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Cost-effectiveness of brachytherapy compared to cystectomy for treatment of muscle-invasive bladder cancer

Master Thesis

Daan Spoor, BSc

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Student:
Daan Spoor, BSc
Master student Health Sciences

Organisation:
University of Twente
Department: Health Technology and Services Research

First supervisor:
Prof. Dr. Maarten J. IJzerman

Second supervisor:
Prof. Dr. Sabine Siesling

External expert team:
Dr. Geert Smits (urologist)
Drs. Elzbieta van der Steen-Banasik (radiotherapist)

Summary

Objective: Most muscle-invasive bladder cancer patients are treated with radical cystectomy. However, multiple articles have proven that for a selected group of patients an initial treatment with brachytherapy results in a comparable survival compared with cystectomy. This study is aimed at determining the health economic impact of brachytherapy as initial treatment compared with radical cystectomy for these selected bladder cancer patients. Within the study will also be looked at the best surgical technique (open or robot-assisted).

Method: A Markov Monte-Carlo cost-effectiveness model was created to simulate the outcome of a cohort of patients with a solitary T1G3, T2 or T3a bladder tumor, with a diameter smaller than 5 centimeter without lymph node involvement or metastasis. Treatment options were open radical cystectomy, robot-assisted cystectomy and robot-assisted brachytherapy. Also deterministic and probabilistic sensitivity have been performed to analyze the outcome.

Results: Cost-effectiveness analysis has shown that robot-assisted brachytherapy is a more expensive treatment but also has a better effectiveness compared to open radical cystectomy and robot-assisted radical cystectomy. The incremental cost-effectiveness ratio was €15.578,96 per QALY which is below a willingness-to-pay threshold of €25.000,-. Deterministic sensitivity analysis showed that long term utilities experienced after cystectomy and brachytherapy had the biggest impact on the cost-effectiveness of brachytherapy compared to cystectomy. These were also the only input parameters for which a variation of base value could result in decision for radical cystectomy as preferred treatment strategy. Probabilistic sensitivity analysis showed that, if uncertainties of all input parameters were taken into account, the chance is 67,3% that brachytherapy is the preferred treatment.

Conclusion: Robot-assisted brachytherapy is the most cost-effective treatment strategy and should therefore be the preferred treatment strategy for a selected group of muscle-invasive bladder cancer patients. Further research should be done to obtain more accurate values for the post treatment utilities.

Contents

Introduction

In 2014 3152 persons were diagnosed with bladder cancer in the Netherlands. In terms of most occurring types of cancer bladder cancer is at 6th place for men and at the 10th place for women. Every year on average 1200 persons die from bladder cancer so it can be said that the disease has a relatively high mortality rate[1][2][3]. Another problem with bladder cancer is its excessive costs because bladder cancer management is very expensive. It is the most expensive malignancy to treat from diagnosis until death. These high costs are caused by a high recurrence rate and because most cases are nonlethal, requiring frequent surgical resections and lifelong surveillance.

Transitional-cell carcinoma comprises nearly 90% of all primary bladder tumors. Depending on to which extent these tumors have invaded the bladder wall bladder it is treated in different ways. For muscle-invasive bladder cancer radical cystectomy, which has a 5-year overall survival of 66% and a 10-year overall survival of 43% is currently standard treatment[4][5]. This includes en bloc resection of the bladder, iliac lymph node dissection and some form of lower urinary tract reconstruction. In case of micrometastates, chemotherapy is given before surgery to improve overall survival[8]. Radical cystectomy has become the golden standard in high grade invasive bladder tumors because it provides the highest survival as well as the lowest recurrence rate in these patients[10]. After radical cystectomy an accurate evaluation of the primary bladder tumor as well as the regional lymph nodes can be done which allows for adjuvant treatment strategies to be based on pathologies rather than on clinical staging[5].

Despite its good overall survival, radical cystectomy also has certain disadvantages. Although the morbidity of radical cystectomy is clearly lower than in previous decades, the rate still remains higher than 30% in the early postoperative period. Common morbidities are loss of normal bladder function, erectile dysfunction, urinary leakage and urinary tract infections. These morbidities have a considerable negative impact on quality of life[11]. Also 27% of the patients having an open radical cystectomy surgery develops a perioperative complication like excessive blood loss[12]. Other disadvantages are that the open surgery leads to much pain, large scars and a long recovery time.

In order to reduce the high perioperative complication rate, minimally invasive techniques for radical cystectomy have been explored[13]. Examples of minimally invasive techniques are laparoscopic and robot-assisted radical cystectomy. Although these techniques might require more operation time, it also leads to a significant reduction in early postoperative morbidity and fewer postoperative complications. In particular major complications occur less frequent after a robot-assisted surgery[14].

Other improvements for treatment of bladder cancer lie within the field of conservative treatment. For example bladder preserving therapy may offer an alternative to radical cystectomy with a possible reduction of side effects[21]. An example of such a new treatment strategy has been developed in recent years and consists of a combination of transurethral resection (TUR), external beam radiotherapy (EBRT) and interstitial brachytherapy[14]. Research has shown that for selected cases this treatment leads to at least similar overall survival compared to radical cystectomy and it is currently already often used as an alternative for radical cystectomy[24][16][17].

Van der Steen et al. [18] looked at the effects of brachytherapy in bladder cancer patients compared to radical cystectomy and showed that brachytherapy can be applied successfully in a selected patient population. However, as far as known, there has not yet been a study that also took the associated health-related quality of life into account.

Bladder cancer is also the most expensive malignancy to treat from diagnosis until death. These high costs are a result of the fact that bladder cancer often recurs and that most cases are nonlethal, requiring frequent surgical resections and lifelong surveillance[22]. At the same time there is growing pressure on health-care policy-makers to allocate resources on the basis of the economic benefit of various therapies it is important to look at costs that are made during both treatment processes.

This research is aimed at determining whether brachytherapy is a more cost-effective treatment compared with radical cystectomy for selected bladder cancer patients. Within the study will also be looked at whether it is better in terms of cost-effectiveness to perform the operation open or robot-assisted.

Following main research question will be answered within this research:

What is the health economic impact of brachytherapy as a new standard treatment for muscle-invasive bladder cancer compared to the current standard radical cystectomy?

To answer this main question a cost-effectiveness study will be performed in which decision analytic modeling techniques are used to analyze performances of the treatment strategies. A state-transition Markov model will be built to describe the clinical course of the bladder cancer patients over time. To build such a model it is important to know which treatment options there are and what their treatment processes look like. Therefore, first a literature study needs to be performed to identify these aspects. This literature study can be found in the appendix of this report. After this section the report will continue with a method which will describe how the study is executed. Then a section will discuss how a model can be built to determine the health-economic impact of the treatment strategies, after which results of analysis of this model will be given. These results will then be discussed and criticized. Also limitations will be mentioned and advises for future research will be given. The report ends with the conclusion of this study.

Methods

Main goal of this study is to determine the health-economic impact of multiple treatment options for muscle-invasive bladder cancer. This can be achieved by performing a cost-effectiveness analysis. To be able to perform this analysis, it has to be clear which treatment options there are and what their processes look like. Virtual patients can then be simulated through these processes over time using a state-transition Markov model. Identification of these treatment processes requires a literature study. Since this study has the design of a cost-effectiveness analysis, it was chosen to place this literature study in the Appendix of this report.

The literature study and the cost-effectiveness analysis both require different methods. For the literature study scientific articles were needed. These articles were mainly found with Scopus and Google Scholar. It was important to use the right combinations of search terms to be sure that only useful articles were found. Only articles written in Dutch or English were used and the full text version had to be available. No limitations were made on the time since publication of articles because sometimes old articles, for example about the history of brachytherapy, were needed. However it was always taken into account that quality of care and treatments techniques have developed over recent years. Besides these articles also a database with information on all bladder cancer patients in the Netherlands since 1995 provided by the Netherlands Cancer Registry was used. Different patient populations could be selected and information about these patients, like survival rates, could be used to confirm estimations done within the research so the model can be validated. Modeling in this research was performed with the decision analysis software package (TreeAge Pro 2015; TreeAge Software, Inc, Williamstown, MA). The structure of this model was made based on findings of the literature study and opinions of an expert team, which consisted of urologist dr. Geert Smits and radiotherapist dr. Elzbieta van der Steen-Banasik from the Rijnstate hospital. Outcomes of the model are given as costs per quality-adjusted life years (QALY). Input parameters were required to obtain these outcomes and were mainly provided by literature. However, sometimes the required data was not available. For example data on the utility of bladder cancer patients that have been treated with brachytherapy. This data was collected with an EQ-5D questionnaire which was filled in by patients from the Rijnstate hospital in Arnhem. Some input parameters could not be found or collected and therefore they had to be estimated.

