brachytherapy	Brachytherapy	Brachytherapy
0,2	Brachytherapy	Brachytherapy	Brachytherapy
0,15	Brachytherapy	Brachytherapy	Brachytherapy
0,1	Brachytherapy	Brachytherapy	Brachytherapy
0,05	Brachytherapy	Brachytherapy	Brachytherapy
0	Brachytherapy	Brachytherapy	Brachytherapy

It can be seen that the high toxicity rates of brachytherapy are leading to this treatment not being the optimal treatment if initial toxicity rates are reduced by less than 60%. If the toxicity rates of the treatment were only 35% of the values used initially, meaning a 65% reduction in toxicity rates, brachytherapy becomes the optimal treatment to select for high-risk patients. Brachy monotherapy becomes more attractive than Brachytherapy and SBRT combined for intermediate- and low-risk patients at toxicity rates being at 35% and 30%, respectively. The fact that Brachytherapy is the optimal treatment to select for higher risk groups at higher rates of toxicity can be explained by the differences of biochemical recurrence rates between Brachy monotherapy and Brachytherapy combined with SBRT. There are significant differences in rates of biochemical recurrence between the risk groups for the initially optimal treatment. High-risk patients are more likely to develop recurring cancer than intermediate- or low-risk patients, which leads to Brachytherapy being a better treatment even if toxicity is relatively high. For intermediate-risk patients, the probability of developing recurring cancer is not as high, meaning that the treatment SBRT + Brachytherapy is more attractive to them. Hence, lower toxicity rates of Brachytherapy are needed such that the benefits of lower toxicity rates make brachytherapy more attractive for intermediate-risk patients.

Since Elekta produces equipment for Brachytherapy, it is important to be aware of areas of improvement for that treatment. This sensitivity analysis can be used to help Elekta to find directions in portfolio developments. In order for brachytherapy to be the optimal treatment to select, toxicity rates should decrease by more than 60% as compared to the initial values we use in the model.

In Table 6, the reduced toxicity values can be seen. Interestingly, when toxicity rates are reduced by 70% and brachytherapy is hence the most attractive treatment for all patient risk-categories, the toxicity rates of brachytherapy are still higher than for SBRT + brachytherapy, as shown in the right two columns in Table 6. Brachytherapy as a monotherapy is thus a more attractive treatment option than Brachytherapy combined with SBRT even if the toxicity levels for Brachytherapy are slightly higher. This can mainly be explained through the cost of performing the treatment, where Brachy monotherapy is significantly cheaper than combining it with SBRT.

Table 6: toxicity rates for brachytherapy as optimal treatment

Symptoms	**Brachy initially**	**60% reduction**	**70% reduction**	**Brachy + SBRT**
Sexual				
1 year	*27,50%*	*11,00%*	*8,25%*	*7,38%*
2 years	*34,27%*	*13,71%*	*10,28%*	*9,01%*
3 years	*42,00%*	*16,80%*	*12,60%*	*10,70%*
Urinary				
1 year	*6,44%*	*2,58%*	*1,93%*	*0,78%*
2 years	*13,06%*	*5,22%*	*3,92%*	*1,57%*
3 years	*20,60%*	*8,24%*	*6,18%*	*2,37%*
Bowel				
1 year	*0,00%*	*0,00%*	*0,00%*	*0,00%*
2 years	*0,00%*	*0,00%*	*0,00%*	*0,00%*
3 years	*0,00%*	*0,00%*	*0,00%*	*0,00%*

7 Conclusion and Discussion

We developed a Markov model that determines the optimal primary treatment for low-, intermediate- or high-risk prostate cancer patients in Germany. The output shows that a combination of SBRT and Brachytherapy is the optimal treatment choice for general input parameter values as derived from current state-of-the-art literature. Even if the direct treatment costs of treating a patient with both SBRT and Brachytherapy is more expensive than most other treatments, a better clinical outcome leads to long-term expected treatment-related costs being reduced by 40,4%, 29,7% and 31,7% compared to the second-best treatment option for low-, intermediate-, and high-risk patients, respectively.

Particularly the costs assigned to lost utility of a patient have a high impact on the total costs, contributing up to 94% of the total costs. The sensitivity analysis of Section 6 shows that with increasing costs assigned to lost utility, this part of the costs gains importance such that for the 36570€ used consists of up to 94% of costs due to lost utility, while for input values for costs assigned to lost utility below 3200€, the cheaper radiation monotherapies are chosen to be the optimal treatment, since the relative contribution of treatment costs to total costs is larger and hence, lower treatment costs outweigh the slightly worse clinical outcome.

The model is structured in a way that it allows treating recurring localized prostate cancer and compares the most commonly used treatments for localized prostate cancer patients. Thereby, our research improves the realism of the decision process as it had been researched in the publications discussed in Section 3, since Weng et al. (2022) do not specify whether or how salvage treatment options are considered, and Naser-Tavakolian et al. (2023) do not consider salvage treatment options at all, nor do they distinguish between the existing different types of radiation therapy. There are differences in optimal treatment selection of our research compared to the two other publications mentioned.

Weng et. al (2022) conclude that Brachytherapy is the most cost-effective treatment option when including direct treatment costs and costs of managing treatment-related toxicity for all risk categories. Nevertheless, they do not assign any cost to lost utility in that comparison of the cost-effectiveness of the primary treatments, while stating that a combination of brachytherapy and SBRT improves the QALY of a patient such that it becomes the optimal treatment whenever an increase of QALY is valued more than 8562$ or 4450$ for low- and intermediate- risk patients, respectively. Hence, if a value of 36570€ is used as WTP and assigned to the equivalent of one year of lifetime utility lost, the outcome of our model suggests that treatment selection for low- and intermediate-risk patients is the same as Weng et al (2022). However, a difference is that for high-risk patients, they suggest that brachytherapy is the optimal treatment to select independent of the WTP input, while our model shows that combining SBRT and Brachytherapy leads to lower expected costs than SBRT monotherapy for WTP values exceeding 3200€. A possible explanation for that is that Weng et al. (2022) only assign a cost to managing sexual symptoms, while for instance urinary toxicity only affects the utility, not the costs directly. Hence, in our model, the combination of SBRT and Brachytherapy is more attractive than Brachytherapy, since the toxicity rates are lower for the combined treatment than for monotherapy.

