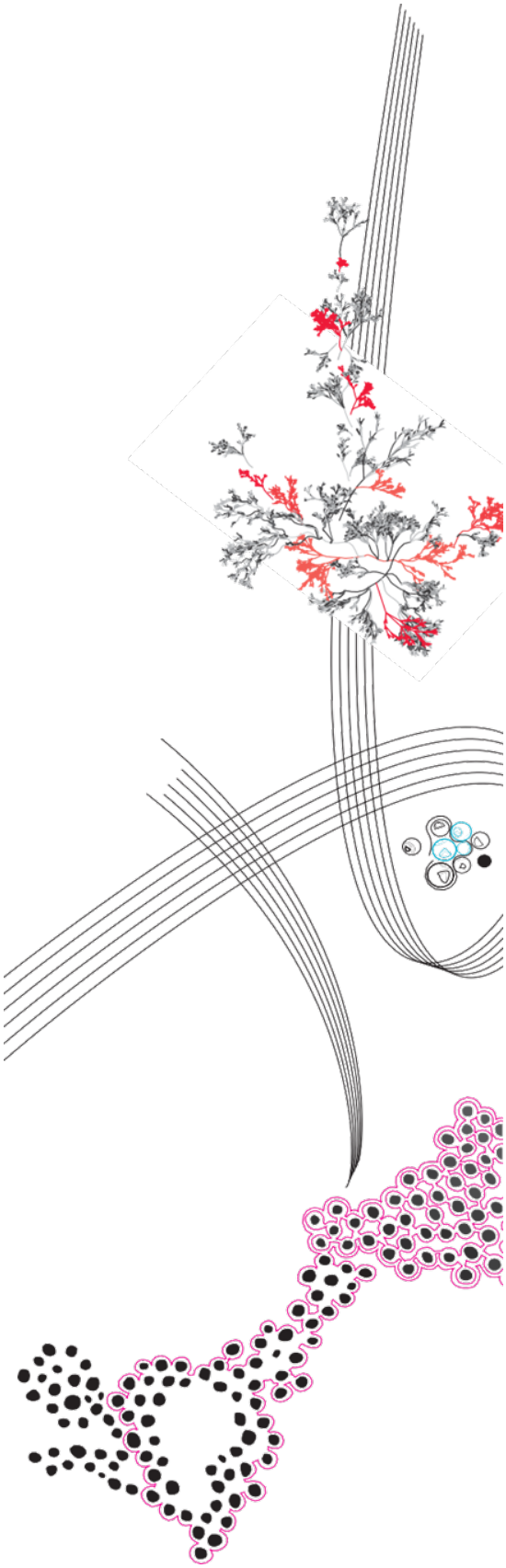


BSc Thesis Industrial Engineering & Management Science

Faculty of Behavioural, Management and Social Sciences

Optimizing the Reimbursement for Brachytherapy: A Critical Factor in Controlling Total Healthcare Expenditure for Prostate Cancer in Italy

Areeba Ahmed

April 2024

Supervisors

University of Twente: Dr. S. Saing & Dr. D. Guericke

Elekta: A. Loonstra

UNIVERSITY OF TWENTE.

Elekta

Optimizing the Reimbursement for Brachytherapy: A Critical Factor in Controlling Total Healthcare Expenditure for Prostate Cancer in Italy

Areeba Ahmed
April, 2024

VERSION
Version 1

AUTHOR
Areeba Ahmed – [s2584506]

EMAIL
a.aahmed@student.utwente.nl

POSTAL ADDRESS
University of Twente, Industrial Engineering and Management
PO Box 217, 7500 AE Enschede
Tel. +31(0)53489911

University Supervisors
1st supervisor: Dr. S. Saing
2nd supervisor: Dr. D. Guericke

Elekta Supervisor
A. Loonstra

WEBSITE
www.utwente.nl

FILENAME
BSc Thesis Industrial Engineering and Management Science

Preface

Dear Reader,

This thesis is written as a final part of my Bachelor of Industrial Engineering and Management Science at the University of Twente. To complete my research, I have worked together with Elekta, the world leader in brachytherapy for cancer treatment.

Firstly, I extend my heartfelt gratitude to my parents for their emotional and motivational support throughout my bachelor studies. I thank my brothers and my friend, Laura Eekelder, for their feedback, motivational support, and readiness to help me whenever needed.

I want to thank my supervisors at Elekta. Ate Loonstra played an important role in the completion of this research and throughout my research project, offering invaluable assistance, readily addressing my questions, and engaging in insightful discussions. I want to thank Alice Di Giacinto for her feedback and discussions. Additionally, I thank Dirk Binnekamp for his contributions to our discussions, which helped me explore diverse perspectives. From the beginning, Elekta provided a welcoming environment, and I thoroughly enjoyed my time there while conducting my research. The practical experience gained during my tenure at Elekta has been valuable to me.

Finally, I thank my academic supervisors, Dr. Sopany Saing and Dr. Daniela Guericke. Their feedback and support were instrumental in guiding my research during moments of uncertainty, ensuring its progression remained on course and enhancing the overall quality of my thesis.

Doing this research has been an honour, and it has been a lot easier with all the support I have received.

Areeba Ahmed

22nd of April 2024

Management Summary

Problem description- This research is conducted at Elekta, a leading manufacturer of radiation therapy solutions and market leader for brachytherapy solutions. Elekta observed that in Italy, brachytherapy treatment for prostate cancer is relatively underutilized compared to Spain, where brachytherapy is used at least 40% more. Literature suggests that an important contributing factor to this underutilization is unfavourable reimbursement for brachytherapy in Italy. Therefore, our research question is:

*"What is the **economic value** and **current reimbursement** of brachytherapy treatment in Italy compared to alternative treatment options for prostate cancer patients and how does changing the reimbursement of brachytherapy influence the allocation of patients among the treatment modalities and subsequently impact the economic value for the population undergoing these treatments?"*

This thesis aims to create a simulation model that allows us to study the effect of reimbursement changes on patient distribution over the treatment options and subsequently, the economic outcomes that result from the survival, toxicity, and quality of life impact of these treatments. This will eventually allow us to determine optimal reimbursement rates for brachytherapy to maintain cost-effectiveness and minimize the overall total cost.

Methods - We developed a model with two components. Firstly, we created a patient allocation model to simulate the distribution of patients to treatment modalities such as brachytherapy. It considers specific decision factors, including reimbursement. The allocation model was populated with input data from six healthcare professionals, including radiation oncologists and urologists, and was validated using real-world data from Spain and Italy. Secondly, we developed a Markov model that captured treatment costs and outcomes, to evaluate the incremental cost-effectiveness ratio (ICER) of brachytherapy versus its treatment alternatives. Input data for this model was gathered from the scientific literature and by interviewing experts from Spain and Italy. In addition to the cost-effectiveness analysis, we conducted a budget impact analysis (BIA). This aimed to find the optimal reimbursement rate by modifying the reimbursement for brachytherapy and identifying the reimbursement at which the total treatment-associated costs for the population was the lowest.

Results – The patient outcomes predicted by the allocation model showed a satisfactory alignment with the actual patient distribution in Italy compared to Spain. Cost-effectiveness analysis results indicate that brachytherapy offers cost savings with better clinical outcomes compared to alternative treatments across all risk groups, except when compared to EBRT in low intermediate-risk and surgery in low-risk, where it demonstrates lower effectiveness. In cases where brachytherapy is not dominant but still cost-effective, such as compared to Active Surveillance in low intermediate-, high intermediate-, and high-risk groups, it remains below the Willingness-to-Pay Threshold (WTP) of €30.000. Sensitivity analysis on the ICER and budget impact reveals that the optimal reimbursement rate for brachytherapy is €7.700, which is €3.000 higher than the current reimbursement level.

Discussion & Conclusion – Our findings indicate that brachytherapy outperforms alternatives in terms of effectiveness, advocating a higher reimbursement to encourage its wider adoption among patients. Input parameters for the model were sourced from different literature, with heterogeneity in the population of the literature and estimation of some of the data due to their availability across sources. Therefore, it is important to review and update these input parameters before implementing our findings in practice. However, the sensitivity analysis confirms the model's responsiveness to parameter changes, presenting it as a powerful tool for healthcare decision-makers seeking reliable comparisons of prostate cancer treatment options and finding the optimal reimbursement. Moreover, our tool can be adopted to assess various diseases, particularly cancer. By validating input parameters and decision factors with experts and optimizing reimbursement using the model, more patients can access brachytherapy, reducing overall costs and saving financial resources.

Table of Contents

Terms of Glossary

AIRO	Italian Association of Radiation Oncology
AS	Active Surveillance
BIA	Budget Impact Analysis
BT	Brachytherapy
CEA	Cost-Effectiveness Analysis
CRPC	Castration Resistant Prostate Cancer
DIRAC	Directory of Radiotherapy Centres
EAU	European Association of Urology
EBRT	External Beam Radiation Therapy
ESTRO	European Society of Radiation Oncology
ESMO	European Soceity for Medical Oncology
HDR	High Dose Rate
ICER	Incremental Cost Effectiveness Ratio
KOL	Key Opinion Leader
LDR	Low Dose Rate
LY	Life Year
MCDA	Multi-Criteria Decision Analysis
mHSPC	Metastatic Hormone-sensitive Prostate Cancer
NCCN	National Comprehensive Cancer Network
QALY	Quality Adjusted Life Years
QOL	Quality of Life
RT	Radiotherapy
SLR	Systematic Literature Review
VBA	Visual Basics of Application

1 Introduction

Prostate cancer forms the most prevalent type of cancer affecting men on a global scale [1] Internationally, it held the fourth position in terms of newly diagnosed cases in 2020, with 1.414.259 cases reported [2]. This importance is not limited to a global context; in 2023, prostate cancer is documented as the most frequently occurring cancer in men in both Spain and Italy [3]. In Italy, it forms 16.4%, with 38.180 cases, and in Spain, it represents 20.8%, with 32.967 cases in 2022, of all tumours diagnosed in males of all ages [4].

For patients with prostate cancer, a range of treatment modalities is available, depending on several factors including risk categorisation, physician preferences, the patient's preferences, expected outcome and the financial considerations associated with the treatment [5]. Treatment options include Active Surveillance, brachytherapy, External Beam Radiation Therapy (EBRT), and surgery [6]. Additionally, a combination of treatments, like EBRT and brachytherapy, may be considered a possibility.

1.1 Brachytherapy

This research focuses on the role of brachytherapy in the treatment of prostate cancer. Brachytherapy is a type of internal radiotherapy treatment, where a radioactive source is positioned close to or into a lesion. This source releases ionizing radiation to eliminate the tumour. Brachytherapy is distinguished into two different types: low-dose rate (LDR) brachytherapy and high-dose-rate (HDR) brachytherapy. In LDR brachytherapy for prostate cancer, the radioactive seeds stay in the prostate, slowly releasing radiation over a few months. In HDR brachytherapy, the radioactive source emits its radiation at several positions in the prostate for several minutes each and is then taken out.

Brachytherapy has significant benefits, especially its ability to precisely target the tumour while minimizing harm to nearby healthy tissues [7]. It focuses the radiation dose on the cells near the source, allowing for a higher dose delivery with fewer needed treatments compared to EBRT [7]. However, like any medical procedure, brachytherapy for prostate cancer has downsides. These include the need for anaesthesia, the potential risk of bleeding and infection, and difficulties in reaching the tumour itself [7]. Brachytherapy is primarily utilized for prostate cancer patients classified as higher-risk groups.

1.2 Elekta and its Role in Brachytherapy Treatment

Elekta is a Swedish medical technology company that specializes in providing equipment and software solutions for advanced cancer treatments such as brachytherapy. Elekta was established in 1970 and has the vision to create a world where "everyone has access to the best cancer care" [8]. They are one of the world's largest producers of radiation therapy equipment. Elekta's products are used in hospitals and clinics worldwide including Spain and Italy. The reason for focusing on brachytherapy for prostate cancer lies in Elekta's strategic emphasis on prostate cancer within their broader vision of ensuring access to the best cancer care for everyone.

1.3 Problem Description

1.3.1 Observed Difference

The initial motivation for undertaking this research originated from the observed difference in the utilization of brachytherapy between Spain and Italy (Table 1). Data were obtained from online databases, literature, and sales & service data by Elekta.

Table 1 Overview of Brachytherapy Products installed in Spain and Italy

	Spain	Italy
Population males	22.969.645	29.379.058
Prostate cancer cases (2022)	32.967	38.180
Afterloaders installed (Elekta afterloader)	147 (65) [48]	61 (56) [48]
Elekta sources used (2022)	216	164
Elekta Source transfers (2022)	158.148	111.051
Elekta disposable needles sold (ProGuides) (2022)	15.670	830
Elekta Metal needles sold over the past three years	560*	20*

*Since these products have a life expectancy of three years the cumulative number of products sold in 2021-2023 indicates how many are currently in use in these countries.

Despite the similarity in annual reported cases of prostate cancer in both countries, a notable difference emerged in the utilization of brachytherapy as a treatment option, with Italy demonstrating a lower adoption rate compared to Spain, as demonstrated by the lower number of afterloaders installed, the lower number of source transfers and especially the lower number of brachytherapy needles used in Italy.

We calculate the utilization of brachytherapy sources per prostate cancer patient in both countries by dividing source transfers by the number of prostate cancer patients per country. Our analysis reveals that brachytherapy sources are employed approximately 4,80 times for each case of prostate cancer in Spain, whereas in Italy, brachytherapy sources are used approximately 2,90 times for each case of prostate cancer. Consequently, brachytherapy is utilized at least 40% less in Italy compared to Spain. The actual difference in utilization for prostate cancer is probably even bigger since brachytherapy is predominantly used for other indications such as cervical cancer. Examining the numbers of brachytherapy needles being used in each country indicates a 15 – 20 times difference in brachytherapy utilization for prostate cancer between these countries.

1.3.2 Factors Responsible for the Observed Difference

When delving into the underlying cause of the lower brachytherapy utilization in Italy compared to Spain, two countries with relatively comparable levels of development and wealth, we began by identifying the [1]factors that could potentially play a role. As previously mentioned, the choice of a particular treatment option for prostate cancer is influenced by various factors, including the cancer's risk category, physician, and patient's preferences, expected outcomes, and the financial considerations associated with the treatment. Since Italy and Spain are both European countries located in the same region, there is no reason to expect significant differences in the distribution of patients across risk categories, especially given that there are no active prostate cancer screening programmes in either country. The expected treatment outcomes of the main treatment options would be similar; therefore, they cannot explain the difference in brachytherapy utilization. Furthermore, the pre-research revealed that there are no distinctions in the healthcare systems, brachytherapy costs, number of prostate cancer cases or any other demographic variables between the countries.

An Elekta survey aimed at analysing brachytherapy workflows for prostate cancer treatment, distributed among customers in Italy and Spain, did not identify differences in treatment practices between the countries. This led to the conclusion that the difference in utilization cannot be explained by difference

[1] Pre-research comparing Spain and Italy was conducted based on specific criteria to identify factors affecting brachytherapy utilization. See Appendix A for details.

in the costs of the treatment. Therefore, the choice of treatment must be related to either physician and patient preferences or difference in reimbursement.

1.3.3 Problem Statement

A report published by Cancer World [7] provided a suggestive insight into a distinction in the reimbursement systems of the two countries. It was observed that healthcare providers (hospitals, doctors) in Spain, who deliver brachytherapy as a treatment for prostate cancer patients, receive a favourable reimbursement, allowing them to benefit from this highly effective treatment modality. Conversely, the article describes that in Italy, healthcare providers do not receive sufficient reimbursement, leading them to pursue alternatives. This observation leads to the following action problem:

"In Italy, healthcare providers that perform/offer brachytherapy treatment receive an unfavourable reimbursement."

In other words, the core problem is that the Italian National Health Service that decides on reimbursement rates has no understanding of the complex procedure of brachytherapy, the actual costs of the therapy, and the benefits related to clinical outcomes. Therefore, the Italian National Health Service does not provide favourable reimbursement for brachytherapy, causing physicians to prefer alternative treatments with better reimbursement and a more profitable economic profile. This preference results in some patients not receiving the best possible treatment, sub-optimal clinical outcomes, a loss of Quality-Adjusted Life Years (QALY), and higher expenditures on the treatment of side effects. In (Figure 1) the problem cluster of the highlighted action problem is depicted.

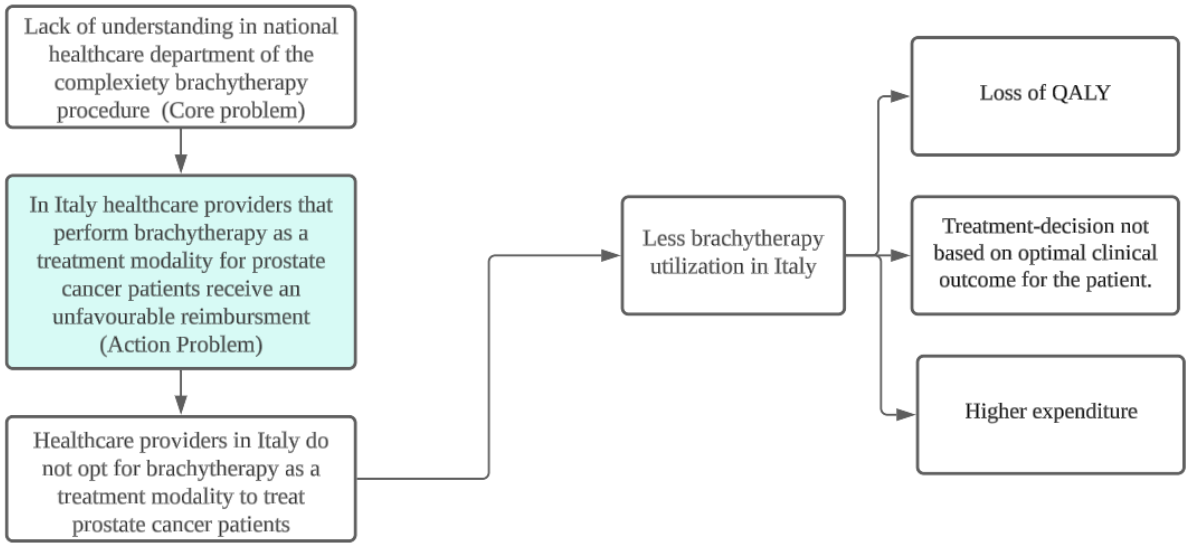


Figure 1 Problem Cluster

1.4 Research Aim

The objective of this research is to demonstrate that the current reimbursement for brachytherapy in Italy results in sub-optimal treatment decisions and increased costs related to toxicity treatment and loss of quality of life. The aim is to present this information to the Italian healthcare department and show how optimizing reimbursement will benefit the patients and the economic profile of the treatment of this patient population.

This will be achieved by simulating the impact of reimbursement changes on treatment decisions and subsequently on the economic profile of the improved clinical outcome for this population. This allows for the identification of an optimal reimbursement level associated with the lowest overall treatment costs. Such optimization supports the establishment of an efficient framework wherein healthcare

providers receive sufficient reimbursement for their services, thereby incentivizing the utilization of this crucial therapeutic modality.

Ultimately, it is the aim to create a favourable environment wherein patients in Italy, particularly those fighting prostate cancer, have access to cost-effective and high-quality brachytherapy treatment.

1.5 Research Question

As a next step, it was necessary to identify knowledge gaps for this research. Identifying these gaps allows for the formulation of specific knowledge questions that guide the research process. Based on the identified Action Problem in section 1.3.3 the research question is defined as follows:

*"What is the **economic value** and **reimbursement** of brachytherapy treatment in Italy compared to alternative treatment options for prostate cancer patients and how does changing the reimbursement of brachytherapy influence the allocation of patients among the treatment modalities and subsequently impact the economic value for the population undergoing these treatments?"*

To address the research question, a simulation model consisting of two components is required. The first component is a patient allocation model, which focuses on depicting how prostate cancer patients are distributed among different treatment modalities based on specific decision factors.

The second component involves assessing the economic value associated with each treatment modality through a cost-effectiveness analysis conducted using a Markov model.

When both components are combined, the simulation should allow us to assess the influence of changing the reimbursement for brachytherapy on the economic value (Figure 2).

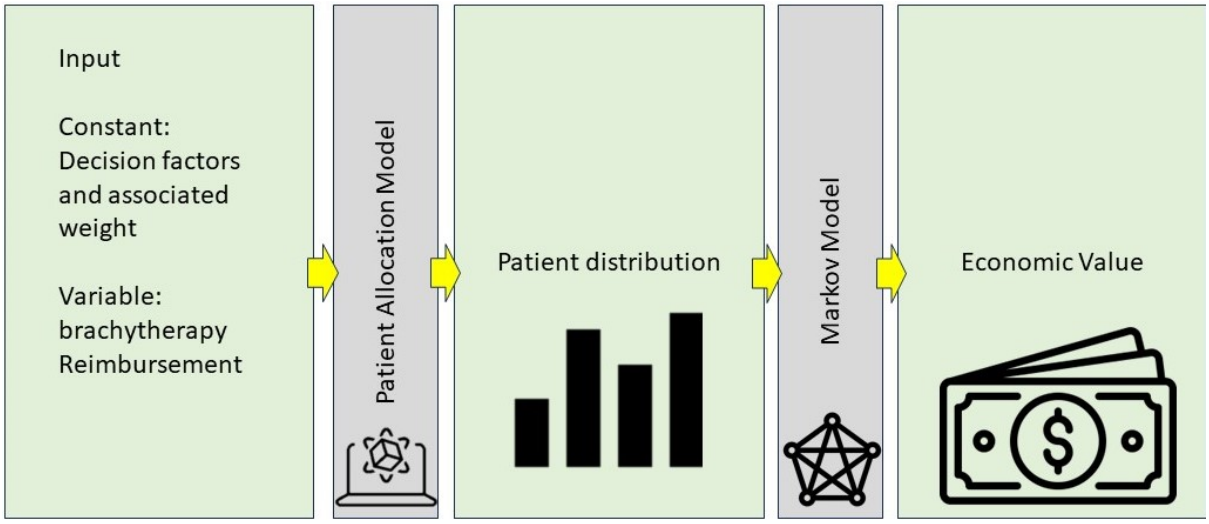


Figure 2 Model to Solve the Research Question

Ultimately, to find an answer to the research question and build the simulation model, we must first address knowledge problems formulated as sub-questions. These sub-questions are described in more detail in the next section.

1.6 Sub-Questions

To effectively address the main research question, it is necessary to adopt a step-by-step approach. This involves breaking down the main question into smaller sub-questions. By solving these sub-questions sequentially, we can gradually arrive at the comprehensive answer we seek. Questions 1 to 5 deal with the patient distribution among the treatment modalities. Whereas Questions 6 to 9 deal with the economic value assessment. The sub-questions are defined as follows:

1. *What are the most relevant alternatives to brachytherapy to treat prostate cancer patients in Spain and Italy?*

This research aims to demonstrate that the current reimbursement for brachytherapy in Italy results in sub-optimal treatment decisions and subsequently increased costs related to the associated sub-optimal clinical outcomes. Therefore, we first need to identify the most relevant treatment modalities employed in these countries to make an effective comparison.

2. *What are the guidelines for selecting a treatment for a prostate cancer patient and what do these guidelines recommend for the different risk categories?*

To accurately simulate patient distribution to treatment modalities, reflecting real-world practices, it is essential to study guidelines governing treatment selection. This ensures a comprehensive understanding of how treatments are chosen in practice.

3. *Which factors are taken into consideration when choosing a particular treatment for a patient, and how do these factors interact?*

Although guidelines will shed some light on how treatment decisions are being made, in practice centers and caregivers may deviate from these guidelines. To determine how a particular treatment is selected for a specific patient, what additional factors influence the treatment decision and how these factors interact, to eventually measure the effect of changing the reimbursement on this decision process we must identify these factors that cause centers to deviate and how they interact.

4. *What are current reimbursement rates and how does changing the reimbursement of brachytherapy affect the distribution of prostate cancer patients among treatment modalities?*

Next, we must study the existing reimbursement systems in Italy in Spain, understand current reimbursement rates and decide on representative numbers to be entered into the allocation model to reflect the existing situation. In addition, we must understand the impact of reimbursement on treatment decisions.

5. *How are patients with prostate cancer currently distributed over the treatment options in Spain and Italy?*

We aim to understand how changes in reimbursement rates for brachytherapy affect the use of different treatments. To explore this, we will create a patient allocation model. The model will make use of the information collected using sub-questions 1-4 and create a patient distribution that will respond to changing reimbursement. To validate the model, we will fine-tune the outcome based on actual distribution in Italy and compare the effect of increasing reimbursement with the actual situation in Spain. For this, we need insight into actual patient distributions in Spain and Italy. Therefore, we must analyse the current patient distributions over the treatment modalities.

To understand how to perform an economic value assessment, of a treatment modality using a Markov model, we must identify what is currently the gold standard for this type of analysis in the clinical arena. This leads to sub-question 6:

6. *What knowledge exists on conducting an economic value assessment using a Markov model in healthcare?*

We will investigate how to integrate the results of the patient allocation model into a Markov model.

7. *How can the cost-effectiveness analysis of prostate cancer treatment modalities be formulated in a Markov model?*

To build the model we require some input variables. To identify those, we formulate the following questions:

7.1 What are the possible health states associated with prostate cancer treatment modalities?

7.2 What are the probabilities of the utility corresponding to each health state?

7.3 What are the costs of the different health states associated with the treatment modalities?

When the model has been created, we will analyse the effect of changing brachytherapy reimbursement on the output of the model.

8. *What are the results of the cost-effectiveness analysis?*

In addition to the cost-effectiveness analysis, we will conclude our research by conducting an additional budget impact analysis (BIA) to help identify the optimal reimbursement rate that can be presented to the Italian decision-makers.

9. What is the optimal reimbursement rate for brachytherapy in Italy?

2 Methodology

This chapter presents the methodology for answering the nine sub-questions described in section 1.6.

2.1 Methods to answer Sub-Questions

Sub-question 1: *What are the most relevant alternatives to brachytherapy to treat prostate cancer patients in Spain and Italy?*

To identify the most relevant treatment options for prostate cancer patients we conducted a systematic literature review (SLR). The details of how the SLR was performed, including search terms, criteria for inclusion and exclusion, databases scrutinized, and description of outcomes are presented in Appendix B. The outcomes of the SLR were validated by comparing outcomes with Elekta's '*Prostate Cancer Care Path,* 2023'[6], an internal analysis of how prostate cancer patients are currently treated, and by consulting experts at Elekta.

Sub-question 2: *What are the guidelines for selecting a treatment for a prostate cancer patient and what do these guidelines recommend for the different risk categories?*

To investigate treatment selection for prostate cancer patients, we aimed to identify relevant guidelines. Since all prostate cancer patients are initially seen by urologists, we looked for treatment guidelines published by the national urological associations of Italy (Società Italian di Uro-Oncologia), Spain (La Asociación Española de Urología), and Europe (the European Association of Urology, EAU), and their recommendations.

To validate our findings and incorporate the identified guidelines into our model, we included a question regarding guideline usage in a survey we conducted. Respondents were asked an open-ended question about the guidelines they employ to confirm our identified guidelines and find additional relevant guidelines. Once confirmed, we reviewed these guidelines to ascertain risk categories for prostate cancer patients, the criteria for assigning patients to risk categories, and the recommended treatments for each risk group.

Sub-question 3: *Which factors are taken into consideration when choosing a particular treatment for a patient, and how do these factors interact?*

To address this question, a customer survey was distributed via E-mail to 20 healthcare professionals in Europe, who are involved in making treatment decisions for prostate cancer patients. Radiation Oncologists were selected from Elekta's overview of Key Opinion Leaders (KOLs), Urologists from the same hospitals as the Radiation Oncologists were identified using google searches. The survey aimed to gather information on relevant decision factors and the weight attributed to these factors, and to confirm treatment guidelines that are currently being employed. For details of the survey design, please refer to Appendix C. The survey questions can be found in Appendix D.

Sub-question 4.1: *What are current reimbursement numbers?*

To understand the reimbursement systems in Italy and Spain literature searches were performed to identify relevant publications that contain information on this topic. In addition, two Elekta regional representatives were asked to contact relevant customers in representative regions in Spain and Italy and collect information on how these centers are reimbursed for brachytherapy. To help them collect the right information, we sent them a list of questions to be answered. They then collected the information we asked for. The questions can be found in Appendix E.

Sub-question 4.2: *How does changing the reimbursement of brachytherapy affect the distribution of prostate cancer patients among treatment modalities?*

Using the information collected in sub-questions 1, 2, 3 and 4.1 a patient allocation model was developed in Excel using the pre-installed coding language Visual Basic for Applications (VBA).

We utilized the Multi-Criteria Decision Analysis (MCDA) method to simulate the distribution of patients among different treatment modalities for each risk category, considering various decision factors such as effectiveness, safety, costs etc. MCDA is a structured process used for comparative analysis of different options based on multiple criteria [9]. Within this approach, we implemented the weighted-sum method, wherein weights are assigned to individual criteria (decision factors), a score is computed for each treatment modality by considering these weighted criteria, and finally, patients are distributed to specific treatment modalities based on the computed scores.

This approach involves several steps [9]:

- Step 1: Identify the treatment modalities to be compared.
- Step 2: Define factors that influence treatment selection decisions.
- Step 3: Allocate weights to each factor.
- Step 4: Normalize the values.
- Step 5: Calculate the score.
- Step 6: Decision rule to allocate patients.

These steps form the basis of our simulation to assess the distribution of patients across treatment options within the identified risk categories. It is worth noting that in clinical practice, MCDA may be used in conjunction with other approaches such as clinical expertise, evidence-based medicine, and shared decision-making to ensure comprehensive and patient-centred care.

Execution of steps 1, 2 and 3 have been described above. Steps 4, 5 and 6 will be executed as described in the following.

Step 4: Normalize Data

To ensure that all values for the input data are on a consistent scale we used the following formula:

$$Normalized\ Value_i = \frac{(Actual\ Value_i - Min\ Value_i)}{(Max\ Value_i - Min\ Value_i)}$$

$$i = factor$$

We utilized the widely accepted Min-Max normalization method to scale the input values between 0 and 1. This choice was deliberate, aiming for simplicity, interpretability, and alignment with existing literature in MCDA. Min-Max normalization ensures that each criterion, irrespective of its measurement scale, contributes proportionally to the overall evaluation, preventing any single criterion from dominating. The formula's straightforwardness enhances its interpretability, particularly for stakeholders without an extensive quantitative background in healthcare decision-making. While alternative methods like Z-Score normalization and Decimal Scaling were considered, Min-Max normalization emerged as the optimal choice due to its ease of interpretation, flexibility across diverse criteria, and its established use in MCDA literature, ensuring coherence with existing research in the field [9].

Step 5: Score calculation

Guideline recommendations are typically considered the gold standard for treatment decisions. For that reason, guideline recommendations are taken as a starting point for the patient allocation model. Deviations from the starting point based on other decision factors such as reimbursement, are calculated by multiplying the fraction of patients receiving a particular therapy based on guidelines with the respective weights and normalized values of other decision factors.

To prevent that, based on guideline recommendations, a particular therapy receives a score of 0 and thus will never be selected, we use exponential scaling for the guideline percentage ($e^{(guideline\ weight * guideline\ percentage)}$). This adjustment ensures that the guideline percentage does not overly dominate the calculation during multiplication, preventing a treatment modality from receiving a score of 0.

Deviations from guideline recommendations can be based on additional factors such as profitability (positive influencer) or toxicity, and complexity (negative influencer). The combined score for each treatment modality is calculated by multiplying the weight of each factor with its normalized value and summing up the combined outcomes.

To address the possible negative influence of factors like toxicity, we applied a 'Detrimental adjustment' using the formula: *Detrimental adjustment = Maximum possible Normalized score – actual Normalized score*. Whereas the Maximum possible normalized score is 1.

The formula below illustrates how guideline recommendations and the combined score for decision factors that could be a reason to deviate result in a score for each treatment modality:

$$Score\ of\ Treatment\ Modality = (\ weight\ Factor\ A * (1 - Normalized\ complexity\ score) + \ weight\ Factor\ B * (1 - Normalized\ toxicity\ score) + \ weight\ Factor\ C * (Normalized\ profitability\ score)) * e^{(guideline\ weight * guideline\ percentage)}$$

Step 6: Decision-rule

In the final step we applied the following decision rule: Allocate patients to treatment modalities proportionally based on the calculated score.

$$Allocate\ Patients\ to\ each\ Treatment\ Modality = \left(\frac{^{2}Score\ of\ Treatment\ Modality\ x}{^{3}Total\ Score}\right) * Number\ of\ Patients\ in\ Risk\ Group$$

This formula ensures that the allocation of patients is proportionally influenced by the scoring system. Whereas the decision factors influence the score.

Validation of the model can be done with information collected to answer question 5.

Sub-Question 5: *How are patients with prostate cancer currently distributed over the treatment options in Spain and Italy?*

To validate the patient allocation model, we collected information on actual patient distributions in Spain and Italy. To collect this information, we performed literature searches to identify recent (less than 5 years old) publications describing actual distributions of patients over the risk categories and over the treatments and compared these with the output of the model.

Sub-question 6: *What knowledge exists on conducting an economic value assessment using a Markov model in healthcare?*

We conducted a search using Google Scholar, focusing on "cost-effectiveness analysis brachytherapy" for the years 2020-2023. The literature we found served as a foundation and guide for constructing our Markov model.

[2] **Score of Treatment Modality :** The score assigned to the identified treatment modality.
[3] **Total Score:** The sum of scores across all treatment modalities.

Sub-question 7*: How can the cost-effectiveness analysis of prostate cancer treatment modalities be formulated in a Markov model?*

Cost-effectiveness analysis

We have chosen cost effectiveness analysis (CEA) as the preferred economic evaluation method. CEA compares treatments by evaluating their effectiveness in terms of health outcomes gained for a given cost. It requires the cost and a common health outcome for each alternative, resulting in an incremental cost-effectiveness ratio (ICER) [10].

To conduct a CEA, we followed these steps:

1. Identify the treatment alternatives for comparison (Sub-question 1).
2. Quantify the health outcome measures for brachytherapy and the identified alternatives.
3. Calculate the costs (treatment cost plus toxicity management cost plus follow-up care cost) associated with brachytherapy and the alternatives using the same Markov model.
4. Compute the ICER for each comparison.

The ICER is calculated by dividing the difference in total cost by the difference in health outcome between brachytherapy and alternatives. In our research, we use Quality-Adjusted Life Years (QALY) and Life Years (LY) as health outcome measures. QALY combines both the quantity and quality of life into a single measure. LY, on the other hand, focuses only on the quantity of life. The ICER can be described as the additional cost per QALY gained or the additional cost per LY gained from brachytherapy.

$$ICER\_1 = \frac{Cost_{brachytherapy} - Cost_{alternatives}}{QALY_{brachytherapy} - QALY_{alternatives}} = additional\ cost\ per\ QALY\ gained$$

$$ICER\_2 = \frac{Cost_{brachytherapy} - Cost_{alternatives}}{LY_{brachytherapy} - LY_{alternative}} = additional\ cost\ per\ LY\ gained$$

The QALYs, LYs, cost and ultimately the ICER of brachytherapy versus its alternatives were assessed utilizing a Markov model. To construct the Markov model the following sub-questions needed to be answered:

Sub-question 7.1: *What are the possible health states associated with prostate cancer treatment modalities?*

To construct a Markov model for prostate cancer, the disease is initially divided into distinct health states. Subsequently, transition probabilities are assigned to represent the movement of patients between these health states over discrete time periods, known as Markov cycles. Transition probabilities were determined by analyzing publications comparing the outcomes of treatment options for the specific risk categories. In case no reliable data was available from scientific literature experts from Elekta were asked to provide estimations of transition probabilities.