In cost-effectiveness analyses it is usual to compare a current standard treatment called the base-case with a new treatment, the experimental treatment. The experimental treatment(s) will then be compared to this base-case. However, for muscle-invasive bladder cancer this is somewhat different. According to the national guidelines open radical cystectomy should be the standard treatment for these patients. However this treatment can also be executed with robot assistance. Though, a substantial part of all Dutch hospitals performs brachytherapy to treat muscle-invasive bladder cancer. This means that there is not one current standard treatment. Because there is not one strictly defined standard treatment option the choice has been made to evaluate the cost-effectiveness of all treatments and rank them on rising costs. If it turns out one treatment strategy is dominated by the two other treatments, further analysis, like the deterministic and probabilistic sensitivity analysis, will only focus comparison on these treatments. Then again the most expensive treatment will be compared to the other one. More information about identifying of the treatment strategies can be found in the literature study located in the Appendix of this report.

Modeling the treatment process

In this section of the report will be discussed how a state-transition Markov model will be used to analyze the cost-effectiveness of the treatment strategies identified in the literature study ; open radical cystectomy, robot-assisted radical cystectomy and EBRT + brachytherapy. In succession will be discussed what study population will be simulated, how their treatment processes can be modeled, what input is required for this model and ends with describing which analyses will be performed. During development of the model many assumptions had to made. Most important assumptions are discussed within this section. All other assumptions are summarized in one overview and can be found in the Appendix of this report.

Study population

To determine the health-economic impact of certain treatment strategies it is important that a comparable patient population is simulated for all strategies. The reason for this is that multiple risk factors like for example age, non-organ confined pathological tumor stage, lymph node involvement, total number of lymph nodes removed and positive surgical margins have found to be independent risk factors for overall survival and bladder cancer specific survival after radical cystectomy[28]. Therefore, to be able to make a valid comparison between the effectiveness of different treatments of bladder cancer, risk factors for both groups have to be comparable.

As already mentioned in the introduction of this report, brachytherapy is only a good alternative for radical cystectomy in a selected group of bladder cancer patients. This study population has been identified in the literature study which can be found in the Appendix. With this literature study has been found that patients who qualify for a brachytherapy treatment are those patients that have a solitary T1G3, T2 or T3a bladder tumor, with a diameter smaller than 5 centimeter, vital enough to undergo a surgical procedure[21]. There should not be too much lymph node involvement and there should be no metastasis at the start of the treatment. Also the EBRT followed by brachytherapy or radical cystectomy should be the initial treatment for the bladder cancer.

Before building the model, it can be useful to verify whether this patient population indeed might benefit from treatment with brachytherapy instead of a radical cystectomy. Since a database provided by the Dutch Cancer Registration with information on all patients diagnosed with bladder cancers in the Netherlands from 1995 until 2013 is available, this can be used to indicate a possible added value of brachytherapy. Two survival curves are made. Only those patients that satisfy the earlier mentioned characteristics are included. The red curve shows the survival of those patients that were treated with brachytherapy and the blue one for radical cystectomy. Also the 5- and 10 year overall survival rates for both treatments are shown in table 1**.**

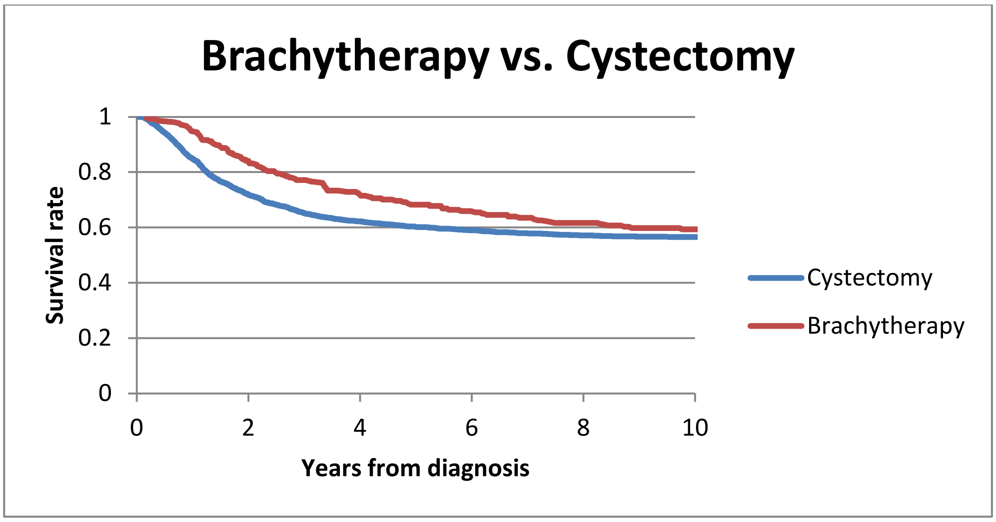

Figure 1: Overall survival of patients treated with cystectomy and brachytherapy. Comparable patients groups are created by filtering on the indications for brachytherapy.

Treatment	5 year overall survival	10 year overall survival
Cystectomy	60%	57%
Brachytherapy	68%	59%

Table 1: 5- and 10 year overall-survival for the survival curves in Figure 1.

When only looking at their survival, it can be seen that patients treated with brachytherapy have a higher survival rate compared to a comparable group of patients treated with radical cystectomy. Difference in survival is larger for the first few years after initial treatment. After 5 years 68% of the patients in the brachytherapy group is still alive whereas this is only 60% for patients treated with cystectomy. After 10 years survival are nearly equal for both treatments (59% for brachytherapy vs. 57% for cystectomy). These results cannot be seen as scientific proof, however it gives an indication that brachytherapy might indeed be beneficial for this group of patients. Further analysis has to be performed to give accurate results.

Model Structure

A state-transition model is built in TreeAge to evaluate health-related quality of life, expected life years and medical costs for the three treatment strategies for MIBC which were identified with the literature study. These strategies are open radical cystectomy, robot-assisted radical cystectomy and EBRT followed by robot-assisted brachytherapy. The moment a patient enters the model is after they have had a TUR and have were diagnosed with MIBC. For each patient one of the treatment strategies can be chosen. After this decision the patient moves through the Markov model. For all treatment strategies only one Markov model has been built. Since patients treated with radical cystectomy do no longer have a bladder, it is not possible for them to develop a recurrence in the bladder wall. However, it is possible for these patients to develop a local recurrence at the original position of the bladder. Though these recurrences are treated the same as distant recurrences and they also lead to a comparable prognosis compared to distant recurrences. For these reasons the assumption has been made that if a patient develops a local recurrence after radical cystectomy this will be modeled as a distant recurrence. Therefore these probabilities can be neglected. Cycle-length for the model is three months, since this is the time between follow-up moments in practice which are the moments in time changes in health-states will be detected. Time horizon is longer than the patient's maximum lifetime so at the end of every simulation there are no patients alive anymore. For each cycle costs related to the health-states are made together with an experienced quality of life associated with this health-state. These costs and experienced are added up for each patient throughout the simulation. In healthcare, effects and costs often increase over time. Therefore both utilities and costs were discounted at 3% to reflect society's rate of time preference[22].

Clinical pathways for both radical cystectomy and brachytherapy differ a lot. Open radical cystectomy and robot-assisted radical cystectomy broadly have the same clinical pathway. It only differs in the fact that input parameters are slightly different. A literature study, which can found in the Appendix of this report, has been performed to identify the clinical pathways of both radical cystectomy as well as brachytherapy. Both pathways will now shortly be discussed, starting with radical cystectomy.

At cycle 0 the patient undergoes radical cystectomy. At that moment three things can happen; 1) the patient has no complications. 2) the patient gets complications and 3) the patient dies during the operation. It was assumed that the patient could not have a metastasis because this is in fact still at the moment after diagnosis and there were no metastasis discovered with diagnosis. Three months later the patient will go to the hospital for follow-up research in to search for any distant recurrences. Every follow-up moment the patient can get a new complication related to the treatment. Most complications are solved shortly after they occur although others can lead to consequences over a longer period. To make a good estimation within making modeling too complicated for this model it is assumed that each complication is solved after exactly three months. It is also possible that the patient develops a distant recurrence in the time between two cycles. As mentioned earlier, since the bladder is removed with radical cystectomy these patients cannot develop a local recurrence in the bladder. Therefore it is impossible for these patients to develop non-invasive or invasive local recurrences. However, it is possible that these patients develop distant recurrences. When a patient develops a distant recurrence, curative treatment is not longer possible. From that moment the patient stays in the distant recurrence health-state (or gets a cystectomy related complication) until the patient dies and moves to the health-state 'dead'. Off course patients can also die at any moment in time from every health-state.

The clinical pathway of treatment with brachytherapy treatment is more complicated since there are more health-states involved throughout the process. After the patient has received both EBRT and brachytherapy three things can happen; 1) the patient does not get any complication, 2) the patient gets a complication 3) the patient dies during or shortly after surgery. Again it is assumed to be impossible that the patient has any recurrence right after the treatment since there was no recurrence found during diagnostics and all suspected areas have been removed with TUR. After the next cycle four things can happen; 1) the patient still has no recurrence, 2) the patient gets a non-invasive local recurrence, 3) the patient get an invasive local recurrence or 4) the patient gets a distant recurrence. A recurrence at same position of the original tumor always invades the muscle layer of the bladder wall. Just as with radical cystectomy the patient can develop a complication related to brachytherapy for each possible health-state and off-course the patient can die. So many different things can happen. If a patient develops multiple recurrences it is assumed that the patient goes to the health-state associated with the recurrence with the worst prognosis. When a patient gets a non-invasive recurrence they will be treated with intravesical chemotherapy or intravesical immunotherapy to prevent this non-invasive of progressing to an invasive local recurrence or cause a distant recurrence. The next cycle the tumor can either progress to an invasive local recurrence, a distant recurrence or stays stable. When a patient gets an invasive local recurrence they get a salvage cystectomy, meaning that the bladder will yet be removed. These patients remain in this health-state until they die. The same applies if a distant recurrence is detected.