Since Naser-Tavakolian et al. (2023) do not consider the possibility to treat recurring cancer and they do not distinguish between the different types of radiation therapy being brachytherapy and SBRT as monotherapy or a combination of the two, it is not surprising that our research finds different optimal

treatments for all risk-categories. To find exact reasons for the different outputs, we should get in contact with Naser-Tavakolian (2023), since their input data is available on request from the authors.

Our model proposes that a combination of SBRT and Brachytherapy is the optimal treatment for all risk groups. The output of the model created shows that an optimal treatment selection can lead to a cost reduction of more than 30% as compared to alternative treatments. Nevertheless, we found that there is a lack of reliable input data that can be used for our calculations, especially with regard to treatment outcomes of salvage treatments, which depend on the initial treatment performed. That is why we must make assumptions about some input parameters required for the model, that are not sufficiently available in the literature. This mainly refers to the differences in treatment outcomes of salvage treatments after initial radiation therapy, because we found that currently, in the literature, outcomes of salvage treatments after initial radiation therapy are researched, but there is not sufficient reliable information about the differences in salvage treatment outcomes between brachytherapy or SBRT as monotherapy or a combination of the two as initial treatment. Discussions with experts in the field of radiation therapy indicated that there might be major differences, since for instance, HDR brachytherapy reduces the radiation to healthy tissue surrounding the tumour significantly and thus, does not affect treatment outcomes as much as SBRT primary treatments, in which surrounding tissue is radiated, and thus, damaged, more.

The sensitivity analysis in Chapter 6 shows the effect a single input parameter can have on the model's outcome. Even though the effect of changing other input parameters is expected to not be as significant, the model is surely presenting different total costs and possibly different optimal treatments if other input parameters are changed.

A simplification we make in the model is that we kept the option to treat metastasized cancer as an extension for future research. We are aware of the fact that this offers room for criticism of the reliability and usability of the model and its outcomes. Nevertheless, comparing the structure of the Markov model we created to existing research, we state that our research is more relevant for treatment selection in practice because it represents reality better.

Given the limitations and simplifications discussed and the heterogeneity of the populations in the studies of which input parameters are used in the model, we cannot decide on the superiority of one technique over the others with complete certainty. Nevertheless, despite the limitations discussed, already now, our research provides insight into the main differences among treatments such as the ratio between treatment costs and toxicity management costs for different treatments and risk groups. Therefore, the model can be used to provide decision-makers and developers of cancer treatment equipment insight into the main differences and costs arising from the different treatments. For our research to be used in practice, mainly input parameters need to be reviewed and more reliable data should be gathered, which should be the focus of future research. Given the current input values found in literature, we recommend Elekta to research on how to reduce the side effects of brachytherapy treatments, since the second sensitivity analysis performed shows that toxicity levels of brachytherapy need to be reduced by around 60% in order for brachytherapy to be the optimal treatment to choose.

For future research, we therefore recommend input parameters to be reviewed and thereby validated or updated. Furthermore, additional data points can be included. Even if it requires slightly adapting the model, individual patient characteristics such as age or comorbidities could be included. An idea of how to do so would be to include the lifetime-adjusted PCCI values in the decision-making. Additionally, since the model we implemented in VBA can be solved within a few seconds, we expect that it is possible to extend the model such that it includes treatments for metastasized cancer. That

would imply that not only for the primary treatment selection, a larger group of patients is considered in the model but also for patients with initial localized cancer who develop metastasized cancer at some point in time, a treatment can be selected again instead of only being able to stay with metastasized cancer until a patient is dead.

This validation of our research and extensions to our model would further increase the reliability and usability of our results. However, we are certain that our model, as it is now, already is a significant improvement of existing research, as it represents reality better and hence allows determining the best treatment per patient better. As said, depending on the primary treatment selected, the long-term expected costs deviate by around 30% at least. That is why we are certain that if treatment selection in practice is improved by our findings, this will lead to reducing the long-term treatment-related costs per patient. Thereby, the negative effect of an increased number of prostate cancer patients in Germany in the near future on healthcare expenditure is reduced. We expect that this reduces the healthcare expenditure for prostate cancer care. As a consequence, financial resources saved on prostate cancer care can be used for other purposes such as early detection of cancer and thereby can help more patients to survive.