Sub-question 7.2: *What are the probabilities of the utility corresponding to each health state?*

We obtained the probabilities of toxicity and the Quality of Life (QOL) for each health state of the prostate cancer treatment modalities from clinical literature. In case no clear data was identified from scientific literature experts from Elekta were asked to provide estimations of these probabilities. Since we aim to compare prostate cancer treatment modalities to show the clinical benefits of brachytherapy over other treatments it is relevant to include health state utility values. We measured utilities in QALYs which are calculated by multiplying the health state utility 'QOL' with the survival. Whereas the

survival is the 'Markov Trace', the percentage of patients in each health state per Markov cycle (Appendix J).

Sub-question 7.3: *What are the costs of the different health states associated with the treatment modalities?*

We obtained the [4]costs of the different health states from clinical literature. In case no clear data was available from scientific clinical literature experts from Elekta were asked to make estimations of these costs.

Sub-question 8: *What are the results of the cost-effectiveness analysis?*

When combining the patient allocation model with the Markov model and entering data relevant to the existing situation in Italy the output of the model showed the cost-effectiveness of each treatment modality and how these compare. The CEA deliverables include ICERs for each comparison (brachytherapy versus each of the alternative therapies).

In addition to the CEA, we conducted a budget impact analysis (BIA), which is increasingly used alongside a CEA when evaluating healthcare interventions. It is both useful and required for reimbursement approvals [11]. We carried out a BIA for all four risk groups in Spain and Italy, where we multiplied the number of patients in each treatment modality by the cost per patient over a period of six years, using the results of the Markov model. The outcome provides the overall total costs considering all the treatment modalities summed together.

Sub-question 9: *What is the optimal reimbursement rate for brachytherapy in Italy?*

The effect of changing reimbursement for brachytherapy on patient distribution and thereby the economic outcome of the treatments was evaluated and optimum reimbursement values for the total population were determined.

2.2 Sensitivity Analysis

To assess the robustness of the model, we conducted a one-way deterministic sensitivity analysis on the transition probabilities. This analysis aimed to examine how changes in the transition probabilities affect the results of the cost-effectiveness analysis. Due to time constraints, the sensitivity analysis was performed using a three-point range, the minimum, mean, and maximum only on one risk group, specifically the high intermediate risk group. This choice was made because brachytherapy is predominantly utilized in this risk group, and it includes the combination of brachytherapy plus EBRT, enabling a comprehensive comparison of brachytherapy with all identified alternatives. The minimum and maximum values for the sensitivity analysis were obtained from the 95% confidence interval (CI), calculated after estimating the standard deviation of the parameters with input from Elekta experts. Since no data were available in the scientific literature specifically for the risk groups, treatment modalities, and parameters required for our analysis, input from with Elekta experts was essential. Tornado diagrams were generated to visually present the results of the sensitivity analysis.

[4] Treatment cost, reimbursement cost and follow up care cost.

3 Results

This chapter presents the answers to the sub-questions described in the section 1.6.

3.1 Sub-Question 1

What are the most relevant alternatives to brachytherapy to treat prostate cancer patients in Spain and Italy?

The results of the SLR to identify the most relevant treatment alternatives for brachytherapy are presented in Appendix B. The primary treatments utilized for prostate cancer patients, besides brachytherapy, include EBRT, Active Surveillance, surgery/radical prostatectomy, and the combination of brachytherapy and EBRT. These therapies can be combined with hormonal therapy or chemotherapy. Focusing on these modalities ensures an investigation of major approaches applicable to prostate cancer patients in Italy and demonstrates the differences in cost and outcomes between brachytherapy and alternative treatments for decision-makers in Italy. The sections below provide some information on these treatment options.

Brachytherapy

See section 1.1 of this thesis.

EBRT

Similar to brachytherapy, EBRT employs ionizing radiation to damage cancer cells while attempting to minimize harm to surrounding healthy tissues. However, the approach of EBRT differs significantly from brachytherapy. In EBRT, high doses of radiation are delivered precisely at a specific, well-defined target area in the body from outside the body. In contrast, brachytherapy involves placing radiation sources inside the body near or within the tumor [12]. Consequently, external beam radiation must travel through healthy tissues, making it inherently less precise than brachytherapy. This broader irradiation may decrease the risk of tumor spread, especially in higher-risk patients, but will also elevate the likelihood of increased toxicity compared to a more targeted treatment approach.

Combination of brachytherapy and EBRT

The combination of brachytherapy and EBRT is predominantly used for patients with high-risk prostate cancer [6]. This treatment process initially starts with EBRT sessions to shrink the tumor, followed by brachytherapy to increase the dose to the lesion without surpassing thresholds of permanent damage to healthy tissues. This combination offers various advantages. By combining the localized dose from brachytherapy with the broader coverage of EBRT, higher overall radiation doses can be delivered to the tumor, increasing treatment effectiveness. The synergistic effect of using both therapies can improve the likelihood of controlling the tumor, especially in cases where cancer cells might have spread beyond the primary site or when the tumor has complex shapes.

Active Surveillance

Active Surveillance involves closely monitoring the tumour instead of promptly opting for active interventions like surgery or radiation therapy. The benefit of actively observing the tumour is to mitigate the negative health impact or complications associated with an intervention, and it is primarily employed for patients with early-stage prostate cancer that is anticipated to have a slow growth rate [13].

Surgery

Surgery is a traditional method used in the treatment of prostate cancer, commonly known as prostatectomy. The primary form of prostatectomy is termed "radical" prostatectomy, involving the

surgical removal of the entire prostate gland along with surrounding tissues [14]. Similar to EBRT, surgery is mainly used for patients in intermediate- and high-risk groups.

3.2 Sub-Question 2

What are the guidelines for selecting a treatment for a prostate cancer patient and what do these guidelines recommend for the different risk categories?

We looked for treatment guidelines published by the national urological associations of Italy (Società Italian di Uro-Oncologia), Spain (La Asociación Española de Urología), and Europe (the European Association of Urology, EAU), and their recommendations. Since the national urologists associations did not have their own guidelines, but instead refer to the EAU guidelines therefore, we decided to focus on those.

Risk Classification

The patient's risk classification mainly determines the selection of treatment for individuals with prostate cancer. Initially, our examination of the EAU guidelines led to the identification of six distinct risk categories for prostate cancer patients: very low-, low-, low intermediate-, high intermediate-, high-, and very high-risk [15]. These categorizations depend on specific cancer characteristics, including the TNM score, where T describes the tumour size and any spread into nearby tissue; N describes the spread of cancer to nearby lymph nodes; and M describes metastasis (spread of cancer to other parts of the body). The Gleason score is also considered to reflect how abnormal cancer cells look under the microscope and align with the levels of 'prostate-specific antigen' (PSA) detected in a patient's blood. Table 2 below illustrates the various risk groups and their corresponding characteristics.

While our primary focus lies on the EAU guidelines, it is important to note that other guidelines from institutions like the National Comprehensive Cancer Network (NCCN), European Association of Radiation Oncology (ESTRO), or European Society of Medical Oncology (ESMO) may offer distinct recommendations, particularly regarding risk stratification. Since our research is specifically focused on the healthcare systems of Italy and Spain, we present and base our choices upon the guidelines provided by the EAU, with minor modifications to focus on the risk groups relevant for our research.

Table 2 NCCN - EAU Risk Classification

Definition			
Low-Risk	Favourable intermediate-risk	Unfavourable intermediate-risk	High-Risk
PSA < 10 ng/mL **And GS < 7 (ISUP grade 1)** **And cT1-2a***	PSA 10-20 ng/mL Or GS 7 (ISUP grade2/3) Or cT2b*	GS 7 (ISUP grade 3) and/or ≥ 50% positive biopsy cores and/or at least two intermediate risk factors	PSA > 20 ng/mL Or GS > 7 (USUP grade 4/5) Or cT2c*
localised			

* Based on digital rectal examination

Treatment recommendation according to guidelines

Once prostate cancer patients are classified into risk groups, the EAU provides guidelines, as outlined in Appendix F. These guidelines recommend treatment based on the assigned risk categories.

1. ***Very Low-Risk and Low-Risk Groups:***

- Active Surveillance as the primary treatment, given that the tumour itself is unlikely to pose harm. Alternative treatments like radiation and surgery may negatively impact patients.

- If intervention is required or preferred, options include EBRT, brachytherapy, and surgery.

2. ***Low Intermediate-Risk (Favourable Intermediate-Risk) Group:***

- Active Surveillance, surgery, EBRT, and brachytherapy.

3. ***High Intermediate-Risk (Unfavourable Intermediate-Risk) Group:***

- Surgery, EBRT, brachytherapy, and a combination of EBRT plus brachytherapy.

4. ***High-Risk and Very High-Risk Groups:***

- Brachytherapy, EBRT, surgery, and EBRT plus brachytherapy.
- Patient preferences may lead to Active Surveillance in some cases, particularly if medical issues impacting lifespan, are a concern.

Conclusion

We have based our selection of risk categories and treatment options included in our model on the guidelines provided by the EAU. Our model includes the risk categories 'low-risk' and 'low intermediate-risk', with treatment options brachytherapy, EBRT, surgery, and Active Surveillance. Additionally, for 'high intermediate-risk' and 'high-risk' we have included the same treatment options along with the addition of EBRT combined with brachytherapy.

3.3 Sub-Question 3

Which factors are taken into consideration when choosing a particular treatment for a patient, and how do these factors interact?

The literature analysis conducted to address sub-question 1 yielded some insights into the decision factors considered when selecting a therapeutic approach for prostate cancer patients. Articles describe that treatment choices are based on risk classification, patient condition, and comorbidities, expected outcomes, benefits and risks associated with a treatment, patient choice, and health economics. Using these insights, a customer survey was developed and distributed to 20 healthcare professionals (radiation oncologists and urologists) across Europe involved in treatment decision-making for prostate cancer patients. The survey design is attached to this thesis as Appendix C. The survey, detailed in Appendix D, included questions about respondent's roles and experience in treating prostate cancer. The goal is to understand the factors influencing the decision-making process for selecting a treatment for prostate cancer patients and to assign weights to these various decision factors. Questions on the role of reimbursement and costs of the therapies in the decision-making process were included in the survey.

A filled-in survey was returned by 6 healthcare professionals (four Radiation Oncologists, one Urologist and one Radiation Therapist), all from Europe, of which two were from Spain (one Urologist) and one from Italy (Radiation Therapist). Table 3 provides information on the respondent's experience in treating prostate cancer and the process of making treatment decisions.

Table 3 Survey Results Related to Experience and Decision Process

	Rad. Onc. 1	Rad. Onc. 2	Rad. Onc. 3	Rad. Onc. 4	Rad. therapist	Urologist
Country	Spain	France	Netherlands	Germany	Italy	Spain
Years of experience	>15	>15	>15	10-15	>15	5-10
Monthly caseload	4	15	15	20	100	120
Decision process	Patients are referred by	All patients are	Treatment is usually decided	Urology and Radiation	Multi-disciplinary	Localized disease is

	urologists in small hospitals, urologists and Rad Oncs. are involved in decision-making.	discussed in a specific tumour board	in the multidisciplinary tumour board. However, a different treatment can be chosen after shared decision-making with the patient himself.	Oncology work together	team with urologists and medical oncologists	usually decided by the urologist, a multi-disciplinary teams decide on locally advanced mHSPC, CRPC
Guidelines used	ESTRO	Local guidelines	The Dutch Prostate Guideline. In case of ambiguities, the EAU guideline is also considered	NCCN	[5]AIRO, EAU, NCCN	EAU

Since three of the six respondents mention that they follow the EAU guidelines in their decision process, and other options are mentioned only once by the respondents we consider this a confirmation of our choice to focus on the EAU guidelines for our model.

Regarding the treatment decision, all respondents indicated that it was made by a multidisciplinary team. Treatment guidelines emerged as the most significant factor for the model. Other confirmed factors included the risk classification of the tumour, expected toxicity, treatment complexity, and profitability. Suggestions for additional factors in the decision-making process included the patient's preference mentioned three times, comorbidities mentioned twice, and urinary function mentioned once.

Given the interconnected nature of these factors for instance, a patient's preference may correlate with expected toxicity, and expected toxicity may be influenced by the patient's comorbidities (such as poor circulation and erectile dysfunction prevalent among some older men) we opted to focus on the factors analysed in our survey. Consequently, we chose not to conduct a second survey to explore further insights into how these suggestions interact.

Consequently, the decision factors to be included in our patient allocation model are:

I. Guidelines

Since the EAU guidelines recommend treatments based on risk categories first the proportion of patients falling into risk groups had to be determined. A recent publication by Gomez-Veiga in 2017 [16] presented data from Spain on this topic. Based on this publication we used the following input data for patient distribution over the risk categories:

Table 4 Distribution of Patients over the Risk Categories

Risk group	% of PC patients falling into risk group	Reference
Low	45%	[16]
Low intermediate	20%	
High Intermediate	15%	

[5] Italian Association of Radiation Oncology

High	20%	

Guidelines serve as the criteria for allocating treatment among different risk groups. In the conducted survey, participants were asked to evaluate the significance of treatment guidelines in their decision-making for each of the four risk groups. Based on the survey feedback, it was determined that guidelines play the most prominent role in treatment decisions. The input values for the distribution of prostate cancer patients incorporated into the model, based on guidelines as presented in Appendix F, are shown below:

Table 5 Percentage of Patients Distributed to a particular Treatment based on EAU Guidelines

Risk group	Brachytherapy	EBRT	Active Surveillance	Surgery	EBRT + Brachytherapy
Low	12%	13%	50%	25%	n.a.
Low intermediate	12%	33%	10%	45%	n.a.
High Intermediate	6%	20%	4%	48%	22%
High	6%	14%	4%	48%	28%

II. Profitability

In our patient allocation model, we combined reimbursement and cost of a therapy into the factor profitability (***Profitability*** = *Reimbursement – Cost* [5]). We included profitability as a decision factor due to its impact on both patients and the healthcare system. The cost of a treatment can influence the patients' decision-making and the overall sustainability of healthcare. Unfavourable reimbursement rates and high treatment costs can strain resources, compromising care quality and accessibility in the healthcare system.

After consulting with Elekta experts, we strategically determined the cost of treatment and reimbursement rates for brachytherapy in both Spain and Italy (see also sub-question 4.1). Profitability of other therapeutic options has been set at a constant level. Our approach makes sure that brachytherapy generates a higher profit in Spain compared to Italy, highlighting a better reimbursement scenario in Spain assisting us to simulate the current situation in both countries.

III. Complexity of Treatment

It is important to consider the complexity of a treatment, as it influences its suitability for certain patients, considering factors such as possible medical history. Some patients may not be suitable for complex treatments due to various factors like age, overall health, or personal preferences. To quantify the role of complexity, two questions were included in the survey. Firstly, participants were asked to rank each treatment based on its complexity from least to most complex. Subsequently, they were requested to score each treatment's complexity on a scale of 0 to 5 with 0 being the least complex and 5 being the most complex. Based on the survey results average scores for each therapeutic option were calculated, taking into consideration that for the rating of the 'complexity of surgery', only the opinions of urologists were considered relevant, whereas for the 'complexity of radiation therapy' options, only the opinions of radiation oncologists mattered. The treatment complexity scores based on survey results are presented in Table 6.

Table 6 Complexity Score of Treatment

Complexity of	Average score	Range
Surgery	3.6	n.a.
Active Surveillance	1.075	0.9 - 1.5
EBRT	2.275	1.5 - 3.5
Brachytherapy	2.5	2.4 - 3.9
EBRT + Brachytherapy	3.7	2.9 - 4.2

IV. Treatment Toxicity

Next, the patient allocation model incorporates toxicity, to support evidence-based decision-making and enable informed choices for patients. This consideration allows patients to align treatments with their preferences. Toxicity of each treatment modality is independent of the risk group. Literature in general reports on gastrointestinal toxicities, genitourinary toxicities, and sexual toxicities. Since one patient can have multiple toxicities at the same time, we have only incorporated the Erectile toxicity at 5 years, which is the highest toxicity we found in the literature.

Table 7 Toxicity Scores of Treatments

Toxicity	Score (percentage of men reporting problem with erectile dysfunction)	Reference:
Surgery	33%	[47]
Active Surveillance	10%	
EBRT	20%	
Brachytherapy	11%	
EBRT + brachytherapy	20% (extrapolated)	

Incorporating only one toxicity offers better clarity than using an average of toxicities or their total. For the toxicity of EBRT plus brachytherapy, we used the highest toxicity of EBRT and brachytherapy.

Weight of Decision Factors

For each risk level of prostate cancer, respondents were asked to rate the relative importance (weight) of various decision factors in the decision-making process for allocating patients to a particular treatment. A scale between 0 to 10 was provided to give a rating, where 0 represented the least important factor and 10 represented the most important factor. The outcomes of the survey are presented in Tables 8-11 below.

Table 8 Decision Factor Weight Scores for Low-Risk Prostate Cancer

Decision factor	Average Score	Range
The severity class of the patient	6.68	4.8 – 9.3
Guidelines	8.62	5.6 - 10
Toxicity	7.76	2.5 - 10
Costs of the treatment	3.64	1 – 7.7
Reimbursement	2.08	0 - 5
Complexity of the treatment	4.56	2.3 – 7.2

Table 9 Decision Factor Weight Scores for Low Intermediate-Risk Prostate Cancer

Decision factor	Average Score	Range
The severity class of the patient	6.46	4.8 - 9
Guidelines	8.2	4.6 - 10
Toxicity	7.18	2 - 10
Costs of the treatment	3.94	1 – 7.9
Reimbursement	3.04	0 – 6.7
Complexity of the treatment	4.68	3 – 7.3

Table 10 Decision Factor Weight Scores for High Intermediate-Risk Prostate Cancer

Decision factor	Average Score	Range
The severity class of the patient	6.16	3.7 - 10
Guidelines	8.7	5.2 - 10
Toxicity	6.62	2 - 10
Costs of the treatment	4	1 – 7.6
Reimbursement	0 – 6.5	2.08
Complexity of the treatment	4.5	1.9 – 8.5

Table 11 Decision Factor Weight Scores for High-Risk Prostate Cancer

Decision factor	Average Score	Range
The severity class of the patient	5.48	2.3 - 10
Guidelines	9.1	6.7 - 10

Toxicity	6.54	2 - 10
Costs of the treatment	3.72	0.9 – 7.7
Reimbursement	2.56	0 – 6.6
Complexity of the treatment	4.62	2.6 – 6.9

An overview of all input values incorporated into the model are presented in Appendix I.

3.4 Sub-Question 4.1

What are the current reimbursement rates?

When analysing reimbursement situations in Italy and Spain through literature analysis and conversations with regional Elekta representatives we identified that the situations are complex, change over time and are different per region (17 autonomic regions in Spain, 21 with varying autonomy in Italy). Within regions hospitals negotiate their own payments based on previous years case load. It appears that in Spain hospitals get budgets from the Spanish National Health System and in addition are paid for activities performed. This means that costs such as those for brachytherapy treatment, comprising personnel expenses, ancillary services like imaging or anaesthesia, and expenses for brachytherapy devices and disposables, are covered by funds from distinct sources. Based on the literature we estimate 25-50% of the costs of brachytherapy treatment are paid by reimbursement for that activity (fee for service). In Italy the National Health Services provide funding. Also, in Italy besides activity-based fees there are also other sources of funding for the hospitals.

We have [6] interviewed two heads of radiation therapy departments of large therapeutic centres in respectively Barcelona and Milano to obtain reimbursement numbers that can be used for our model. We are aware that the numbers obtained are not representative of Spain and Italy as a whole but merely reflect the current numbers in only these two hospitals. Additional data on surgery and Active Surveillance was obtained from a third subject matter expert (Urologist – surgeon from Spain).

They provided us with the following data:

Table 12 Data obtained from Elekta Experts in Spain and Italy

	ICO Barcelona	IEO Milano
Surgery	Between €2.180,50 and €21.436,00 depending on procedure and complications	No data
Active Surveillance	need to be calculated by adding the reimbursement values of each procedure established in the protocol (annual visit, PSA lab value, biopsy), estimated at 850 € annually.	No data
EBRT	€2.817,11 (complexity 2)	€5.000 – €10.000 SBRT ~€7.000
Brachytherapy	€923,74 / fraction	€4.700(variables are many)
EBRT + Brachytherapy	Summation	Summation

Finally, after consulting Elekta experts in Italy and Spain we included the following reimbursement rates for input in our model for Italy as shown in Table 13. The reimbursement rate for Active Surveillance is calculated over six years to account for the ongoing tumour monitoring. We calculated the annual costs, which include expenses for biopsies, PSA tests, and hospital visits. The combined rate

[6] We send questions to Elekta representatives in both countries. The list of questions can be found in Appendix E.

of EBRT plus brachytherapy is calculated as the sum of the individual reimbursement rates for each of the two treatments. The details of how we calculated the surgery reimbursement are provided in Appendix G.

Table 13 Reimbursement Rates in Spain and Italy

Treatment modalities	Reimbursement rates Italy	Reimbursement rates Spain
Brachytherapy	€4.700	€6.000
EBRT	€7.500	€7.500
Active Surveillance	€4.250	€4.250
Surgery	€7.544	€7.544
EBRT + Brachytherapy	€12.200	€13.500

3.5 Sub-Question 4.2

How does changing the reimbursement of brachytherapy affect the distribution of prostate cancer patients among treatment modalities?

The output of the patient allocation model yields how prostate cancer patients in Italy and Spain are allocated among different treatment modalities within each risk group. Figure 3 and Figure 4 depict the distribution of patients among brachytherapy and the selected alternative treatment modalities in Italy and Spain.

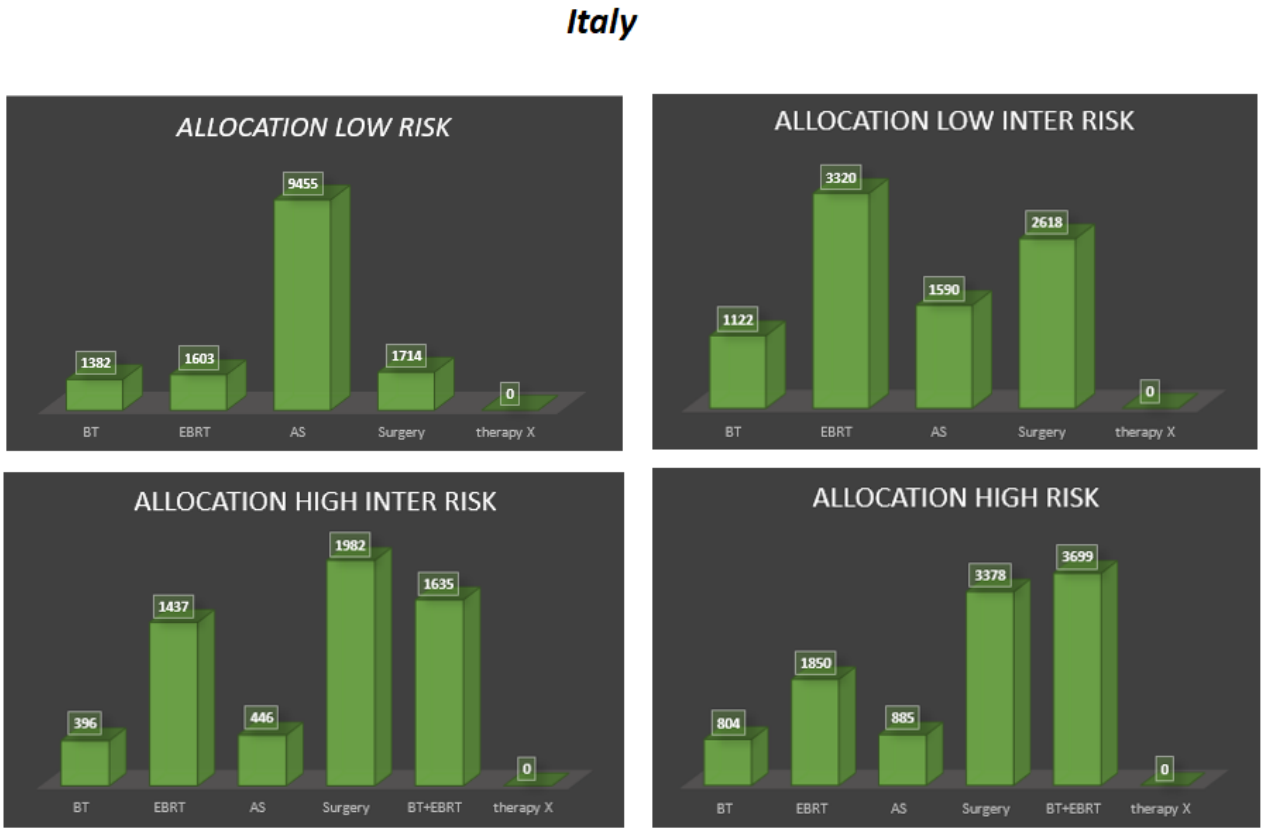


Figure 3 Distribution of Prostate Cancer Patients among Treatment Modalities in Italy

Spain

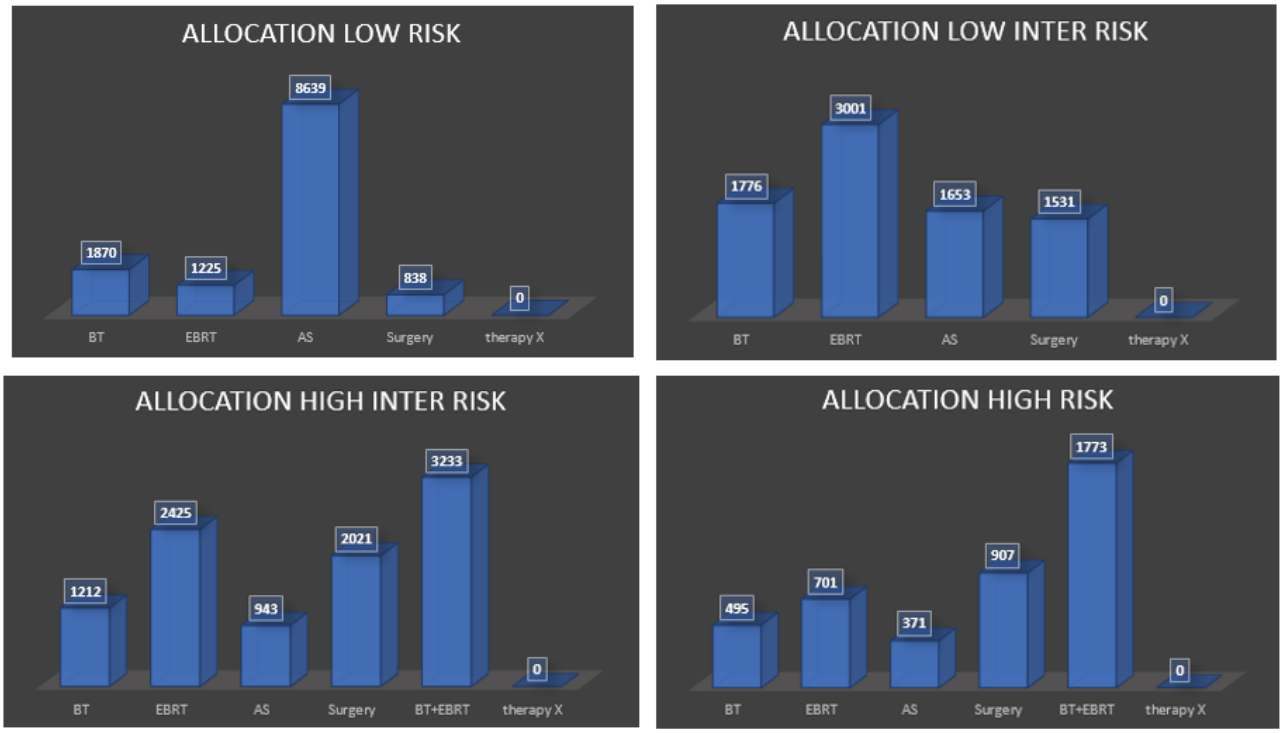


Figure 4 Distribution of Prostate Cancer Patients among Treatment Modalities in Spain

The difference in the distribution of prostate cancer patients among risk groups in Italy and Spain is guided by the inclusion of treatment modality recommendations following established guidelines. The output from both Italy and Spain indicates differences in the utilization of brachytherapy as a primary treatment modality for prostate cancer between the two countries. In Italy, brachytherapy is mainly used in combination with EBRT, particularly for high-risk patients. Whereas the distribution of prostate cancer patients in Spain demonstrates an emphasis on brachytherapy across the different risk groups. Particularly for high intermediate-risk patients, brachytherapy is a prominent choice in the form of combination therapy with EBRT.

Based on the output of the model we identify that the main difference in brachytherapy utilization in Spain and Italy is because of differences in reimbursement rates of brachytherapy. In Spain, there is a higher reimbursement for brachytherapy compared to Italy, leading to its increased utilization. Our model simulation supports this, as the only difference we considered for both countries while modelling was the higher reimbursement for brachytherapy in Spain and the lower reimbursement in Italy.

3.6 Sub-Question 5

How are patients with prostate cancer currently distributed over the treatment options in Spain and Italy?

Recent publications were reviewed to understand the current treatment landscape for prostate cancer patients in Italy and Spain, focusing on articles published within the last five years that reported treatment options. One article describing treatment patterns in Italy was identified [50]. Analysis of this article by Bugoline et al. presented the following distribution of prostate cancer patients among treatment modalities in Italy:

Table 14 Distribution of Prostate Cancer Patients among Treatment Modalities in Italy [50]

	Active Surveillance	Radical Treatment			
		Surgery	EBRT	Brachytherapy	EBRT +Brachytherapy
Low					
Intermediate	17 (1.7%)	44%	54%		
High					

In Spain two relevant articles were found [51][52]. Their analysis demonstrated the following distribution in Spain:

Table 15 Distribution of Prostate Cancer Patients among Treatment Modalities in Spain by Bonfill et al. [51]

	Active Surveillance (+untreated)	Radical Treatment			
		Surgery	EBRT	Brachytherapy	EBRT +Brachytherapy
Low	33 (21%)	66 (41%)	61 (38%)		
Intermediate	23 (21%)	53 (49%)	32 (30%)		
High	41 (29%)	44 (31%)	55 (39%)		

Table 16 Distribution of Prostate Cancer Patients among Treatment Modalities in Spain by Correa et al. [52]

	Active Surveillance (+untreated)	Radical Treatment			
		Surgery	EBRT	Brachytherapy	EBRT +Brachytherapy
Low	40%	58%			
Intermediate	2%	91%			
High	2%	86%			

Based on a publication by Gomez-Veiga et al in 2017 [16] that showed that for clinically localized prostate cancer in Spain, the majority of patients analysed (~ 84%) received treatment, with one-third undergoing radiotherapy; ~ 86% were treated with EBRT and ~ 39% received brachytherapy, combined with the information from the three articles mentioned above, we deducted that the actual patient distribution in Spain and Italy should be close to the numbers presented in Table 17. In this overview almost 80% get treated, a little over one third of all patients (50% of patients that receive treatment) with radiotherapy of which 84% with EBRT, 39% with brachytherapy.

Table 17 Deducted Patient Distribution across Risk Groups

	Active Surveillance (+untreated)	Radical Treatment			
		Surgery	EBRT	Brachytherapy	EBRT + Brachytherapy
Low	40%	30%	20%	10%	0%
Intermediate Low	8%	53%	32.5%	6.5%	0%
Intermediate High	6%	48%	23%	1.5%	21.5%
High	6%	42%	23%	0%	29%

When comparing the simulated data depicted in Figure 3 with the inferred patient distribution data presented in Table 17 through a graph, a high degree of similarity is observed, indicating that the patient allocation model operates as intended. The notable deviation in Active Surveillance among low-risk patients can be attributed to the increasing adoption of Active Surveillance in recent years [53].

The fluctuation in the percentage of patients undergoing surgery versus radiotherapy (RT) is a result of significant variability in the distribution of radical treatments between surgery and RT across the publications. To address this, we opted for an equal distribution in the inferred data.

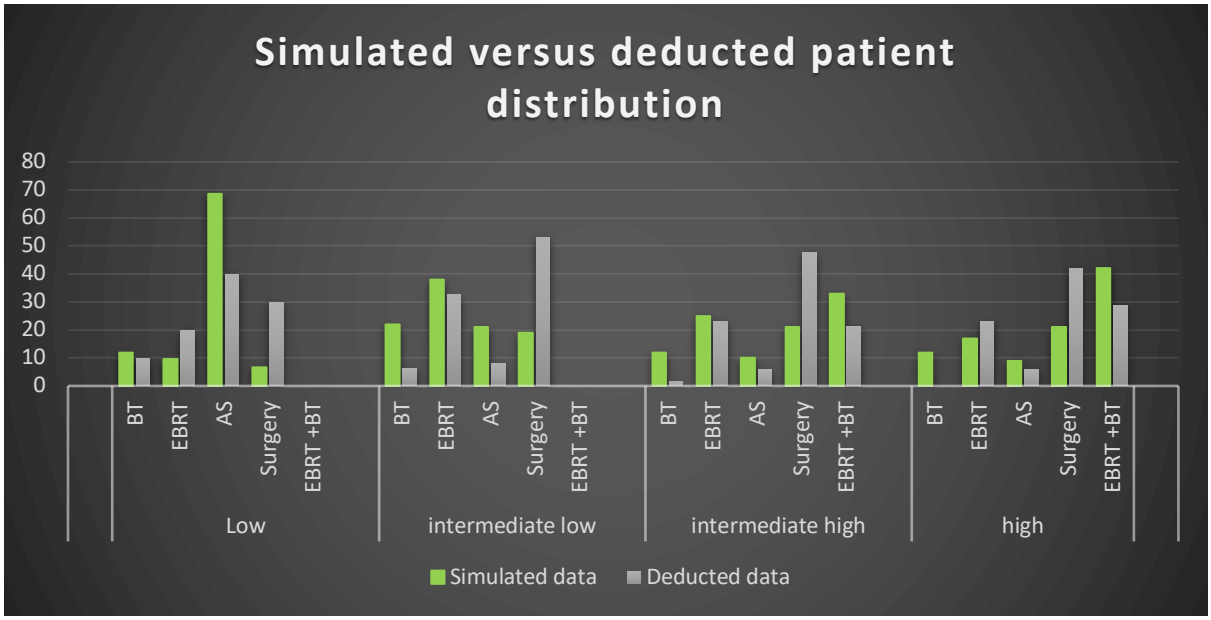


Figure 5 Validation of the Patient Allocation Model with Data Deducted from Clinical Publications

3.7 Sub-question 6

What knowledge exists on conducting an economic value assessment using a Markov model in healthcare?

Markov models are widely utilized in conducting economic evaluations as they provide a method to model random processes evolving over time. In the medical field, these models are particularly useful for simulating the progression of diseases. To construct a Markov model for prostate cancer, the disease is initially divided into distinct health states. Subsequently, transition probabilities are assigned to represent the movement of patients between these health states over discrete time periods, known as Markov cycles. By associating costs and health outcomes with each state and running the model over numerous cycles, the long-term costs and outcomes of the disease can be estimated.

Existing Literature

When conducting a Google Scholar search, focusing on "cost-effectiveness analysis brachytherapy" for the years 2020-2023, we identified two key publications that conducted a CEA utilizing a Markov model: Weng et al. [19] and Naser-Tavakolian et al. [20].

In their publication Weng et al. compared four treatment modalities brachytherapy, EBRT, Surgery, and the combination of brachytherapy plus EBRT for prostate cancer through a CEA using a Markov model. Weng et al performed CEAs for three risk groups (low-, intermediate-, and high-risk) of prostate

cancer patients over an eight-year time horizon. However, Active Surveillance, although cost-effective for low-risk prostate cancer patients [20][21], was not included in Weng et al.'s research.

Naser-Tavakolian et al. limited the scope of comparison by only including three treatment modalities Active Surveillance, surgery, and radiation therapy for the low-risk and intermediate-risk groups. In his research Naser-Tavakolian et al. did not differentiate between the different radiation treatment options, namely brachytherapy and EBRT, despite clinical evidence of distinctions among them [19].