For all treatment strategies the modeling from the moment a patients develops a distant recurrence is very simplified. In reality this can be modeled far more complex since for example sometimes patients react on chemotherapy and sometimes they don't. If a patient reacts on chemotherapy, this will prolong life expectancy. However, the initial treatment does not influence the result of this palliative care pathway. Therefore it also cannot influence the choice for the most cost-effective treatment strategy. So even if this simplified modeling does not perfectly reproduce reality, it will not have any influence on the main goal of this study.

To simulate the treatment processes concrete health-states have to be defined. During simulation the patients will always be in one of those health-states. Each of the health-states will be associated with a certain quality of life and medical costs. All possible health-states for the processes described above are shown in table 2.

Health-States
no recurrence + no complication
no recurrence + complication
non-invasive local recurrence + no complication
non-invasive local recurrence + complication
invasive local recurrence + no complication
invasive local recurrence + complication
distant recurrence + no complication
distant recurrence + complication
dead

Table 2 Health-states of the Markov model

All these treatment processes are translated into one Markov model that only uses the defined health-states shown in table 2. This entire model is relative complicated. To make it more understandable a simplified version of the Markov model is shown below in figure 2. For all health-states that are shown in fact there is also a version of this state in which the patients also has a complication. Also the health-state dead is not shown. It is at any moment, from any health-state possible that the patient moves to this 'dead' state.

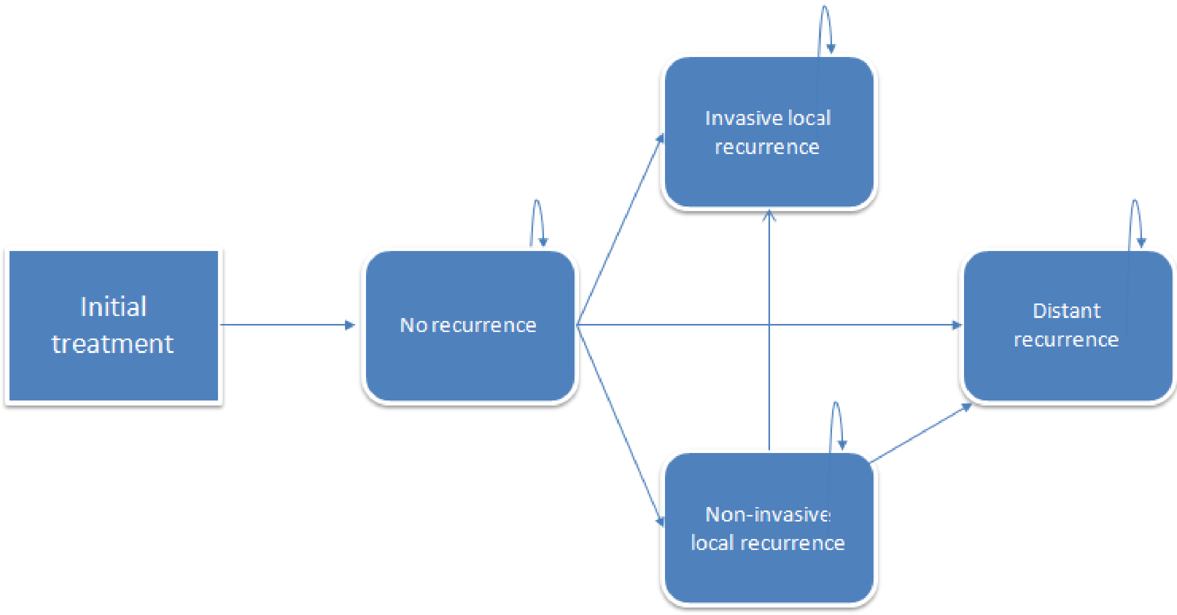

Figure 2. Markov model for both radical cystectomy as well as for brachytherapy. Model is simplified because the four health-states that are shown also exist as a state with a complication. Each arrow has its own transition probability and transitions to death are not shown. Also the values of these probabilities are different for all treatment strategies.

Input

Now that a Markov model has been built, input is required to perform the desired analyses. Most data were obtained from the literature. Mainly articles found with Scopus and Google Scholar were used. It was important to use the right combinations of search terms to be sure that only useful articles were found. Only articles written in Dutch or English were used and the full text version had to be available. No limitations were made on the time since publication of articles. However it was always taken into account that quality of care and treatments techniques have developed over recent years. For example the brachytherapy technique has made many improvements over the years. Therefore it was desirable to search for relatively recent published articles. Also additional data collection was carried out to determine the utility of patients treated with brachytherapy, since this has never been done before (as far as known). This data collection was performed with the EQ-5D questionnaire which was filled in by patients from the Rijnstate hospital in Arnhem. Some other input parameters could not be found or collected and therefore they had to be estimated.

For the modeling following data is required: transition probabilities between the health-states, utilities that are experienced in every health-state and costs associated with all health-states. Data found in literature was assumed to be most reliable. Whenever literature was lacking an expert was consulted. If this was also not possible an assumption was made.

Event Probabilities

First the most important information on the event probabilities for open and robot-assisted radical cystectomy will be discussed. As expected the initial probability of having a complication is lower for robot-assisted cystectomy compared to open surgery (54% vs. 61,5% resp.). Also the long-term complication probability was lower for the robot-assisted treatment (1,4% vs. 1,6% resp.). Since current studies show comparable oncologic outcomes for robot-assisted and open cystectomy[23], it was possible for both treatments to use the information on recurrence rates mentioned in the large-scale study performed by *Stein et al.*[24]. This study showed recurrences in 32% of the patients after a median period of five years, which leads to an event probability of 0,8% every three months (one cycle-length).

Unfortunately, literature on event probabilities after brachytherapy was harder to find. Most information on recurrence probabilities could be extracted from the largest study to brachytherapy for bladder cancer performed by *Koning et al.*[25]. Information on the probabilities of complications was extracted from the article of *van der Steen et al.*[18]. Some assumptions had to be made to determine the separate progression rates when having a non-invasive local recurrence. This was calculated with the ratio of developing an invasive local recurrence/distant recurrence which were known[26]. Also two values relevant for all treatment strategies had to be determined; the age specific mortality rate which could be taken from a life table for United States citizens[27] and the probability of dying from cancer when having metastases[28]. An overview of all event probabilities is shown in the table 3.

Event Probabilities	open cystectomy		robot cystectomy		robot brachytherapy	
	Value (SE)	Ref. (year)	Value (SE)	Ref. (year)	Value (SE)	Ref.(year)
Event						
initial complication	0.62 (0.1)	[29]2009	0.54 (0.1)	[30]2015	0.17 (0.05)	[29]2009
postoperative mortality	0.008 (0.001)	[10]2007	0.007 (0.001)	est.	0.005 (0.0005)	[31]2014
long-term complication	0.016 (0.003)	[29]2009	0.014 (0.003)	[30]2015	0.005 (0.001)	[29]2009
non-invasive local recurrence	n.a.	-	n.a.	-	0.004 (0.0004)	[25]2012
progression to invasive recurrence	n.a.	-	n.a.	-	0.0016 (0.0003)	[25]2012
progression to distant recurrence	n.a.	-	n.a.	-	0.0097 (0.002)	[26]2004
invasive local recurrence	n.a.	-	n.a.	-	0.003 (0.0004)	[26]2004
distant recurrence	0.019 (0.002)	[8]2001	0.019 (0.002)	[32] 2011	0.018 (0.003)	[25]2012
age specific mortality	0.004 (0.0005)	[27]2009	0.004 (0.0005)	[27]2009	0.004 (0.0005)	[27]2009
die from complication	0.002 (0.0005)	[29]2009	0.002 (0.0005)	[29]2009	0.0026 (0.0005)	[29]2009
die from metastases	0.129 (0.02)	[28]2014	0.129 (0.02)	[28]2014	0.129 (0.02)	[28]2014

Table 3 Overview of event probabilities for all treatment strategies. Est. means that a parameter could not be found in literature and was therefore estimated.