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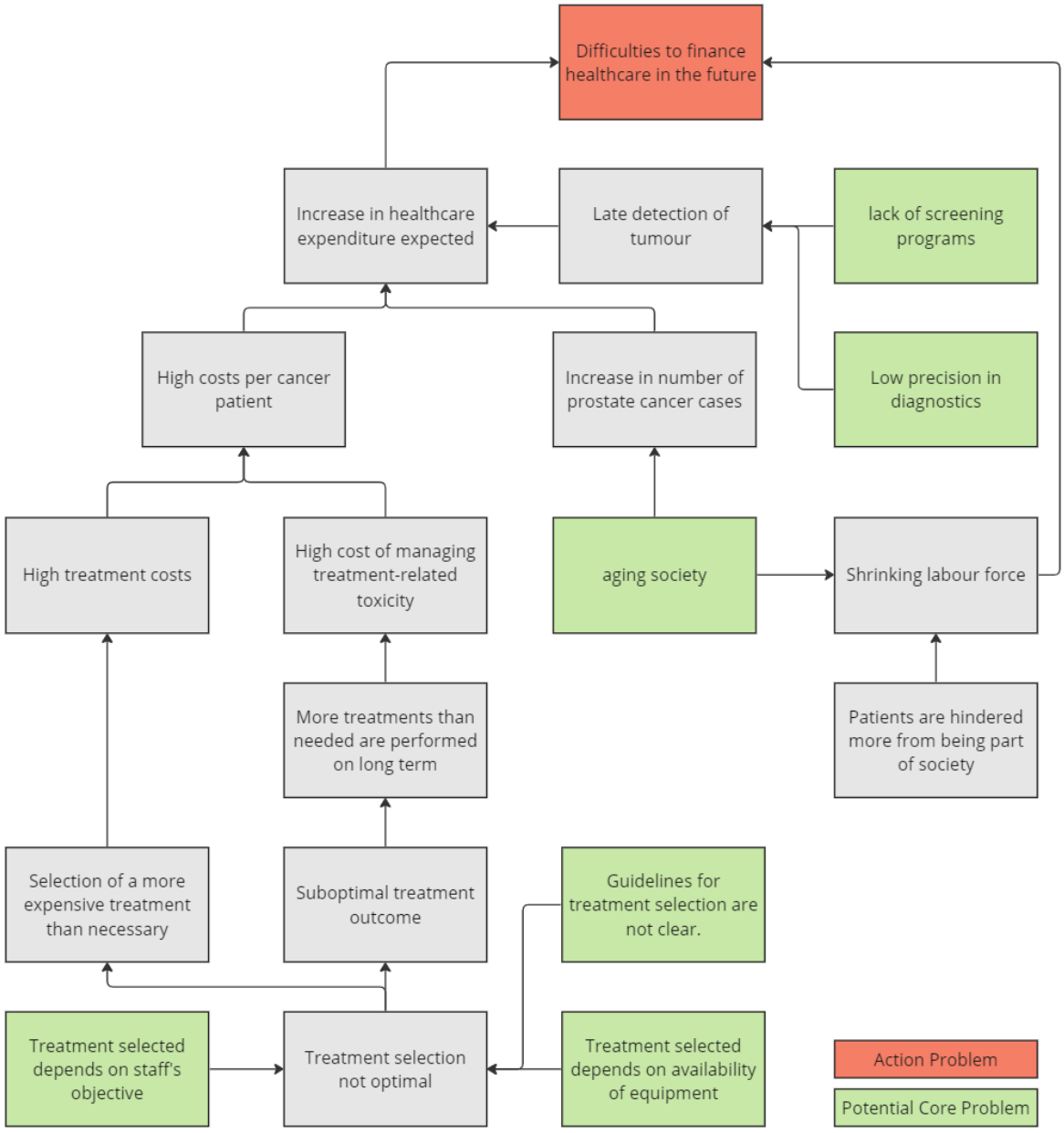
Appendix

Appendix 1.1: Problem Cluster



Appendix 1.2: Elaboration on problems

Our research is aiming to tackle the action problem being that there are difficulties to finance healthcare in the future, focusing on the role prostate cancer care plays in that area, as explained above. That is to a large extent influenced by the fact that not only in Germany but in Europe and the world overall, prostate cancer cases are expected to increase significantly (World Health Organization 2020). From expert interviews including staff who have performed cancer treatments themselves, a financial manager in a hospital or colleagues at Elekta who have worked in the field of cancer care for several years, and literature, we identified a number of factors that lead to that increase. One reason is that the current way screening programs are executed in Germany, they do not promise a very high precision in diagnosing prostate cancer (Al-Monajjed, Arsov, and Albers 2018). Nevertheless, even if screening programs do not always lead to the correct diagnosis, they have still been proven to be

beneficial to a number of patients, especially younger patients such that the tumour is identified at an early stage (Zhang et al. 2012). The low precision and the lack of screening programs overall together with an ageing society leads to the number of prostate cancer cases.

Looking at the action problem, ageing society causes another challenge for society in general apart from the increase in cancer cases mentioned: A larger part of society will retire and fewer younger people will lead to a lower labour force in general having to finance increasing expenditure in healthcare.

The increase in healthcare expenditure is not only caused by the increase in the number of cancer patients expected but is also affected by the fact that the cost per cancer patient is high. In interviews, we identified two main contributors to the high total cost of a cancer patient, namely the relatively high initial treatment cost and the long-term toxicity management cost up to ten years after initial treatment.

Investigating possible reasons for the high costs, we found that the decision, of what treatment to perform for a specific patient, excludes patient-specific information that is expected to have an effect on the treatment such as the patient's age or tumour type. A consequence of that information not being included is that there exists a possibility of selecting a suboptimal treatment with lower outcomes than expected, which might be more expensive than the treatment that best suits this specific patient. Thus, a patient is hindered from being part of society and might cost money, while especially for younger patients, the possibility to positively contribute to the country's economy by working is taken away from that patient for more time than necessary if an optimal treatment was selected. Additionally, if the treatment's outcome is not as good as it would be with the best-suited treatment performed, there is a higher possibility that the patient will have to be treated again in the long term and thereby leads to a higher cost of managing long-term treatment-related toxicity. It can thus be said that the norm of every patient receiving the treatment that suits them best is deviating from reality, in which the selection of treatments does not consider all factors of importance and is hence not optimal.

Lastly, we identified another of the selection of treatment not being optimal, namely that the selection of treatment depends on the medical staff's preferences. Even if the guidelines give recommendations on what treatment to perform, it is in the end up to the staff together with the patient to decide how to proceed. Since there are for instance significant differences in profits that can be made per treatment, which can influence decisions made (Mitchell et al. 2019).