Weng et al. considered four mutually exclusive health states: *(1) no recurrence*, *(2) recurrence*, *(3) recurrence post-salvage*, and *(4) death*, with further subdivisions for the *no recurrence* and *recurrence* states. Figure 6 shows the Markov model structure. We decided to use the Markov model structure by Weng et al. as the foundation for our model.

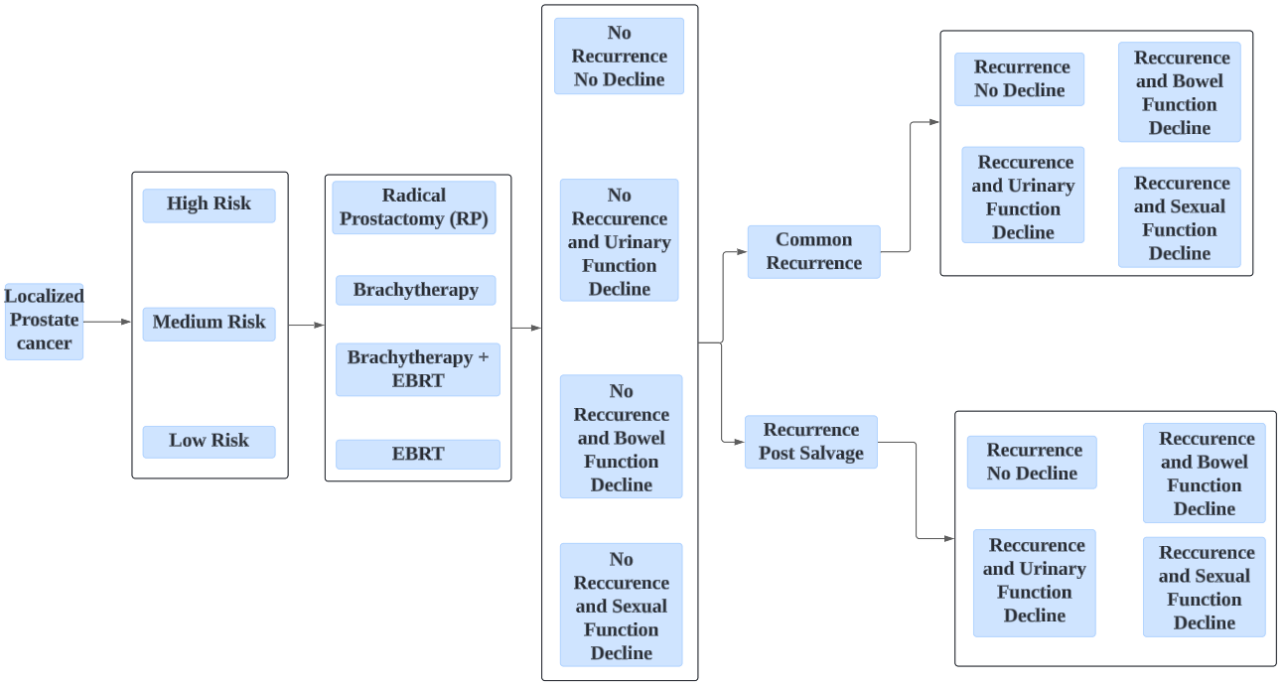


Figure 6 Markov Model [19]

3.8 Sub-Question 7

How can the cost-effectiveness analysis of prostate cancer treatment modalities be formulated in a Markov model?

Sub-question 7.1: *What are the possible health states associated with prostate cancer treatment modalities?*

To create our Markov model simulating prostate cancer progression, we defined five exclusive health states, ensuring a patient occupies only one state at a time [18].

The five states are defined as follows. *(1) Cancer + no toxicity* represents the initial diagnosis without treatment. All patients start in this state in cycle 0 as we deal with patients who have already been diagnosed. From this state patients can move to the states: *(2) Healthy + no toxicity* indicating a successful treatment outcome, and *(3) Healthy + toxicity* signifies successful treatment with side effects. *(4) Cancer + toxicity* reflecting unsuccessful treatment with side effects, *(5) Death*, marking the end of the simulation. Patients may transition between some of these states, e.g. develop late toxicity, toxicities may resolve, or they may experience recurrence of their cancer. These states and their transitions,

depicted in Figure 7, capture pivotal clinical and economic events, guiding the model's representation of prostate cancer progression.

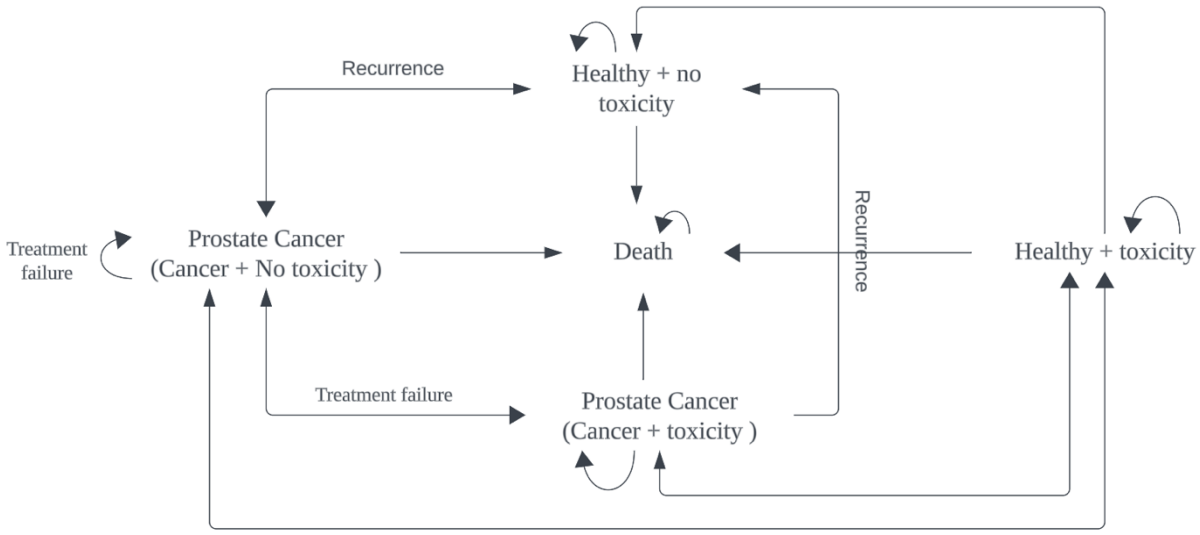


Figure 7 Transition Diagram Markov Model

Sub-question 7.2: *What are the probabilities of the utility corresponding to each health state?*

The transition takes place for each cycle of the Markov model. The transition between the states is given by a n x n transition probability matrix (Table 18), where n represents the number of states. The transition probability is the probability of moving from one state to another or staying in the same state. Since there is no possible movement from the *Death* state to any other state the transition probability is 0. Also, the probability of moving from *healthy + toxicity* or *healthy + no toxicity* to *death* within the six-year time frame is very low that we have assigned a probability value of 0.

Next, the probabilities of moving between each state must sum to a total of 1 therefore, the probability of remaining in a state is 1 minus the probability of moving out of that state, these are the red cells in the matrix. Consequently, we are left with a total of twelve cells for which transition probability data must be entered. These are marked blue. How these are calculated is presented in Appendix H. The input values for these 12 cells (transition probabilities including their sources) are detailed in Appendix I in Table 29.

Table 18 Transition Probability Matrix

Transition probabilities	Cancer + no toxicity	Cancer + toxicity	Healthy + toxicity	Healthy + no toxicity	Death
Cancer + no toxicity	Treatment failure	Treatment failure	0		
Cancer + toxicity	Treatment failure	Treatment failure			
Healthy + toxicity	recurrence	recurrence			0
Healthy + no toxicity	recurrence	recurrence	0		0
Death	0	0	0	0	1

Sub-question 7.3: *What are the costs of the different health states associated with the treatment modalities?*

The costs of health states considered include cost of treatment (reimbursement costs), toxicity management costs, and follow-up costs.

Costs of treatment have been presented when answering sub-question 4.1.

Toxicity management costs specifically apply to the *Cancer + toxicity* and *Health + toxicity* state, covering the management of Erectile dysfunction as discussed when answering sub-question 3. The toxicity management cost is determined to be €960 per patient per year [24].

Follow-up costs are incurred in each state except state death, as in each state there will be active monitoring of the patients. Therefore, the follow-up costs are identical to the cost of Active Surveillance. The Active Surveillance cost is €850 per year.

Since the costs associated with Active Surveillance and toxicity management are uniform across all treatment modalities within each risk group, the only variation lies in the reimbursement costs, which differ between treatments but remain constant for a specific treatment within each risk group. The total cost of each state is computed by summing the three components: reimbursement cost, cost of toxicity management, and follow-up cost.

Sub-question 7: *How can the cost-effectiveness analysis of prostate cancer treatment modalities be formulated in a Markov model?*

With the input from sub-questions 7.1 – 7.3 we can answer this sub-question 7. Building upon the Markov model proposed by Weng et al. [19], we developed a Markov cohort simulation using Microsoft Excel to calculate the costs and assess the QALYs and LYs over a six-year time horizon, with a cycle length of 1 year for each health state (Figure 8). Diverging from Weng et al.'s model, we expanded our Markov model to include four risk groups rather than three. Additionally, we included Active Surveillance as a treatment modality.

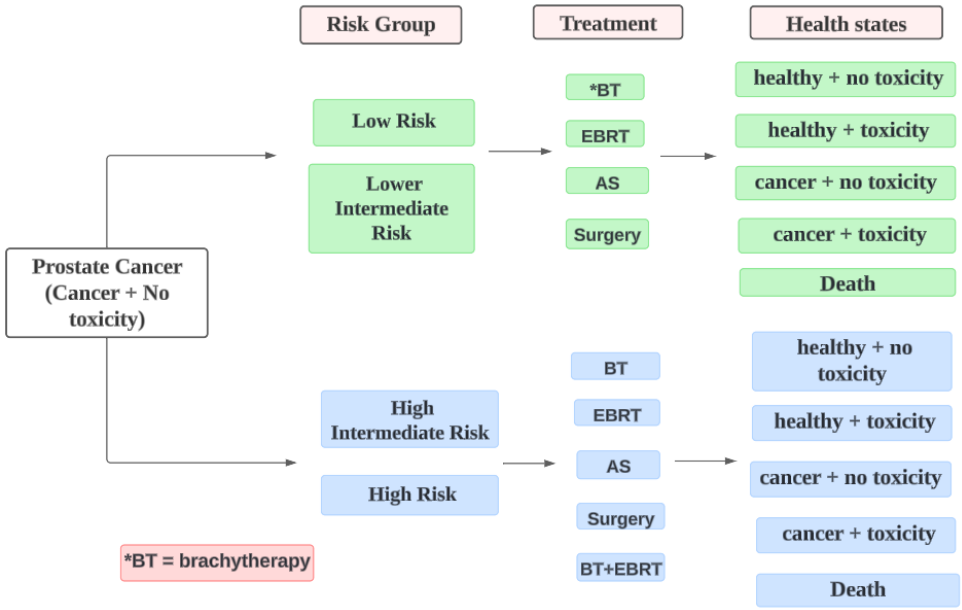


Figure 8 Markov Model Structure

Markov Cohort Simulation

We performed a Markov Cohort simulation to evaluate the cost and QALY for each treatment modality within each risk group, essential for calculating the ICER. This Markov Cohort simulation links the patient allocation model to the Markov model.

In the initial cycle (cycle 0) starting from the state *Cancer + no toxicity*, the cohort consists of the number of patients allocated to the treatment modalities in the patient allocation model. We multiply this initial cohort with the transition probabilities governing movement between states to assess the cohort in each state for every subsequent one-year cycle. We convert this cohort into a 'Markov Trace' translated as the fraction of patients in each state. The Markov Trace graph for each treatment in each risk group is shown in Appendix J. To determine the cost, QALY and LY for each state we multiply the values of these three parameters with the Markov Trace. This process allows us to calculate the ICER, enabling a comparison of brachytherapy with other alternative treatment options.

QALY

Quality-Adjusted Life Years (QALY) serves as a metric to measure the improvement in both the quantity and quality of a patient's life resulting from the treatment [22]. In our model, we computed the QALY for every treatment in each state in each cycle over six years, resulting in a cumulative QALY. The [7]QALY is determined by "multiplying the value of utility associated with a given health state with the years lived in that state" [23]. Where the [8] QOL assigned to each state, ranging from 0 to 1 (0 being the lowest is the death state and 1 being the highest quality of life which is the healthy state) is the utility and the survival rate, representing the percentage of patients in each state is the years lived in that state. The QOL values were derived from relevant literature and are shown in Appendix I.

LY

The LY is another measure of effectiveness of a treatment, representing the health outcomes of the treatment modalities. The probability of LY is 1 for all states except for the state *Death*, where it is 0. This consistency holds across all treatment modalities within each risk group. We calculate the [9]LY for every state in each yearly cycle by multiplying the probabilities of LY associated with each state by the fraction of patients in that state.

3.9 Sub-Question 8

What are the results of the cost-effectiveness analysis?

Analysis of CEA Results

The primary outcome of the Markov model is the ICER, derived by calculating the total cost, QALYs, and LYs for brachytherapy and alternative treatment modalities for different risk groups in both countries. The ICER for each comparison is the cost of gaining an additional unit of QALY and LY. Cost-effectiveness is assessed by comparing the ICER to the Willingness-to-Pay Threshold (WTP), set at €30.000/QALY and €60.000/QALY in both countries [25]. WTP is the cost per additional QALY gained which the society is ready to pay. The results are visualized using a cost-effectiveness plane (Figure 9), where the y-axis represents incremental cost, and the x-axis represents incremental effectiveness. If brachytherapy, compared to alternative treatments, is more effective and cost-saving, then ICER is negative, and it is said to be 'Dominant' and falls into quadrant A. For positive ICERs falling into quadrants C and E, brachytherapy is considered cost-effective and acceptable only if it is below the WTP. Quadrant C indicates higher effectiveness but also higher cost. Quadrant E represents lower cost but also lower effectiveness. Theoretically, acceptable in quadrant E, in practice, a treatment may be less likely to be accepted if it is less effective despite being less costly. Conversely, anything in quadrants B, D, and F is not considered cost-effective, and brachytherapy would not be a choice in these scenarios.

[7] $QALY = Utility * survival = \ QOL\ of\ state * fraction\ of\ patients\ in\ the\ state$
[8] QOL = 0 = state death, QOL=1=state healthy
[9] LY = LY * fraction of patients in state

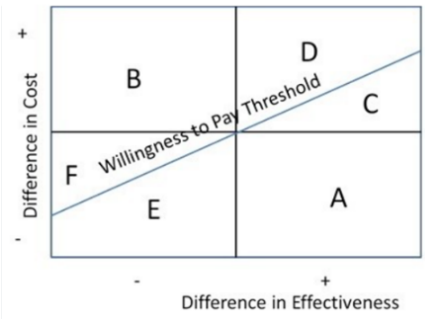


Figure 9 General Cost-effectiveness Plane

Analysis ICER

Analysing the ICERs of the Italian scenario we observe ICERs predominantly falling into quadrant A of the cost-effectiveness plane indicating that brachytherapy is cost-saving, and more effective compared to its alternatives across all risk groups ([10]Figure 10).

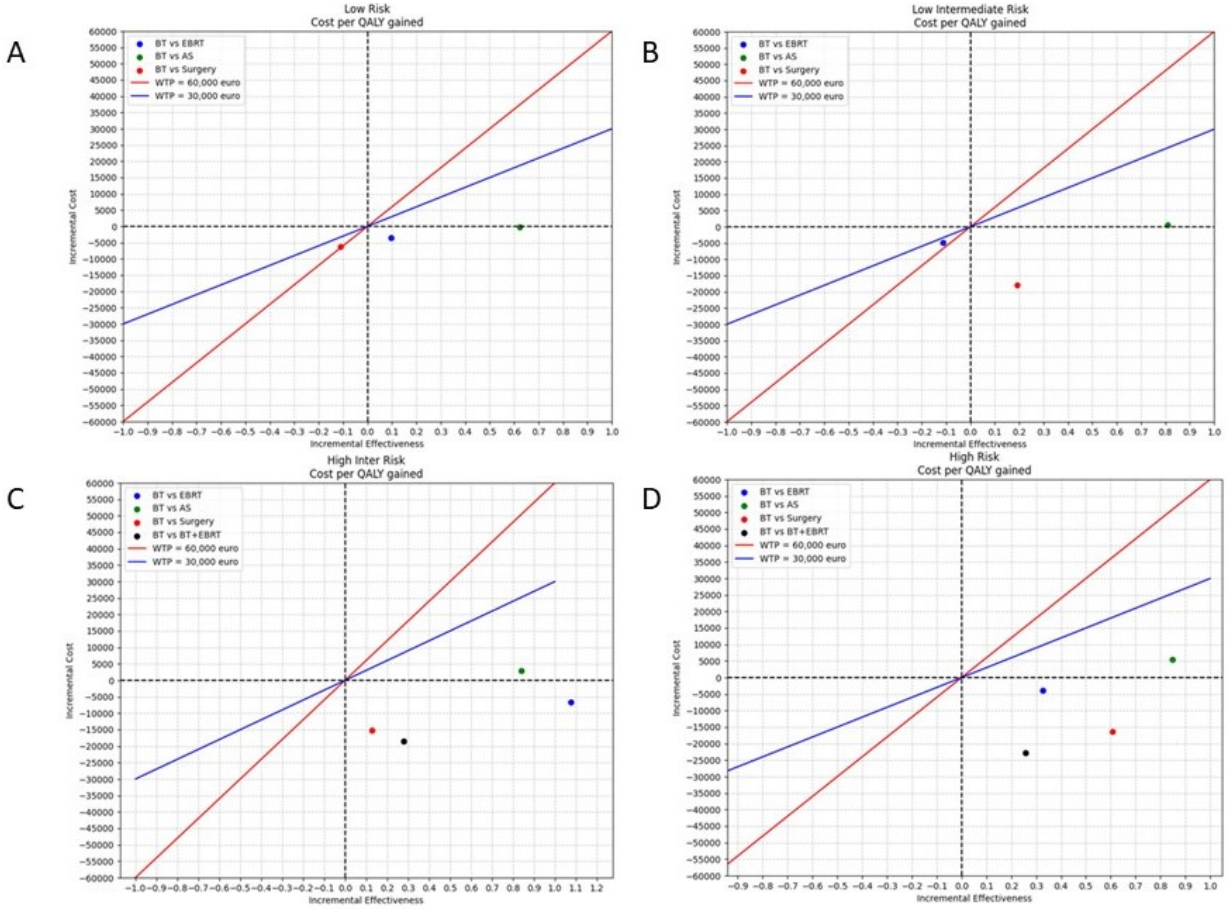


Figure 10 Cost-effectiveness Plane Italy A: Low-Risk, B: Low Intermediate-Risk, C: High Intermediate-Risk, D: High-Risk.

[10] The planes are presented in Appendix K as well for better readability.

Table 19 ICER Outcome Italy

		Cost per QALY gained	Cost per LY gained	
Low-Risk	***Comparison***	***ICER_1***	***ICER_2***	
	BT vs EBRT	-€36.667	-€44.621	**Dominant**
	BT vs AS	-€369	€1.098	**Dominant**
	BT vs Surgery	€57.010	€31.761	-
Low Intermediate-Risk	BT vs EBRT	€42.923	€31.710	-
	BT vs AS	€724	€10.626	-
	BT vs Surgery	-€93.192	€85.829	**Dominant**
High Intermediate-Risk	BT vs EBRT	-€6.220	-€6.743	**Dominant**
	BT vs AS	€3.413	€11.701	-
	BT vs Surgery	-€118.266	€61.409	**Dominant**
	BT vs EBRT + BT	-€65.806	-€123.630	**Dominant**
High-Risk	BT vs EBRT	-€11.827	-€12.932	**Dominant**
	BT vs AS	€6.434	€13.689	-
	BT vs Surgery	-€27.036	-€52.588	**Dominant**
	BT vs EBRT + BT	-€88.350	-€412.507	**Dominant**

In the low-risk group, brachytherapy is dominant over EBRT. For every QALY gained brachytherapy is associated with a cost savings of €36.667 and for every LY gained, there is a cost saving of €44.621. In terms of QALYs brachytherapy dominates Active Surveillance (-€370) with a cost saving of €370 per QALY gained. However, for every LY gained with brachytherapy compared to Active Surveillance there is an additional cost of €1.098. In the low intermediate risk group, for every QALY gained with brachytherapy compared to surgery, there is a cost savings of €93.192 making brachytherapy dominant over surgery in terms of QALYs. For every LY gained, there is an additional cost of €85.829. In the high intermediate and high-risk groups, brachytherapy is dominating over all therapies in terms of QALYs except Active Surveillance. In terms of LYs in high-risk brachytherapy is also dominating its alternatives except Active Surveillance. Whereas in high intermediate risk brachytherapy compared to surgery is dominant in terms of QALYs gained with a cost saving of €118.267. However, in terms of LY gained with brachytherapy compared to surgery there is an additional cost of €61.409.

Compared to surgery in the low-risk group and EBRT in the low intermediate-risk group, brachytherapy is less costly but also less effective, with a positive ICER of €57.010 and €42.923 per QALY gained and falls into quadrant E of the plane. Also, in terms of LYs with brachytherapy compared to surgery and EBRT there is an additional cost of € 31.761; and €31.710 respectively. In both cases (brachytherapy vs surgery and EBRT), the ICER falls above the WTP threshold of €30.000, indicating that brachytherapy is more expensive for an additional QALY gained and will not be paid for. Nevertheless, at a WTP of €60.000, the ICER is below the threshold, making brachytherapy acceptable from a cost-effectiveness perspective. However, in practice, it is less likely for a treatment to be chosen only based on cost if it is less effective. The positive ICER for brachytherapy versus EBRT in the low intermediate-risk group was not as expected. However, this can be explained by the input parameters of the model. We have a higher mortality rate input for brachytherapy compared to EBRT, leading more patients to transition towards the death state, and reducing the QALYs.

In the low intermediate-, high intermediate-, and high-risk groups, brachytherapy compared to Active Surveillance is both more expensive and more costly, with positive ICERs of €724, €3.414, and €6.435, incurring additional cost per QALY gained. Since these ICERs fall below the WTP thresholds of €30.000 and €60.000, they fall into quadrant C, and in all three cases, brachytherapy is cost-effective and therefore acceptable. Additionally, we observe a discrepancy between the cost per QALY gained (ICER_1) and cost per Life Year gained (ICER_2). In the low-risk group, brachytherapy compared to

Active Surveillance, and in the low intermediate- and high intermediate-risk groups, brachytherapy compared to surgery, ICER_1 is negative, but ICER_2 is positive.

In Spain, we observe a similar ICER pattern as in Italy, with the exception that brachytherapy is not dominant over Active Surveillance in the low-risk group (€1.828). In this case, brachytherapy is slightly more expensive but also more effective. However, the cost per QALY gained falls under the WTP thresholds of €30.000 and €60.000, making brachytherapy acceptable (Appendix K).

Budget Impact Analysis

The result of BIA reveals a significant difference in the overall total costs between Italy and Spain. As shown in the figure below, a lower reimbursement in Italy (€4.500) results in fewer patients (1382 (9.4%) in Italy versus 5353 (15.46%) in Spain) receiving brachytherapy, contributing to a higher total cost across all risk groups (€17.435 per patient in Italy versus €16.342 per patient in Spain). This contrast between Spain and Italy underscores the impact of reimbursement rates on total costs. The reduced overall costs in Spain can be attributed to higher reimbursement for brachytherapy, as the treatment's effectiveness remains consistent in both countries.

Analysing both the CEA and BIA together shows that brachytherapy is a beneficial choice for prostate cancer treatment in Italy. It not only provides clear health benefits but also saves money across different risk levels. This makes brachytherapy not just a practical but also a financially sensible option for healthcare decision-makers. The actual savings, amounting to more than 40 million euro annually for the patient population of almost 40.000 patients in Italy, highlight how economically viable brachytherapy is.

Table 20 BIA outcome Italy

	Low-Risk		Low Intermediate-Risk		High Intermediate-Risk		High-Risk	
Treatment	**#of patients**	**Final total cost**	**#of patients**	**Final total cost**	**#of patients**	**Final total cost**	**#of patients**	**Final total cost**
BT	1382	€12.092.302	1122	€10.028.570	396	€4.136.242	804	€10.042.651
EBRT	1603	€19.683.444	3320	€45.741.257	1437	€24.621.800	1850	€30.221.36
AS	9455	€84.454.957	1590	€13.276.053	446	€3.373.992	885	€6.217.520
Surgery	1714	€25.577.860	2618	€70.117.899	1982	€50.709.164	3378	€97.464.212
BT + EBRT	-	-	-	-	1635	€47.267.351	3699	€130.514.708

Table 21 BIA Outcome Spain

	Low-Risk		Low Intermediate-Risk		High Intermediate-Risk		High-Risk	
Treatment	**#of patients**	**Final total cost**	**#of patients**	**Final total cost**	**#of patients**	**Final total cost**	**#of patients**	**Final total cost**
BT	1870	€18.827.78	1776	€18.441.552	1212	€14.930.136	495	€7.392.083
EBRT	1225	€15.037.76	3001	€41.346.438	2425	€41.539.031	701	€11.452.929
AS	8639	€77.168.765	1653	€13.808.538	943	€7.132.65	371	€2.608.233

Surgery	838	€12.507.033	1531	€40.999.06	2021	€51.686.835	907	€26.175.496
BT + EBRT	-	-	-	-	3233	€47.267.351	1773	€62.552.946

3.10 Sub-Question 9

What is the optimal reimbursement rate for brachytherapy in Italy?

By changing the input values for brachytherapy reimbursement, we conducted a sensitivity analysis to determine the optimal reimbursement threshold to which decision-makers can increase reimbursement, maintaining cost-effectiveness and minimizing overall total costs. The maintenance of cost-effectiveness relies on ensuring that the cost per QALY gained (ICER) does not exceed the WTP threshold of €30.000. The option with a WTP of €60.000 is not under consideration, as achieving this would necessitate a brachytherapy reimbursement exceeding €30.000, which is practically not possible. It is important to note that in the comparison between brachytherapy and surgery for low-risk, as well as between brachytherapy and EBRT for low-intermediate risk, we observe lower QALY indicating that brachytherapy is less effective. In these two scenarios, we are not examining the reimbursement where the cost per QALY gained, would reach the WTP of €30.000, as brachytherapy is less effective, and it will not be paid for. The sensitivity analysis was performed on all four risk groups separately on the ICER and the overall total cost.

Sensitivity Analysis reimbursement threshold

After conducting the sensitivity analysis, we determined that the reimbursement threshold for low-risk cases is €10.700, for both low-intermediate and high-intermediate risk it is €15.200. The upper limit was determined in consultation with Elekta experts as the maximum reimbursement amount. We use 22 reimbursement rate values ranging from a base case of €4.700 to €15.200 with incremental steps of €500.

This reimbursement threshold for low intermediate does not reach WTP, we have identified them due to the reimbursement rate limit. For high-risk cases, we identified two reimbursement thresholds: €11.700 for the comparison between brachytherapy and EBRT and €15.200 for the comparison between brachytherapy and Active Surveillance, reaching the WTP limit. However, we consider the threshold to be €11.700, as at this limit, the cost per QALY gained for each comparison falls below the WTP. An overview of these findings is presented in the figure below.

Table 22 Brachytherapy Reimbursement Threshold

					Cost per QALY gained
	Reimbursement BT	Comparison	Incremental Cost	Incremental QALY	ICER
Low-Risk	€10.700	BT vs EBRT	€2.738	0,10	€28.101
		BT vs AS	€6.081	0,62	€9.778
		BT vs Surgery	€91	-0,11	-€838
Low Intermediate-Risk	€15.200	BT vs EBRT	€6.846	-0,11	-€60.697
		BT vs AS	€12.274	0,81	€15.192
		BT vs Surgery	-€6.153	0,19	-€32.41
High Intermediate-Risk	€15.200	BT vs EBRT	€8.504	1,08	€7.896
		BT vs AS	€18.071	0,84	€21.509
		BT vs Surgery	€55	0,13	€433
		BT vs BT+EBRT	€3.266	12,28	-€265

High-Risk	€11.700	BT vs EBRT	€9.351	0,33	€28.718
		BT vs AS	€18.661	0,85	€21.997
		BT vs Surgery	-€3.164	0,61	-€5.227
		BT vs BT+EBRT	-€12.991	0,26	-€50.357
	€15.200	BT vs EBRT	€15.952	0,33	€48.991
		BT vs AS	€25.263	0,85	€29.778
		BT vs Surgery	€3.436	0,61	€5.676
		BT vs BT+EBRT	-€6.389	0,26	-€24.768

Sensitivity Analysis Total Cost

Conducting an additional sensitivity analysis on the budget impact has shown the reimbursement rate at which the total cost is minimized. This analysis was conducted separately for all four risk groups and one combined analysis. Starting at a reimbursement rate of €4.700, we used incremental steps of €1.000. The trade-off between this analysis on the cost per QALY gained and the total cost reveals the optimal reimbursement rate for brachytherapy. This optimal reimbursement is situated below the WTP, representing the society's willingness to pay, and simultaneously ensures the overall total cost is minimized, considering the impact on the total budget.

The graphs below illustrate that, for the low-risk group, the optimal reimbursement for brachytherapy is identified at €5.700, resulting in a minimum overall total cost of €140.318.871 for this Risk Group.

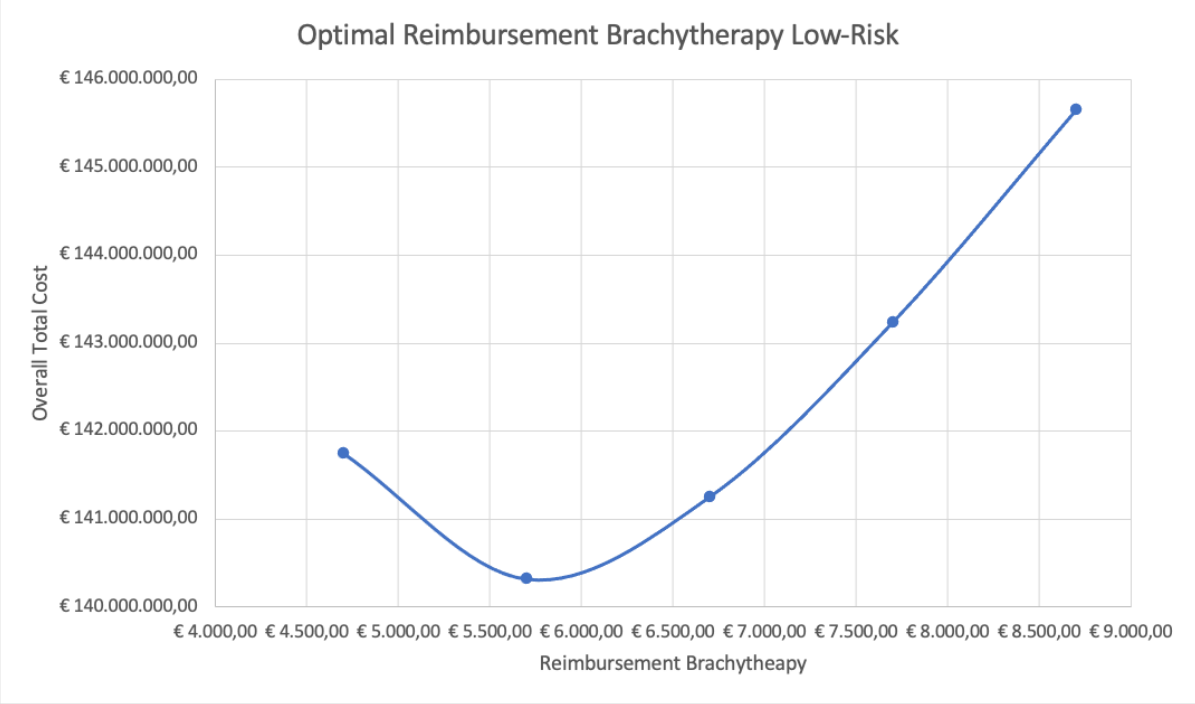


Figure 11 Optimal Reimbursement Brachytherapy Low-Risk

In the low intermediate-risk group, the optimum is at €7.700 with a minimum overall total cost of €124.689.759.

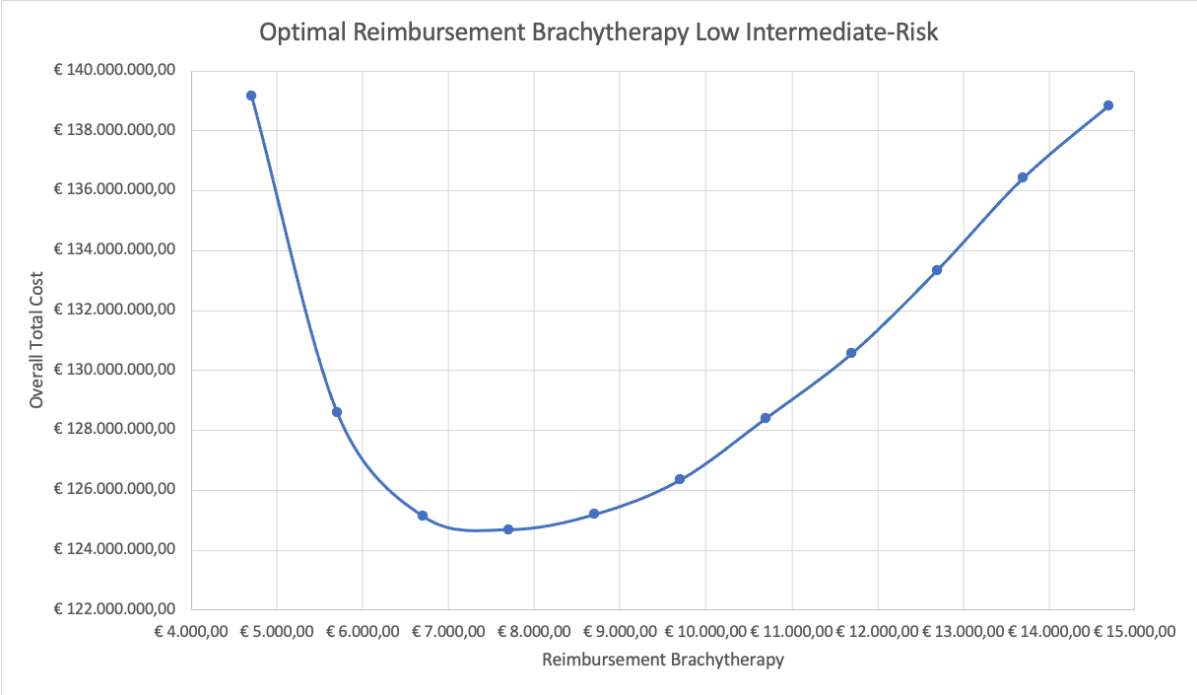


Figure 12 Optimal Reimbursement Brachytherapy Low Intermediate-Risk

For low intermediate-, high intermediate-, and high-risk groups, the optimal reimbursement rate is identified at €7.700, corresponding to minimum overall total costs of €124.689.759; €122.798.781 and €274.749.720, respectively.