Utilities

Unfortunately, data for utilities after treatment for bladder cancer patients was not easily available from the literature. Though, values for the utilities shortly after an open radical cystectomy and the period after first follow-up moment were found in literature and 0,8 and 0,96 respectively[28][33]. Utilities of these health-states after robot-assisted cystectomy were not available and were therefore estimated. Robot-assistance has mainly an advantage for the utility in the first three months after surgery, after this period the utility is comparable to those of patients treated with open radical cystectomy. Values used in the model are 0,85 shortly after the surgery and 0,96 later on. Quality of life assessment of patients treated with brachytherapy for bladder cancer is something that, as far as known, has never been done before so there was no data available on this. Therefore this data was collected by sending EQ-5D questionnaires to patients that were treated with brachytherapy for bladder cancer in Arnhem. Because the test is very easy to fill in and the patients were really enthusiastic, the response rate was very high. From a total of 65 patients that were still 34 patients had filled in the questionnaire. Results of the questionnaire showed a utility of 0,92 after brachytherapy. This is strange because one would expect to see a higher utility for patients treated with brachytherapy compared with patients treated with radical cystectomy since these patients remain their bladder function and have way less complications. This might be caused by the fact that the EQ-5D questionnaire is not a bladder specific quality of life assessment tool. Co-morbidities also lead to a lower utility score. On the other hand the utility for cystectomy only looks at quality of life consequences caused by the cystectomy. Two things can be done to solve this problem: increase utility after brachytherapy or decrease utility after cystectomy. For this research last option is chosen. Later on in the sensitivity analysis can be checked whether this assumption leads to a different treatment preference. Also for some events disutilities were accounted. For example when a patient has to undergo a TUR, the patient experiences a single time utility of 0,1 lower than normally. A summary of all utilities is shown in the table 4. In TreeAge each cycle each patient is given an 'award' for the utility associated with the health-state the patient occupies. Since one cycle is in fact three months, each cycle the award is the utility of that health-state divided by four.

Utilities	**Value (SE)**	**Ref.**
Open cystectomy	0.800 (0.050)	[34]2014, [33]2009
Robot-assisted cystectomy	0.850 (0.170)	estimation
Postcystectomy state	0.910 (0.050)	[34]2014, [33]2009
Brachytherapy	0.900 (0.030)	estimation
Postbrachytherapy state	0.920 (0.070)	EQ-5D Questionnaire
Metastases	0.630 (0.050)	[34]2014, [33]2009
Major complication requiring reoperation	-0.100 (0.020)	estimation
Short-term complication cystectomy	-0.112 (0.022)	estimation
Long-term complication cystectomy	-0.132 (0.026)	estimation
Short-term complication brachytherapy	-0.094 (0.019)	estimation
Long-term complication brachytherapy	-0.090 (0.018)	estimation
Cytoscopy	-0.003 (0.001)	[33]2009
TUR	-0.100 (0.100)	[34]2014,[33]2009
BCG therapy	-0.020 (0.003)	[33]2009

Table 4 Utilities for all heath-states and state-transitions

Costs

The cost-effectiveness of brachytherapy and cystectomy is examined from a healthcare system perspective and therefore only includes direct medical costs. Indirect costs like societal costs of missing work practices for the patient are not included in this analysis. This is not a problem since the average age of patients in the model is 66 years old and therefore most patients will not have a job anymore. This study incorporates tariffs according to guidelines (see 'Instructions for cost analysis in the Netherlands[35]'). This is also the amount of money that plays a role in the allocation of resource by the policy makers. For all costs that are used in the model it is important to calculate weighted average costs per patient. For example patients have follow-up every three months but only have to make a CT scan once a year, the costs of a CT scan should be included into the follow-up costs though the value should four times lower than the actual cost of a scan. Costs in different money units are multiplied with the current currencies into Euros. Reported costs that originate from years ago also have been multiplied with the right yearly discount rate mentioned in Instructions for Cost-Analysis of the Netherlands[35]. Differences in costs of the surgical techniques mostly occur due to differences in costs of robot-assistance during surgery, an increased operation time, decreased length of stay and a reduction in complication rates. Therefore these parameters are all taken into account during the cost analysis. In literature there are several costs mentioned for the usage of robot-assistance calculated per-case. For example *Mmeje et al.*[36] talk about 2.203,- $US per case and this value is used in this study. The article of *Lee et al.*[37] gives a good insight in costs that are made with an open cystectomy and a robot-assisted cystectomy. Some of these values, like costs of utilization per minute could also be used to assess costs of brachytherapy. The same article also gives a good overview for how much costs are made per complication. Complications that occur after cystectomy are not only of larger amounts when compared with brachytherapy, they are also relatively more severe. For this reason it is assumable that cost per complication are also higher so the costs per complication for brachytherapy could be estimated. Costs of chemotherapy could be extrapolated from a study for metastatic long cancer[33]. An overview with all costs and their references is shown in table 5.

	open cystectomy		**robot cystectomy**		**robot brachytherapy**	
Event	€ (SE)	Ref. (year)	€ (SE)	Ref. (year)	€ (SE)	Ref. (year)
Initial Treatment	17.910(3.852)	[37](2011)	20.279(4.056)	[37](2011)	22.997(4.599)	[37](2011), [35](2015)
Cost per compl.	6.735(1.347)	[37](2011)	3.301(660)	[37](2011)	2.500(500)	Estimation
Follow-up	272 (82)	[38](2004)	272(82)	[38](2004)	281(56)	[38](2004), [35](2015)
TUR	n.a.		n.a.		3.124(625)	[38](2004)
BCG instillations	n.a.		n.a.		365(73)	[38](2004)
Chemotherapy	8.941(1.082)	[39](2004)	8.94 (1.082)	[39](2004)	8.941(1.082)	[39](2004)
Living with metas.	280(112)	[38](2004)	280(112)	[38](2004)	280(112)	[38](2004)
Dying from cancer	3.401(680)	[40](2009)	3.401(680)	[40](2009)	3.401(680)	[40](2009)
Dying from other causes	2.2601(453)	[40](2009)	2.2601(453)	[40](2009)	2.2601(453)	[40](2009)

Table 5 Costs accompanied with treatment of bladder cancer with cystectomy or brachytherapy

Analysis

Incremental cost-effectiveness of each strategy

As mentioned in the introduction of this report, the first analysis looks at the incremental cost-effectiveness of all treatment strategies. So for every treatment the costs and the effectiveness will be determined. Incremental cost-effectiveness is defined as the ratio between average cost per patient and average quality-adjusted life-years for one strategy. Effectiveness of a treatment will be expressed both in quality-adjusted life-years and expected life years. With this analysis there is no base-case scenario but the treatments are ranked according to their costs. The incremental cost-effectiveness for all treatment strategies will be visualized in one figure to check which strategies require further analysis and if one of the strategies is dominated by the others. When this is the case, further analysis will only be performed for those strategies that dominate a third strategy. Also an incremental cost per life-year can be determined between two treatment strategies. Most often new techniques lead to a higher effectiveness though it is most often also associated with higher cost. Off course society prefers the most effective treatment. However the budget for healthcare is limited and therefore not every effective technique can be implemented. If a new technique has a better effectiveness and is also cheaper it will always be implemented. However, if the new, effective, technique is more expensive a choice has to be made. A tool for this problem is the 'willingness to pay threshold'. This is the additional amount of money society is prepared to pay to gain one extra quality-adjusted life-year. This value is set at €25.000,- in this study. If one extra QALY has lower additional costs than the willingness to pay compared to the other treatment then it should be implemented.

Deterministic Sensitivity Analysis

Interpretation of the incremental cost QALY will largely depend on the level of uncertainty. Also for this model assumptions had to be made and all input parameter had a certain standard error. Therefore the uncertainty of the outcome from the analysis of this model has to be determined. This can be done with a sensitivity analysis.

First a deterministic sensitivity analysis will be performed to assess the uncertainty of certain model parameters. This will be done in several ways. At first a one-way sensitivity analysis will be performed to assess the influence of the most important parameters of the model. With this analysis will be looked at parameters with high uncertainty used in the model by varying parameter over a certain range. For all analyses this range is 10% for all probabilities and utilities is chosen while for the costs this is 20%. There was not much literature available on the utilities and some assumptions on these values had to be made. The sensitivity analysis will show the impact on the outcome if a different value would have been chosen. Also the recurrence rate after brachytherapy is could possibly be higher than for cystectomy because the bladder is not removed so the tumor could possibly recur on the original location. Not much literature was available on this parameter and therefore the parameter has to be examined. At last the costs of both treatments and the chance of developing initial complications will also be examined since these values are also likely to have a big influence on the outcome of the analysis.

In general most criticism about robot-assisted brachytherapy is about the costs of it. For example because surgery would take more time, new equipment is required and if patients eventually do develop a recurrence they still require an expensive cystectomy. For these reasons cost of brachytherapy requires extra attention and a threshold analysis will be performed. For a range of values for the cost of brachytherapy is calculated whether the incremental cost-effectiveness is under the willingness to pay value, which is set at €25.000,-.

While one-way sensitivity analysis is useful for demonstrating the impact of one parameter varying in the model, it can also be useful to vary two parameters simultaneously. For each potential combination of values of these parameters the result will be given. A two-way sensitivity analysis will be performed to assess the influence of the two most important and uncertain parameters considering the brachytherapy; probability of developing a distant recurrence and cost of initial treatment. These parameters could possible the main reason for brachytherapy to be unsuccessful.