Appendix 1.3: Selection of Core Problem

Potential core problems and their influenceability

Problem	Influenceable	If yes, feasible to be influenced	Reason of influenceability and feasibility
Lack of screening programs	Yes	Yes	Our research could investigate how to increase the number of screening programs.
Low precision on diagnostics	Yes	Yes	Our research could focus on how to improve diagnostics of early stage prostate cancer.
Aging society	To some extent	No	A possible solution is for instance more immigration of qualified workers. However, the scope of that problem is beyond our research.
Treatment selected depends on staff's objective	Yes	No	Since staff and patient in the end are always the ones deciding on a treatment, this cannot be influenced.
Classification of patient excludes important individual characteristics	Yes	Yes	Our research could improve the patient classification such that it includes more patient characteristics of importance when selecting a treatment.
Treatment selection depends on availability of equipment	Yes	Yes	Our research could focus on making the treatment less dependent on specific equipment.

As The table shows, two of the six potential core problems cannot feasibly be influenced by our research. Looking at the remaining four problems, we decided not to focus on improving the number of screening programs or improving methods for diagnostics, because research about optimizing the number of screening programs is already done (Akhavan-Tabatabaei, Sánchez, and Yeung 2017), and requires detailed medical background knowledge, while the problems' impact of it on healthcare expenditure is expected to be limited.

Appendix 1.4: Research design

Research question	MPSM Phase	Research population	Research type	Method of data gathering	Research strategy	Presentation of outcome	Activity Plan
What different treatment options exist for treating localized prostate cancer?	3	Literature, interviews	Descriptive	Literature search, semi-structured interviews	Qualitative	Summary of relevant treatments and brief explanation about each treatment.	Search for treatment options for localized prostate cancer in literature, approve with experts, summarize.
What are the guidelines for selecting a treatment for a patient with localized prostate cancer?	3	Literature	Descriptive	Literature search	Qualitative	Table showing what treatment is selected for specific patient	Search for current guidelines for localized prostate cancer treatments in Germany, summarize findings in table
What research is existing on improving treatment selection?	4	Literature	Descriptive	Literature search	Qualitative	Analysis of existing research in form of a text. Visual presentation if applicable.	Search for existing research, Critically discuss it with experts and evaluate to what extent it can be of use.
How can the treatment selection process be formulated in a mathematical model?	4	Literature, Experts at Elekta or University	Descriptive	Semi-structured interviews, literature search	Qualitative	Section, in which findings are briefly discussed	Conduct literature search and interviews, discuss in report.
What values can be used as unput for the mathematical model?	4	Literature	Descriptive	Systematic literature review	Quantitative	Table showing probabilities per source (treatment outcomes and costs)	Design literature search, Select the ten most recent publications, if needed, Summarize findings per source in table
What are the results of the optimized treatment selection?	5	Mathematical Model	Explanatory	Computations based on previous findings	Qualitative and quantitative	Provide the best suitable treatment for specific patient and related expected total cost.	Design Mathematical Model, Decide on Program to solve it, implement it, test it using examples
How can the optimized treatment selection be implemented?	6&7	Colleagues and Management at Elekta	Descriptive	Semi-structured interviews, observation	Qualitative	Plan of action for Elekta	Observe colleague's reaction to presenting solutions found, Create plan of action

Appendix 2: Treatment selection

Appendix 2.1: TNM classification

Feature	Definition
Size of Tumor	
TX	Primary tumor not assessable
T0	No evidence of primary tumor
T1	Not palpable and not seen with imaging test such as transrectal ultrasound
T2	The tumor can be felt by digital rectal exam. Limited to prostate
T2a	Involves ≤ half of lobe
T2b	Involves > half of 1 lobe, but not both lobes
T2c	Tumor involves both lobes
T3	Extraprostatic extension
T3a	Extends through the prostatic capsule unilaterally or bilaterally; microscopic invasion of the bladder neck
T3b	Invades seminal vesicles
T4	Is fixed or invades adjacent structures other than seminal vesicles
Regional lymph node metastasis	
NX	Not assessed
N0	**None**
N1	Present
Distant metastasis	
M0	None
M1	Present
M1a	Nonregional lymph nodes
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

Appendix 2.2: Gleason Score

Grade	Gleason score	relative risks of progression
1	Gleason score 6	1
	Only individual discrete well-formed glands	
2	Gleason score 3 + 4 = 7	2,6
	Predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands	
3	Gleason score 4 + 3 = 7	8,5
	Predominantly poorly formed/fused/cribriform glands with lesser (>5%) component of well-formed glands	
4	Gleason score 4 + 4 = 8; 3 + 5 = 8; or 5 + 3 = 8	16,8
	Only poorly formed/fused/cribriform glands Predominantly well-formed glands and lesser component lacking glands	
	Predominantly lacking glands and lesser component of well-formed glands	
5	Gleason scores 9–10	29,3
	Lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands	

Appendix 2.3: EUA Guidelines

Information obtained from Guidelines on Prostate Cancer (De Santis et al. 2023)