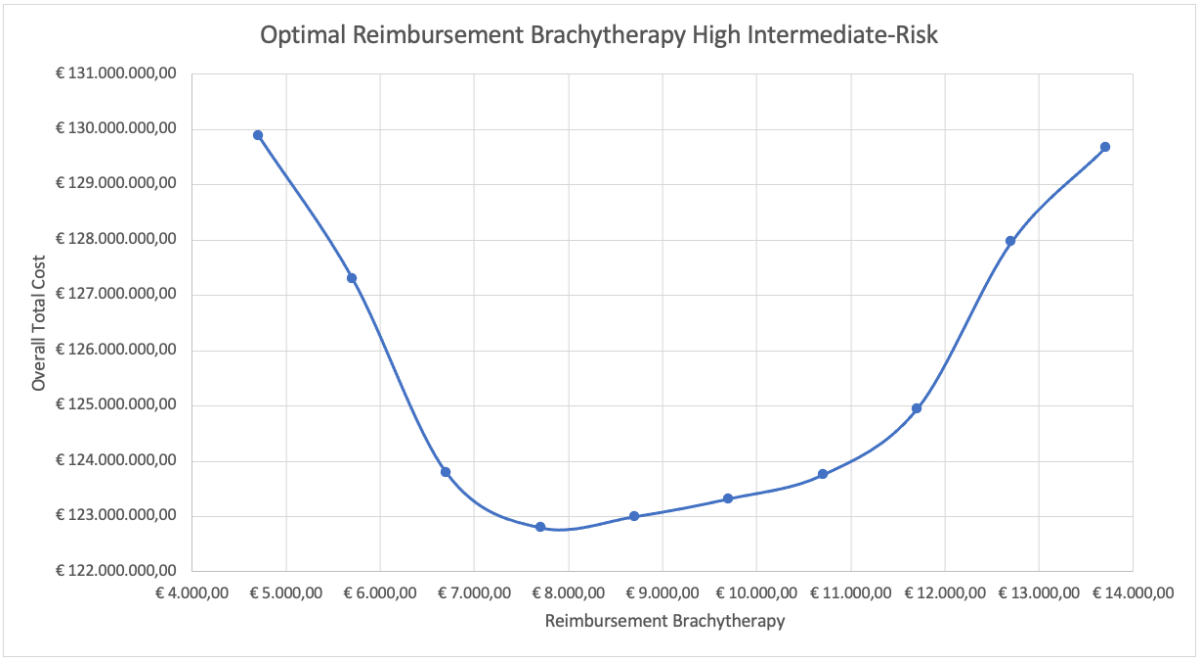


Figure 13 Optimal Reimbursement Brachytherapy High Intermediate-Risk

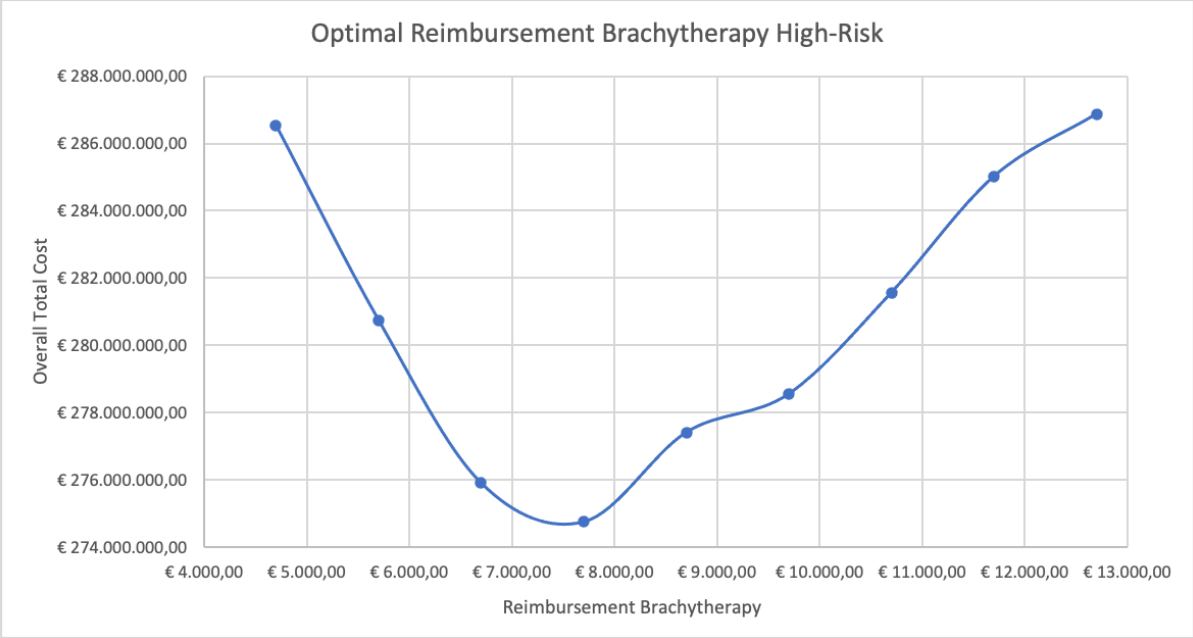


Figure 14 Optimal Reimbursement Brachytherapy High-Risk

When combining all risk groups, the optimal reimbursement rate remains at €7.700.

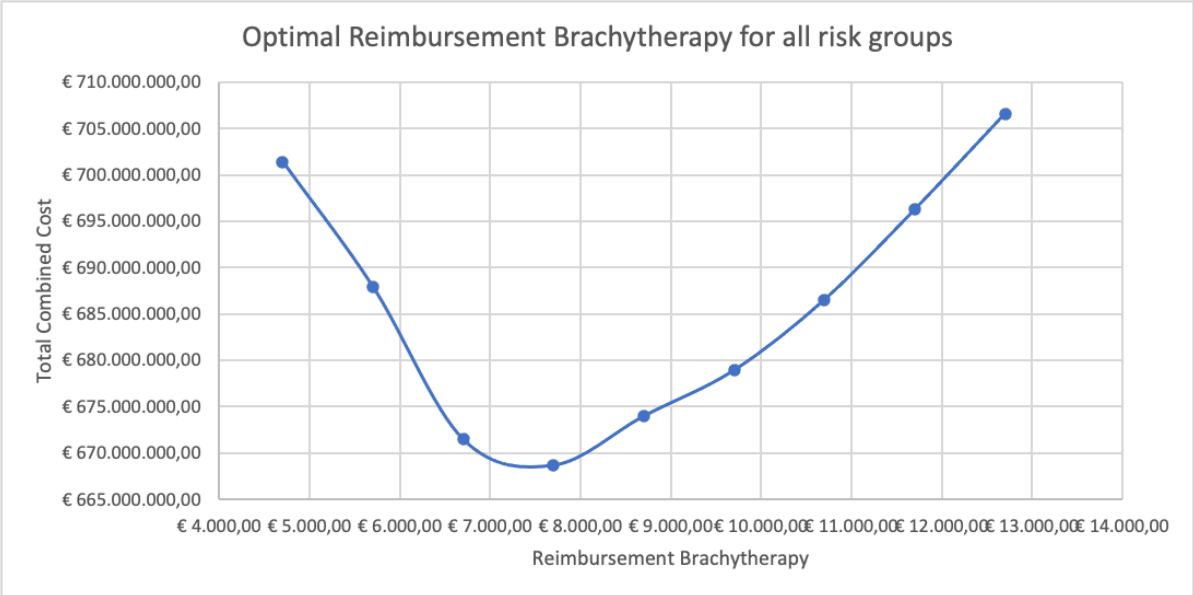


Figure 15 Optimal Reimbursement Brachytherapy for all Risk Groups

3.11 One-way Deterministic Sensitivity Analysis

The sensitivity analysis conducted to evaluate the robustness of the cost-effectiveness model across different comparisons of prostate cancer treatment strategies revealed crucial insights. In the comparison between brachytherapy and EBRT, variations in the probabilities of disease recurrence and treatment failure emerged as the most sensitive parameters affecting the ICER outcomes. Similarly, when comparing brachytherapy with Active Surveillance, the ICER outcomes were primarily sensitive to variations in the recurrence transition probability. For the comparison with surgery, sensitivity to changes in recurrence and treatment failure probabilities was evident, emphasizing the significance of managing these risks for informed treatment decisions. The sensitivity analysis of brachytherapy versus EBRT followed by brachytherapy also highlighted the importance of accurate estimation and management of recurrence and treatment failure risks. Overall, these findings underscore the critical role of addressing recurrence and treatment failure risks in assessing the cost-effectiveness of prostate cancer treatment strategies, with potential implications for clinical decision-making and health policy.

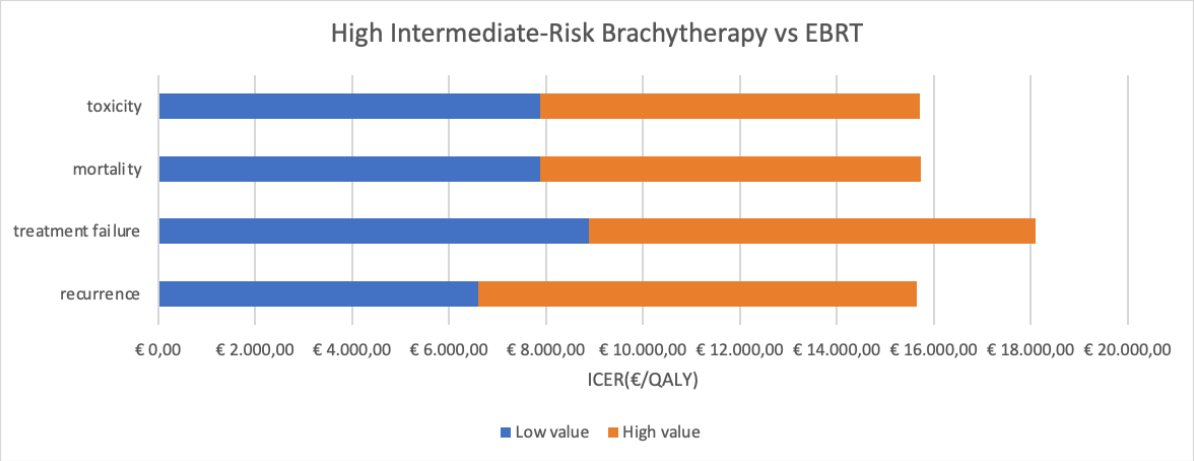


Figure 16 Tornado Diagram Brachytherapy vs EBRT

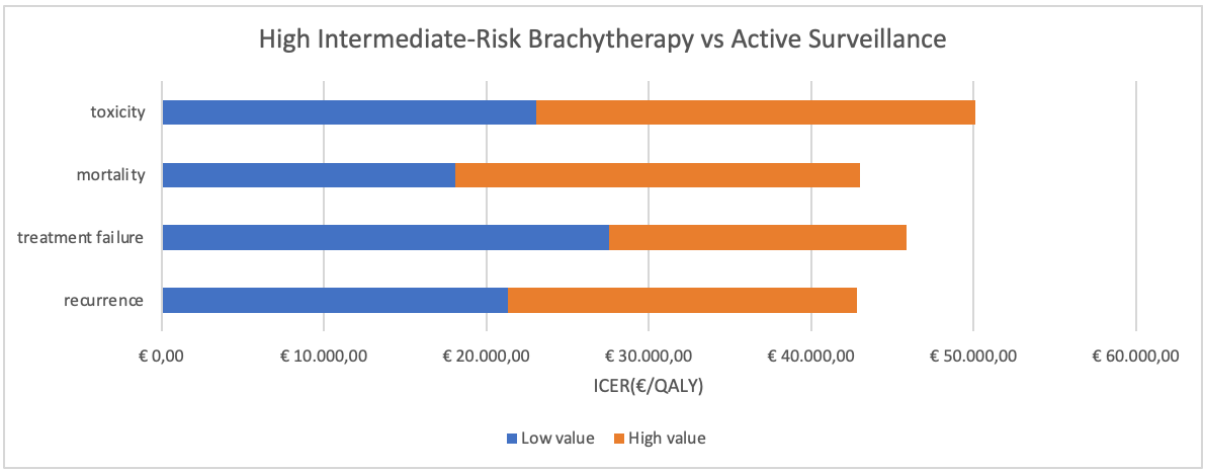


Figure 17 Tornado Diagram Brachytherapy vs Active Surveillance

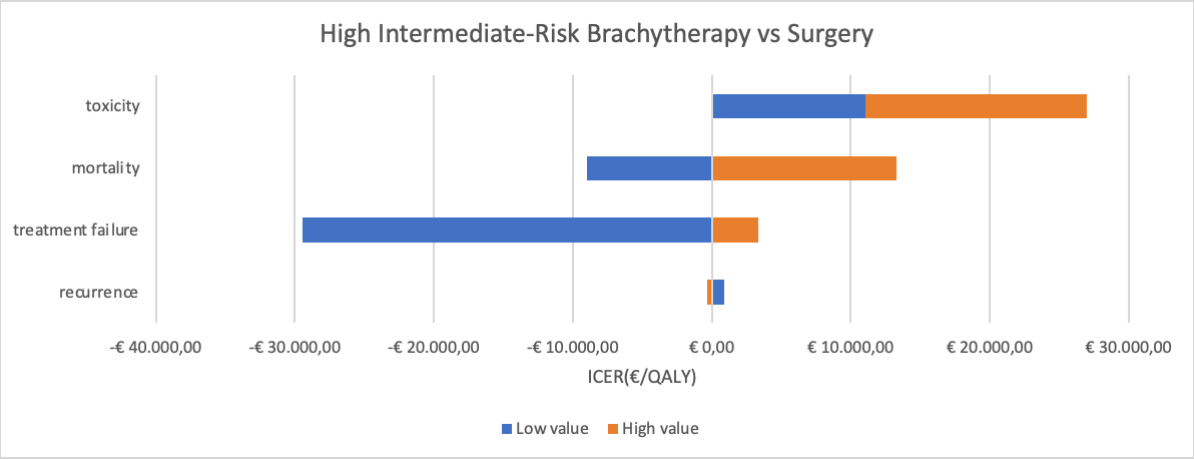


Figure 18 Tornado Diagram Brachytherapy vs Surgery

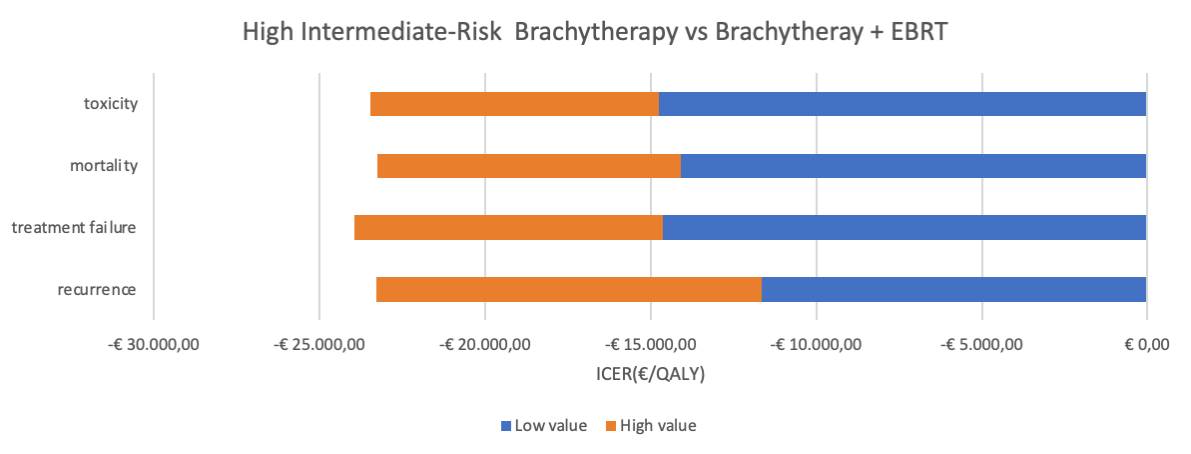


Figure 19 Tornado Diagram Brachytherapy vs Brachytherapy + EBRT

4 Discussion, Recommendation & Conclusion

4.1 Summary of Results

Prostate cancer forms the most prevalent type of cancer affecting men on a global scale [1]. Treatment options include Active Surveillance, brachytherapy, External Beam Radiation Therapy (EBRT), and surgery. We observed that brachytherapy equipment is utilized at least 40% less in Italy compared to Spain, with the actual difference in utilization for prostate cancer probably being even bigger. We show that this difference in brachytherapy utilization can be explained by differences in reimbursement.

This research aims to demonstrate to Italian stakeholders the superior outcomes and cost-effectiveness of brachytherapy compared to alternative treatments. Additionally, it seeks to identify the optimal reimbursement rate for brachytherapy, maximizing outcomes while minimizing costs. We achieved this by integrating a patient allocation model that assigns patients to therapeutic options based, among other factors, on reimbursement levels, alongside a Markov model for comprehensive economic evaluation of outcomes. We confirmed that the outcomes generated by the patient allocation model closely align with published patient distributions across the therapeutic options in the countries of interest.

Our combined model revealed that brachytherapy is cost-effective across all risk groups compared to other treatment modalities. As expected, in the low intermediate, high intermediate, and high-risk groups, brachytherapy is better in outcome but slightly more expensive than Active Surveillance. Compared to EBRT in the low intermediate-risk group, brachytherapy is cost-saving but results in slightly less favourable outcomes. Despite these cases, brachytherapy remains cost-effective as the ICER falls below the WTP threshold. We conducted a sensitivity analysis on the ICER by increasing the reimbursement rate for brachytherapy to identify the limit at which the therapy becomes more costly but still outperforms other modalities. We demonstrated that increasing the reimbursement rate from the current €4.700 minimizes the overall total cost and improves clinical outcomes, with the optimal reimbursement rate identified at €7.700.

4.2 Evaluation and Explanation

The fact that Brachytherapy is both more efficient and less costly than most other therapies is not unexpected. Previous research has shown that brachytherapy results in comparable biochemical control and lower costs compared to EBRT [68] and surgery [69]. The fact that it is more effective but more costly than no treatment cannot be a surprise. In previous research evaluating cost-effectiveness of treatments for localised prostate cancer using a Markov model, Weng et al. [19] concluded that brachytherapy is a cost-effective treatment compared to EBRT, Surgery, and the combination of brachytherapy plus EBRT for low-, intermediate-, and high-risk groups. However, in the low-risk group, EBRT showed better outcomes than brachytherapy. In our research, we divided the intermediate-risk group into low intermediate and high intermediate, as these risk groups are clinically identified in Italy. Additionally, considering Active Surveillance as a possible treatment modality, we included it in our research as a comparator to brachytherapy. In the high-risk group, as expected, our findings showed that brachytherapy is slightly more expensive but yields better outcomes.

While Weng et al. included health states post-salvage and made distinctions between sexual, urinary, and bowel toxicities in their research, we chose to keep our model simpler. We did not include health states post-salvage, and we did not distinguish between toxicities. Instead, we focused on overall costs related to toxicities by considering *Cancer + toxicity* and *Healthy + toxicity*, eliminating the need to consider toxicities separately. Another difference between our research and the research conducted by Weng et al. lies in the analytical approach. While both studies analysed the cost-effectiveness of brachytherapy compared to other treatments, our investigation incorporated a comprehensive analysis centred around the reimbursement rate. In addition to conducting a cost-effectiveness analysis, we expanded our scope to include a thorough budget impact analysis. By combining these two analyses,

we aimed to offer a more comprehensive understanding of the economic considerations associated with brachytherapy, providing valuable insights for healthcare policymakers and stakeholders in making informed decisions regarding the allocation of resources in cancer treatment.

4.3 Methodological Evaluation

4.3.1 Strengths

In the healthcare sector, the intersection of policy and economics often plays a pivotal role in shaping patient outcomes and system-wide efficiency [49]. Across various sectors, including healthcare, political interventions frequently employ monetary incentives to influence behaviour and decision-making. This dynamic is particularly evident in reimbursement policies, where adjustments in funding can impact the accessibility and utilization of treatment modalities.

The innovative model developed in this research offers evidence of how modulating reimbursement rates can not only yield cost savings within the healthcare system but also enhance patient access to critical treatments, ultimately maintaining quality of life. By simulating the effects of changing reimbursement rates, the model provides understanding of how policy adjustments can be leveraged to achieve dual objectives: reducing healthcare expenditure and improving patient outcomes. Such findings underscore the potential of policy interventions to drive meaningful change in healthcare delivery, aligning financial incentives with the broader goals of enhancing patient well-being and system sustainability. In essence, the model highlights the importance of adopting evidence-based reimbursement strategies that prioritize both economic efficiency and patient-centred care, thereby navigating the complex interplay between politics, economics, and healthcare delivery.

Although initially developed for assessing prostate cancer treatments, the model's adaptability extends to other diseases, particularly cancer, and can be tailored for different countries. Adapting the model for other diseases may require additional decision factors, adjustments to health states, and other input values, but its flexibility allows for these modifications. Adjusting VBA code, such as changing the cell reference, allows incorporation of additional factors, treatment modalities and health states.

The reimbursement rate factor is integral to patient allocation and the Markov model, offering insights into both cost-effectiveness and budgetary impact. By enabling adjustments to reimbursement rates, the model facilitates evidence-based decision-making processes, providing a robust foundation for recommending optimal reimbursement rates to decision-makers.

In addition to treatment costs, the analysis incorporates toxicity costs, acknowledging their importance in long-term expenses and quality of life considerations. While recognizing data limitations in our current research, it is essential to highlight the model's flexibility in handling input data, allowing for easy adjustments and refinements over time, potentially enhancing its relevance in evidence-based decision-making.

4.3.2 Weaknesses

Unlike the research by Weng et al. [19], which utilized input data exclusively from one database, our study faced limitations due to data constraints. Gathering specific input data, such as transition probabilities for the Markov model and reimbursement rates, was challenging. Transition probabilities were sourced from different studies, introducing a degree of variability to our data. Despite consulting Elekta experts in both countries for reimbursement rate information, estimations were necessary due to limitations in obtaining precise figures.

Additionally, the survey we conducted faced limitations, as the responses were limited despite being distributed to more than 20 clinical experts. We did not get many responses, which limited the range of insights we could include in our study. As we employed a self-completed questionnaire, there was room for biases and ethical concerns. Firstly, response bias was a concern, as participants who chose to take part may have different opinions or experiences compared to non-participants, potentially skewing the

results. To mitigate this, we emphasized the significance of the survey in the introduction and personalized invitations to encourage participation. Additionally, considering the high risk of a low response rate [26] with self-completed surveys, we collaborated with Elekta experts in Italy and Spain to endorse the survey, leveraging their established relationships with local professionals. Careful timing of survey distribution, avoiding peak periods, and emphasizing the impact of respondent's expertise on research and patient outcomes were also strategies employed. Furthermore, to protect result anonymization [26], we ensured device security using Qualtrics, a trusted survey tool. Secondly, social desirability bias was addressed by emphasizing anonymity and confidentiality in the informed consent process and formulating questions in a neutral tone to avoid leading language, thereby encouraging respondents to provide genuine responses rather than socially desirable ones. In addition to the bias confidentiality was maintained throughout the study to protect participant's privacy. Personal identification information, including names, dates of birth, and hospital details, was not collected, ensuring anonymity of the respondents. Ethical considerations were paramount, with measures implemented to address potential issues. Firstly, a comprehensive informed consent statement was provided to each respondent prior to survey participation. This statement outlined the survey's purpose, the voluntary nature of involvement, assurances of confidentiality, and the option to withdraw at any time without consequence. Secondly, strict confidentiality protocols were adhered to, with all collected data anonymized. Finally, the voluntary nature of participation was emphasized, with participants informed of their right to withdraw from the survey at any point without facing consequences. These ethical protections were integral to upholding the integrity of the study and protecting the rights of the participants.

Another limitation of our research lies within the patient allocation model. We currently included a limited number of factors that play a role in how patients are allocated among the treatment modalities. The factors 'patient preference', suggested by 50% of the survey respondents, has not been included in our model. Conducting a specific patient survey related to this topic could have shed some light on how their preferences influence treatment decisions. However, the lack of patient access due to data protection regulations and limited time available for this project made this unfeasible.

4.4 Relevance for Clinical Practice and Policymakers

The developed model represents a significant advancement in clinical practice, offering a multifaceted approach to decision-making in prostate cancer treatment. Clinicians are empowered to make more informed treatment decisions by leveraging insights from the model, which integrates clinical expertise, treatment costs, and budgetary implications. This allows for tailored treatment plans that optimize patient outcomes while efficiently utilizing resources. Moreover, healthcare providers and policymakers benefit from evidence-based recommendations on reimbursement strategies, ensuring fair compensation for providers while incentivizing the use of cost-effective treatments. The model's adaptability enables customization for different patient populations and diseases, fostering personalized approaches to care. Furthermore, its continuous refinement based on real-world feedback and emerging research ensures its ongoing relevance and effectiveness in informing clinical practice. Overall, the developed model serves as a valuable tool in improving the quality, efficiency, and cost-effectiveness of prostate cancer care and has the potential for broader applications across various healthcare settings.

The model developed as a result of this research holds significant potential to impact government decision-making in healthcare. By providing insights into the cost-effectiveness and budgetary impact of various treatment modalities, the model allows policymakers to make informed decisions regarding resource allocation, reimbursement strategies, and healthcare policy formulation. Through tailored reimbursement rates and optimized resource allocation, governments can ensure that limited healthcare budgets are directed towards interventions that deliver the greatest value for money and maximize population health outcomes. Furthermore, the model's adaptability to other diseases and countries enhances its utility and relevance on a global scale, enabling governments to address a wide range of healthcare challenges while promoting evidence-based decision-making and healthcare system

sustainability. Overall, such a model serves as a valuable tool for governments striving to improve healthcare efficiency, equity, and effectiveness.

4.5 Recommendations

Elekta could consider prioritizing efforts to expand access to brachytherapy technology, particularly in regions where it is underutilized or where barriers to access exist. Through collaboration with healthcare providers, advocacy organizations, and policymakers, Elekta can help raise awareness about the benefits of brachytherapy and facilitate its adoption as a standard treatment modality for prostate cancer. Targeted initiatives could ensure that patients in all regions have equitable access to this effective and cost-efficient treatment option. Additionally, Elekta might advocate for policy changes that support the integration of brachytherapy into standard treatment protocols and ensure equitable reimbursement for brachytherapy services. Collaborating with professional societies, patient advocacy groups, and policymakers, Elekta could support policies that incentivize the use of brachytherapy and remove barriers to access. By advocating for supportive policies, Elekta could contribute to creating an environment where brachytherapy is accessible to all patients who may benefit from it. Moreover, Elekta could engage in global outreach efforts and partnerships to address disparities in access to cancer care, particularly in underserved regions. Collaboration with international organizations, non-profit groups, and governmental agencies could enable Elekta to provide resources, expertise, and technology to improve cancer care infrastructure and capacity in low- and middle-income countries. Leveraging its global presence and expertise, Elekta could play a role in closing the gap in access to cancer care and contribute to the goal of ensuring that everyone has access to the best cancer care, regardless of geography.

For future research, we recommend reviewing and updating the input data. As our model is implemented within VBA, incorporating additional data can be easily achieved within a few minutes. We see the possibility of extending the model by including more treatment modalities or decision factors or adapting it to address an entirely different disease for any country. Validating the input data and the research would further increase the reliability and usability of the model. Nevertheless, we are confident that our current model is a significant addition to existing research. Thus far, our research of prostate cancer treatment modalities and cost-effectiveness analyses has revealed a gap in research from the perspective of reimbursement. Our research not only demonstrates the cost-effectiveness of brachytherapy but also shows how increasing reimbursement can lead to a decrease in overall total costs, establishing an optimal reimbursement rate. We are confident that, in practice, a thorough review of the input data will facilitate the determination and enhancement of an optimal reimbursement rate, justifying the cost and outcomes of the treatment. This, in turn, will likely result in a substantial reduction in long-term costs by encouraging more patients to opt for brachytherapy as a prostate cancer treatment, leading to a significant reduction in healthcare expenditures for prostate cancer in Italy. The practical insights gained from our analysis have the potential to not only influence decision-making within prostate cancer treatment but also inform broader discussions on healthcare resource allocation. For future research, it is also recommended to perform a probabilistic sensitivity analysis on transition probabilities, costs, and utilities to assess the robustness further besides the small one-way sensitivity analysis we conducted only on one risk group. Conducting a sensitivity analysis of the parameters will make the model a more reliable and more powerful tool to be used in practice.

4.6 Conclusion

Our research demonstrates that brachytherapy is a cost-effective and clinically beneficial treatment option for prostate cancer patients in Italy. Analysis of ICERs reveals its dominance over alternative treatments across various risk groups, highlighting its cost-saving nature and superior outcomes. Additionally, BIA underscores the importance of reimbursement rates in influencing treatment utilization and overall healthcare costs.

After conducting the research, we are able to answer the research question of this study:

*"What is the **economic value** and **reimbursement** of brachytherapy treatment in Italy compared to alternative treatment options for prostate cancer patients and how does changing the reimbursement of brachytherapy influence the allocation of patients among the treatment modalities and subsequently impact the economic value for the population undergoing these treatments?"*

We demonstrated that increasing the brachytherapy reimbursement rate from the current €4.700 has the potential to enhance patient access to effective treatment while minimizing healthcare expenditures. Increasing the reimbursement of brachytherapy minimizes the overall total cost and improves clinical outcomes, with the optimal reimbursement rate identified at €7.700. Thus, aligning reimbursement policies with evidence-based practices is crucial for optimizing the economic value of brachytherapy and improving patient outcomes in Italy.

References

[1] Cancer today. (n.d.). https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=cancer&mode_population=continents&population=900&populations=900

[2] WCRF International. (2022, April 14). Worldwide cancer data | World Cancer Research Fund International. https://www.wcrf.org/cancer-trends/worldwide-cancer-data/

[3] Statista. (n.d.). https://www.statista.com/statistics/1325894/cases-of-prostate-and-testicular-cancer-in-italy/#:~:text=Cases%20of%20prostate%20and%20testicular%20cancer%20in%20Italy%20as%20of%202023&text=As%20of%202023%2C%20more%20than,or%20testicular%20cancer%20in%20Italy.

[4] Globocan. (2022). https://gco.iarc.who.int/media/globocan/factsheets/populations/724-spain-fact-sheet.pdf

[5] Salek, M., Silverstein, A., Tilly, A., Gassant, P. Y., Gunasekera, S., Hordofa, D. F., Hesson, D., Duffy, C., Malik, N., McNeil, M., Force, L. M., Bhakta, N., Rodin, D., & Kaye, E. C. (2023). Factors influencing treatment decision-making for cancer patients in low- and middle-income countries: A scoping review. *Cancer medicine*, *12*(17), 18133–18152. https://doi.org/10.1002/cam4.6375

[6] *Prostate Cancer Care Path.* 2023. An Elekta Internal document.

[7] Cancer World. (2019, March 18). Brachytherapy: halting the spiral of decline. https://archive.cancerworld.net/cover-story/brachytherapy-halting-the-spiral-of-decline/

[8] Elekta. (2023). 'About Elekta'. https://www.elekta.com/company/about-us/ (April 13, 2023).

[9] Gongora-Salazar, P., Rocks, S., Fahr, P., Rivero-Arias, O., & Tsiachristas, A. (2023). The use of multicriteria decision analysis to support decision making in healthcare: an updated systematic literature review. *Value in Health*, *26*(5), 780-790.

[10] Simoens, S. (2009). Health economic assessment: a methodological primer. *International journal of environmental research and public health*, *6*(12), 2950-2966.

[11] Jamshidi, H. R., Foroutan, N., & Salamzadeh, J. (2014). "Budget Impact Analyses": A Practical Policy Making Tool for Drug Reimbursement Decisions. *Iranian Journal of Pharmaceutical Research: IJPR*, *13*(3), 1105.

[12] American Cancer Society. (2023). 'Initial Treatment of Prostate Cancer, by Stage and Risk Group' https://www.cancer.org/cancer/types/prostate-cancer/treating/by-stage.html

[13] Prostate Cancer Free Foundation. 2021. 'Active Surveillance - What's New'. https://www.prostatecancerfree.org/pcacommentary-148-active-surveillance-whats-new/

[14] John Hopkins Medicine. (n.d.). 'Prostate Cancer: Surgery' https://www.hopkinsmedicine.org/health/conditions-and-diseases/prostate-cancer/surgery-for-prostate-cancer#:~:text=Radical%20(Open)%20Prostatectomy&text=During%20a%20radical%20retropubic%20prostatectomy,Read%20more%20about%20radical%20prostatectomy.

[15] Mohler, J. L. (2010). The 2010 NCCN clinical practice guidelines in oncology on prostate cancer. *Journal of the national comprehensive cancer network*, *8*(2), 145-145.

[16] Gómez-Veiga, F., Rodríguez-Antolín, A., Miñana, B., Hernández, C., Suárez, J. F., Fernández-Gómez, J. M., Unda, M., Burgos, J., Alcaraz, A., Rodríguez, P., Medina, R., Castiñeiras, J., Moreno, C., Pedrosa, E., Cózar, J. M., & GESCAP (2017). Diagnosis and treatment for clinically localized prostate cancer. Adherence to the European Association of Urology clinical guidelines in a nationwide population-based study - GESCAP group. Diagnóstico y tratamiento del cáncer de prostata clínicamente localizado. Adherencia a las guías clínicas en un estudio poblacional nacional – GESCAP. *Actas urologicas espanolas*, *41*(6), 359–367. https://doi.org/10.1016/j.acuro.2016.10.009

[17] Data, M. C., Komorowski, M., & Raffa, J. (2016). Markov models and cost effectiveness analysis: applications in medical research. *Secondary analysis of electronic health records*, 351-367.
[18] Briggs, A., & Sculpher, M. (1998). An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics*, *13*(4), 397-409.
[19] Weng, Xiuhua et al. 2022. 'Cost-Effectiveness Analysis of Primary Treatments for Localised Prostate Cancer: A Population-Based Markov Analysis Using Real-World Evidence'. European Journal of Cancer Care 31(6): e13740. https://onlinelibrary.wiley.com/doi/full/10.1111/ecc.13740 (May 10, 2023).
[20] Naser-Tavakolian, Aurash et al. 2023. 'The Impact of Life Expectancy on Cost-Effectiveness of Treatment Options for Clinically Localized Prostate Cancer'. Urologic Oncology: Seminars and Original Investigations 41(4): 205.e1-205.e10.
[21] Noble, Sian M. et al. 2020. 'The ProtecT Randomised Trial Cost-Effectiveness Analysis Comparing Active Monitoring, Surgery, or Radiotherapy for Prostate Cancer'. British Journal of Cancer 2020 123:7 123(7): 1063–70. https://www.nature.com/articles/s41416-020-0978-4 (May 11, 2023).
[22] dos Santos Silva, E. K., Cruz, J. A. W., da Cunha, M. A. V. C., de Moraes, T. P., Marques, S., & da Silva, E. D. (2021). Cost-effectiveness in health: consolidated research and contemporary challenges. *Humanities and Social Sciences Communications*, *8*(1), 1-10.
[23] Prieto, L., & Sacristán, J. A. (2003). Problems and solutions in calculating quality-adjusted life years (QALYs). *Health and quality of life outcomes*, *1*, 80. https://doi.org/10.1186/1477-7525-1-80
[24] Bundesministerium für Gesundheit. 2023. 'Krankenhausreform'. https://www.bundesgesundheitsministerium.de/themen/gesundheitswesen/krankenhausreform.html (June 4, 2023).
[25] Messori, A., & Trippoli, S. (2022). Estimation of value-based price for five high-technology medical devices approved by a regional health technology assessment committee in Italy. *Cureus*, *14*(5).
[26] [Schindler, 2019] Schindler, P. S. (2019). Business Research Methods, 13th edition. McGraw-Hill/Irwin.
[27] Kittel, J. A., Reddy, C. A., Smith, K. L., Stephans, K. L., Tendulkar, R. D., Ulchaker, J., Angermeier, K., Campbell, S., Stephenson, A., Klein, E. A., Wilkinson, D. A., & Ciezki, J. P. (2015). Long-Term Efficacy and Toxicity of Low-Dose-Rate ^{125}I Prostate Brachytherapy as Monotherapy in Low-, Intermediate-, and High-Risk Prostate Cancer. *International journal of radiation oncology, biology, physics*, *92*(4), 884–893. https://doi.org/10.1016/j.ijrobp.2015.02.047
[28] Smith, G. D., Pickles, T., Crook, J., Martin, A. G., Vigneault, E., Cury, F. L., ... & Rodrigues, G. (2015). Brachytherapy improves biochemical failure–free survival in low-and intermediate-risk prostate cancer compared with conventionally fractionated external beam radiation therapy: a propensity score matched analysis. *International Journal of Radiation Oncology* Biology* Physics*, *91*(3), 505-516.
[29] Wenzel, M., Würnschimmel, C., Nocera, L., Colla Ruvolo, C., Tian, Z., Shariat, S. F., ... & Karakiewicz, P. I. (2021). The effect of lymph node dissection on cancer-specific survival in salvage radical prostatectomy patients. *The prostate*, *81*(6), 339-346.
[30] Chu, C. E., Cowan, J. E., Fasulo, V., Washington III, S. L., de la Calle, C., Shoemaker, J., & Carroll, P. R. (2021). The Clinical Significance of Multiple Negative Surveillance Prostate Biopsies for Men on Active Surveillance—Does Cancer Vanish or Simply Hide?. *The Journal of urology*, *205*(1), 109-114.
[31] Lo, A. C., Morris, W. J., Pickles, T., Keyes, M., McKenzie, M., & Tyldesley, S. (2015). Patterns of recurrence after low-dose-rate prostate brachytherapy: a population-based

study of 2223 consecutive low-and intermediate-risk patients. International Journal of Radiation Oncology* Biology* Physics, 91(4), 745-751.