Probabilistic Sensitivity Analysis

In the previous incremental cost-effectiveness analysis each parameter is assigned a point estimate value. However, in practice there is a certain amount of reality around this value. A probabilistic sensitivity analysis can be performed to assess the uncertainty of the outcome of the analysis caused by these uncertainties. Rather than assigning a base value, in probabilistic sensitivity analysis for each parameter a value is picked from a distribution around the mean value. The range of values around the mean value for both utilities and probabilities is determined by a Beta-distribution whereas a Gamma distribution was used for the costs. A scatter plot will be made with all outcomes of the analysis, each with a different combination of values of the parameters. Since it is hard to say based on such a figure which treatment is more cost-effective also an ICER plot will be made. In this ICER plot will be looked how many of the results have an incremental cost-effectiveness below a willingness to pay of €25.000,-. However, this willingness to pay level can also be different in most cases. Sometimes society is willing to pay more money for one additional quality-adjusted life-year. For example this depends on how many life-years can be gained with the new treatment. If a patient is expected to die shortly after diagnosis, they are willing to pay relatively more money for one extra life-year compared to a disease with a long life expectancy after diagnosis. Therefore also a cost-effectiveness acceptability curve is made. This figure shows for multiple willingness-to-pay values what the chance is for brachytherapy to be to preferred treatment strategy.

Results

Incremental cost-effectiveness of each strategy

A Markov cohort simulation is performed in TreeAge. All patients had died at the end of the simulation. The model gave following results for the three treatment strategies:

	Cost (€)	Incr. Cost (€)	LY's	Incr. LY's
Robot-Assisted Radical Cystectomy	35.340,17	0,00	9.317	0.000
Open Radical Cystectomy	38.983,71	3.643,54	9.305	-0.012
Robot-Assisted Brachytherapy	49.828,60	14.488,43	9.786	0.469

Effect. (QALY)	Incr. Effect. (QALY)	Incr. C/E (€/QALY)
8.046	0.000	0,00
8.030	-0.016	-227.721,30
8.976	0.930	15.578,96

Table 6 Results of the Markov cohort simulation

Robot-assisted radical cystectomy is the cheapest treatment strategy. Therefore, as already announced in the introduction, the incremental cost-effectiveness of robot-assisted brachytherapy and open radical cystectomy will be compared to robot-assisted radical cystectomy. The values shown in table 6 can all also be visualized with the ICER-plot shown in figures 3 and 4. In figure 3 the effectiveness is expressed in expected life-years and in figure 4 in quality-adjusted life-years.

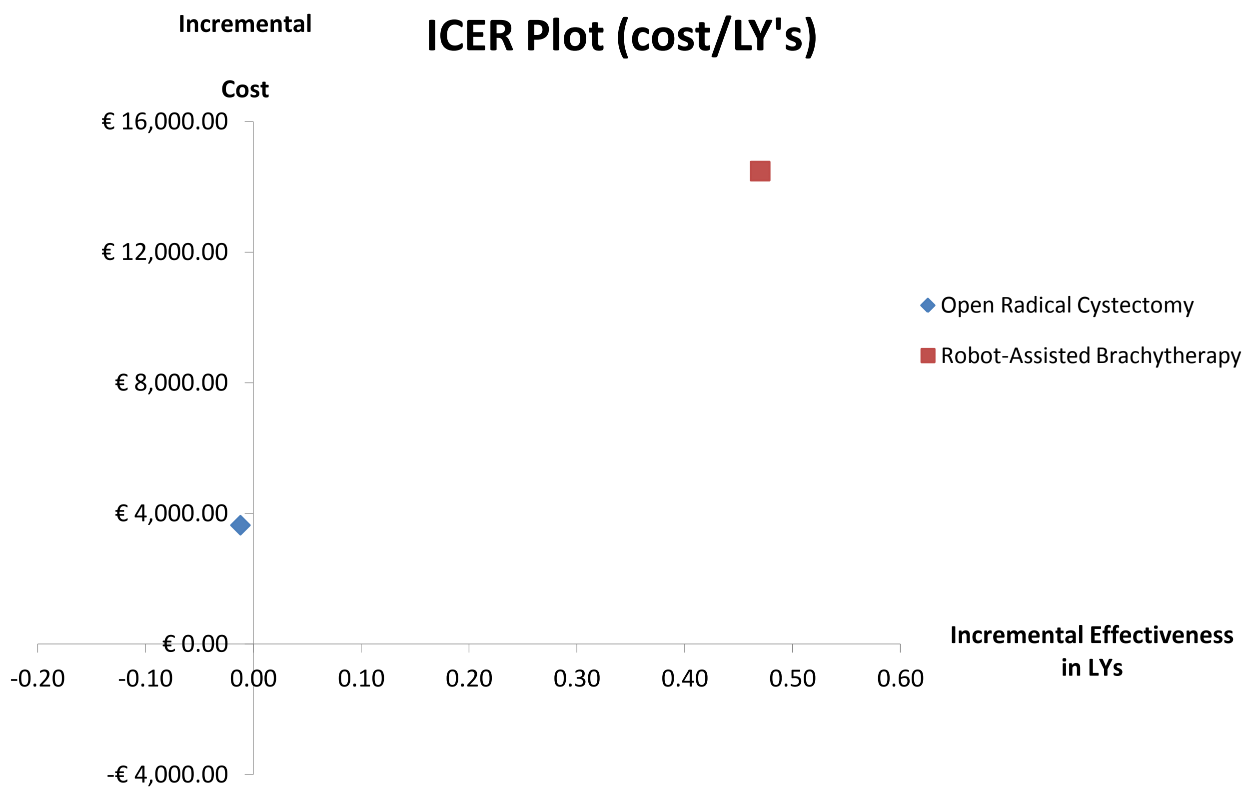

Figure 3 ICER plot with robot-assisted brachytherapy and open radical cystectomy compared to robot-assisted radical cystectomy with effectiveness defined as expected life-years

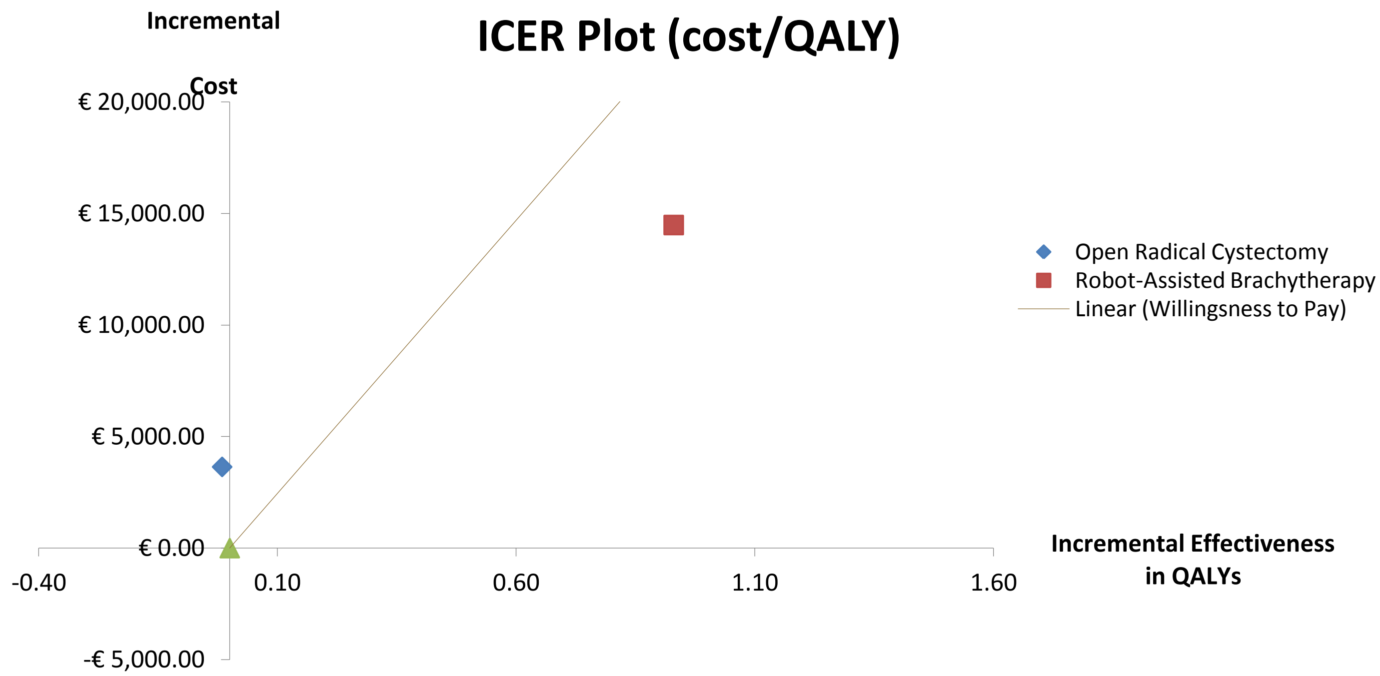

Figure 4 ICER plot with robot-assisted brachytherapy and open radical cystectomy compared to robot-assisted radical cystectomy with effectiveness given in quality-adjusted life years.