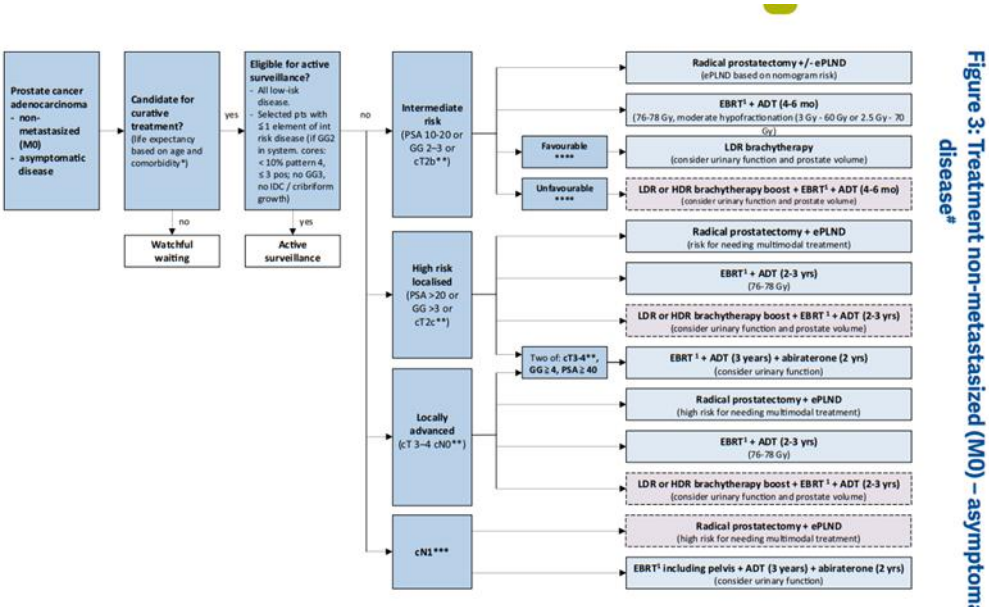


Figure 3: Treatment non-metastasized (M0) – asymptomatic disease#

** Rule of thumb: Life expectancy 10 years.*
*** Recommendation based on clinical staging using digital rectal examination, not imaging.*
**** Recommendation based on staging using combination of bonescan and CT.*
***** See text, dependent on GG and (biopsy) volume*
[1]EBRT: IMRT/VMAT + IGRT of the prostate
[ ] = weak recommendation
ADT = androgen deprivation therapy; EBRT =external beam radiotherapy; ECE = extracapsular extension; ePLND = extended pelvic lymph node dissection; GG = grade group; HDR = high-dose rate; IDC = intraducal carcinoma; IGRT = image-guided radiotherapy; IMRT = intensity-modulated radiotherapy; LDR = low-dose rate; VMAT = volumetric modulated arc therapy.

Appendix 2.3.1: EAU Guidelines on low-risk patients

Recommendations	Strength rating
Watchful Waiting	
Manage patients with a life expectancy < 10 years by watchful waiting.	Strong
Active surveillance (AS)	
Manage patients with a life expectancy > 10 years and low-risk disease by AS.	Strong
Selection of patients	
Patients with intraductal histology on biopsy should be excluded from AS.	Strong
Perform magnetic resonance imaging (MRI) before a confirmatory biopsy if no MRI has been performed before the initial biopsy.	Strong
Take both targeted biopsy (of any PI-RADS ≥ 3 lesion) and systematic biopsy if a confirmatory biopsy is performed.	Strong
If MRI is not available, per-protocol confirmatory prostate biopsies should be performed.	Weak
If a patient has had upfront MRI followed by systematic and targeted biopsies there is no need for confirmatory biopsies.	Weak
Follow-up of patients	
Repeat biopsies should be performed at least once every 3 years for 10 years.	Weak
In case of prostate-specific antigen progression or change in digital-rectal examination or MRI findings, do not progress to active treatment without a repeat biopsy.	Strong

**All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.*

Appendix 2.3.2: EAU Guidelines on Intermediate-risk Patients

Recommendations	Strength rating
Watchful Waiting (WW)	
Offer WW in asymptomatic patients with life expectancy < 10 years.	Strong
Active surveillance (AS)	
Offer AS to highly selected patients with ISUP grade group 2 disease (i.e. < 10% pattern 4, PSA < 10 ng/mL, ≤ cT2a, low disease extent on imaging and low biopsy extent [defined as ≤ 3 positive cores and cancer involvement ≤ 50% core involvement [CI]/per core]), or another single element of intermediate-risk disease with low disease extent on imaging and low biopsy extent, accepting the potential increased risk of metastatic progression.	Weak
Patients with ISUP grade group 3 disease should be excluded from AS protocols.	Strong
Re-classify patients with low-volume ISUP grade group 2 disease included in AS protocols, if repeat non-MRI-based systematic biopsies performed during monitoring reveal > 3 positive cores or maximum CI > 50%/core of ISUP 2 disease.	Weak
Radical prostatectomy (RP)	
Offer RP to patients with a life expectancy of > 10 years.	Strong
Radical prostatectomy can be safely delayed for at least 3 months.	Weak
Offer nerve-sparing surgery to patients with a low risk of extra-capsular disease on that side.	Strong
Extended pelvic lymph node dissection (ePLND)	
Perform an ePLND based on predicted risk of lymph node invasion (validated nomogram, see Section 6.1.2.3.2.)	Weak
Radiotherapeutic treatment	
Offer low-dose rate (LDR) brachytherapy to patients with good urinary function and NCCN favourable intermediate-risk disease.	Strong
Offer intensity-modulated radiotherapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiotherapy (IGRT), with a total dose of 76–78 Gy or moderate hypofractionation (60 Gy/20 fx in 4 weeks or 70 Gy/28 fx in 6 weeks), in combination with short-term androgen deprivation therapy (ADT) (4–6 months).	Strong
Offer LDR brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and NCCN unfavourable intermediate-risk disease, in combination with short-term ADT (4–6 months).	Weak
Offer high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and NCCN unfavourable intermediate-risk disease, in combination with short-term ADT (4–6 months).	Weak
Other therapeutic options	
Only offer whole-gland ablative therapy (such as cryotherapy, high-intensity focused ultrasound, etc.) or focal ablative therapy within clinical trials or registries.	Strong
Do not offer ADT monotherapy to asymptomatic men not able to receive any local treatment.	Weak

**All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.*

Appendix 2.3.3: EAU Guidelines on high-risk patients

Recommendations	Strength rating
Watchful Waiting (WW)	
Offer WW to asymptomatic patients with life expectancy < 10 years.	Strong
Radical prostatectomy (RP)	
Radical prostatectomy can be safely delayed for at least 3 months.	Weak
Offer RP to selected patients as part of potential multi-modal therapy.	Strong
Extended pelvic lymph node dissection (ePLND)	
Perform an ePLND in high-risk PCa.	Strong
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure (see Section 6.2.4.1).	Strong
Radiotherapeutic treatment	
Offer patients intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT) with 76–78 Gy in combination with long-term androgen deprivation therapy (ADT) (2 to 3 years).	Strong
Offer patients with good urinary function IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT (2 to 3 years).	Weak
Therapeutic options outside surgery or radiotherapy	
Do not offer either whole gland or focal therapy.	Strong
Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a prostate-specific antigen (PSA)-doubling time < 12 months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour.	Strong