[32] Stone, N. N., Stock, R. G., White, I., & Unger, P. (2007). Patterns of local failure following prostate brachytherapy. The Journal of urology, 177(5), 1759-1764.

[33] Gomez-Iturriaga, A., Buchser, D., Mayrata, E., San Miguel, I., Gonzalez, A., Suarez, F., ... & Casquero, F. (2020). Pattern of relapse and dosimetric analysis of a single dose 19 Gy HDR-brachytherapy phase II trial. *Radiotherapy and Oncology*, *146*, 16-20.`

[34] Taira, A. V., Merrick, G. S., Butler, W. M., Galbreath, R. W., Fiano, R., Wallner, K. E., & Adamovich, E. (2013). Time to failure after definitive therapy for prostate cancer: implications for importance of aggressive local treatment. *Journal of contemporary brachytherapy*, *5*(4), 215-221.

[35] Spratt, D. E., Zumsteg, Z. S., Pei, X., Romesser, P. B., Yamada, J., Kollmeier, M. A., ... & Zelefsky, M. J. (2015). Predictors of castration-resistant prostate cancer after dose-escalated external beam radiotherapy. *The Prostate*, *75*(2), 175-182.

[36] Miszczyk, L., Namysł-Kaletka, A., Napieralska, A., Kraszkiewicz, M., Miszczyk, M., Woźniak, G., ... & Tukiendorf, A. (2019). Stereotactic Ablative Radiotherapy for Prostate Cancer—The Treatment Results of 500 Patients and Analysis of Failures. *Technology in Cancer Research & Treatment*, *18*, 1533033819870815.

[37] Goy, B. W., Burchette, R., Soper, M. S., Chang, T., & Cosmatos, H. A. (2020). Ten-year treatment outcomes of radical prostatectomy vs external beam radiation therapy vs brachytherapy for 1503 patients with intermediate-risk prostate cancer. *Urology*, *136*, 180-189.

[38] Åström, L., Grusell, E., Sandin, F., Turesson, I., & Holmberg, L. (2018). Two decades of high dose rate brachytherapy with external beam radiotherapy for prostate cancer. *Radiotherapy and Oncology*, *127*(1), 81-87.

[39] Castiglione, F., Dell'Oglio, P., Tosco, L., Everaerts, W., Albersen, M., Hakim, L., ... & European Multicenter Prostate Cancer Clinical and Translational Research Group (EMPaCT). (2017). Tumor volume and clinical failure in high-risk prostate cancer patients treated with radical prostatectomy. *The Prostate*, *77*(1), 3-9.

[40] Hamdy, F. C., Donovan, J. L., Lane, J. A., Mason, M., Metcalfe, C., Holding, P., ... & Neal, D. E. (2016). 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *New England Journal of Medicine*, *375*(15), 1415-1424.

[41] Katz, A., Formenti, S. C., & Kang, J. (2016). Predicting biochemical disease-free survival after prostate stereotactic body radiotherapy: risk-stratification and patterns of failure. *Frontiers in Oncology*, *6*, 168.

[42] Galdos-Bejar, M., Belanovic-Ramirez, I., Alvarado, G. F., & Del Castillo, R. (2022). Biochemical failure and toxicity in treatment with brachytherapy and external beam radiotherapy compared with radical prostatectomy in localized prostate cancer. reports of practical Oncology and radiotherapy, 27(4), 644-654.

[43] Tosoian, J. J., Mamawala, M., Epstein, J. I., Landis, P., Wolf, S., Trock, B. J., & Carter, H. B. (2015). Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. *Journal of Clinical Oncology*, *33*(30), 3379.

[44] Godtman, R. A., Holmberg, E., Khatami, A., Pihl, C. G., Stranne, J., & Hugosson, J. (2016). Long-term results of active surveillance in the Göteborg randomized, population-based prostate cancer screening trial. *European urology*, *70*(5), 760-766.

[45] Yoshioka, Y., Suzuki, O., Isohashi, F., Seo, Y., Okubo, H., Yamaguchi, H., ... & Ogawa, K. (2016). High-dose-rate brachytherapy as monotherapy for intermediate-and high-risk prostate cancer: clinical results for a median 8-year follow-up. *International Journal of Radiation Oncology* Biology* Physics*, *94*(4), 675-682.

[46] Glaser, S. M., Dohopolski, M. J., Balasubramani, G. K., Benoit, R. M., Smith, R. P., & Beriwal, S. (2017). Brachytherapy boost for prostate cancer: trends in care and survival outcomes. *Brachytherapy*, *16*(2), 330-341.

[47] Lane, J. A., Donovan, J. L., Young, G. J., Davis, M., Walsh, E. I., Avery, K. N., ... & Goepel, J. (2022). Functional and quality of life outcomes of localised prostate cancer treatments (Prostate Testing for Cancer and Treatment [ProtecT] study). *BJU international*, *130*(3), 370-380.

[48] The IAEA Directory of Radiotherapy Centres (DIRAC), Division for Human Health: DIRAC (DIrectory of RAdiotherapy Centres) (iaea.org) (November,2023).

[49] Kruk, M. E., Gage, A. D., Arsenault, C., Jordan, K., Leslie, H. H., Roder-DeWan, S., Adeyi, O., Barker, P., Daelmans, B., Doubova, S. V., English, M., García-Elorrio, E., Guanais, F., Gureje, O., Hirschhorn, L. R., Jiang, L., Kelley, E., Lemango, E. T., Liljestrand, J., Malata, A., … Pate, M. (2018). High-quality health systems in the Sustainable Development Goals era: time for a revolution. *The Lancet. Global health*, *6*(11), e1196–e1252. https://doi.org/10.1016/S2214-109X(18)30386-3.

[50] Buglione, M., Noale, M., Bruni, A., Antonelli, A., Bertoni, F., Corvo', R., Ricardi, U., Borghetti, P., Maddalo, M., Simeone, C., Mazzeo, E., Porreca, A., Serni, S., Bassi, P., Gacci, M., Mirone, V., Montironi, R., Tubaro, A., Berruti, A., Conti, G. N., … Pros-IT CNR study group (2019). Treatment paths for localised prostate cancer in Italy: The results of a multidisciplinary, observational, prospective study (Pros-IT CNR). *PloS one*, *14*(11), e0224151. https://doi.org/10.1371/journal.pone.0224151

[51] Bonfill, X., Martinez-Zapata, M. J., Vernooij, R. W., Sánchez, M. J., Morales-Suárez-Varela, M., Emparanza, J. I., Ferrer, M., Pijoan, J. I., Palou, J., Madrid, E., Abraira, V., Zamora, J., & EMPARO-CU study group (2021). Follow-up care over 12 months of patients with prostate cancer in Spain: A multicenter prospective cohort study. *Medicine*, *100*(47), e27801. https://doi.org/10.1097/MD.0000000000027801

[52] Correa, R., Vidal, N., Quesada-García, A., Marcos, R., Muñoz Del Toro, J., & Muñoz-Rodríguez, J. (2024). Management of patients with localized prostate cancer and biochemical recurrence in Spain: A medical survey. *Actas urologicas espanolas*, *48*(3), 218–227. https://doi.org/10.1016/j.acuroe.2023.08.002

[53] Ciccone, G., De Luca, S., Oderda, M., Munoz, F., Krengli, M., Allis, S., ... & Rossi, R. (2023). Patient and Context Factors in the Adoption of Active Surveillance for Low-Risk Prostate Cancer. *JAMA Network Open*, *6*(10), e2338039-e2338039.

[54] The World Bank. (2022). https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?locations=IT-ES&name_desc=false

[55] InterNation. (n.d.). https://www.internations.org/italy-expats/guide/healthcare

[56] Statista. (n.d.). 'Health care system in Italy – Statistics&Facts'. https://www.statista.com/topics/6349/healthcare-system-in-italy/#topicOverview

[57] Statista. (n.d.). 'Number of public and private hospitals in Spain in 2020'. https://www.statista.com/statistics/486355/number-of-public-and-private-hospitals-in-spain-by-region/

[58] Statista. (2023). 'Number of public and private inpatient care facilities in Italy in 2020'. https://www.statista.com/statistics/1372611/number-of-public-and-private-inpatient-care-facilities-by-region-italy/

[59] Statistia. (2023). 'Number of hospitals in Italy 2014 to 2021'. https://www.statista.com/statistics/557042/hospitals-in-italy/

[60] The IAEA Directory of Radiotherapy Centres (DIRAC). https://dirac.iaea.org/Query/Map2?mapId=2 (September, 2023).

[61] Statista. (2023). 'Estimated number of new cases of cancer diagnosed among men in Spain in 2023.' https://www.statista.com/statistics/779849/most-common-cancer-types-diagnosed-among-men-in-spain/
[62] Statista. (2023). 'Estimated number of new cases of cancer diagnosed among men in Italy in 2023.' https://www.statista.com/statistics/588600/number-of-new-cancer-cases-in-italy-by-type-of-cancer-males/
[63] HPVV. (2019). 'FACT SHEET: SPAIN'. https://www.hpvworld.com/articles/fact-sheet-spain-www-hpvcentre-net-human-papillomavirus-and-related/#:~:text=Spain%20has%20a%20population%20of,825%20die%20from%20the%20disease.
[64] The Lancent Oncology. (2001). 'A new alternative for prostate cancer treatment in Spain'. https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(00)00375-2/abstract
[65] Statista. (2023). 'Number of radiation therapy equipment units in Spain from 2012 to 2021.' https://www.statista.com/statistics/771539/radiation-therapy-equipment-in-spain/
[66] Statista. (2023). 'Number of radiation therapy equipment units in Italy from 2012 to 2021.' https://www.statista.com/statistics/535399/radiation-therapy-equipment-in-italy/
[67] Corkum, M., Loblaw, A., Hasan, Y., Chung, H. T., Tseng, C. L., McGuffin, M., Cheung, P., Szumacher, E., Liu, S., Chu, W., Zhang, L., Mamedov, A., & Morton, G. (2021). Prostate high dose-rate brachytherapy as monotherapy for prostate cancer: Late toxicity and patient reported outcomes from a randomized phase II clinical trial. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology*, *156*, 160–165. https://doi.org/10.1016/j.radonc.2020.12.021
[68] Shah, C., Lanni Jr, T. B., Ghilezan, M. I., Gustafson, G. S., Marvin, K. S., Ye, H., ... & Martinez, A. A. (2012). Brachytherapy provides comparable outcomes and improved cost-effectiveness in the treatment of low/intermediate prostate cancer. *Brachytherapy*, *11*(6), 441-445.
[69] Moll, M., & Goldner, G. (2023). Comparison of treatment costs for primary localized prostate cancer in Austria and Vienna: an economic analysis. *Frontiers in Public Health*, *11*, 1016860.
[70] Cruz-Martínez, R. R. (2022). Practice guide: Setting up your systematic search strategy. https://doi.org/10.5281/ZENODO.7062727

Appendix A Pre-Research

To identify the factors that contribute to the difference in the utilization of brachytherapy for prostate cancer between Italy and Spain, we conducted a comparative analysis of the two countries based on specific criteria, as outlined in the following table. For some criteria, no information was available in the literature, and due to time constraints, we were unable to consult experts in the field. Our analysis revealed that both European countries are similar in various aspects, such as healthcare systems, GDP, and brachytherapy facilities. However, a difference was observed in the reimbursement system in both countries.

Table 23 Pre-Research

Criteria	Spain	Italy	Difference?
Country level comparison			
Economic indicators			
GDP per capita	29.350 USD (2022) [54]	34.158 USD (2022) [54]	No difference that can explain under-utilization in Italy
Political system and Governance			
Political stability	yes	yes	similar
State/provinces	17 autonomous communities, 2 autonomous cities. Each autonomous community has its own regional government with varying degrees of legislative and administrative autonomy	20 regions. These regions are the primary subdivisions of the country and have varying degrees of autonomy in areas such as education, healthcare, and transportation	-
a) Health care			
Are people insured?	Universal health insurance available to every citizen: old, unemployed or children. free of charge; it's financed by public taxes. Citizens have access to public healthcare automatically. In addition to public healthcare citizen can acquire private health care for faster service which has annual payments	Universal health insurance for residents, free of charge; it's financed by public taxes. Citizens have access to public healthcare automatically and this option can be opted out. In addition to public healthcare citizen can acquire private health care for faster service which has annual payments.	similar

Access to Health care service/system	Mix of public-private healthcare system Healthcare is decentralized. Patients are allowed to have direct access to specialists without referral from GP (less strict than Italy) Pharmaceutical reimbursement: prescription-based medication is partially covered. <u>Public health care (same as Italy):</u> - Free of charge - covers the direct family of a beneficiary. - waiting times for surgeries, procedures, and treatment from specialist doctors is too long. - do not allow you to choose your doctor or specialist. - difficulty finding English-speaking staff. <u>Private health care</u> - allows quicker access to doctor, specialists. - the possibility of choosing English-speaking healthcare providers, - and overall more comfortable hospitals and medical centers. - 19% of Spanish resident use private health insurance.	A mix of public-private healthcare system Healthcare is decentralized and managed on regional level by 19 regions and 2 autonomous provinces. Italy has a co payment system for specialist physician care. Means patients must share cost. For a general practitioner a copayment does not happen. - Patients need a referral from GP to access specialized care. - Pharmaceutical reimbursement: prescription-based medication is partially covered for drugs in outpatient and ambulatory care, and free of charge for drugs for severe and chronic illness. - inequalities between levels of service provision in the North and South of the country, favouring the North. <u>Public healthcare (same as Spain):</u> - free of charge. - Difficult to find English speaking doctors, mostly Italian speaking.	-

- cost will depend on your age, gender, and any pre-existing conditions.
- cost is between 100 to 200 EUR per month.
- Primary care consultations and specialists in the private sector usually cost between 100 and 150 EUR per consultation.
- Common to have private health insurance to supplement public health coverage

- Long waiting times
- A specialist of own choice cannot be chosen when being referred by family doctor.
- Seeing a specialist can take months. Delay of diagnosis, treatment.

Private healthcare:

- Fast appointments, test, diagnosis, procedures, more personalized attentive care.
- English speaking doctor and staff available.
- Private Health insurance scheme:
    1. Basic level: 500€ annually. Does not cover serious medical condition.
    2. 1000€ annually. Allows to visit private doctors, specialists for fast consultancy, treatment in private hospitals. (Takes too long in public health care).
    3. 3000€ annually. Covers all medical needs, covers medical care abroad.

Assumption: BT treatment falls under private healthcare with the last insurance option.

		[55] - Not so common to have private health insurance. 10% of population has private health insurance in addition to public health insurance which can not be opted out. [56]	
Reimbursement system	Adequate reimbursement for BT [7]	Inadequate reimbursement for BT [7]	different
Healthcare expenses	Expenses only occur in private health insurance: - cost is between 100 to 200 EUR per month. - Primary care consultations and specialists in the private sector usually cost between 100 and 150 EUR per consultation.	Expenses only occur in private health insurance as following: - <u>Private Health insurance scheme:</u> 4. Basic level: 500€ annually. Doesn not cover serious medical condition. 5. 1000€ annually. Allows to visit private doctors, specialists for fast consultancy, treatment in private hospitals. (Takes too long in public health care). 6. 3000€ annually. Covers all medical needs, covers medical care abroad.	Different, but does not directly explain difference in treatment selection
# of public/private inpatient care facilities	[57]	[58]	similar
# of hospitals	-	[59]	similar

Availability and effectiveness of healthcare programs	good	good	similar
Unemployment benefits	Unemployed also have access to public health insurance	Unemployed also have access to public health insurance.	similar
How are healthcare payments organized/ professional payment model	Salary or capitation model for healthcare professionals. Fixed salary, does not depend on number of patients they see.	- Fee-for-service model for specialist. Specialists get a fee every time a patient visits them. So, their payment depends on number of patients they see. - co-payment for specialist ambulatory care.	May partly explain the difference. Brachytherapy is less profitable, and reimbursement does not compensate for increased time expenditure
# of RT facilities/centers	130 RT centers [60]	194 RT centers [60]	Similar, difference can be explained by size of the population
b) Prostate cancer management			
# of new prostate cancer cases	In 2020 34.613 new cases of prostate cancer. [1] 29.002 cases of prostate cancer in 2023. Prostate cancer is the most common type of cancer among men in Spain. [61]	39.217 new cases of prostate cancer in 2020. [1] Prostate cancer is the most common type of cancer in Italy among men. [62]	Similar, difference is related to size of the population
Cases of cervical cancer	1942 cases every year. [63]	2400 cases in 2020. Cervical cancer elimination in Italy: Current scenario and future endeavours for a value-based prevention	Difference is related to difference in population. Does not explain difference in brachytherapy utilization since brachytherapy is gold standard for CC

Screening programs	PSA test, Spain is in favor of prostate cancer screening. Cancer screening recommendations: an international comparison of high-income countries. Page 5	PSA test, prostate Specific Antigen, Italy is in favor of prostate cancer screening. Cancer screening recommendations: an international comparison of high-income countries. Page 5	similar
How is prostate cancer treated?	Spain has an ageing population therefore they prefer brachytherapy over external beam and radical surgery. [64]	intensity-modulated radiotherapy and stereotactic radiotherapy were preferred to brachytherapy in Italy since they are non-invasive, and because the Italian National Health Service pays more for these advanced external beam radiotherapy techniques. Moved to External Beam RT because of its technical improvement	Observed difference in brachytherapy
# of hospitals with BT units (providing BT)	73 [60]	54 [60]	different
# of BT units	147	61	different
#RT equipment units including linear accelerators	[64]	[66]	Similar taking the size of the country into consideration
# of Linear accelerator units/linacs	283 [60]	433 [60]	Does not explain lower brachytherapy utilization
Image/awareness of BT			
efforts taken to promote BT (among young doctors)	- There is a Spanish Brachytherapy group since 2001 which promotes BT and spreads awareness among patients an attracts young doctors.	- No such group exists. - No strong community exists that promotes BT.	Different, but does not explain lower brachytherapy use in existing centers

	- They have written 2 textbooks on brachytherapy. - Spain has a strong community to promote BT		
Guidelines			
Clinical guidelines prostate cancer	EAU	EAU	similar

Appendix B Systematic Literature Review

Research Question and Approach

To answer the research question: "*What are the most relevant alternatives to brachytherapy to treat prostate cancer patients in Spain/Italy?"* we conducted a systematic literature review (SLR) in line with the guidance provided by Cruz-Martinez [70]. Background information on this question can be found in other sections of this thesis.

Database

We chose PubMed, a widely respected academic database specializing in healthcare, on the advice of Elekta experts. Given our research's sole focus on healthcare, PubMed was the obvious selection. Additionally, we referred to the University of Twente database, further confirming PubMed's appropriateness.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were defined as shown in Table 24 Inclusion and Exclusion criteria. This crucial step was performed before commencing the search process to prevent a biased selection of literature.

Table 24 Inclusion and Exclusion criteria

Inclusion criteria	Reasoning
The literature should be about non metastatic Prostate Cancer.	This is the topic of the research.
The literature should provide information on treatment modalities used to treat PC patients	Our research question aims to identify alternative therapies
The literature should be relevant to Italy or Spain	We want to understand differences in treatment patterns between these countries.
The literature should not be published before 2017.	Cancer treatments are rapidly changing, recent publications are more likely to provide information on why the situation currently is as it is.
The literature should be peer-reviewed.	Peer-reviewed articles are more likely to provide reliable and validated information for academic research.
The literature should be in the following language: German or English	This is for easy understanding as these are the two languages I understand.
Exclusion criteria	Reasoning
Literature about other cancer types than prostate cancer.	Restricting to prostate cancer ensures relevance to the specific condition being investigated.
Studies focusing solely on brachytherapy.	The literature should help identify the most relevant alternatives to BT
Literature older than 2017	Since publication describe practices that happened in the past, an especially since cancer research usually has a 5 year follow up period, older articles may be describing practices that are no longer standard of care.

Search Matrix

The next step involves defining a search matrix based on the [11]PICO search methodology that represents potential research terms for the key concepts of the question to be answered.

Table 25 Search Matrix

	Key concept	Related Terms/synonyms	Narrower terms	Broader terms
Problem	Prostate cancer	Prostatic Neoplasms, Prostate Tumour, cancer of the prostate.	Prostate cancer	Cancer, tumor, oncology, urology
Intervention	Brachytherapy	Radioactive Seed Implantation, Radiotherapy	HDR Brachytherapy, LDR Brachytherapy	Brachytherapy
Comparison	Alternative Treatments	Other Treatments, Non-Brachytherapy Treatments	Surgery, Radiation Therapy, EBRT, SBRT, External beam radiation therapy, watchful waiting, prostatectomy, Active Surveillance	Prostate Cancer Treatments, Cancer Treatment Options
Outcome/ additional filter	Spain and Italy	Spanish Healthcare, Italian Healthcare	Spain, Italy	European Healthcare Systems, Southern Europe

Search Log

Table 26 Search Log

Date	Source	Search Query	Total Hits	Remarks
16.11.2023	PubMed	("Prostate cancer" OR "cancer of the prostate" OR "prostate tumor" OR "Prostatic Neoplasm*") AND (brachytherapy OR treatment OR surgery OR "External beam" OR EBRT OR SBRT OR surgical OR prostatectomy OR "watchful waiting" OR "Active Surveillance") AND (Spain [Title] OR Italy [Title]) AND ("2017/01/01"[Date - Publication]: "3000"[Date - Publication])	44	Conducted initial search; Found relevant articles focusing on alternative treatments for prostate cancer in Spain and Italy. Noted studies on different therapies like surgery, radiation, and EBRT.
17.11.2023	Google Scholar	"prostate Cancer" treatment brachytherapy "Italian healthcare" Filters: last 5 years	6	Conducted supplementary search for literature. Found additional articles on brachytherapy treatments for prostate cancer in the context of Spanish and Italian healthcare systems.

[11] PICO stands for "problem", "Intervention", "comparison" and "Outcome"

Results

Table 27 SLR Results

Search ID	Reference	Inclusion/Exclusion	Therapies
PM1	Corrao G, Franchi M, Zaffaroni M, Vincini MG, de Marinis F, Spaggiari L, Orecchia R, Marvaso G, Jereczek-Fossa BA. Upfront Advanced Radiotherapy and New Drugs for NSCLC Patients with Synchronous Brain Metastases: Is the Juice Worth the Squeeze? A Real-World Analysis from Lombardy, Italy. Cancers (Basel). 2023 Feb 9;15(4):1103. doi: 10.3390/cancers15041103.	Excluded, not related to prostate cancer.	
PM2	Borsoi L, Ciani O, Fornarini G, Oderda M, Sciarra A, Vetrini D, Luccarini I. Direct healthcare costs of non-metastatic castration-resistant prostate cancer in Italy. Int J Technol Assess Health Care. 2023 Jan 6;39(1):e2. doi: 10.1017/S0266462322003336.	included	Surgery (radical prostatectomy), radiotherapy, chemotherapy (as neoadjuvant therapy in localized high-risk PCa), or combination approaches such hormonal therapy (androgen-deprivation therapy, ADT) before prostatectomy
PM3	Bonfill-Cosp X, Auladell-Rispau A, Gich I, Zamora J, Saiz LC, Pijoan JI, Urreta I, Cordero JA. Prevalence study of intermittent hormonal therapy of Prostate Cancer patients in Spain. F1000Res. 2021 Oct 21;10:1069. doi: 10.12688/f1000research.53875.2. eCollection 2021.	Excluded, mainly metastatic prostate cancer	
PM4	Ippoliti S, Orecchia L, Esperto F, Langer Wroclawski M, Manenti G, Barrett T, Kastner C, Miano R. Survey on prostate MRI reading and interpretation among urology residents in Italy, Brazil and the UK: a cry for help. Minerva Urol Nephrol. 2023 Jun;75(3):297-307. doi: 10.23736/S2724-6051.22.05043-1. Epub 2022 Oct 26.	Excluded, not describing treatment modalities	
PM5	Guijarro A, Castro A, Hernández V, de la Peña E, Sánchez-Rosendo L, Jiménez E, Pérez-Férnandez E, Llorente C. Population based study of morbidity and mortality rates associated to radical prostatectomy cases in Spain. Actas Urol Esp (Engl Ed). 2022 Dec;46(10):619-628. doi: 10.1016/j.acuroe.2022.10.005. Epub 2022 Oct 21.	included	Radical prostatectomy
PM6	de Velasco Oria de Rueda G, Plata Bello AC, Landeira M, Mateo M, Anguita P, Pranzo A, Snijder R, Garnham A, Hernández I. Incidence, prevalence, and treatment patterns in metastatic hormone-sensitive prostate cancer in Spain: ECHOS study. Actas Urol Esp (Engl Ed). 2022 Nov;46(9):557-564. doi: 10.1016/j.acuroe.2022.02.009. Epub 2022 Oct 7.	Excluded, metastatic, no local treatment.	
PM7	Taborelli M, Toffolutti F, Bidoli E, Dal Maso L, Del Zotto S, Clagnan E, Gobbato M, Serraino D, Franceschi S. The use of PSA testing over more	Included	Active Surveillance, surgery or radiotherapy

	than 20 years: A population-based study in North-Eastern Italy. Tumori. 2023 Aug;109(4):406-412. doi: 10.1177/03008916221128343. Epub 2022 Oct 10.		
PM8	Verzoni E, Pappagallo G, Alongi F, Arcangeli S, Francolini G, Galanti D, Galli L, Maruzzo M, Rossetti S, Siepe G, Triggiani L, Zucali PA, D'Angelillo RM. Achieving Consensus for Management of Hormone-Sensitive, Low-Volume Metastatic Prostate Cancer in Italy. Curr Oncol. 2022 Jun 28;29(7):4578-4586. doi: 10.3390/curroncol29070362.	Excluded, metastatic, no local treatment.	
PM9	Leith A, Kim J, Ribbands A, Clayton E, Yang L, Ghate SR. Real-World Treatment Patterns in Metastatic Castration-Resistant Prostate Cancer Across Europe (France, Germany, Italy, Spain, and the United Kingdom) and Japan. Adv Ther. 2022 May;39(5):2236-2255. doi: 10.1007/s12325-022-02073-w. Epub 2022 Mar 22.	Excluded, metastatic, no local treatment.	
PM10	Bonfill X, Martinez-Zapata MJ, Vernooij RW, Sánchez MJ, Morales-Suárez-Varela M, Emparanza JI, Ferrer M, Pijoan JI, Palou J, Madrid E, Abraira V, Zamora J; EMPARO-CU study group. Follow-up care over 12 months of patients with prostate cancer in Spain: A multicenter prospective cohort study. Medicine (Baltimore). 2021 Nov 24;100(47):e27801. doi: 10.1097/MD.0000000000027801.	included	Surgery, radiotherapy, hormone therapy, watchful waiting (no therapy), Active Surveillance.
PM11	Montaño JJ, Barceló A, Franch P, Galceran J, Ameijide A, Pons J, Ramos M. Prostate Cancer Survival by Risk and Other Prognostic Factors in Mallorca, Spain. Int J Environ Res Public Health. 2021 Oct 24;18(21):11156. doi: 10.3390/ijerph182111156.	included	Prostatectomy, radiotherapy, cryosurgery, hormonal therapy, chemotherapy, Active Surveillance, expectant attitude and unknown.
PM12	Spadea T, Di Girolamo C, Landriscina T, Leoni O, Forni S, Colais P, Fanizza C, Allotta A, Onorati R, Gnavi R; Mimico-19 working group. Indirect impact of Covid-19 on hospital care pathways in Italy. Sci Rep. 2021 Nov 2;11(1):21526. doi: 10.1038/s41598-021-00982-4.	Excluded, not related to prostate cancer.	
PM13	Barrios-Rodríguez R, García-Esquinas E, Pérez-Gómez B, Castaño-Vinyals G, Llorca J, de Larrea-Baz NF, Olmedo-Requena R, Vanaclocha-Espi M, Alguacil J, Fernández-Tardón G, Fernández-Navarro P, Cecchini L, Lope V, Gómez-Acebo I, Aragonés N, Kogevinas M, Pollán M, Jiménez-Moleón JJ. Prostate cancer genetic propensity risk score may modify the association between this tumour and type 2 diabetes mellitus (MCC-Spain study). Prostate Cancer Prostatic Dis. 2022 Apr;25(4):694-699. doi: 10.1038/s41391-021-00446-w. Epub 2021 Oct 2.	Excluded, not describing treatment modalities	
PM14	Zapatero A, Maldonado Pijoan X, Gómez-Caamaño A, Pardo Masferrer J, Macías Hernández V, Hervás Morón A, Muñoz García JL, Palacios Eito A, Anguita-Alonso P, González-Junco C, López Torrecilla J. Health-related quality	Included	external beam radiotherapy (EBRT) or brachytherapy

	of life in men with localized prostate cancer treated with radiotherapy: validation of an abbreviated version of the Expanded Prostate Cancer Index Composite for Clinical Practice in Spain. Health Qual Life Outcomes. 2021 Sep 25;19(1):223. doi: 10.1186/s12955-021-01856-z.		
PM15	Santucci C, Medina HN, Carioli G, Negri E, La Vecchia C, Pinheiro PS. Cancer mortality in Italian populations: differences between Italy and the USA. Eur J Cancer Prev. 2022 Jul 1;31(4):393-399. doi: 10.1097/CEJ.0000000000000712. Epub 2021 Aug 26.	Excluded, not related to prostate cancer.	
PM16	Mazzeo E, Triggiani L, Frassinelli L, Guarneri A, Bartoncini S, Antognoni P, Gottardo S, Greco D, Borghesi S, Nanni S, Bruni A, Ingrosso G, D'Angelillo RM, Detti B, Francolini G, Magli A, Guerini AE, Arcangeli S, Spiazzi L, Ricardi U, Lohr F, Magrini SM. How Has Prostate Cancer Radiotherapy Changed in Italy between 2004 and 2011? An Analysis of the National Patterns-Of-Practice (POP) Database by the Uro-Oncology Study Group of the Italian Society of Radiotherapy and Clinical Oncology (AIRO). Cancers (Basel). 2021 May 30;13(11):2702. doi: 10.3390/cancers13112702.	included	radical external beam radiotherapy (EBRT)
PM17	Spandonaro F, D'Angela D, Polistena B, Bruzzi P, Iacovelli R, Luccarini I, Stagni P, Brigido A. Prevalence of Prostate Cancer at Different Clinical Stages in Italy: Estimated Burden of Disease Based on a Modelling Study. Biology (Basel). 2021 Mar 10;10(3):210. doi: 10.3390/biology10030210.	Excluded, not describing treatment modalities	
PM18	Oderda M, Calleris G, Falcone M, Fasolis G, Muto G, Oderda G, Porpiglia F, Volpe A, Bertetto O, Gontero P. How uro-oncology has been affected by COVID-19 emergency? Data from Piedmont/Valle d'Aosta Oncological Network, Italy. Urologia. 2021 Feb;88(1):3-8. doi: 10.1177/0391560320946186.	included	Radical prostatectomies
PM19	López-Torrecilla J, González Sanchis D, Granero Cabañero D, García Miragall E, Almendros Blanco P, Hernandez Machancoses A, Brualla González L, Pastor Peidro J, Gordo Partearroyo JC, Rosello Ferrando J. Pattern of care in radiotherapy at a University Hospital in Spain: the RENORT project. Clin Transl Oncol. 2021 Aug;23(8):1657-1665. doi: 10.1007/s12094-021-02564-2. Epub 2021 Feb 14.	Excluded, not related to prostate cancer.	
PM20	Fusco V, Cabras M, Erovigni F, Dell'Acqua A, Arduino PG, Pentenero M, Appendino P, Basano L, Ferrera FD, Fasciolo A, Caka M, Migliario M. A multicenter observational study on Medication-Related Osteonecrosis of the Jaw (MRONJ) in advanced cancer and myeloma patients of a cancer network in North-Western Italy. Med Oral Patol Oral Cir Bucal. 2021 Jul 1;26(4):e466-e473. doi: 10.4317/medoral.24318.	Excluded, not related to prostate cancer.	
PM21	Aschele C, Negru ME, Pastorino A, Cavanna L, Zagonel V, Barone-Adesi F, Blasi L. Incidence of	Excluded, not related to prostate cancer.	

	SARS-CoV-2 Infection Among Patients Undergoing Active Antitumor Treatment in Italy. JAMA Oncol. 2021 Feb 1;7(2):304-306. doi: 10.1001/jamaoncol.2020.6778.		
PM22	Gacci M, Greco I, Artibani W, Bassi P, Bertoni F, Bracarda S, Briganti A, Carmignani G, Carmignani L, Conti GN, Corvò R, DE Nunzio C, Fusco F, Graziotti P, Maggi S, Magrini SM, Mirone V, Montironi R, Muto G, Noale M, Pecoraro S, Porreca A, Ricardi U, Russi E, Salonia A, Simonato A, Serni S, Tubaro A, Zagonel V, Crepaldi G; Pros-IT CNR Study Group. The waiting time for prostate cancer treatment in Italy: analysis from the PROS-IT CNR Study. Minerva Urol Nephrol. 2022 Feb;74(1):38-48. doi: 10.23736/S2724-6051.20.03925-9. Epub 2020 Nov 17.	Included	Active Surveillance (AS), surgery (radical prostatectomy, RP), radiotherapy (RT) and androgen deprivation therapy (ADT).
PM23	Gacci M, Artibani W, Bassi P, Bertoni F, Bracarda S, Briganti A, Carmignani G, Carmignani L, Conti G, Corvò R, De Nunzio C, Fusco F, Graziotti P, Greco I, Maggi S, Magrini SM, Mirone V, Montironi R, Morgia G, Muto G, Noale M, Pecoraro S, Porreca A, Ricardi U, Russi E, Russo G, Salonia A, Simonato A, Serni S, Tomasini D, Tubaro A, Zagonel V, Crepaldi G; MIRROR-SIU/LUNA Study Group and the Pros-IT CNR Study Group. How radical prostatectomy procedures have changed over the last 10 years in Italy: a comparative analysis based on more than 1500 patients participating in the MIRROR-SIU/LUNA and the Pros-IT CNR study. World J Urol. 2021 May;39(5):1445-1452. doi: 10.1007/s00345-020-03350-5. Epub 2020 Aug 1.	Included	prostatectomy
PM24	Di Lorenzo G, Buonerba L, Ingenito C, Crocetto F, Buonerba C, Libroia A, Sciarra A, Ragone G, Sanseverino R, Iaccarino S, Napodano G, Imbimbo C, Leo E, Kozlakidis Z, De Placido S. Clinical Characteristics of Metastatic Prostate Cancer Patients Infected with COVID-19 in South Italy. Oncology. 2020;98(10):743-747. doi: 10.1159/000509434. Epub 2020 Jun 22.	Excluded, metastatic, no local treatment.	
PM25	Larrea L, López E, Antonini P, González V, Berenguer MÁ, Baños MC, Bea J, Domingo J. COVID-19: hypofractionation in the Radiation Oncology Department during the 'state of alarm': first 100 patients In a private hospital in Spain. Ecancermedicalscience. 2020 May 28;14:1052. doi: 10.3332/ecancer.2020.1052. eCollection 2020.	Excluded, not related to prostate cancer.	
PM26	Couñago F, Martínez-Ballesteros C, Artigas C, Díaz-Gavela AA, Gómez LLG, Lillo-García ME, Chicharo JR, Recio M, Maldonado A, Thuissard IJ, Andreu-Vázquez C, Sanz-Rosa D, Conde-Moreno AJ, Marcos FJ, García SS, Martínez-Salamanca JI, Carballido-Rodríguez J, Hornedo J, Cerro ED. Impact of (68)Ga-PSMA PET/CT in the treatment of prostate cancer: Initial experience in Spain. Rep Pract Oncol Radiother. 2020 May-Jun;25(3):405-411. doi: 10.1016/j.rpor.2020.03.024. Epub 2020 Apr 12.	included	Active Surveillance, radical treatment (RP or primary radiotherapy), hormonal therapy.