Figure 3 shows that patients treated with robot-assisted brachytherapy have a longer life-expectancy compared to those treated with robot-assisted radical cystectomy and those treated with open radical cystectomy a shorter life-expectancy. Both robot-assisted brachytherapy and open radical cystectomy are more expensive than robot-assisted radical cystectomy. Since not only the life-expectancy of the treatments is important but also the quality of life during this period, figure 4 gives even more insight on the situation. If we look at the incremental cost-effectiveness of open radical cystectomy compared to robot-assisted radical cystectomy in figure 4, it can be seen that this treatment strategy is dominated because this treatment has a lower effectiveness and higher costs. Therefore further analysis will only focus on comparing robot-assisted radical cystectomy to robot-assisted brachytherapy.

Both figures show that robot-assisted brachytherapy is the most expensive as well as the most effective treatment. Apparently, for this selected group of patients it is the case that those who are treated with brachytherapy have the longest life expectance with the best quality of life. The question is though whether the extra costs justify the increased effectiveness. This can be determined by comparing the ICER (incremental cost-effectiveness ratio) to the willingness-to-pay threshold. The willingness to pay was set at a value of €25.000,- in this study. The ICER of robot-assisted brachytherapy is €15.578,96 per QALY which is below the threshold. Therefore, based on this analysis can be stated that for this selected group of patient robot-assisted brachytherapy is the most cost-effective treatment and should therefore always be the treated of choice for these patients.

Deterministic Sensitivity Analysis

One-way sensitivity analysis

After performing the base incremental cost-effectiveness analysis it is important to look at the influence of some important parameters on this result. To do this a one-way sensitivity analysis has been performed to provide insight into the effect of a change in an input parameter on the outcome. The resulting Tornado diagram for the ICER is shown in figure 5.

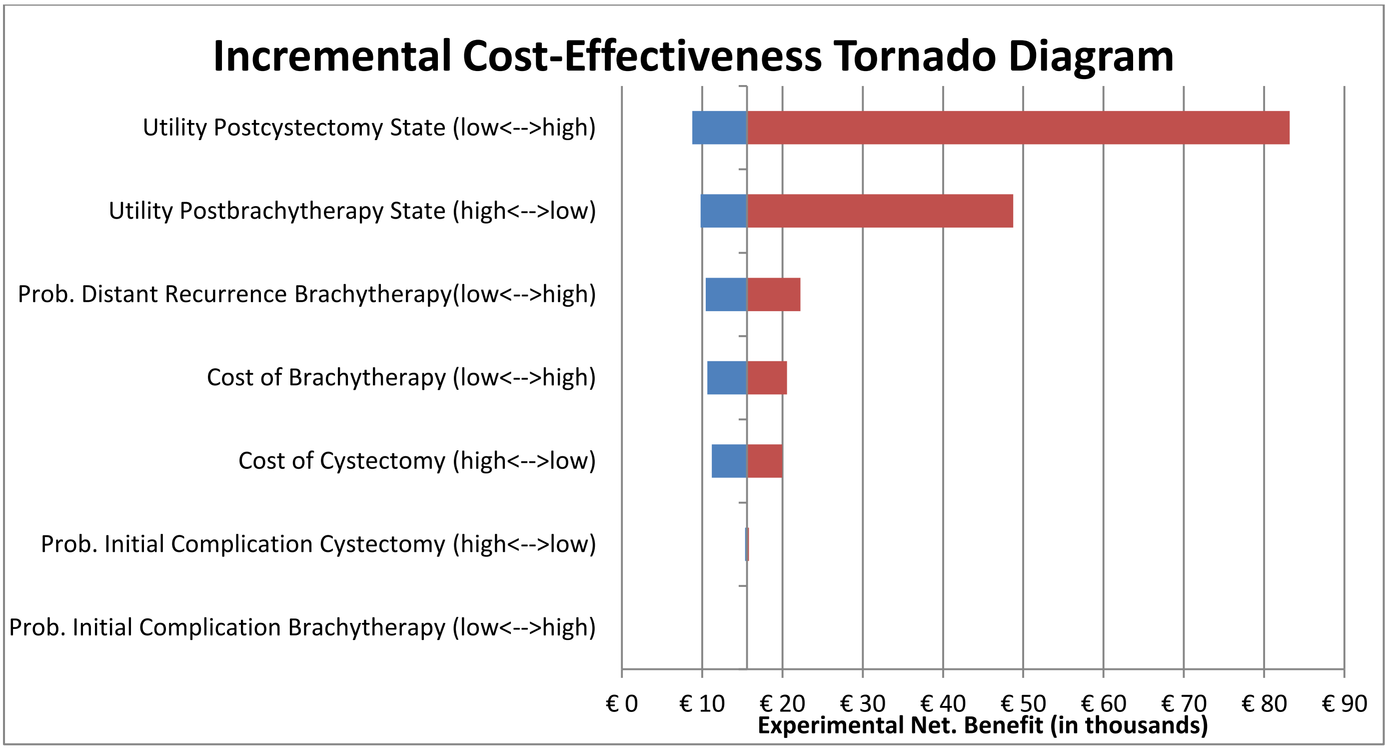

Figure 5 One-way deterministic sensitivity analysis. Effect of input parameters on Incremental Cost-Effectiveness of Robot-Assisted Brachytherapy compared to Robot-Assisted Cystectomy

When all input parameters have their normal value, the incremental cost-effectiveness was €15.578,96 per QALY. When the values of the input parameters are changed, also this outcome will change. First thing that stands out is that figure 5 shows that except for the long-term utilities none of the parameters can lead to a different preferred treatment strategy. For these cases robot-assisted brachytherapy always stays the most cost-effective treatment strategy.

So only for the long-term utilities the preferred treatment strategy can change. Even only a small change in utilities experienced on long term has a large impact on the cost-effectiveness of brachytherapy. In particular, a change in the benefit of cystectomy leads to a large different outcome and makes cystectomy the preferred treatment strategy. On the other hand, if the parameter of postcystectomy utility would have been lower this would have led to an increased benefit of brachytherapy. The opposite applies for postbrachytherapy utility. If this value would have been chosen higher it would have led to a higher preference for brachytherapy compared to cystectomy. However, if this utility would have been lower the ICER for brachytherapy compared to cystectomy would have been way above the WTP, making cystectomy the preferred treatment strategy. These findings are important since the important assumption was made to lower the postcystectomy utility. Now we can see that if the old value would have been used, brachytherapy probably would no longer be more cost-effective when compared to radical cystectomy. Therefore further research should be aimed at obtaining more accurate utilities.

Figure 5 shows that the probability of developing a distant recurrence after brachytherapy has a significant influence on the cost-effectiveness of brachytherapy. However, even if this probability would have had the highest possible value, brachytherapy still would have been the most cost-effective treatment.

The tornado diagram also shows that even a change of 20% in costs of both treatments only has a small influence on the cost-effectiveness of brachytherapy compared to cystectomy. So even though some assumptions have been made in calculating these costs, it does not change the decision for the preferred treatment.

Finally the initial chance of developing a short-term complication is evaluated for both treatment strategies since this is one of the major advantages of brachytherapy. However, it turns out that this parameter barely influences the incremental cost-effectiveness ratio.

Threshold analysis

The result of the threshold analysis for the cost of brachytherapy is shown in figure 6.

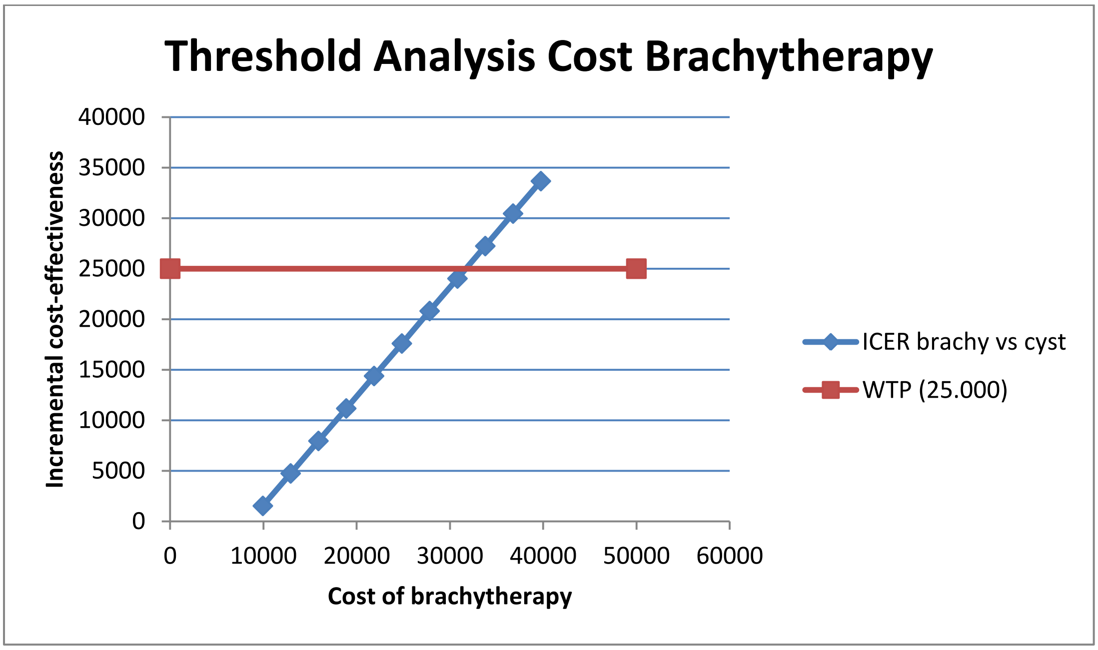

Figure 6 threshold analysis of cost of brachytherapy

The figure shows that as long as the treatment cost of brachytherapy can be hold below the €32.000,- the treatment can be interpreted as more cost-effective than cystectomy. The base value of the cost of brachytherapy was around €23.000,- which is way below this threshold. So even if the initial treatment will be more expensive than estimated, the robot-assisted brachytherapy will still be expected to be the preferred treatment strategy for the selected group of patients.