**All recommendations are based on conventional imaging with isotope bone scan and CT/MR abdomen/pelvis.*

Appendix 3: Literature search strategy

Appendix 3.1: Inclusion / Exclusion Criteria

Inclusion criteria	**Reasoning**
The publication should be about cancer	This is the overarching disease the research is about.
The publication should compare different treatments.	Our research is comparing different treatment options.
The Publication date should be in or after 2018	Treatment options and outcomes seem to be changing rapidly. After consulting experts in the field, we limit publications about treatment comparisons to no longer than five years old.
Publications coming from Western Europe or the US	Information should be representative of the population of our research. There are similar guidelines and standards of care.
Language: English or German	That is not only linked to an easier understanding but also the criterion above stating that papers should be from Western Europe or the US
Exclusion Criterion	**Reasoning**
Publications on specific patients groups	We want to cover a large sample of patients in our research and are hence not interested in research that has been performed on some specific patient groups such as high-risk or radiotherapy-resistant patients.
Publications focusing on patients who receive their second treatment are excluded.	This is not the population of interest in our research.

Appendix 3.2: Search Matrix

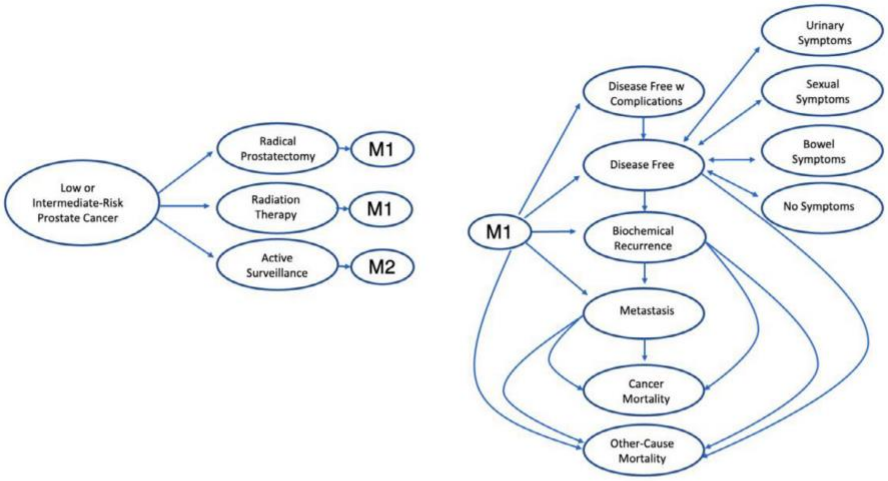
Key Concept	**Related Terms/synonyms**	**Narrower terms**	**Broader terms**
Treatment	Intervention, operation	SBRT, Brachytherapy, prostatectomy,	Radiotherapy, radiation therapy, cancer treatment
Clinical outcome	Reaction, Result	local control, overall survival, toxicity	Outcome, consequences
Prostate cancer	Prostate carcinoma	Localized cervical cancer	cancer, tumour, oncology
Germany			EU, Western world, Europe, Developed countries

Appendix 3.3: Search Log

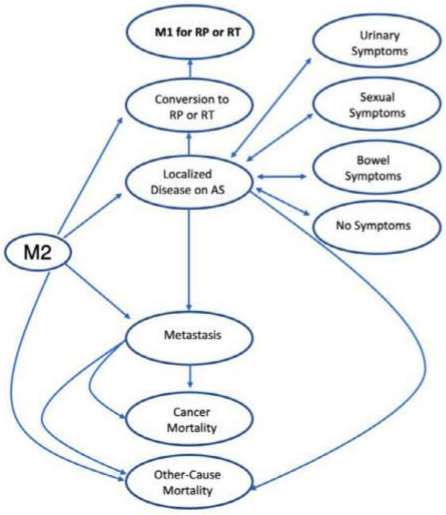
Source	**Search Query**	**Total Hits**	**Remarks**
PubMed	(((Cost) AND (Cancer)) AND ("treatment")) AND (optim*)	1435	Too many results. Scanning a few publications shows that several are not of relevance for our research. I narrow the search as described below.
PubMed	(((Cost) AND (Cancer)) AND ("treatment")) AND (optim*) AND (decision)	232	Still many results. Decisions seem to often not only be about treatment selection. I adjust the search query accordingly.
PubMed	(((Cost) AND (Cancer)) AND ("treatment selection")) AND (optim*)	15	Reasonable number of results. The following articles satisfy inclusion criteria - Davies et al. (2022) - Jongeneel et al (2023)
PubMed	(("prostate cancer") AND (treatment)) AND (cost) AND (Markov)	60	Reasonable number of publications. Out of the first 20, we find two that satisfy the search criteria: - Naser-Tavakolian et al. (2023) - Weng et al. (2022)

Appendix 4: Markov Model Naser-Tavakolian et al. (2023)

(A)



(B)