PM27	Mangone L, Ferrari F, Mancuso P, Carrozzi G, Michiara M, Falcini F, Piffer S, Filiberti RA, Caldarella A, Vitale F, Tumino R, Brustolin A, Tagliabue G, Giorgi Rossi P, Ottini L. Epidemiology and biological characteristics of male breast cancer in Italy. Breast Cancer. 2020 Jul;27(4):724-731. doi: 10.1007/s12282-020-01068-1. Epub 2020 Feb 29.	Excluded, not related to prostate cancer.	
PM28	Buglione M, Noale M, Bruni A, Antonelli A, Bertoni F, Corvo' R, Ricardi U, Borghetti P, Maddalo M, Simeone C, Mazzeo E, Porreca A, Serni S, Bassi P, Gacci M, Mirone V, Montironi R, Tubaro A, Berruti A, Conti GN, Maggi S, Magrini SM, Triggiani L; Pros-IT CNR study group. Treatment paths for localised prostate cancer in Italy: The results of a multidisciplinary, observational, prospective study (Pros-IT CNR). PLoS One. 2019 Nov 1;14(11):e0224151. doi: 10.1371/journal.pone.0224151. eCollection 2019.	Included	Surgery and radiotherapy (RT) with or without androgen deprivation therapy (ADT) are widely adopted treatment options for localized PCA together with Active Surveillance (AS),
PM29	Lloret-Durá MA, Panach-Navarrete J, Martínez-Jabaloyas JM, Valls-González L, Cózar-Olmo JM, Miñana-López B, Gómez-Veiga F, Rodríguez-Antolín A; Grupo Español de Cáncer de Próstata. Factors related to early castration resistance in metastatic prostate cancer. Results from the National Prostate Cancer Registry in Spain. Actas Urol Esp (Engl Ed). 2019 Dec;43(10):562-567. doi: 10.1016/j.acuro.2019.04.001. Epub 2019 Jul 10.	Excluded, metastatic, no local treatment.	
PM30	Cernigliaro A, Santangelo OE, Maniglia M, Pollina Addario S, Usticano A, Marras A, Ciranni P, Dardanoni G, Saporito L, Tavormina E, Fantaci G, Scondotto S. [The epidemiological surveillance in the programme of public health intervention in the national priority contaminated sites of Sicily Region (Southern Italy): update of mortality, hospitalization, and cancer incidence]. Epidemiol Prev. 2019 Mar-Jun;43(2-3):132-143. doi: 10.19191/EP19.2-3.P132.052.	Excluded, article in Italian	
PM31	Faccio F, Gandini S, Renzi C, Fioretti C, Crico C, Pravettoni G. Development and validation of the Family Resilience (FaRE) Questionnaire: an observational study in Italy. BMJ Open. 2019 Jun 5;9(6):e024670. doi: 10.1136/bmjopen-2018-024670.	Excluded, not related to prostate cancer.	
PM32	Cordero JA, Sancho G, Bonfill X. Population-based estimate of the use of intermittent androgen deprivation therapy in prostate cancer patients in Catalonia, Spain. Pharmacoepidemiol Drug Saf. 2019 Jun;28(6):796-803. doi: 10.1002/pds.4744. Epub 2019 Mar 6.	Excluded, mainly metastatic prostate cancer	
PM33	Jereczek-Fossa BA, Bortolato B, Gerardi MA, Dicuonzo S, Arienti VM, Berlinghieri S, Bracelli S, Buglione M, Caputo M, Catalano G, Cazzaniga LF, De Cicco L, Di Muzio N, Filippone FR, Fodor A, Franceschini D, Frata P, Gottardo S, Ivaldi GB, Laudati A, Magrini SM, Mantero E, Meaglia I, Morlino S, Palazzi M, Piccoli F, Romanelli P, Scorsetti M, Serafini F, Scandolaro L, Valdagni R, Orecchia R, Antognoni P; Lombardy Section of	Excluded, metastatic, no local treatment.	

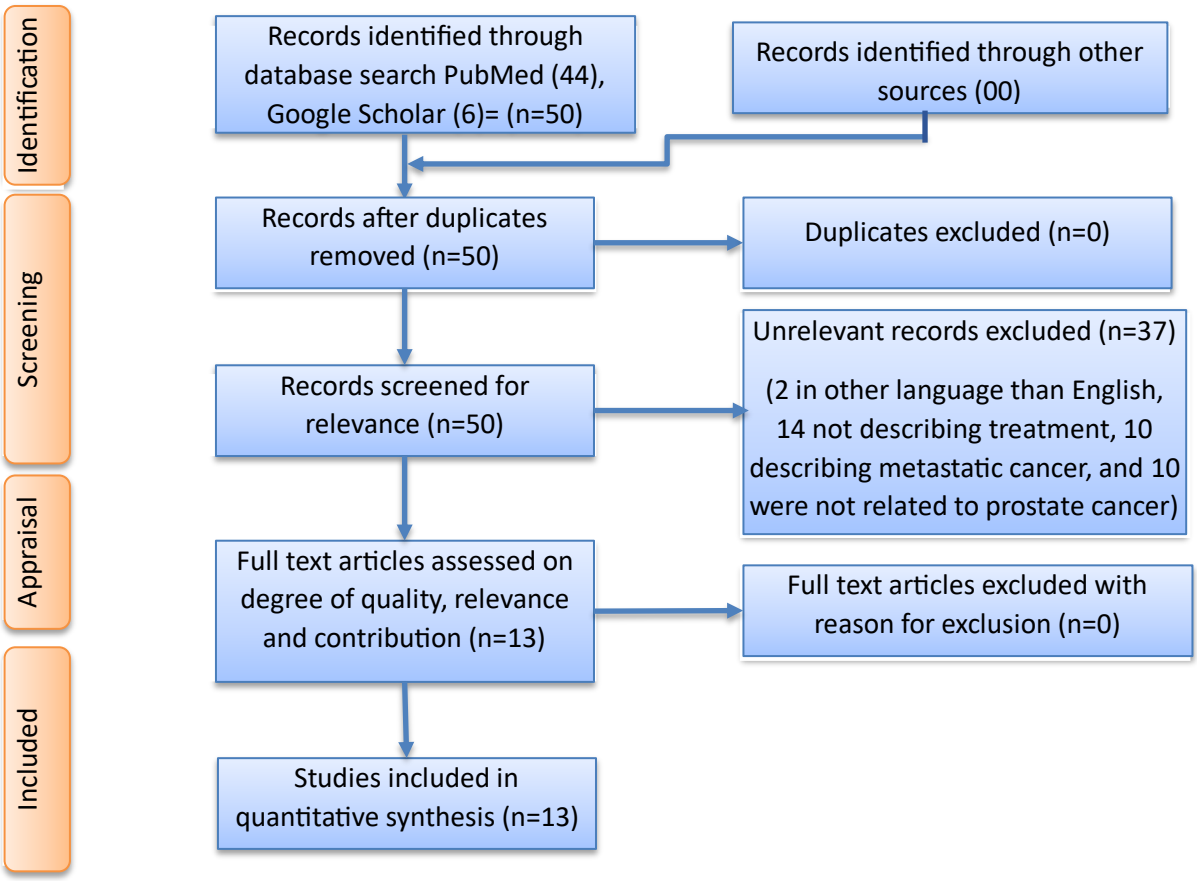
	the Italian Society of Oncological Radiotherapy (Associazione Italiana di Radioterapia Oncologica-Lombardia, AIRO-L). Radiotherapy for oligometastatic cancer: a survey among radiation oncologists of Lombardy (AIRO-Lombardy), Italy. Radiol Med. 2019 Apr;124(4):315-322. doi: 10.1007/s11547-018-0972-6. Epub 2018 Dec 15.		
PM34	Peremiquel-Trillas P, Benavente Y, Martín-Bustamante M, Casabonne D, Pérez-Gómez B, Gómez-Acebo I, Oliete-Canela A, Diéguez-Rodríguez M, Tusquets I, Amiano P, Mengual L, Ardanaz E, Capelo R, Molina de la Torre AJ, Salas Trejo D, Fernández-Tardón G, Lope V, Jimenez-Moleon JJ, Marcos-Gragera R, Dierssen-Sotos T, Azpiri M, Muñoz M, Guevara M, Fernández-Villa T, Molina-Barceló A, Aragonés N, Pollán M, Castaño-Vinyals G, Alguacil J, Kogevinas M, de Sanjosé S, Costas L. Alkylphenolic compounds and risk of breast and prostate cancer in the MCC-Spain study. Environ Int. 2019 Jan;122:389-399. doi: 10.1016/j.envint.2018.12.007. Epub 2018 Dec 13.	Excluded, not related to treatment of PCa	
PM35	Couñago F, Sancho G, Gómez-Iturriaga A, Henríquez I; Urological Tumours Working Group of the Spanish Society of Radiation Oncology (URONCOR/SEOR). Multiparametric MRI for prostate cancer: a national survey of patterns of practice among radiation oncologists in Spain. Clin Transl Oncol. 2018 Nov;20(11):1484-1491. doi: 10.1007/s12094-018-1919-z. Epub 2018 Jul 10.	Excluded, not related to treatment of PCa	
PM36	Taborelli M, Piselli P, Ettorre GM, Lauro A, Galatioto L, Baccarani U, Rendina M, Shalaby S, Petrara R, Nudo F, Toti L, Sforza D, Fantola G, Cimaglia C, Agresta A, Vennarecci G, Pinna AD, Gruttadauria S, Risaliti A, Di Leo A, Burra P, Rossi M, Tisone G, Zamboni F, Serraino D; Italian Transplant & Cancer Cohort Study. Risk of virus and non-virus related malignancies following immunosuppression in a cohort of liver transplant recipients. Italy, 1985-2014. Int J Cancer. 2018 Oct 1;143(7):1588-1594. doi: 10.1002/ijc.31552. Epub 2018 May 10.	Excluded, not related to prostate cancer	
PM37	Tirado Mercier E, Callejo Velasco D, Rubio Cabezas M, Moretones Agut C, Granell Villalón M. Cost-effectiveness Analysis of Radium-223 Dichloride in Metastatic Castration-Resistant Prostate Cancer Patients Without Previous Chemotherapy Treatment in Spain. J Health Econ Outcomes Res. 2018 Jan 29;6(1):1-14. doi: 10.36469/9777. eCollection 2018.	Excluded, metastatic, no local treatment.	
PM38	Restelli U, Ceresoli GL, Croce D, Evangelista L, Maffioli LS, Gianoncelli L, Bombardieri E. Economic burden of the management of metastatic castrate-resistant prostate cancer in Italy: a cost of illness study. Cancer Manag Res. 2017 Dec 7;9:789-800. doi: 10.2147/CMAR.S148323. eCollection 2017.	Excluded, metastatic, no local treatment.	

PM39	Russo GI, Campisi D, Di Mauro M, Regis F, Reale G, Marranzano M, Ragusa R, Solinas T, Madonia M, Cimino S, Morgia G. Dietary Consumption of Phenolic Acids and Prostate Cancer: A Case-Control Study in Sicily, Southern Italy. Molecules. 2017 Dec 5;22(12):2159. doi: 10.3390/molecules22122159.	Excluded, not related to treatment of PCa	
PM40	Alcaraz A, Martínez-Piñeiro L, Rodríguez A, Rubio J, Borque Á, Burgos J, Carballido J, Cózar JM, Crespo I, Esquena S, Gómez-Veiga F, López D, Miñana B, Morote J, Ribal MJ, Solsona E, Suárez JF, Unda M. [Consensus on castration-resistant prostate cancer management in Spain.]. Arch Esp Urol. 2017 Nov;70(9):777-791.	Excluded article in Spanish	
PM41	Ballotari P, Vicentini M, Manicardi V, Gallo M, Chiatamone Ranieri S, Greci M, Giorgi Rossi P. Diabetes and risk of cancer incidence: results from a population-based cohort study in northern Italy. BMC Cancer. 2017 Oct 25;17(1):703. doi: 10.1186/s12885-017-3696-4.	Excluded, not related to prostate cancer	
PM42	Morlando M, Pelullo CP, Di Giuseppe G. Prostate cancer screening: Knowledge, attitudes and practices in a sample of men in Italy. A survey. PLoS One. 2017 Oct 12;12(10):e0186332. doi: 10.1371/journal.pone.0186332. eCollection 2017.	Excluded, not related to treatment of PCa	
PM43	Castelló A, Boldo E, Amiano P, Castaño-Vinyals G, Aragonés N, Gómez-Acebo I, Peiró R, Jimenez-Moleón JJ, Alguacil J, Tardón A, Cecchini L, Lope V, Dierssen-Sotos T, Mengual L, Kogevinas M, Pollán M, Pérez-Gómez B; MCC-Spain Researchers. Mediterranean Dietary Pattern is Associated with Low Risk of Aggressive Prostate Cancer: MCC-Spain Study. J Urol. 2018 Feb;199(2):430-437. doi: 10.1016/j.juro.2017.08.087. Epub 2017 Aug 23.	Excluded, not related to treatment of PCa	
PM44	Romaguera D, Gracia-Lavedan E, Molinuevo A, de Batlle J, Mendez M, Moreno V, Vidal C, Castelló A, Pérez-Gómez B, Martín V, Molina AJ, Dávila-Batista V, Dierssen-Sotos T, Gómez-Acebo I, Llorca J, Guevara M, Castilla J, Urtiaga C, Llorens-Ivorra C, Fernández-Tardón G, Tardón A, Lorca JA, Marcos-Gragera R, Huerta JM, Olmedo-Requena R, Jimenez-Moleon JJ, Altzibar J, de Sanjosé S, Pollán M, Aragonés N, Castaño-Vinyals G, Kogevinas M, Amiano P. Adherence to nutrition-based cancer prevention guidelines and breast, prostate and colorectal cancer risk in the MCC-Spain case-control study. Int J Cancer. 2017 Jul 1;141(1):83-93. doi: 10.1002/ijc.30722. Epub 2017 Apr 21.	Excluded, not related to treatment of PCa	
GS1	López Torrecilla, J., Marín i Borràs, S., Ruiz-Alonso, A., Jaen Olasolo, J., Vázquez de la Torre, M. L., Bóveda Carro, E., ... & Ferrer Albiach, C. (2019). Quality indicators in radiation oncology: proposal of the Spanish Society of Radiation Oncology (SEOR) for a continuous improvement of the quality of care in oncology. Clinical and Translational Oncology, 21, 519-533.	Excluded, not related to treatment of PCa	
GS2	Andrade, P., Sacristan, J. A., & Dilla, T. (2017). The economic burden of cancer in Spain: a	Excluded, not related to treatment of PCa	

	literature review. Health Econ Outcome Res Open Access, 3(125), 2.		
GS3	Corrao, G., Bergamaschi, L., Zaffaroni, M., Sarra Fiore, M., Bufi, G., Leonardi, M. C., ... & Jereczek-Fossa, B. A. (2021). COVID-19 impact in radiotherapy practice in an oncology hub: a screenshot from Lombardy, Italy. *Tumori Journal*, *107*(6), 498-503.	Excluded, not related to treatment of PCa	
GS4	Pagliarulo, V., Alba, S., Gallone, M. F., Zingarelli, M., Lorusso, A., Minafra, P., ... & Ditonno, P. (2021). Athermal versus ultrasonic nerve-sparing laparoscopic radical prostatectomy: A comparison of functional and oncological outcomes. *World Journal of Urology*, *39*, 1453-1462.	Included	Radical prostatectomy
GS5	Sulsenti, R. (2023). *Intracellular osteopontin controls the release of TNFα by mast cells to restrain neuroendocrine prostate cancer* (Doctoral dissertation, The Open University).	Excluded, not related to treatment of PCa	
GS6	Ammer, K. (2019). Medical Thermology 2018-a computer-assisted literature survey. *Thermology International*, *29*(1).	Excluded, not related to treatment of PCa	

Summary

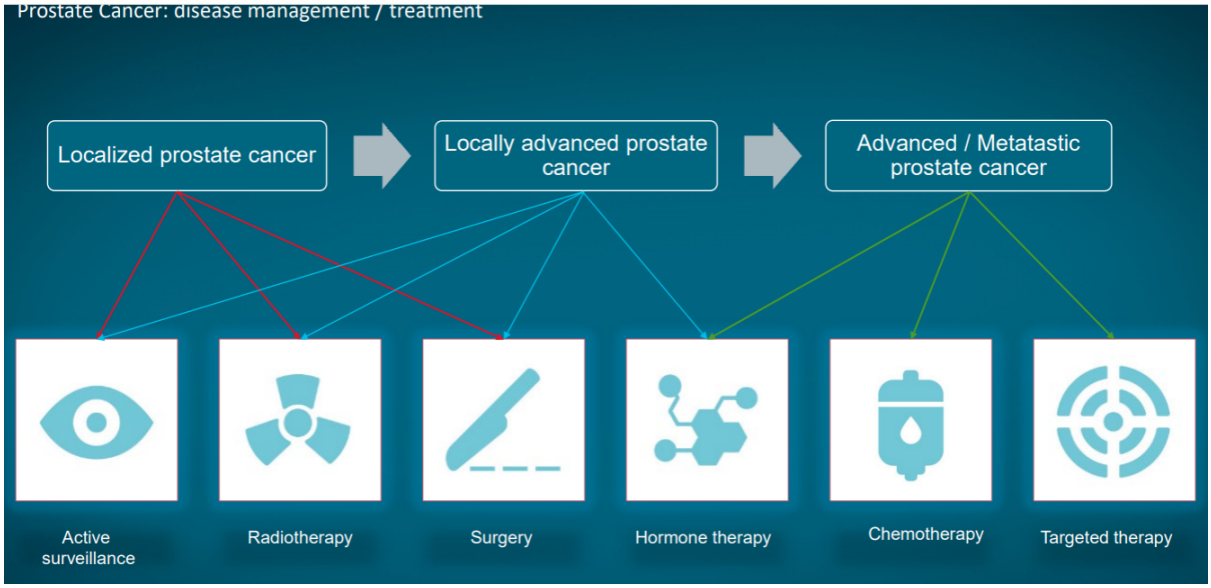
Figure 20: Literature Search Results



Thirteen articles described treatment options, of which 11 describe surgery/radical prostatectomy, 9 describe radiotherapy (including external beam radiotherapy and brachytherapy), Active Surveillance

is described in 6 articles, combinations of these therapies with hormonal therapies or chemotherapy are described in 6 articles, and watchful waiting or cryotherapy are each mentioned once.

Comparison with Elekta's care path 2023:



Conclusion

The primary treatments utilized for prostate cancer patients, besides brachytherapy, include EBRT, Active Surveillance, surgery/radical prostatectomy, and the combination of brachytherapy and EBRT. These can be combined with hormonal therapy or chemotherapy, especially in more advanced disease.

Appendix C Survey Design

We opted for designing an online survey for systematic collection of data from healthcare professionals, offering a comprehensive view of treatment practices, decision-making factors, and patient outcomes in real-world settings.

Objective of the Survey

The objective of this survey is to systematically gather essential information from Urologists and Radiation Oncologists actively practicing in Italy and Spain. The goal is to understand the factors influencing the decision-making process for selecting a treatment for prostate cancer patients and to assign weights to these various decision factors.

The collected information is pivotal for constructing a comprehensive model, designed to efficiently allocate patients with prostate cancer among different treatment modalities. Insights derived from survey responses will contribute to the development of a robust and effective model for the allocation of prostate cancer patients to suitable treatment approaches.

Scope

The information collected through the survey will be regarding the treatment decision taken for newly identified prostate cancer patients of all identified risk categories in Europe, preferably in Italy and Spain. The focus will be on the regions Rome in Italy and Catalonia in Spain since we have selected these to provide input into the model. We aim to collect information from Urologists and Radiation Oncologists from these areas since these are the main professions deciding on prostate cancer treatments. If we cannot identify sufficient experts in Italy and Spain, we will expand the scope to other countries in Europe.

Target Groups

The target groups include Urologists and Radiation Oncologists. We have approached sales representatives of Elekta in the respective regions to obtain contact details for radiation oncologists. Specifically, we have requested names and email addresses of individuals whom they identify as decision-makers in prostate cancer treatment and who are likely to be willing to participate in the survey.

Sampling

To describe the scope of the survey and to ensure comparable results we have set inclusion and exclusion criteria as follows:

Inclusion Criteria

The survey targets certified urologists and radiation oncologists actively practicing in medical facilities within Spain and Italy (Europe in case we do not obtain sufficient contact details from these countries). All participating clinical experts are required to specialize in prostate cancer treatment, focusing on brachytherapy, EBRT, AS, or surgery, or demonstrate significant knowledge of these treatment modalities. The selection process ensures representation from specific regions: Catalonia in Spain and Rome in Italy.

Exclusion Criteria

Medical experts not actively involved in the treatment decision of prostate cancer patients are excluded from participation.

Sample Size

The survey will be distributed to 10 Radiation Oncologists and 10 Urologists. Names and contact details of radiation oncologists are obtained from local Elekta representatives. In case not sufficient contact details are retrieved from these representative, additional contact data will be extracted from Elekta's overview of Key Opinion Leaders in Europe. Urologists from the same centres will be identified using Google searches and contacted via their contact details in scientific publications. Anticipating a response rate of 50% for Elekta's customers (Rad. Oncs) and 25% for Urologists, we expected five Radiation Oncologists and two or three Urologists to respond. Subsequently, decisions regarding input data for the model will be made based on the received feedback.

Survey Design

To collect data in a structured and low-cost way and obtain responses quickly, which is a requirement given the relatively short time frame available, we decided to use an online survey tool with a limited number of questions.

Self-completed Quantitative Questionnaire

We will employ a self-completed quantitative survey to gather data from radiation oncologists and urologists in Spain and Italy for our patient allocation model. This method, chosen over a literature search due to limited available data, aims to quantify treatment modality factors with the expertise of clinical professionals familiar with the complexities and outcomes of various prostate cancer treatments. The self-completed survey offers a convenient means of accessing medical professionals, who are often challenging to reach for face-to-face interviews. This approach enhances accessibility, ensuring a diverse range of expertise contributed to the research. Additionally, it facilitates reaching a broad audience of clinical experts, including those in remote locations, without incurring high costs. The survey, that will be conducted in English via Qualtrics, maintains respondent anonymity, encourages open and honest responses, and allowes for straightforward data collection and efficient quantitative analysis.

Survey Implementation

Invitations to participate, along with the survey link and a brief explanation of the study's purpose, will be sent via email to radiation oncologists and urologists in Spain and Italy. The survey will be designed using Qualtrics, a verified survey tool prioritizing the security of personal data. Conducted in English, the self-completed survey involves a structured list of questions, allowing respondents to maintain anonymity and providing straightforward data for efficient collection and quantitative analysis.

Survey Validation (pilot testing)

We will sent out the survey to 20 clinical experts. The clinicians we will send the survey to are decision-makers in the hospitals with at least 5 years of treatment experience. To validate the survey, we will first do a limited release to a) two independent validators. This allowes us to improve questions if the responses indicate that we would not be able to meet our objective with the current survey.

Survey Structure

The following figure shows how we structure our survey.

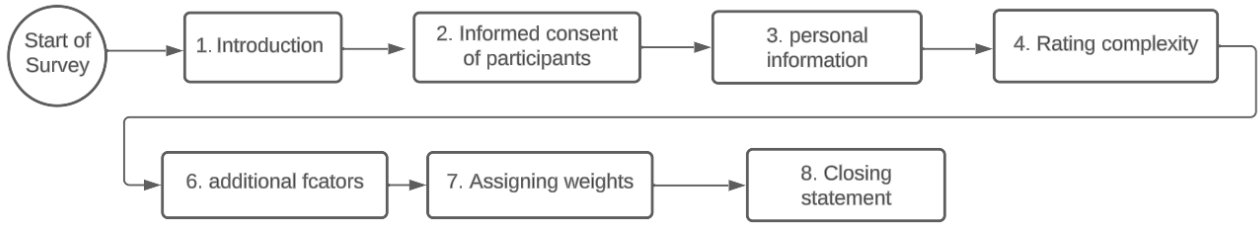


Figure 22 Survey Structure

The starting point of the survey is the introduction, where participants are provided with a brief background of our research and the survey's aim. Subsequently, respondents are asked about their profession, years of experience, the number of patients they manage monthly, and the guidelines they follow in treatment selection. This information confirms participants eligibility for the survey.

Next, the survey proceeds to have participants rate the complexity of different treatment modalities for the four identified risk groups of prostate cancer patients. To validate the complexity score, participants are first asked to rank the treatment modalities from least to highest complexity. Following this, they provide a score between 0 and 5 for each treatment modality based on complexity, with 0 indicating no complexity and 5 representing the highest complexity.

Afterward, respondents are asked to assign weights to the different decision factors influencing treatment selection for prostate cancer patients in each risk group. A sliding scale from 0 to 10 is provided for each decision factor within each risk group, where 0 to 10 represents 0% to 100%. The weight is assigned as a percentage, and normalization is done using [12]min-max normalization for consistency across factors.

To quantify the different factors, respondents are presented with a sliding scale in the survey, allowing them to choose a score for each factor of each treatment modality, including the option to choose decimal numbers for practical quantification.

Lastly, an open-ended question invites participants to add any additional factors they believe play a role in treatment selection based on their expertise. This helps validate the factors included in our model. Following this, respondents can provide any concluding remarks they may have. The survey concludes with a closing statement, expressing acknowledgment for the respondent's valuable insights and time, highlighting their contribution to our research.

Design Considerations

As respondents are not compensated financially or otherwise, the questionnaire is designed to take a maximum of five minutes to complete.

Implementation

Qualtrics will be used to design the survey, distribute it, and collect data. The data will be exported to Excel for analysis. After designing the questionnaire, it will be tested and validated by colleagues and two Key Opinion Leaders with whom we collaborate. Selected participants will be approached by E-mail, personally inviting them to participate in the survey. After one week, a reminder will be sent to those who have not yet participated.

Data Analysis

Based on the response, we will gain insight into the various factors that play a role in the decision-making process for prostate cancer treatment. Factors may be considered for addition to or deletion

[12] Normalized Value = (Actual Value – Min Value) / (Max Value – Min Value)

from the model based on the perceived relevance to the responses. We will calculate the mean of the complexity scores and weights for each factor within each risk group based on the answers gathered from the radiation oncologists and urologists to add as input to our model. Mean will be calculated for the opinions of Radiation Oncologists and Urologists. We anticipate that decisions are made in multidisciplinary teams, especially for higher-risk categories. Therefore, we will pool the data from urologists and Radiation Oncologists for these risk categories.

Response Rate and non-respondent characteristics

By keeping the survey short and approaching participants individually with personalized email invitations, along with a reminder sent after one week to non-responders, we expect to achieve a high response rate. A high response rate is crucial to minimize sampling bias and enhance the validity of the outcomes.

Appendix D Survey Questions

INTRODUCTION

Dear Participants,

We've created this survey to gain insights into how decisions about treating prostate cancer are made. We value your expertise in determining the factors that influence the allocation of different severity classes of prostate cancer patients to various treatment options within the European healthcare system. The survey will only take about 5-10 minutes of your time.

**The information collected in this survey will be anonymous. Please do not provide any personally identifiable information within the free text boxes from which it would be possible to identify you. If you do share personal data in free text boxes, it will be processed and protected in accordance with our privacy notice. For further information, please go to www.elekta.com/privacy. For any other questions relating to the mail and data privacy feel free to contact us at privacy@elekta.com. **

Please indicate your specialized field:

- Radiation Oncology
- Medical Oncologist
- Urology
- Other - please name your specialization bellow:

How many years of experience do you have treating prostate cancer?

- less than 5 years
- 5 to 10 years
- 10 to 15 years
- more than 15 years

On average, how many patients diagnosed with prostate cancer do you manage per month?

Briefly describe the process by which the patients' treatment is decided. Do you meet with doctors from other specializations? Which specializations are involved?

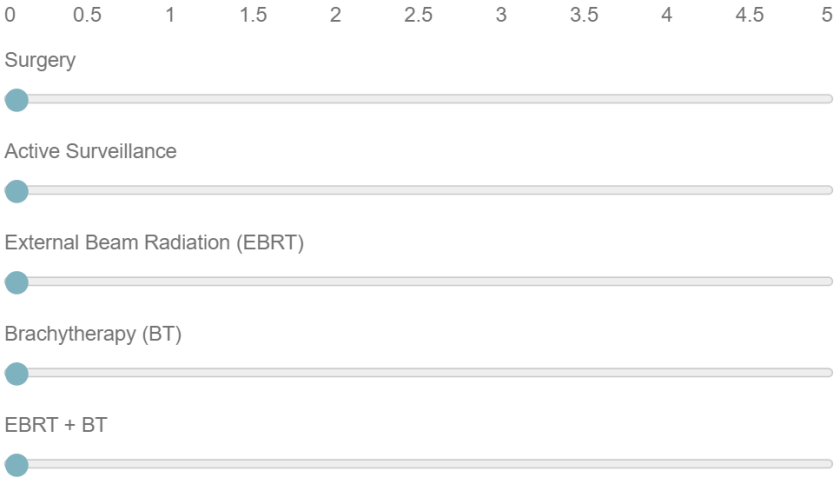
COMPLEXITY

Please rank how complex the following treatments are, with '1' being the most complex and '4' being the least complex (drag and drop).
**Note that for complexity we mean: procedure difficulty, resources needed, patient specific factor difficulty and number of fractions/sessions.*

- Surgery
- Active Surveillance
- External Beam Radiation (EBRT)
- Brachytherapy (BT)
- EBRT + BT

Do you follow any guidelines in specific for the treatment selection? Which one? (for example the EUA)

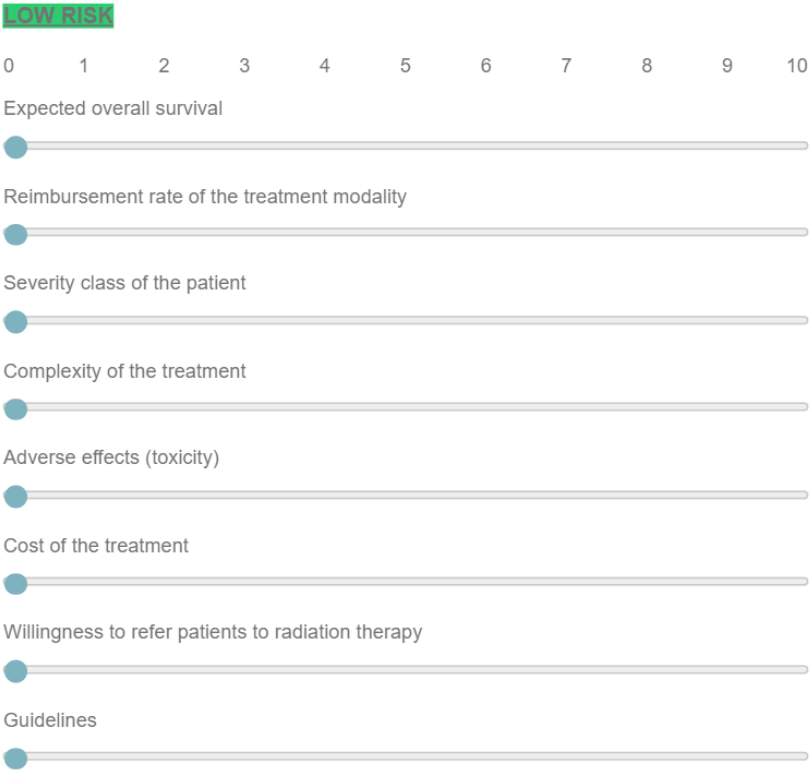
On a scale of 0 to 5, with 0 being the least complex and 5 being the most complex, please rate the perceived relative complexity of the following treatments of prostate cancer patients.
**Note that for complexity we mean: procedure difficulty, resources needed, patient specific factor difficulty and number of fractions/sessions.*



Factors Influencing Patient Allocation to Different Treatments

Allocate the relative importance in your decision-making process when allocating patients to a treatment modality, being 0 least important and 10 most important.

Please do this for each of the following 4 risk levels of prostate cancer:



INTERMEDIATE-LOW RISK

0 1 2 3 4 5 6 7 8 9 10

Expected overall survival

Reimbursement rate of the treatment modality

Severity class of the patient

Complexity of the treatment

Adverse effects (toxicity)

Cost of the treatment

Willingness to refer patients to radiologiation therapy

Guidelines

INTERMEDIATE-HIGH RISK

0 1 2 3 4 5 6 7 8 9 10

Expected overall survival

Reimbursement rate of the treatment modality

Severity class of the patient

Complexity of the treatment

Adverse effects (toxicity)

Cost of the treatment

Willingness to refer patients to radiologiation therapy

Guidelines

HIGH RISK

0 1 2 3 4 5 6 7 8 9 10

Expected overall survival

Reimbursement rate of the treatment modality

Severity class of the patient

Complexity of the treatment

Adverse effects (toxicity)

Cost of the treatment

Willingness to refer patients to radiation therapy

Guidelines

Are there other factors that affect this decision (please add level of importance)

Final remarks

Do you have any other remarks on this subject?

Appendix E Interview Questions

To investigate the reimbursement situation for prostate cancer treatment modalities in Spain and Italy, we queried Elekta representatives by sending them our questions. They collected this information from various sources, including clinical experts. The questions we asked are as follows:

1. How are prostate cancer treatment modalities (brachytherapy, EBRT, Active Surveillance, Surgery, and brachytherapy plus EBRT) reimbursed in Italy/Spain? (What is the procedure of getting reimbursement, how are they granted etc.)

2. What are the current reimbursement rates of brachytherapy, EBRT, Active Surveillance, Surgery, and brachytherapy plus EBRT?

3. Is the reimbursement for brachytherapy sufficient? If not and the reimbursement for brachytherapy is low, then is this the reason for low utilization of brachytherapy?

4. What is the current distribution of prostate cancer patients among the treatment modalities per risk group (Low-risk, low intermediate-risk, high intermediate-risk, and high-risk)? For example, for low risk how many patients are allocated to brachytherapy, EBRT, Active Surveillance and Surgery. This informs us about how prostate cancer patients of each risk group (low-risk, low intermediate-, high intermediate- and high-risk) are currently being treated in Italy/Spain.