Two-way sensitivity analysis

Figure 7 shows the two-way sensitivity analysis that has been executed for the probability of development of a distant recurrence after robot-assisted brachytherapy and the cost of initial treatment of brachytherapy.

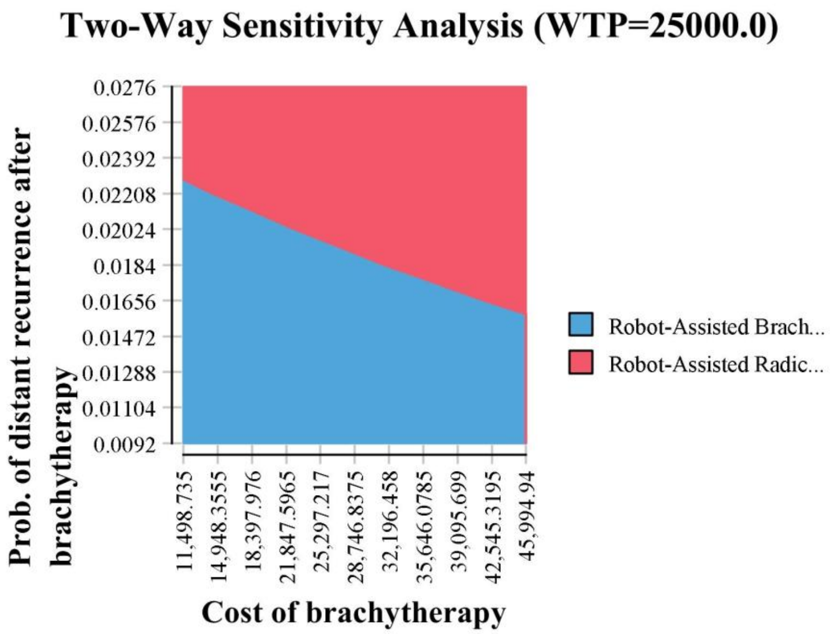

Figure 7 Two-way sensitivity analysis. Effect on preferred treatment strategy when both the cost of brachytherapy and the probability of developing distant recurrences after brachytherapy are changed.

Previously, the one-way sensitivity analysis showed that no matter which parameter was changed, as long as only one parameter was changed at a time, robot-assisted brachytherapy always stayed the preferred treatment for this selected group of patients. However, this two-way sensitivity analysis shows us that if two of the most important input parameter, cost of brachytherapy and probability of developing a distant recurrence after brachytherapy, both would have been worse than expected, robot-assisted radical cystectomy would have been the preferred treatment. Therefore costs should not become too high and also the recurrence rate has to be monitored very careful. If both of these parameters are not as positive as expected the implementation of brachytherapy could become a failure.

Probabilistic Sensitivity Analysis

A total of 1000 iterations have been executed with the probabilistic sensitivity analysis. The results and their interpretations are shown in this section.

Cost-effectiveness scatterplot

The outcomes of a probabilistic sensitivity analysis are many different values for the cost-effectiveness for both treatment strategies. When all these outcomes are plotted into one figure a scatterplot is result. The scatterplot of the analysis for this study is shown in figure 8. Only the first 500 iterations are shown because otherwise the dots could not be distinguished.

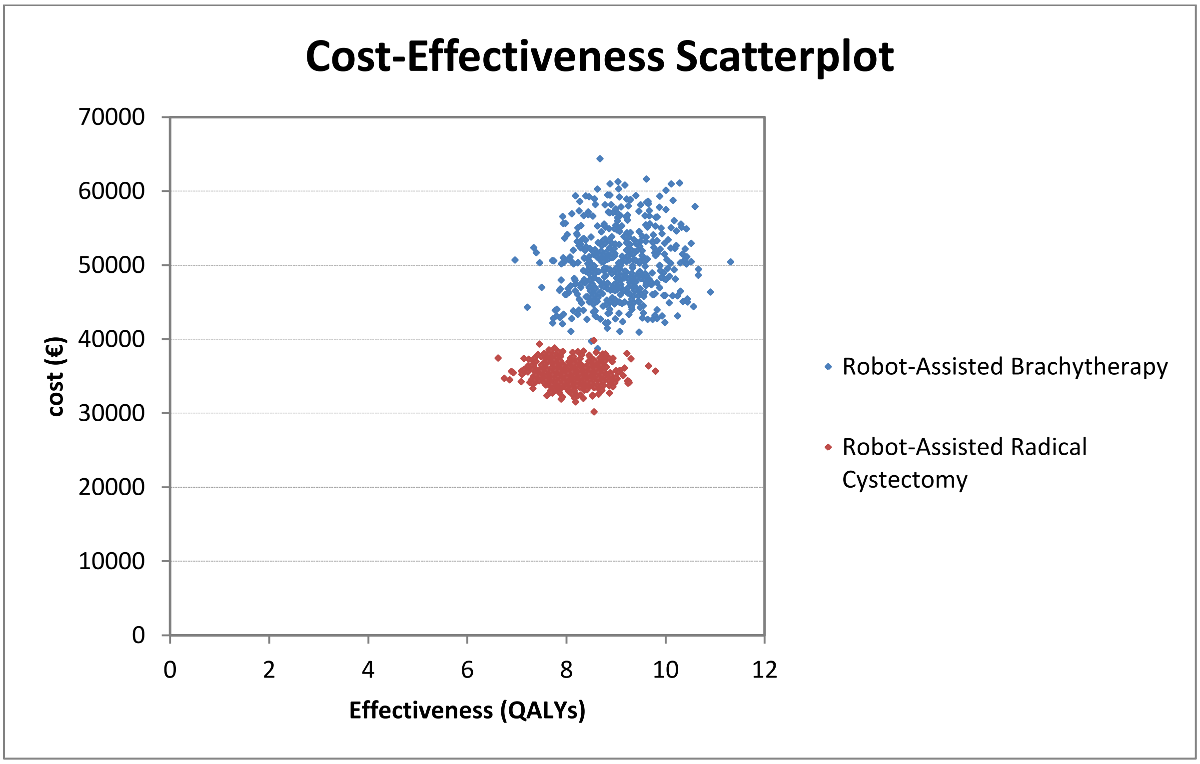

Figure 8 Cost-effectiveness scatterplot for 500 iterations with the probabilistic sensitivity analysis

First thing that is remarkable about figure 8 is that robot-assisted brachytherapy is always more expensive than robot-assisted radical cystectomy. However, for many cases it is also has a higher effectiveness. The outcomes for brachytherapy are also more spread, meaning that the cost-effectiveness of this treatment has a higher variance compared to cystectomy.

Based on figure 8 it is hard to tell if the extra costs of brachytherapy can also be justified by the higher effectiveness. This is easier to interpret when the incremental costs and incremental effectiveness are visualized for these treatments.

ICER plot

From the results of the probabilistic sensitivity analysis an ICER plot can be made to give more insight on the likelihood that robot-assisted brachytherapy should indeed be the preferred treatment strategy for the selected group of patients. Figure 9 shows this ICER plot.