Appendix 5: Sources for input data

Data	Source	Comments
Transition Probability of Mortality as a Function of PCCI and Time Since Diagnosis	(Naser-Tavakolian et al. 2023)	
Transition probability of severe toxicity after initial RP and AS	(Naser-Tavakolian et al. 2023)	
Transition probability of severe toxicity after initial Brachytherapy	(Harris et al. 2020)	
Transition probability of severe toxicity after initial SBRT	(Fuller et al. 2018a)	
Transition probability of sexual toxicity after initial Brachy + SBRT	(Shahid et al. 2017)	
Transition probability of toxicity after initial Brachy	(Ghadjar et al. 2009)	
Transition probability of urinary toxicity after initial SBRT	(Fuller et al. 2018b)	
Transition probability of urinary toxicity after initial Brachy + SBRT	(Shahid et al. 2017)	
Transition Probability of Severe toxicity as a Function of Treatment and Time Since Treatment	(Naser-Tavakolian et al. 2023)	
Transition Probability of Metastasis on AS as a Function of Cancer Risk and Duration.	(Naser-Tavakolian et al. 2023)	
Transition Probability of BCR after initial RP as a Function of Cancer Risk and Duration.	(Naser-Tavakolian et al. 2023)	
Transition Probability of BCR after initial Brachytherapy as a Function of Cancer Risk and Duration.	(Mendez and Morton 2018)	4,7 years 4;4;8%
Transition Probability of BCR after initial Brachytherapy as a Function of Cancer Risk and Duration.	(Strouthos et al. 2018)	Assumption: constant over 10 years
Transition Probability of BCR after initial SBRT as a Function of Cancer Risk and Duration.	(Fuller et al. 2022b)	10 years: 0; 15,7;45,2%. Assumption: constant over 10 years
Transition Probability of BCR after initial SBRT + Brachy as a Function of Cancer Risk and Duration.	(Phan et al. 2007)	4.9 years: 2;10;22%. Assumption: Constant over 10 years
Probability of Metastasis as function of Cancer risk and Duration of BCR	(Naser-Tavakolian et al. 2023)	
Transition Probability of Prostate Cancer- Specific Death in RP/RT as a Function of Cancer Risk and BCR Duration.	(Naser-Tavakolian et al. 2023)	
Transition Probability of Death in RP/RT/AS as a Function of Metastasis Duration.	(Naser-Tavakolian et al. 2023)	

Transition Probability of BCR for recurring Pca after primary radiation salvage RP	(Valle et al. 2021)	Assumption: risk after 5 years does not change
Transition Probability of BCR for recurring Pca after primary radiation salvage RP	(Chade et al. 2011)	
Transition Probability of BCR for recurring Pca after primary radiation salvage SBRT	(Henderson et al. 2023)	
Transition Probability of BCR for recurring Pca after primary radiation salvage SBRT	(Valle et al. 2021)	Assumption: risk after 5 years does not change
Transition Probability of BCR for recurring Pca after primary radiation salvage Brachytherapy	(Valle et al. 2021)	Assumption: risk after 5 years does not change
Transition Probability of BCR for recurring Pca after primary radiation salvage Brachytherapy + SBRT	(Steele and Holmes 2019)	
Probabilities of toxicity after salvage treatments for recurring Pca after primary radiation	(Valle et al. 2021)	
Probabilities of urinary symptoms after salvage RP for recurring Pca after primary radiation	(Henderson et al. 2023)	
Probabilities of urinary symptoms after salvage SBRT for recurring Pca after primary radiation	(Leroy et al. 2017)	8 months: 8,7%. Assumption: follows same pattern as after RP.
Probabilities of urinary symptoms after salvage Brachy for recurring Pca after primary radiation	(Henderson et al. 2023)	5 year: 2%. Assmuption: follows same pattern as RP
Probabilities of urinary symptoms after salvage Brachy + SBRT for recurring Pca after primary radiation		Assumption: same ratio of patients with severe toxicity as compared to Brachy for primary treatments
Probabilities of bowel symptoms after salvage RP for recurring Pca after primary radiation	(Steele and Holmes 2019)	
Probabilities of bowel symptoms after salvage SBRT for recurring Pca after primary radiation	(Leroy et al. 2017)	
Probabilities of bowel symptoms after salvage Brachy for recurring Pca after primary radiation	(Wojcieszek et al. 2016)	
Probabilities of bowel symptoms after salvage SBRT + Brachy for recurring Pca after primary radiation		Assumption: same ratio of patients with severe toxicity as compared to Brachy for primary treatments
Probabilities of sexual symptoms after salvage RP for recurring Pca after primary radiation		Assumption: Same as for primary treatments

Probabilities of sexual symptoms after salvage SBRT for recurring Pca after primary radiation	(Steele and Holmes 2019)	2 years: 30%. Assumption: Constant over 3 years
Probabilities of sexual symptoms after salvage Brachy for recurring Pca after primary radiation	(van Son et al. 2020)	31 months: 22%. Assumption: same ratio of patients with severe toxicity as compared to Brachy for primary treatments
Probabilities of sexual symptoms after salvage SBRT + Brachy for recurring Pca after primary radiation		Similar to primary treatment: 30% of Brachytherapy
Transition Probability of BCR for recurring Pca after primary radical prostatectomy	(Schröder et al. 2022)	When investigating outcomes of Radiation therapies for salvage treatments, they argue it is only essential to evaluate whether a patient has already been radiated. Thus, if a patient has received prostatectomy as initial treatment, the outcomes of radiation therapy can be approximated as the same as for initial treatments.
	(Naser-Tavakolian et al. 2023)	Hence, values of intermediate risk prostate cancer patients of initial treatment are used.
Fraction of recurrences with localized Pca	(Baty et al. 2019)	
Utility values	(Naser-Tavakolian et al. 2023)	

Appendix 6: Input Values

Toxicity after initial treatment					
Symptoms	**Active Surveillance**	**Radical Prostatectomy**	**Brachy**	**SBRT**	**Brachy + SBRT**
Sexual					
1 year	*2,20%*	*43,10%*	*27,50%*	*22,40%*	*7,38%*
2 years	*8,09%*	*40,27%*	*34,27%*	*27,93%*	*9,01%*
3 years	*14,70%*	*37,60%*	*42,00%*	*34,09%*	*10,70%*
Urinary					
1 year	*0,00%*	*18,50%*	*6,44%*	*0,22%*	*0,78%*
2 years	*1,82%*	*17,85%*	*13,06%*	*0,43%*	*1,57%*
3 years	*3,70%*	*17,20%*	*20,60%*	*0,65%*	*2,37%*
Bowel					
1 year	*0,00%*	*0,00%*	*0,00%*	*0,00%*	*0,00%*
2 years	*0,25%*	*0,00%*	*0,00%*	*0,00%*	*0,00%*
3 years	*0,50%*	*0,00%*	*0,00%*	*0,00%*	*0,00%*