Appendix F Guidelines for Treatment

EAU guidelines for 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.*

EAU guidelines for 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.*

EAU guidelines for 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 G Reimbursement

Reimbursement Rate Surgery

Please find in the following links the document with reimbursement values for procedures in the Catalonian hospitals (DOGC):

-DOGC 2013 according to the complexity of the hospital: 1286874.pdf (gencat.cat)
306 Prostatectomy with complications or comorbidity (6.948,53 € 5.850,78 € 4.140,65 €)
307 Prostatectomy without complications or comorbidity (3.659,16 € 3.081,07 € 2.180,50 €)
336 Transurethral prostatectomy with complications or comorbidity (4.414,77 € 3.717,31 € 2.630,77 €)
337 Transurethral prostatectomy without complications or comorbidity (2.848,76 € 2.398,70 € 1.697,58 €)

-DOGC 2020: ORDRE SLT/63/2020, de 8 de març, per la qual s'aproven els preus públi (gencat.cat)
GRD 482.01 Transurethral prostatectomy, minor severity 4.511,00 €
GRD 482.02 Transurethral prostatectomy, moderate severity 5.929,00 €
GRD 482.03 Transurethral prostatectomy, high severity 10.695,00€
GRD 482.04 Transurethral prostatectomy, extreme severity 21.346,00€

	€ 6.948,53
	€ 3.659,16
	€ 4.414,77
	€ 2.848,76
	€ 4.511,00
	€ 5.929,00
	€ 10.695,00
	€ 21.346,00
Average surgery	€ 7.544,03

Reimbursement Rates EBRT and BT Spain

At follow-up level, we classify treatment according to the criteria provided by the Radiotherapy Oncology Service:

External radiotherapy:
Complexity 1, 2, 3 and 4 (4 levels)
Radiosurgery Brain tumors single dose and fractional dose (2 types)

brachytherapy
Standard, complexities 1,2,3 and 4 (4 levels)
Permanent prostate
ophthalmic

In terms of payment, our insurer (CatSalut , CatSalut is the Health Care Regional for Catalonia one of the 17 provinces) recognizes fewer levels:

External Beam Radiotherapy (The above levels 3 and 4 are converted in one unique level (level 3)
Radioteràpia complexitat 1 (Tractament) 998,42
Radioteràpia complexitat 2 (Tractament) 2.817,11
Radioteràpia complexitat 3 (Tractament) 4.264,89
Radiocirurgia TC DU (Tractament) 11.367,90
Radiocirurgia TC DF (Tractament) 12.504,70

Braquiteràpia
Braquiteràpia (Sessió, means..... fraction) 923,74
Braquiteràpia oftàlmica (Tractament) 12.572,79
Braquiteràpia prostàtica (Tractament) 18.091,53

I hope this information could be interesting for the project analysis

Appendix H Transition Probabilities

Table 28 Transition Probabilities

$\boldsymbol{cancer + no\ toxicity \rightarrow cancer + toxicity = P(\text{treatment failure}) * P(\text{toxicity})}$
$\boldsymbol{cancer + no\ toxicity \rightarrow cancer + no\ toxicity = P(\text{treatment failure}) - P(\text{cancer + no toxicity} \rightarrow \text{cancer + toxicity})}$
$\boldsymbol{cancer + no\ toxicity \rightarrow healthy + no\ toxicity = 1 - P(\text{treatment failure}) - P(^{13}\text{mortality})}$
$\boldsymbol{cancer + no\ toxicity \rightarrow death = P(\text{mortality})}$
$\boldsymbol{cancer + toxicity \rightarrow cancer + no\ toxicity = \big(P(\text{treatment failure}) * P(\text{toxicity})\big) + (P(\text{treatment failure}) * P(\text{toxicity after 1 year}))}$
$\boldsymbol{cancer + toxicity \rightarrow cancer + toxicity = P(\text{treatment failure}) - P(\text{cancer + toxicity} \rightarrow \text{cancer + no toxicity})}$
$\boldsymbol{cancer + toxicity \rightarrow healthy + toxicity = \big(1 - P(\text{treatment failure}) - p(\text{mortality})\big) * P(\text{toxicity after 1 year})}$
$\boldsymbol{cancer + toxicity \rightarrow healthy + no\ toxicity = \big(1 - P(\text{treatment failure}) - p(\text{mortality})\big) * (1 - P(\text{toxicity after 1 year}))}$
$\boldsymbol{cancer + toxicity \rightarrow death = P(\text{mortality})}$
$\boldsymbol{healthy + toxicity \rightarrow cancer + toxicity = P(\text{recurrence}) * P(\text{toxicity})}$
$\boldsymbol{healthy + toxicity \rightarrow cancer + no\ toxicity = P(\text{recurrence}) - P(\text{healthy + toxicity} \rightarrow \text{cancer + toxicity})}$
$\boldsymbol{healthy + toxicity \rightarrow healthy + toxicity = 1 - p(\text{recurrence})}$
$\boldsymbol{healthy + no\ toxicity \rightarrow cancer + toxicity = \big(P(\text{recurrence}) * P(\text{toxicity})\big) * \big(P(\text{recurrence}) * P(\text{toxicity after 1 year})\big)}$
$\boldsymbol{healthy + no\ toxicity \rightarrow cancer + no\ toxicity = P(\text{recurrence}) - P(\text{healthy + no toxicity} \rightarrow \text{cancer + toxicity})}$
$\boldsymbol{healthy + no\ toxicity \rightarrow healthy + no\ toxicity = 1 - P(\text{recurrence})}$

[13] 1-survival

Appendix I Overview Input Values

Table 29 Treatment failure, Recurrence and Overall survival Input Values

	Treatment failure	Reference	Recurrence	Reference	Overall survival	Reference
Low-risk:						
BT	0.3%	[27]	1.3%	[34]	95%	[27]
EBRT	7.2%	[28]	1.6%	[36]	93.8%	[28]
Surgery	8%	[29]	0.89%	[40]	98%	[29]
BT+EBRT	0.8%	[28]	0%	[38]	96.6%	[28]
AS	15% will have two negative biopsies so 100-15-8.4-0.6 = 76%	[30]	8.4% (need treatment)	[43]	99.4%	[43]
Low intermediate-risk:						
BT	2.8%	[27]	2.29% 4.8%	[33] [34]	92.8%	[27]
EBRT	21%	[28]	1.4%	[36]	96.3%	[28]
Surgery	21%	[29]	57.1%	[37]	94%3	[29]
BT+EBRT	3.5%	[28]	21%	[38]	95.8%	[28]
AS	15% will have two negative biopsies so 100-15-10.9-2 = 72.1%	[30]	10.9% (need treatment)	[43]	98%	[44]
High intermediate-risk:						
BT	10.2%	[27]	10%	[34]	88%	[45]
EBRT	21.1%	[28]	25%	[35]	75.2%	[28]
Surgery	39%	[29]	57.1%	[37]	86%3	[29]
BT+EBRT	11.8%	[28]	33%	[38]	87.6%	[28]
AS	-	-	-		40%	Elekta expert
High-risk:						
BT	17%	[27]	22.86%	[31]	86.5% 80	[45]
EBRT	7.9%	[41]	35%	[35]	82%	[46]
Surgery	50%	[29]	65.3%	[39]	75%	[29]
BT+EBRT	26.1%	[42]	65%	[38]	88.7%	[46]
AS	-	-	-		5%	Elekta Expert

Table 30 Cost of Treatment Input Values

Treatment Modality	Cost of treatment
BT	€4.500
EBRT	€6.500
AS	€3.250
Surgery	€6.544
BT+EBRT	€11.200

Table 31 Percentage of patients distributed to a particular treatment based on EAU Guideline Input Values

Risk group	Brachytherapy	EBRT	Active Surveillance	Surgery	EBRT + Brachytherapy
Low	12%	13%	50%	25%	n.a.
Low intermediate	12%	33%	10%	45%	n.a.
High Intermediate	6%	20%	4%	48%	22%
High	6%	14%	4%	48%	28%

Table 32 Complexity Score of Treatment Input Values

Complexity of	Average score	Range
Surgery	3.6	n.a.
Active Surveillance	1.075	0.9 - 1.5
EBRT	2.275	1.5 - 3.5
Brachytherapy	2.5	2.4 - 3.9
EBRT + Brachytherapy	3.7	2.9 - 4.2

Table 33 Toxicity Score of Treatment Input Values

Toxicity	Score (percentage of men reporting problem with erectile dysfunction)	Reference:
Surgery	33%	[47]
Active Surveillance	10%	
EBRT	20%	
Brachytherapy	11%	
EBRT + Brachytherapy	20% (extrapolated)	

Table 34 Decision factor weight scores for Low-Risk prostate cancer

Decision factor	Average Score	Range
The severity class of the patient	6.68	4.8 – 9.3
Guidelines	8.62	5.6 - 10
Toxicity	7.76	2.5 - 10
Costs of the treatment	3.64	1 – 7.7
Reimbursement	2.08	0 - 5
Complexity of the treatment	4.56	2.3 – 7.2

Table 35 Decision factor weight scores for Low Intermediate-risk prostate cancer

Decision factor	Average Score	Range
The severity class of the patient	6.46	4.8 - 9
Guidelines	8.2	4.6 - 10
Toxicity	7.18	2 - 10
Costs of the treatment	3.94	1 – 7.9
Reimbursement	3.04	0 – 6.7
Complexity of the treatment	4.68	3 – 7.3

Table 36 Decision factor weight scores for High Intermediate-risk prostate cancer

Decision factor	Average Score	Range
The severity class of the patient	6.16	3.7 - 10
Guidelines	8.7	5.2 - 10
Toxicity	6.62	2 - 10
Costs of the treatment	4	1 – 7.6
Reimbursement	0 – 6.5	2.08
Complexity of the treatment	4.5	1.9 – 8.5

Table 37 Decision factor weight scores for High-Risk prostate cancer

Decision factor	Average Score	Range
The severity class of the patient	5.48	2.3 - 10
Guidelines	9.1	6.7 - 10
Toxicity	6.54	2 - 10
Costs of the treatment	3.72	0.9 – 7.7
Reimbursement	2.56	0 – 6.6
Complexity of the treatment	4.62	2.6 – 6.9

Table 38 Reimbursement rates in Spain and Italy

Treatment modalities	Reimbursement rates Italy	Reimbursement rates Spain
Brachytherapy	€4.700	€6.000
EBRT	€7.500	€7.500
Active Surveillance	€4.250	€4.250
Surgery	€7.544	€7.544
EBRT + Brachytherapy	€12.200	€13.500

Table 39 QOL Input Values

Health state	QOL	Reference
Cancer + no toxicity	0,83	[67]
Cancer + toxicity	0,77	
Healthy + no toxicity	0,8	
Healthy + toxicity	1	
death	0	

Appendix J Markov Trace

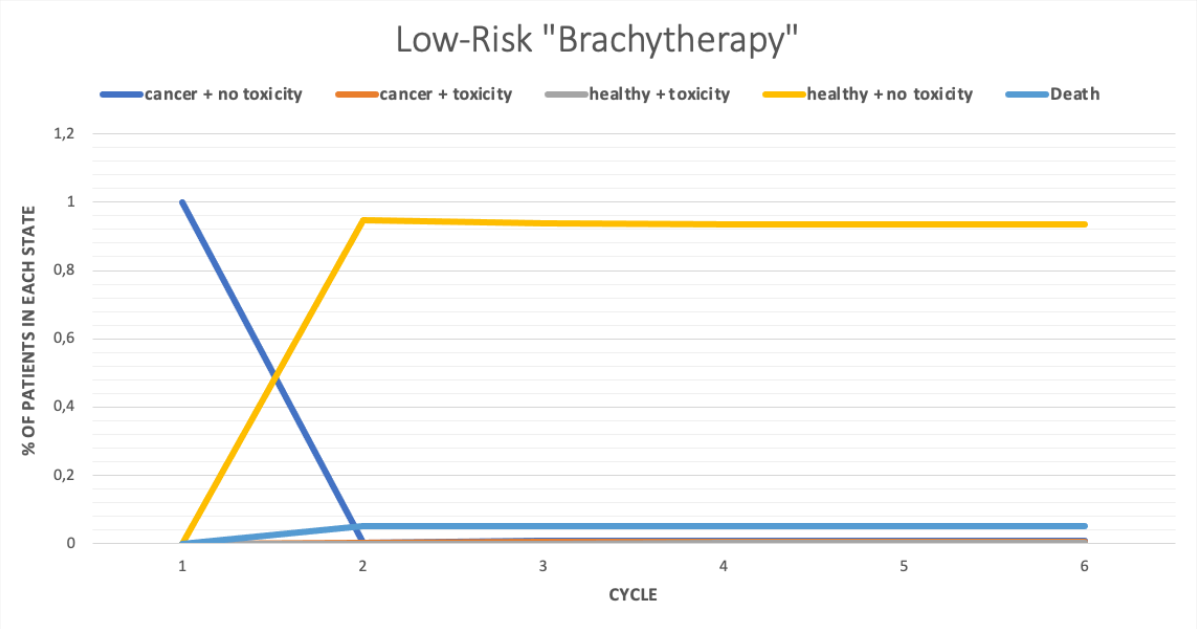


Figure 23 Markov Trace Low-Risk Brachytherapy

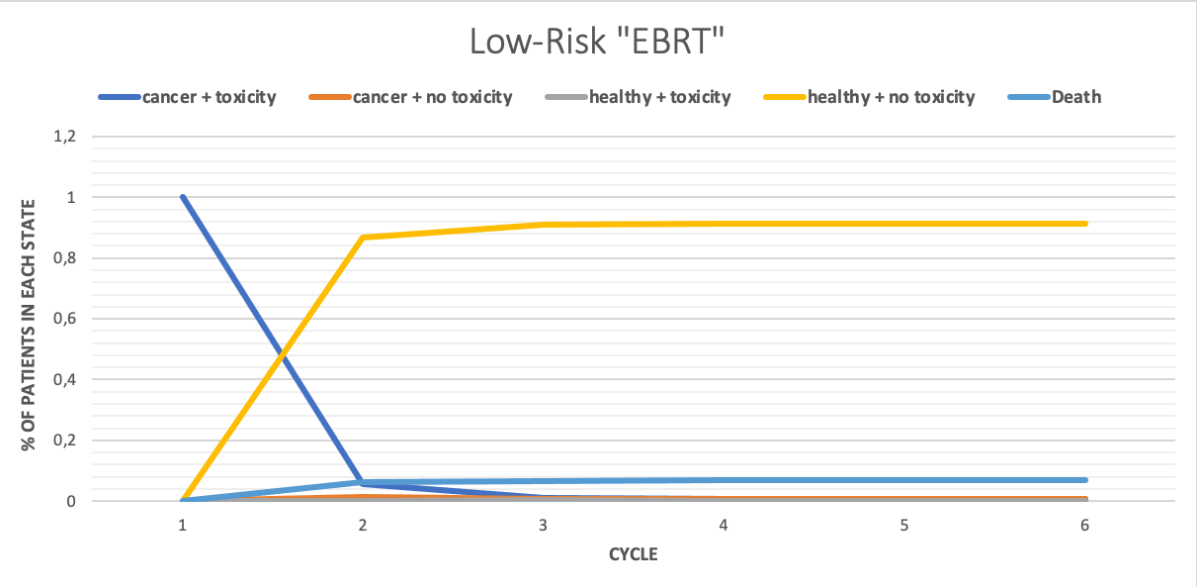


Figure 24 Markov Trace Low-Risk EBRT

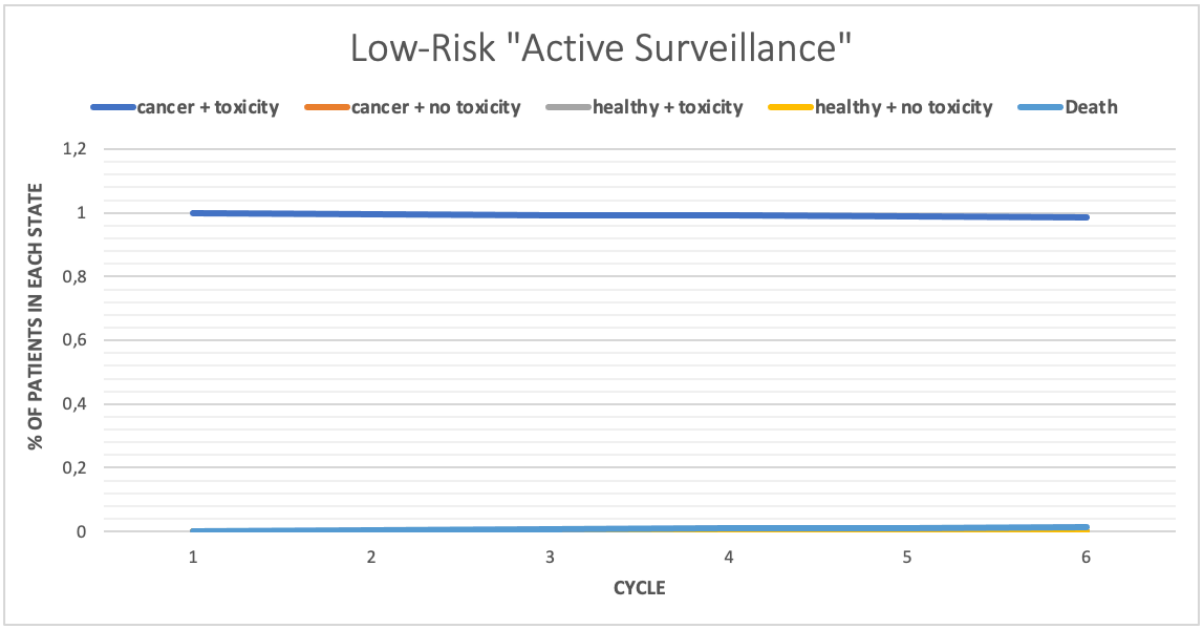


Figure 25 Markov Trace Low-Risk Active Surveillance

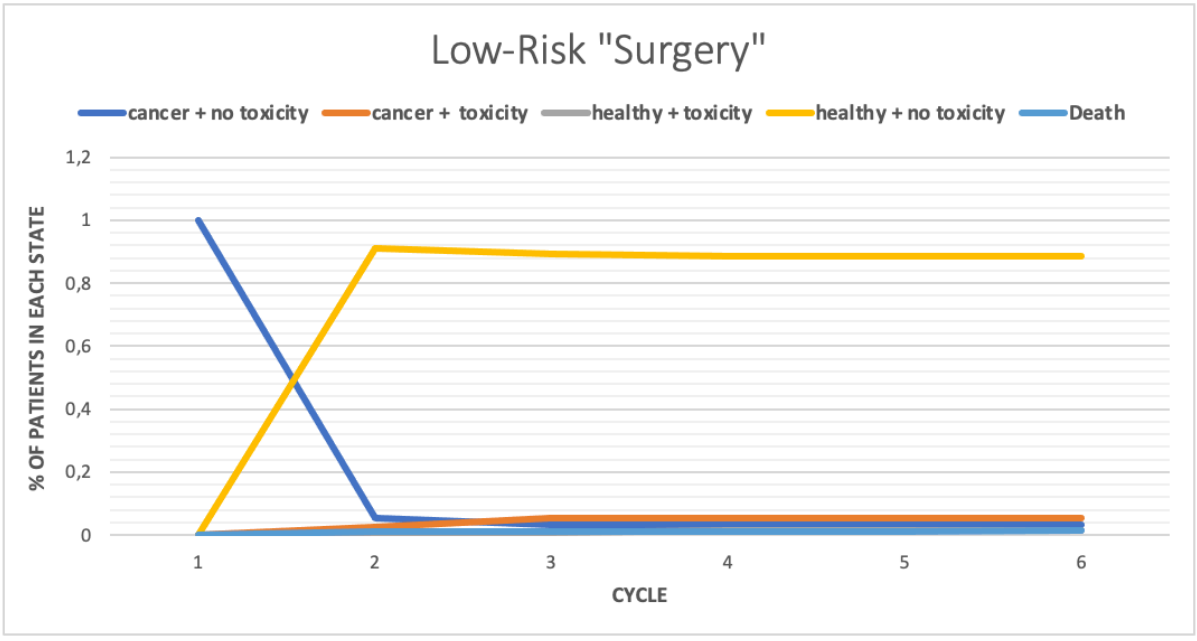


Figure 26 Markov Trace Low-Risk Surgery

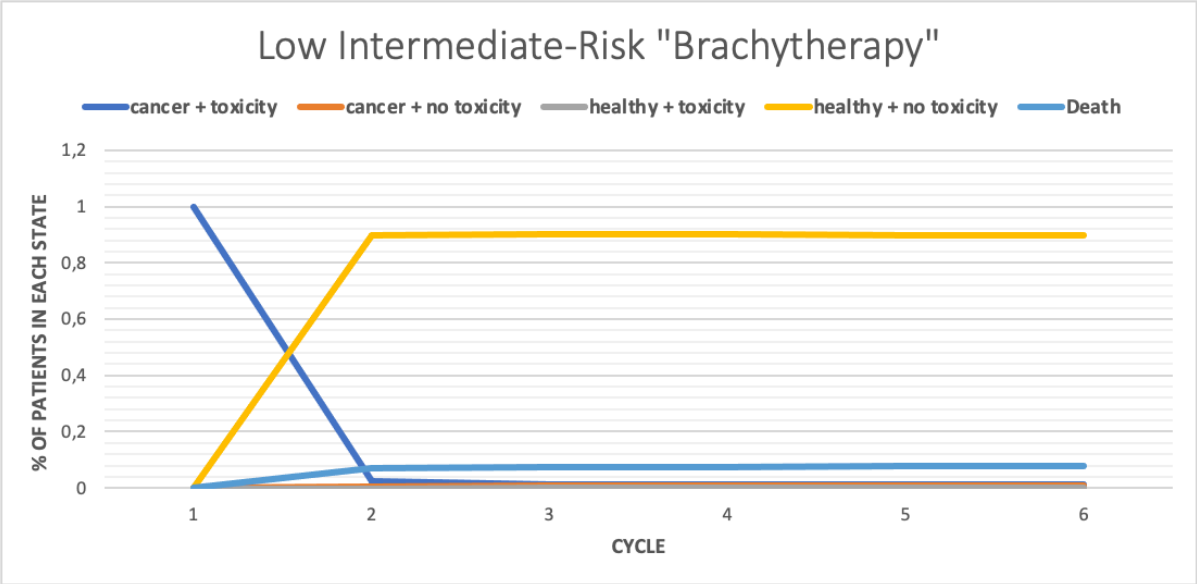


Figure 27 Markov Trace Low Intermediate-Risk Brachytherapy

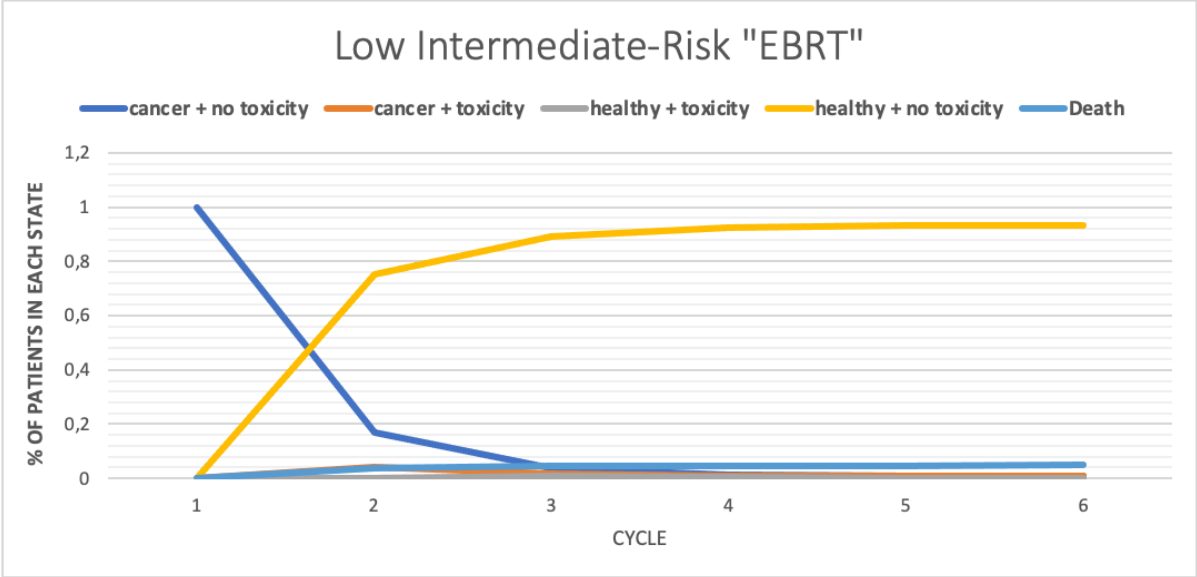


Figure 28 Markov Trace Low Intermediate-Risk EBRT

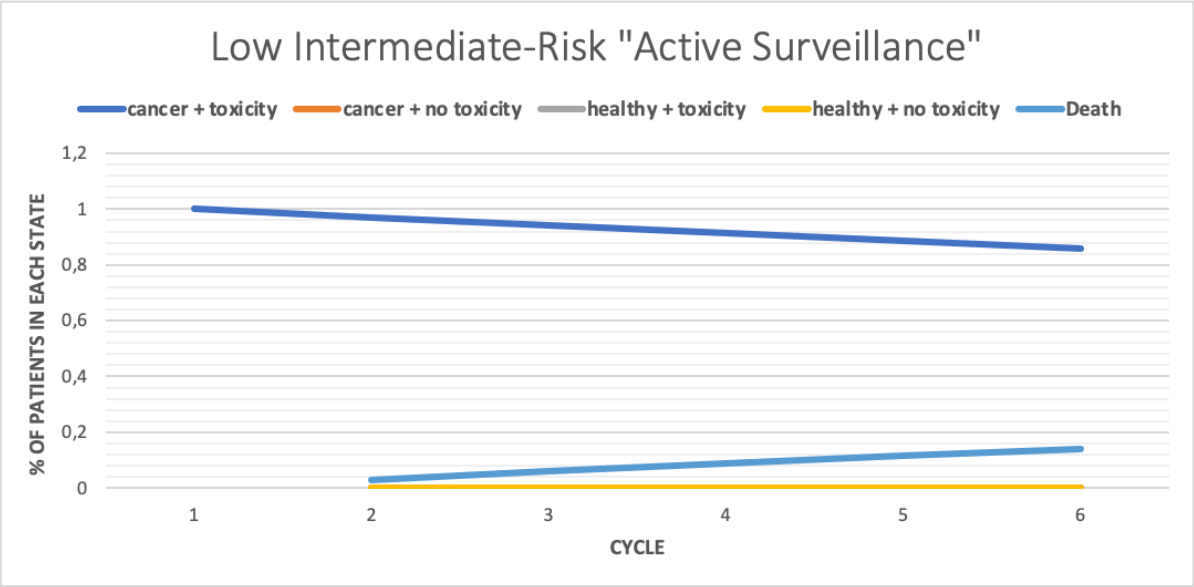


Figure 29 Markov Trace Low Intermediate-Risk Active Surveillance

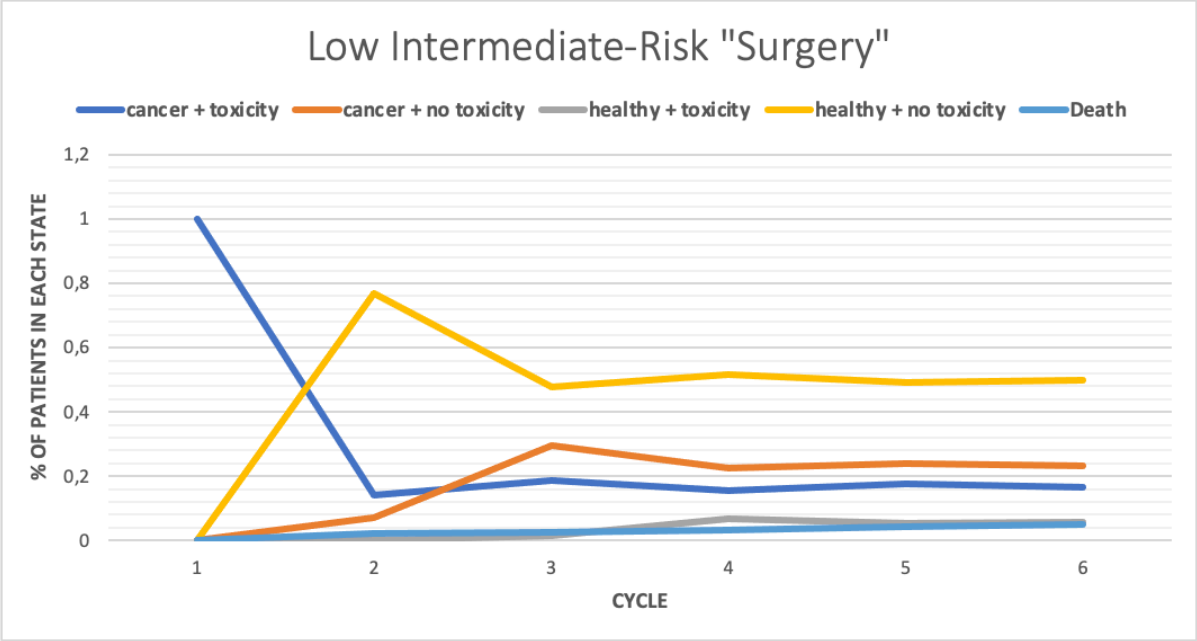


Figure 30 Markov Trace Low Intermediate-Risk Surgery

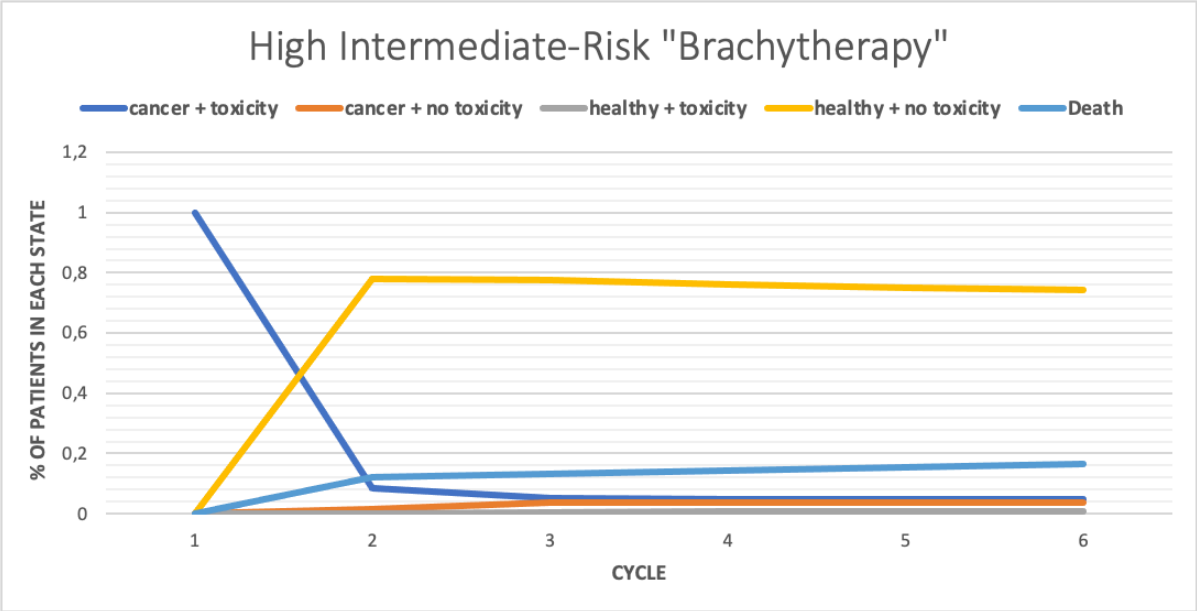


Figure 31 Markov Trace High Intermediate-Risk Brachytherapy

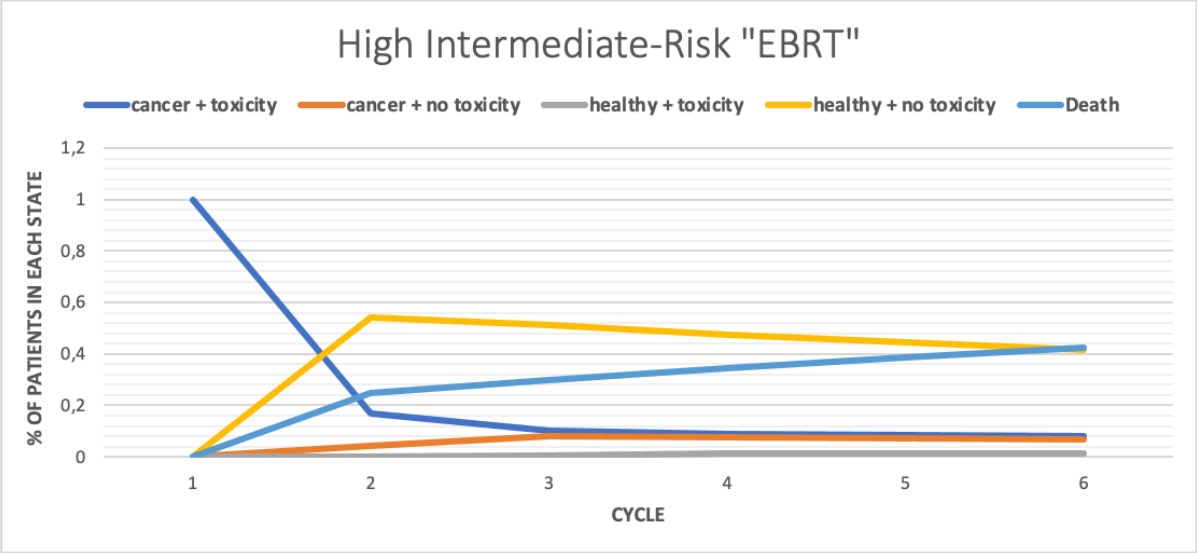


Figure 32 Markov Trace High Intermediate-Risk EBRT

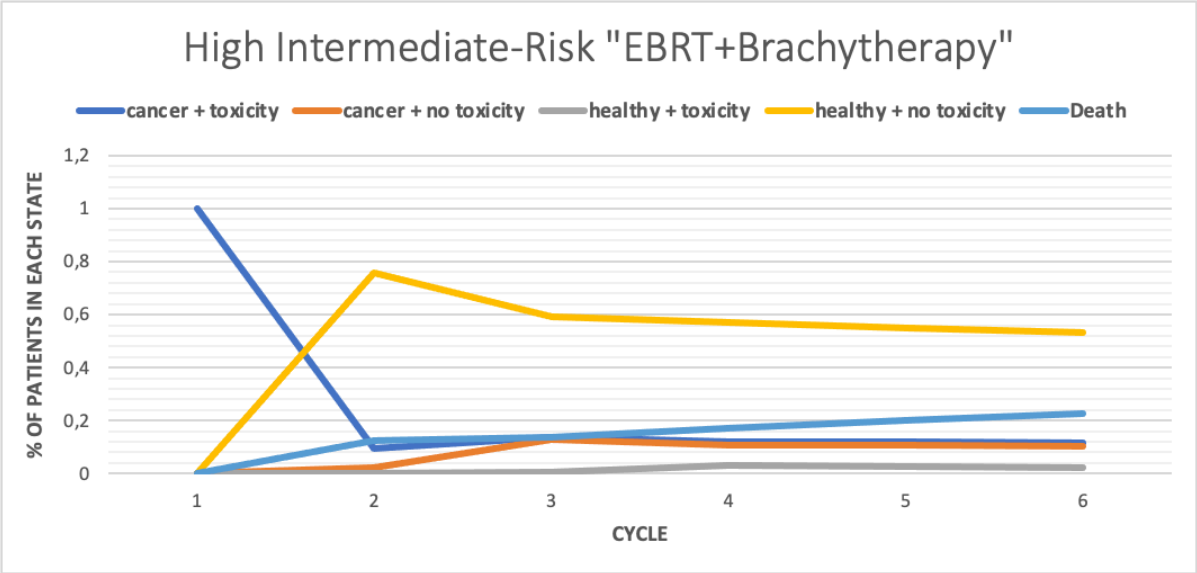


Figure 33 Markov Trace High Intermediate-Risk EBRT + Brachytherapy

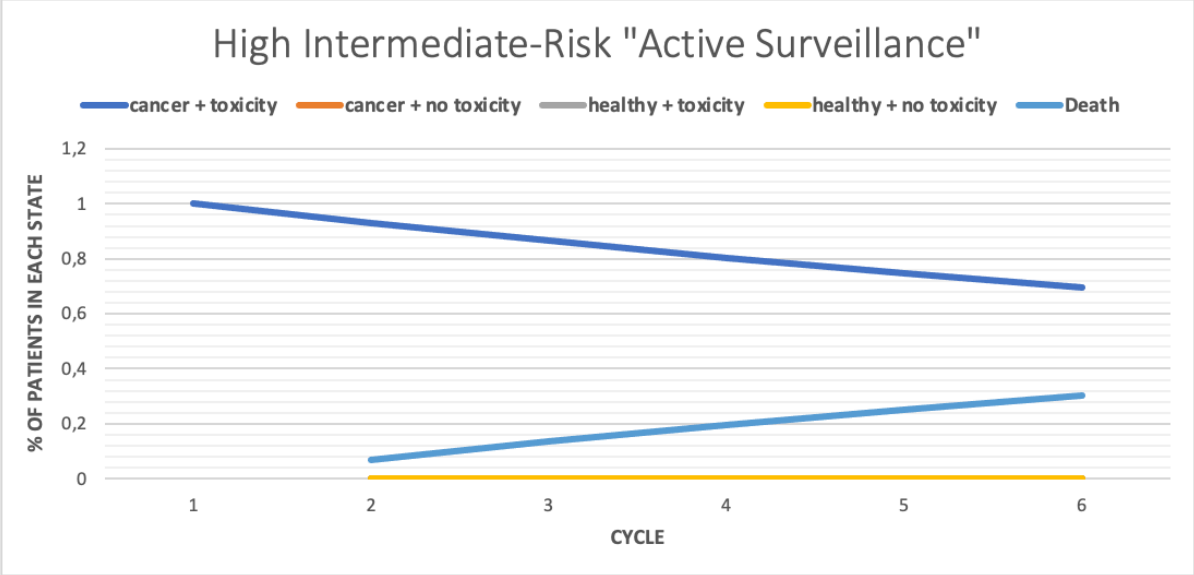


Figure 34 Markov Trace High Intermediate-Risk Active Surveillance

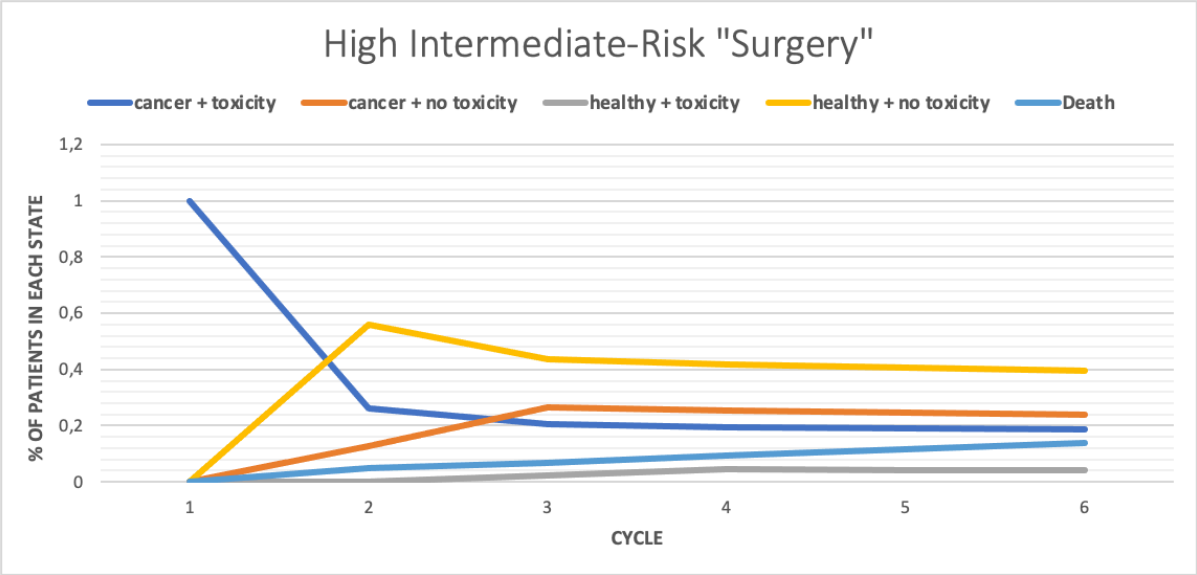


Figure 35 Markov Trace High Intermediate-Risk Surgery

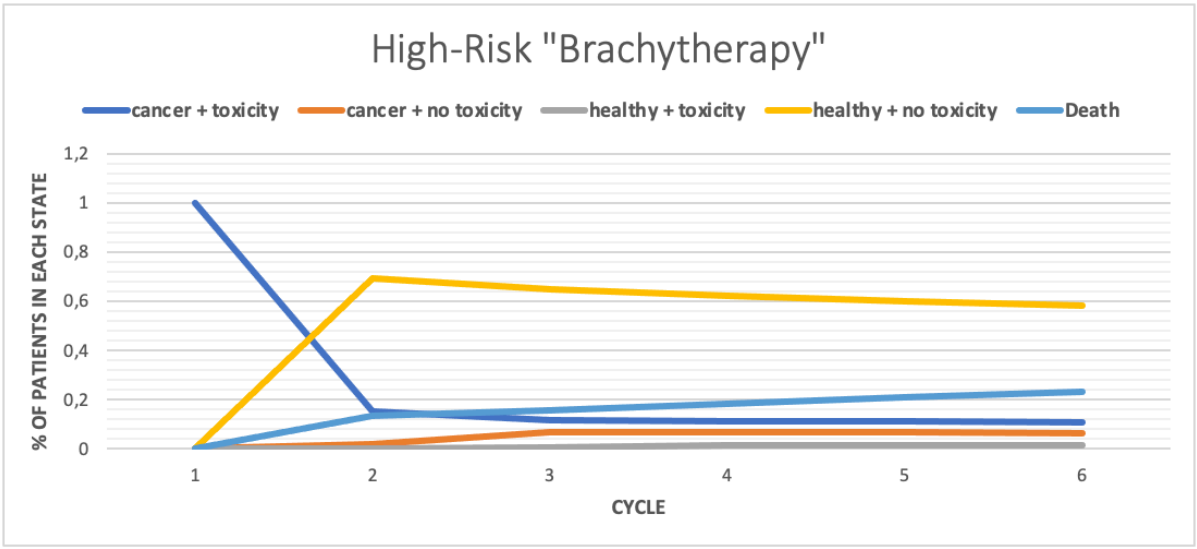


Figure 36 Markov Trace High-Risk Brachytherapy

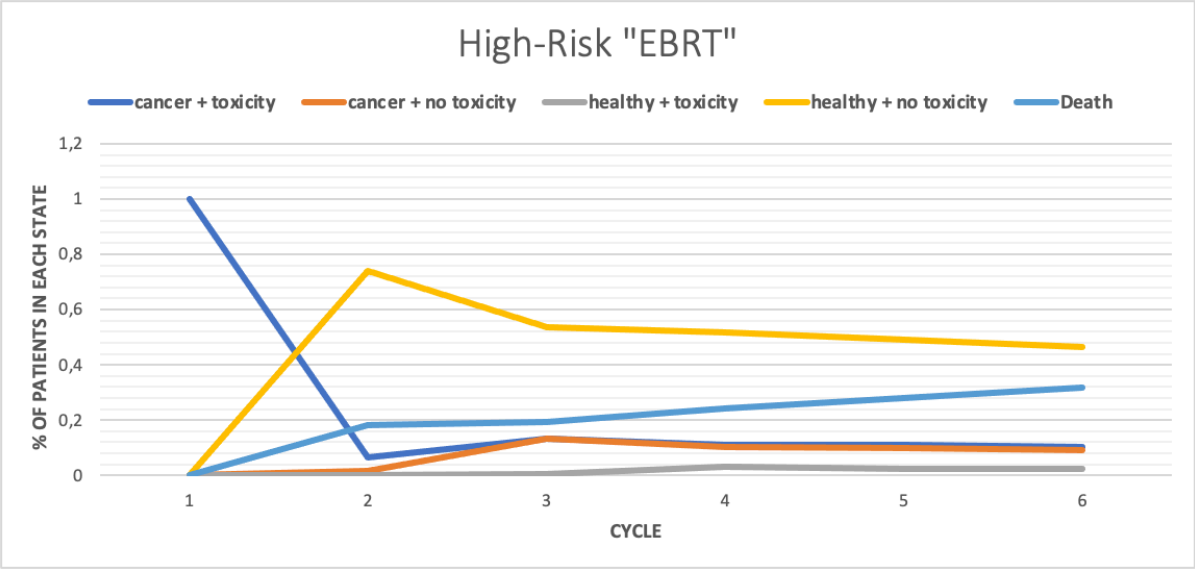


Figure 37 Markov Trace High-Risk EBRT

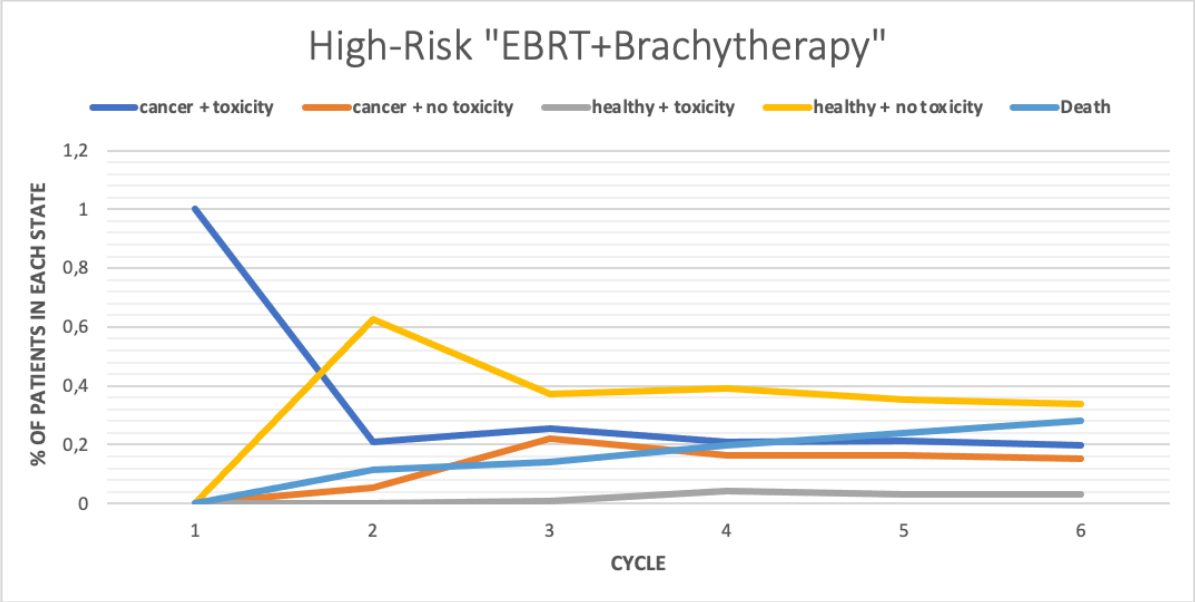


Figure 38 Markov Trace High-Risk EBRT + Brachytherapy

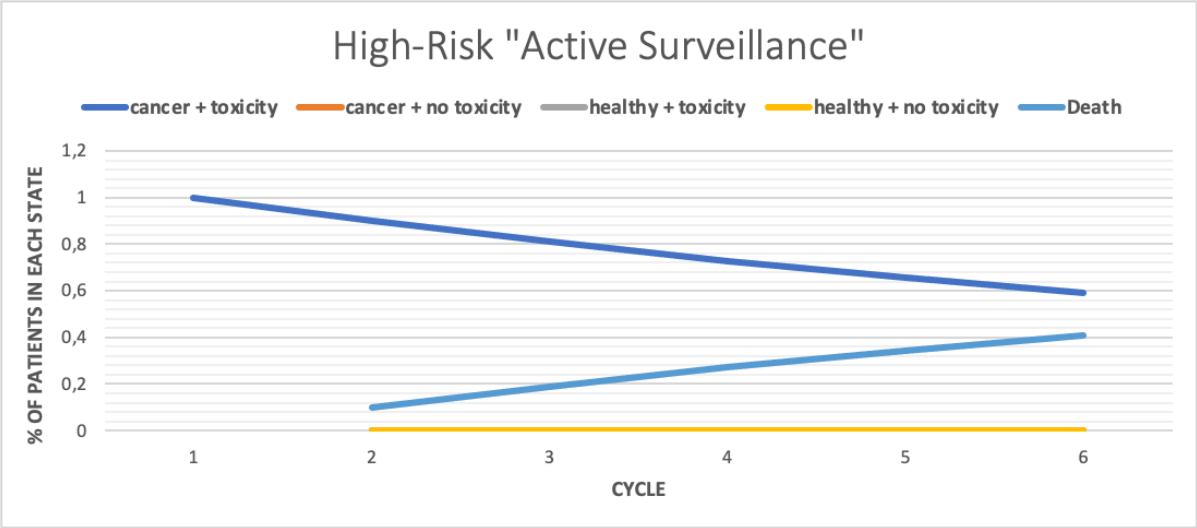


Figure 39 Markov Trace High-Risk Active Surveillance

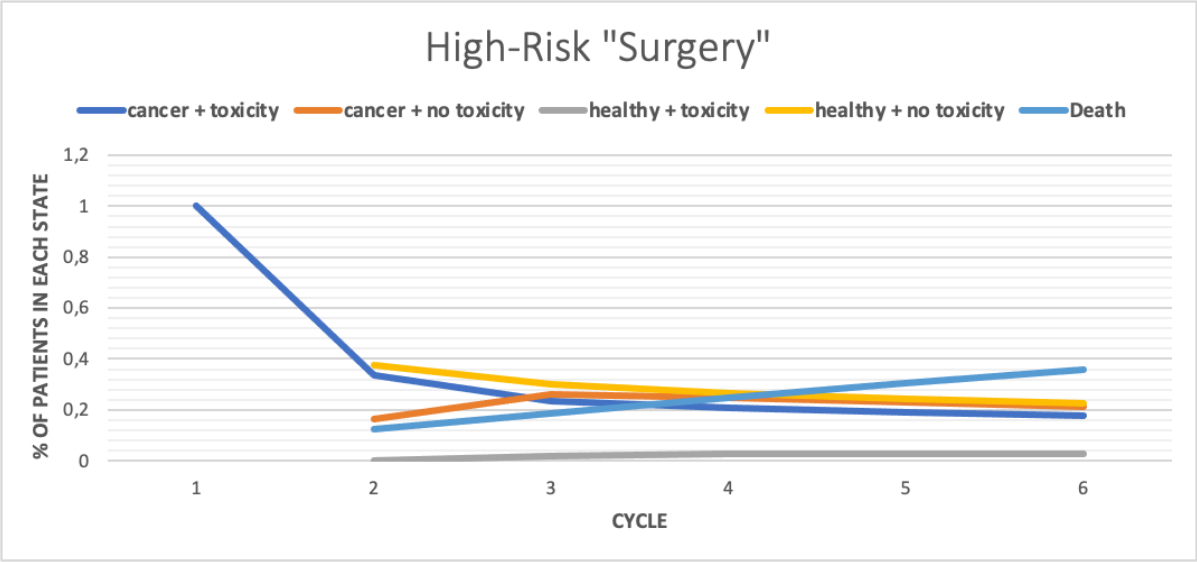


Figure 40 Markov Trace High-Risk Surgery

Appendix K Additional Analysis of outcomes of the Markov Model

The figures below present findings of the analysis, such as costs, QALY's, LY's, and Incremental costs, per risk group for both Italy and Spain. Although the treatment modalities show consistent effectiveness, due to the two countries having the same transition probabilities and utility values, differences occur in terms of cost. The difference between the two countries is the reimbursement cost for brachytherapy which leads to different costs in the CEA output.

Analysis costs

The CEA results for Italy show that brachytherapy is the cheapest across all risk groups in comparison with EBRT, surgery and brachytherapy plus EBRT. This conclusion is drawn from the incremental costs (brachytherapy cost – cost of alternative) which consistently show a negative value, signifying that brachytherapy is more economical than its competitors. While brachytherapy shows lower costs compared to Active Surveillance in the low-risk group, Active Surveillance is more cost-saving in the low-intermediate, high-intermediate, and high-risk groups. The rationale lies in the fact that, in the low-risk group under Active Surveillance, a high percentage (99%) of patients remain in the state of *cancer + no toxicity*, incurring a high cost of €1.500 per cycle due to a low probability of transitioning to the death state. Conversely, with brachytherapy in the low-risk group over 90% of patients transition annually to the state *healthy + no toxicity*, incurring a lower cost of €650, which is the follow-up care cost. In higher-risk groups Active Surveillance has a higher mortality than brachytherapy, and since the death state produces no costs, this results in lower overall costs for Active Surveillance compared to brachytherapy. This cost disparity is particularly notable, as illustrated in the Markov Trace provided in the Appendix. Throughout all risk groups, the combination of brachytherapy plus EBRT consistently incurs the highest costs, followed by surgery as the second highest, and EBRT as the third highest.

We observe a similar pattern of cost outcomes in Spain. However, in Spain, brachytherapy is less costly compared to the other treatment modalities in each risk group except for Active Surveillance. In comparison to Active Surveillance, brachytherapy is consistently more expensive. This contrasts with the findings in Italy, where, in the low-risk group, brachytherapy was cheaper. The difference is attributed to the higher total cost of cycle 0 for brachytherapy in Spain, which exceeds the total cost per cycle in the low-risk Active Surveillance category.

	Comparison	*cost BT*	*cost Alt*	*Incremental Cost:*
Low Risk	BT vs EBRT	€ 8.702,76	€ 12.276,07	-€ 3.573,31
	BT vs AS	€ 8.702,76	€ 8.932,77	-€ 230,01
	BT vs Surgery	€ 8.702,76	€ 14.923,08	-€ 6.220,32
Low Inter Risk	BT vs EBRT	€ 8.937,08	€ 13.779,02	-€ 4.841,94
	BT vs AS	€ 8.937,08	€ 8.351,40	€ 585,68
	BT vs Surgery	€ 8.937,08	€ 26.779,93	-€ 17.842,85
High Inter Risk	BT vs EBRT	€ 10.432,67	€ 17.131,55	-€ 6.698,87
	BT vs AS	€ 10.432,67	€ 7.564,50	€ 2.868,18
	BT vs Surgery	€ 10.432,67	€ 25.580,07	-€ 15.147,40
	BT vs BT+EBRT	€ 10.432,67	€ 28.901,56	-€ 18.468,89
High Risk	BT vs EBRT	€ 12.487,60	€ 16.338,92	-€ 3.851,32
	BT vs AS	€ 12.487,60	€ 7.028,39	€ 5.459,21
	BT vs Surgery	€ 12.487,60	€ 28.855,29	-€ 16.367,69
	BT vs BT+EBRT	€ 12.487,60	€ 35.280,25	-€ 22.792,65

Figure 41 Costs Italy

	Comparison	cost BT	cost Alt	Incremental Cost:
Low Risk	BT vs EBRT	€ 10.070,32	€ 12.276,07	-€ 2.205,74
	BT vs AS	€ 10.070,32	€ 8.932,77	€ 1.137,55
	BT vs Surgery	€ 10.070,32	€ 14.923,08	-€ 4.852,76
Low Inter Risk	BT vs EBRT	€ 10.384,28	€ 13.779,02	-€ 3.394,74
	BT vs AS	€ 10.384,28	€ 8.351,40	€ 2.032,88
	BT vs Surgery	€ 10.384,28	€ 26.779,93	-€ 16.395,65
High Inter Risk	BT vs EBRT	€ 12.314,94	€ 17.131,55	-€ 4.816,61
	BT vs AS	€ 12.314,94	€ 7.564,50	€ 4.750,44
	BT vs Surgery	€ 12.314,94	€ 25.580,07	-€ 13.265,13
	BT vs BT+EBRT	€ 12.314,94	€ 31.568,88	-€ 19.253,94
High Risk	BT vs EBRT	€ 14.939,54	€ 16.338,92	-€ 1.399,38
	BT vs AS	€ 14.939,54	€ 7.028,39	€ 7.911,15
	BT vs Surgery	€ 14.939,54	€ 28.855,29	-€ 13.915,75
	BT vs BT+EBRT	€ 14.939,54	€ 35.280,25	-€ 20.340,71

Figure 42 Cost Spain

Analysis health outcomes

In terms of effectiveness, positive values for incremental QALY's (QALY brachytherapy – QALY alternative) demonstrate that brachytherapy consistently achieves the highest QALY when compared to EBRT, Active Surveillance, surgery, and the combination of brachytherapy plus EBRT in the high intermediate and high-risk group. In the low intermediate-risk group, brachytherapy shows a higher QALY compared to Active Surveillance and surgery, while in the low-risk group, brachytherapy shows a higher QALY compared to EBRT and Active Surveillance. The higher QALY for brachytherapy in the higher-risk groups is attributed to its low mortality, recurrence, and persistence rates. However, in the low intermediate risk and low risk, contrary to expectations, brachytherapy shows a lower QALY compared to EBRT and surgery. This discrepancy can be explained by our input data, which indicates a higher mortality rate associated with brachytherapy in low-risk groups compared to EBRT and surgery.

Given that QALY's and LY's both measure the effectiveness of the treatment, we expected them to show the same pattern. However, there are discrepancies in some of the results of incremental LYs (LY brachytherapy – LY alternative treatment) compared to incremental QALYs. For instance, in the low-risk group, brachytherapy showed a higher QALY, but a shorter LY compared to Active Surveillance. Similar discrepancies were observed in the comparison of brachytherapy with surgery in the low-intermediate and high-intermediate-risk groups. These differences in patterns between QALY and LY can be explained by the transition probabilities: Active Surveillance and surgery have lower mortality compared to brachytherapy, which reduces the number of years lived, directly affecting the LY. Because QALY accounts not only for the quantity but also the quality of life, then it is not directly affected by mortality but also by other factors like toxicity, which are lower in brachytherapy. This leads to the observed differences in QALY and LY patterns.

	Comparison	cost BT	cost Alt	Incremental Cost:	QALY BT	QALY Alt	Incremental QALY:	LY BT	LY Alt	Incremental LY:
Low Risk	BT vs EBRT	€ 8.702,76	€ 12.276,07	-€ 3.573,31	5,56	5,47	0,10	5,75	5,67	0,08
	BT vs AS	€ 8.702,76	€ 8.932,77	-€ 230,01	5,56	4,94	0,62	5,75	5,96	-0,21
	BT vs Surgery	€ 8.702,76	€ 14.923,08	-€ 6.220,32	5,56	5,67	-0,11	5,75	5,94	-0,20
Low Inter Risk	BT vs EBRT	€ 8.937,08	€ 13.779,02	-€ 4.841,94	5,43	5,54	-0,11	5,62	5,78	-0,15
	BT vs AS	€ 8.937,08	€ 8.351,40	€ 585,68	5,43	4,62	0,81	5,62	5,57	0,06
	BT vs Surgery	€ 8.937,08	€ 26.779,93	-€ 17.842,85	5,43	5,24	0,19	5,62	5,83	-0,21
High Inter Risk	BT vs EBRT	€ 10.432,67	€ 17.131,55	-€ 6.698,87	5,03	3,95	1,08	5,29	4,29	0,99
	BT vs AS	€ 10.432,67	€ 7.564,50	€ 2.868,18	5,03	4,19	0,84	5,29	5,04	0,25
	BT vs Surgery	€ 10.432,67	€ 25.580,07	-€ 15.147,40	5,03	4,90	0,13	5,29	5,53	-0,25
	BT vs BT+EBRT	€ 10.432,67	€ 28.901,56	-€ 18.468,89	5,03	4,75	0,28	5,29	5,14	0,15
High Risk	BT vs EBRT	€ 12.487,60	€ 16.338,92	-€ 3.851,32	4,74	4,41	0,33	5,08	4,79	0,30
	BT vs AS	€ 12.487,60	€ 7.028,39	€ 5.459,21	4,74	3,89	0,85	5,08	4,69	0,40
	BT vs Surgery	€ 12.487,60	€ 28.855,29	-€ 16.367,69	4,74	4,13	0,61	5,08	4,77	0,31
	BT vs BT+EBRT	€ 12.487,60	€ 35.280,25	-€ 22.792,65	4,74	4,48	0,26	5,08	5,03	0,06

Figure 43 QALYs and LYs Italy and Spain

		Cost per QALY gained	Cost per LY gained	
	Comparison	ICER (€/QALY):	ICER (€/LY) :	
Low Risk	BT vs EBRT	-€ 22.634,18	-€ 27.543,93	dominant
	BT vs AS	€ 1.828,90	-€ 5.430,87	
	BT vs Surgery	€ 44.476,42	€ 24.778,82	
Low Inter Risk	BT vs EBRT	€ 30.093,91	€ 22.232,81	
	BT vs AS	€ 2.516,07	€ 36.885,21	
	BT vs Surgery	-€ 85.633,65	€ 78.867,95	dominant
High Inter Risk	BT vs EBRT	-€ 4.472,55	-€ 4.848,39	dominant
	BT vs AS	€ 5.654,37	€ 19.380,56	
	BT vs Surgery	-€ 103.570,35	€ 53.778,50	dominant
	BT vs BT+EBRT	-€ 68.604,16	-€ 128.885,24	dominant
High Risk	BT vs EBRT	-€ 4.297,52	-€ 4.699,03	dominant
	BT vs AS	€ 9.325,09	€ 19.837,90	
	BT vs Surgery	-€ 22.986,04	-€ 44.710,41	dominant
	BT vs BT+EBRT	-€ 78.846,47	-€ 368.132,01	dominant

Figure 44 ICER Spain

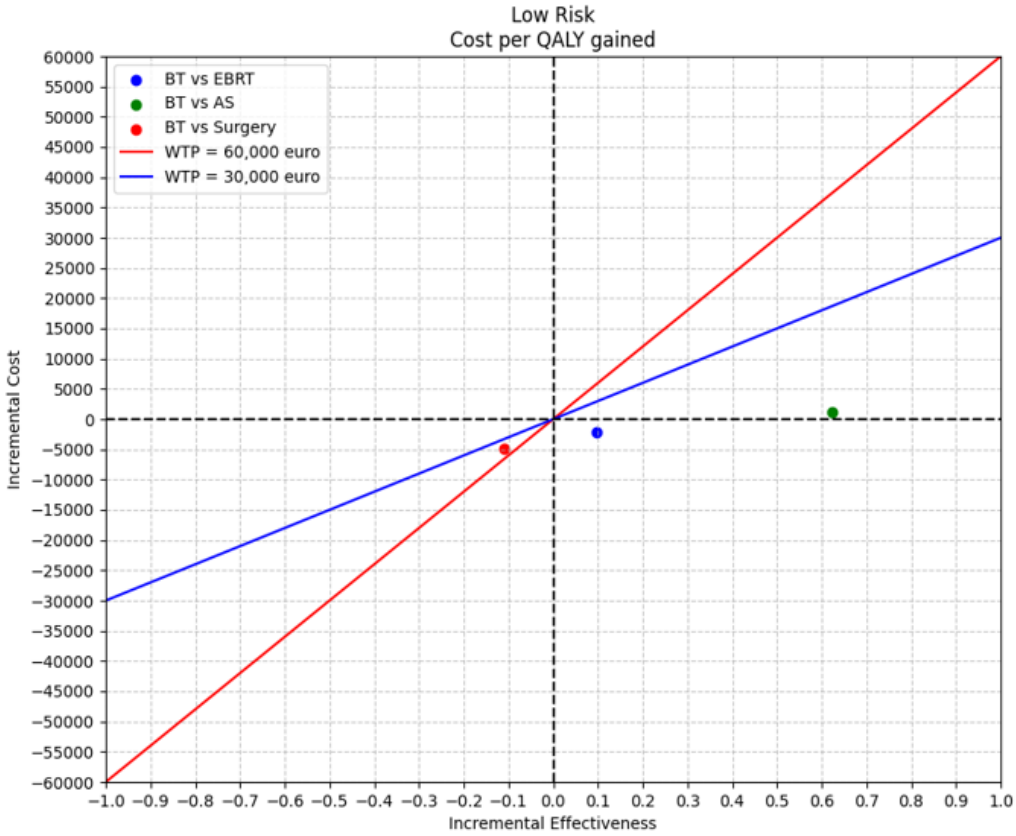


Figure 45 Cost-effectiveness Spain "Low-Risk"

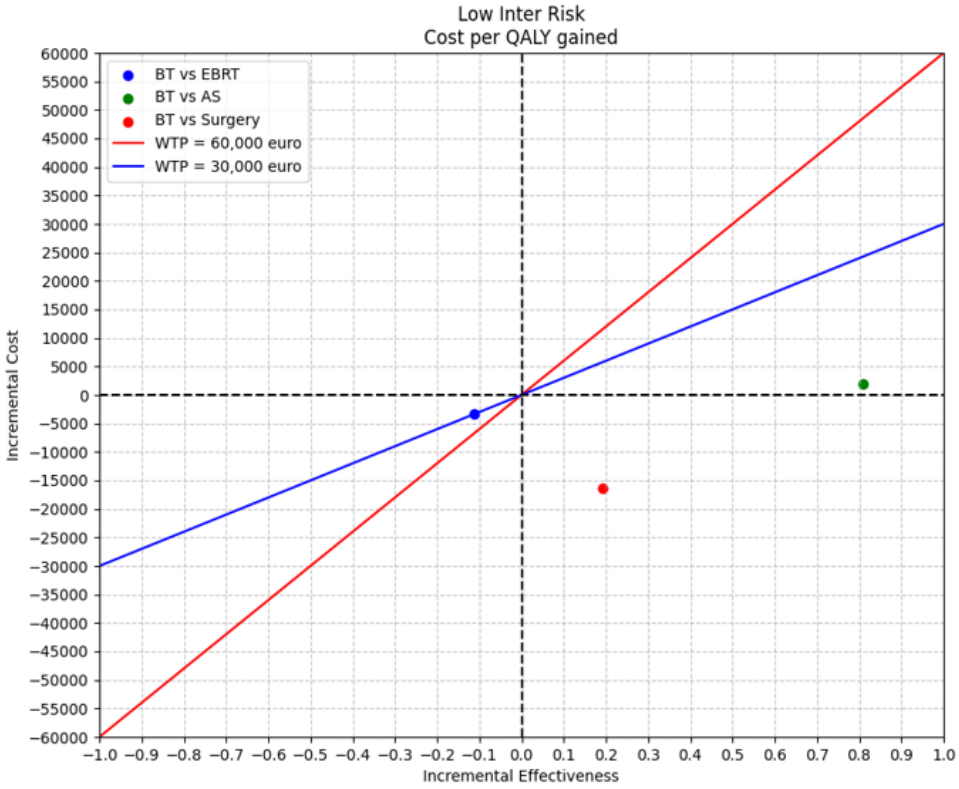


Figure 46 Cost-effectiveness Plane Spain "Low Intermediate-Risk"

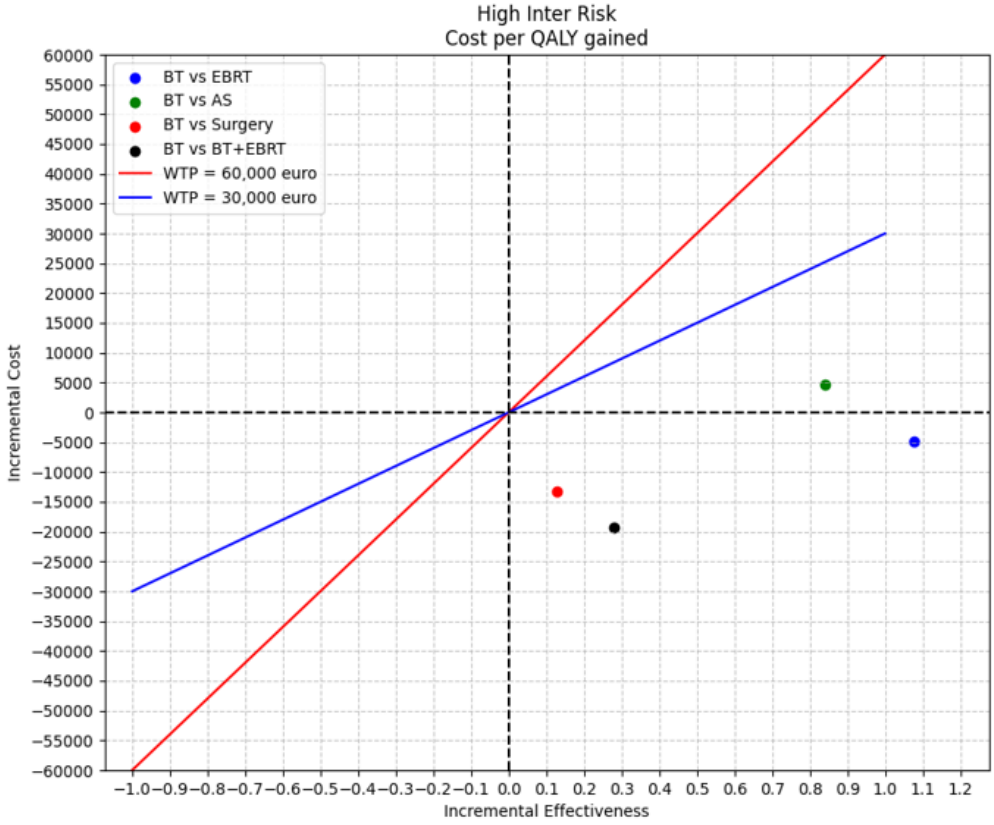


Figure 47 Cost-effectiveness Plane Spain "High Intermediate-Risk"

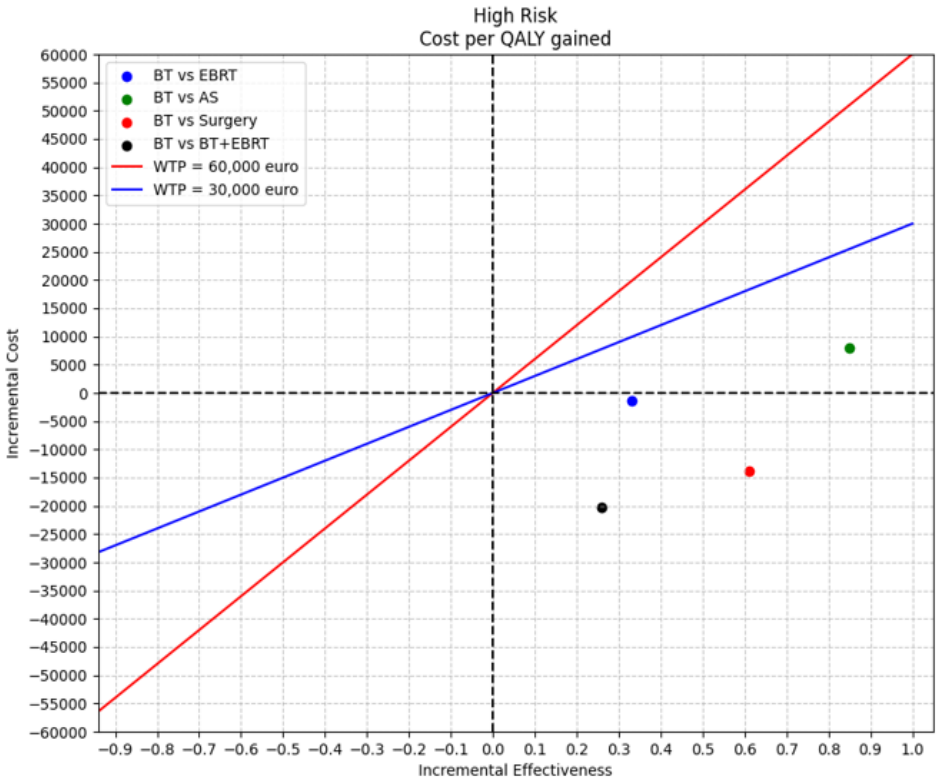


Figure 48 Cost-effectiveness Plane Spain "High-Risk"