Transition Probability of Definitive Treatment on Active Surveillance cdf			
Time	**Low Risk**	**Intermediate Risk**	**High Risk**
1 year	2,50%	2,81%	1,08%
2 years	5,13%	5,78%	2,19%
5 years	9,09%	48,60%	18,20%

Transition Probability of Metastasis on Active Surveillance		
Time	**Low Risk**	**Intermediate**
1 year	0,00%	1,00%
2 years	0,00%	0,80%
5 years	0,20%	0,90%

Probability of Biochemical Recurrence cdf

Radical Prostatectomy

Time (Cancer Durati	Low Risk	Intermediate	High Risk
1 year	*0,41%*	*0,98%*	*1,48%*
2 years	*0,83%*	*1,97%*	*3,01%*
5 years	*2,10%*	*5,00%*	*7,70%*

Brachytherapy

Time (Cancer Durati	Low Risk	Intermediate	High Risk
1 year	*5,00%*	*5,00%*	*1,59%*
2 years	*1,70%*	*1,70%*	*3,24%*
5 years	*4,30%*	*4,30%*	*8,53%*

SBRT

Time (Cancer Durati	Low Risk	Intermediate	High Risk
1 year	*0,00%*	*1,41%*	*3,41%*
2 years	*0,00%*	*2,86%*	*7,06%*
5 years	*0,00%*	*7,30%*	*18,60%*

SBRT + Brachytherapy

Time (Cancer Durati	Low Risk	Intermediate	High Risk
1 year	0,40%	1,91%	3,98%
2 years	0,80%	3,89%	8,28%
5 years	2,00%	10,00%	22,00%

Probability of Metastasis cdf

Duration of BCR	Low Risk	Intermediate Risk	High Risk
1 year	0,30%	0,70%	1,05%
2 years	0,60%	1,40%	2,10%
5 years	1,60%	3,55%	5,35%

Prostate Cancer Death Probability cdf

Duration of BCR	Low Risk	Intermediate Risk	High Risk
1 year	0,00%	0,05%	0,15%
2 years	0,00%	0,10%	0,30%
5 years	0,35%	0,60%	1,70%

Probability of Prostate Cancer D	
Duration of Metastasis	**Probability**
1 year	27,40%
2 years	27,90%
5 years	24,00%

Treatment outcomes post primary RT

Probability of Biochemical Recurrence				
Time	**RP**	**Brachytherapy**	**SBRT**	**SBRT + Brachythe**
1 year	**13,50%**	**10,35%**	**16,10%**	**3,11%**
2 years	**31,00%**	**23,00%**	**38,00%**	**6,90%**
5 years	**46,00%**	**40,00%**	**40,00%**	**12,00%**

Probability of Biochemical Recurrence cdf				
Symptoms	**Radical Prostatectomy**	**Brachy**	**SBRT**	**Brachy + SBRT**
Sexual				
1 year	*43,10%*	*27,50%*	*22,40%*	*7,38%*
2 years	*40,27%*	*34,27%*	*27,93%*	*9,01%*
3 years	*37,60%*	*42,00%*	*34,09%*	*10,70%*
Urinary				
1 year	*6,46%*	*45,00%*	*6,46%*	*0,20%*
2 years	*3,25%*	*38,25%*	*3,25%*	*0,17%*
3 years	*0,05%*	*31,50%*	*0,05%*	*0,14%*
Bowel				
1 year	*0,00%*	*0,00%*	*0,00%*	*0,00%*
2 years	*0,00%*	*0,00%*	*0,00%*	*0,00%*
3 years	*0,00%*	*0,00%*	*0,00%*	*0,00%*

Treatment outcomes post RT

Probability of Biochemical Recurrence				
Time	**RP**	**Brachytherapy**	**SBRT**	**SBRT + Brachythe**
1 year	**13,50%**	**10,35%**	**16,10%**	**3,11%**
2 years	**31,00%**	**23,00%**	**38,00%**	**6,90%**
5 years	**46,00%**	**40,00%**	**40,00%**	**12,00%**

Probability of Biochemical Recurrence cdf				
Symptoms	**Radical Prostatectomy**	**Brachy**	**SBRT**	**Brachy + SBRT**
Sexual				
1 year	*43,10%*	*27,50%*	*22,40%*	*7,38%*
2 years	*40,27%*	*34,27%*	*27,93%*	*9,01%*
3 years	*37,60%*	*42,00%*	*34,09%*	*10,70%*
Urinary				
1 year	*6,46%*	*45,00%*	*6,46%*	*0,20%*
2 years	*3,25%*	*38,25%*	*3,25%*	*0,17%*
3 years	*0,05%*	*31,50%*	*0,05%*	*0,14%*
Bowel				
1 year	*0,00%*	*0,00%*	*0,00%*	*0,00%*
2 years	*0,00%*	*0,00%*	*0,00%*	*0,00%*
3 years	*0,00%*	*0,00%*	*0,00%*	*0,00%*

Utility	
Cancer Diagnosis	0,95
Peri-Op Complications	0,67
Radical Prostatectomy	0,67
Radiation Therapy	0,73
Urinary Incontinence	0,83
Erectile Dysfunction	0,89
Bowel Dysfunction	0,71
Metastatic Disease	0,25

Toxicity	*Related management costs in € per year*
Urinary	*800*
Sexual	*882*
Bowel	*1200*

Treatment	Average price per patient in €	Comment
Prostatectomy	18 000	
Active Surveillance	543	yearly
Brachytherapy	6 000	
SBRT	10 000	
Brachytherapy + SBRT	15 000	Estimate: Slightly lower than Brachytherapy and SBRT as monotherapies