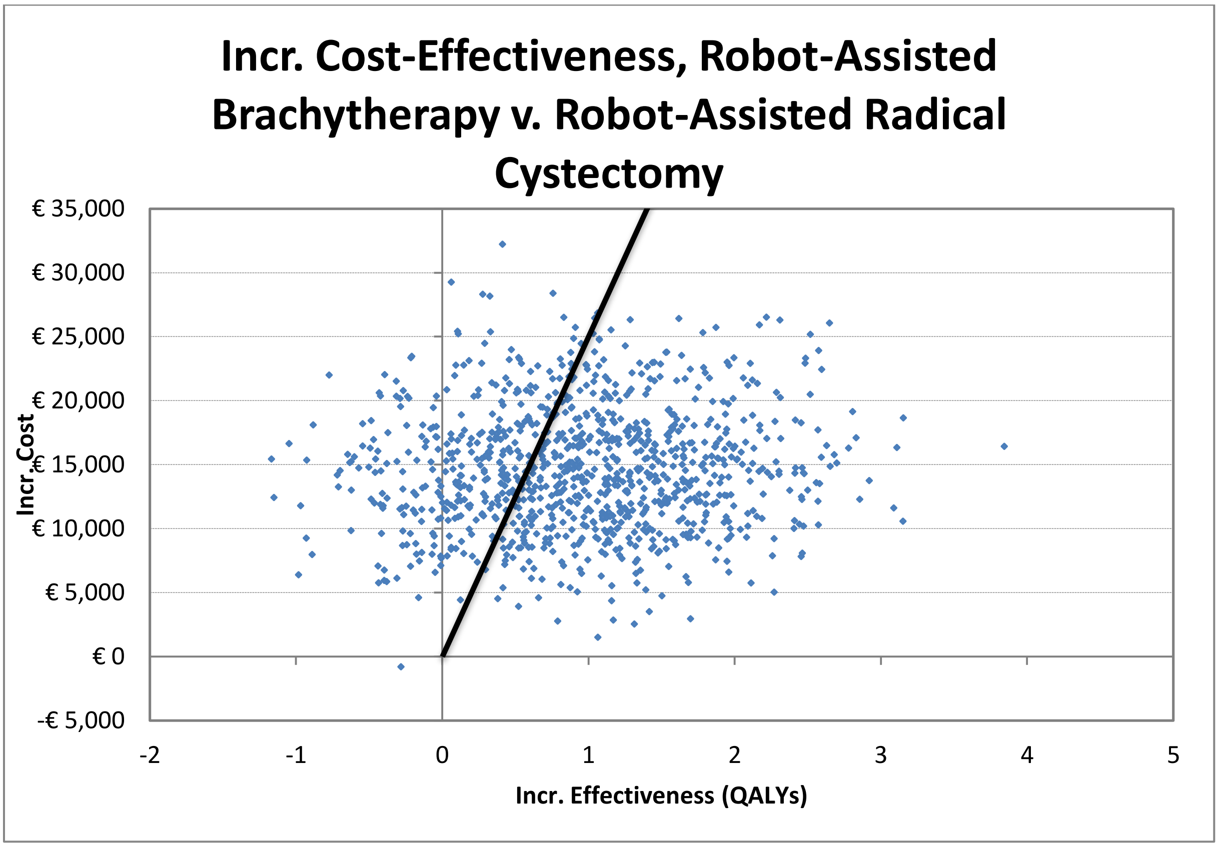

Figure 9 Incremental cost-effectiveness of robot-assisted brachytherapy compared to robot-assisted radical cystectomy. Outcomes are gained with a probabilistic sensitivity analysis.

As we say earlier, all outcomes of this analysis show higher costs for robot-assisted brachytherapy and it can also be seen that most outcomes show a better effectiveness for brachytherapy. Again raises the question if these additional costs can be justified by the better effectiveness. For this reason also the black line, which represents the willingness-to-pay threshold, is included in figure 9. For all points below this line brachytherapy is the more cost-effective treatment and for points above the line cystectomy is the preferred strategy. Because of the high density of the dots it is hard to see but for 67,3% of the 1000 iterations robot-assisted brachytherapy is the preferred treatment strategy. So it is most likely that robot-assisted brachytherapy will be more cost-effective than robot-assisted radical cystectomy though it is not completely certain.

Cost-effectiveness acceptability curve

Previous analysis showed that with a willingness to pay of €25.000,- the chance that robot-assisted brachytherapy should be the preferred treatment strategy is 67,3%. As discussed earlier this willingness-to-pay threshold can vary a lot for different diseases. To visualize which treatment strategy is expected to be more cost-effective for multiple willingness-to-pay values a cost-effectiveness acceptability curve is made.

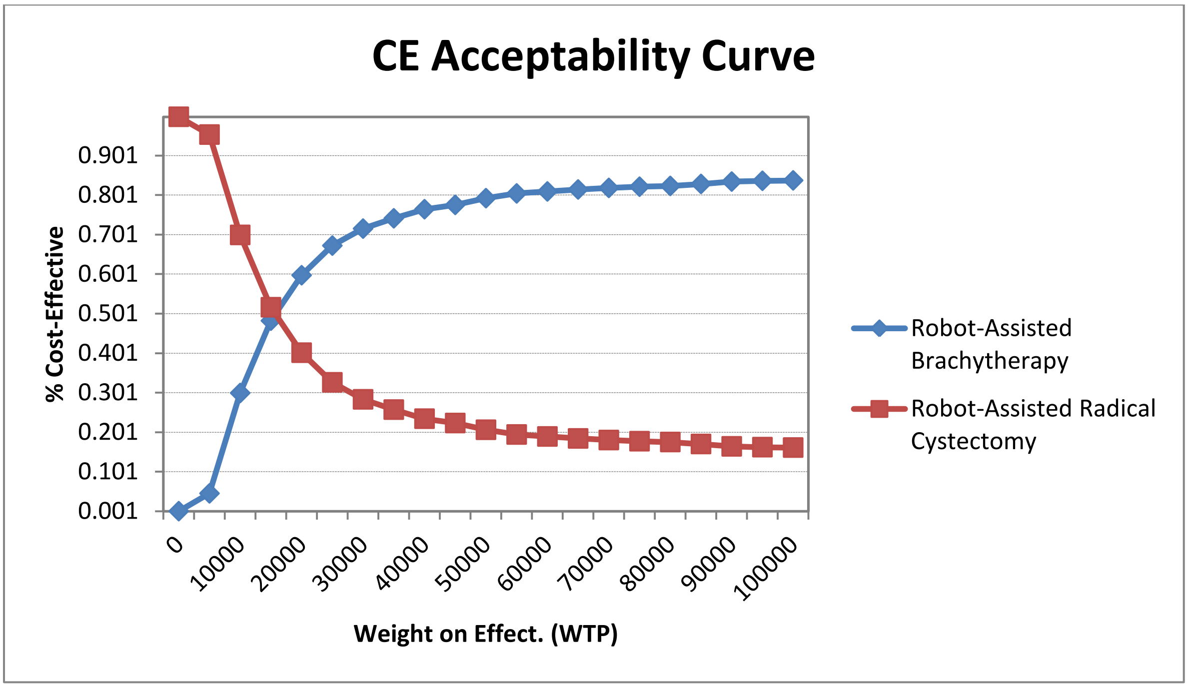

Figure 10 Cost-effectiveness acceptability curves showing the chances of being the preferred treatment strategy for both treatment strategies at multiple willingness-to-pay values.

Figure 10 shows that the higher the willingness-to-pay threshold, the higher the chance that robot-assisted brachytherapy is the preferred treatment strategy. For example a willingness-to-pay threshold of €50.000,- , which is also mentioned many times in literature sometimes, already gives a chance of 79,3% that brachytherapy should be the preferred strategy. Although it never becomes completely certain that it is the best treatment for muscle-invasive bladder cancer, this analysis again shows that it is most likely that robot-assisted brachytherapy is the preferred treatment strategy for a selected group of muscle-invasive bladder cancer patients.

Discussion

Main goal of this study was to determine the health-economic impact of brachytherapy as a new standard treatment for muscle-invasive bladder cancer compared to the current standard radical cystectomy. A cost-effectiveness analysis has shown that brachytherapy is a more expensive treatment but also has a better effectiveness compared to the other treatment strategies. Expected life-years after brachytherapy is at least comparable to treatment with cystectomy, which was also found in the article of *Konng et al.*[25] The incremental cost-effectiveness ratio is below a willingness-to-pay threshold of €25.000,-. and therefore it is most likely that robot-assisted brachytherapy is the most cost-effective treatment strategy for a selected group of muscle-invasive bladder cancer patients. Main reason to start this research was because literature already showed a comparable survival for patients treated brachytherapy and cystectomy though the health economic impact was never measured. The expectation was that this would be beneficial for brachytherapy. The fact that this study seems to confirm this expectation can only give more impulses to improve implementation of this treatment for muscle-invasive bladder cancer patients.

On forehand three treatment strategies had been identified in the literature study; open radical cystectomy, robot-assisted radical cystectomy and robot-assisted brachytherapy. However, the analysis showed that open radical cystectomy was dominated by the other treatment strategies and was therefore eliminated from further analyses. A deterministic sensitivity analysis showed that the only parameter that could lead to a change in preferred treatment strategy are the long term utilities experienced after both treatments. Even a small change for these parameters leads to a large difference in the outcome of the cost-effectiveness analysis. Therefore more research should be done to obtain more accurate values for these utilities. Threshold analysis showed that costs of initial treatment of brachytherapy should not be higher than €32.000,- or, according to a two-way sensitivity analysis, even less expensive if also the probability of developing a distant recurrence after brachytherapy is higher than expected. Also a probabilistic sensitivity analysis has been performed and showed that, if uncertainties of all input parameters are taken into account, the chance is 67,3% that brachytherapy is the preferred treatment. However, this is at a willingness-to-pay threshold of €25.000,- which is estimated quite low. The higher this threshold, the higher the chance that robot-assisted brachytherapy is more cost-effective than robot-assisted radical cystectomy for a selected group of muscle-invasive bladder cancer patients.

Strength of this analysis lies within the fact that a model has been built that reproduces reality quite well. The model has been built in collaboration with an expert team that treats bladder cancer patients with cystectomy and brachytherapy in daily practice. Also a literature study has been performed to perfectly identify the real treatment processes. For most input parameters sufficient literature could be found and for those cases where literature was lacking good estimations could be made. The only parameter that was not easy to estimate was the health-related quality of life of bladder cancer patients treated with brachytherapy. Therefore this data had to be collected which was done by sending EQ-5D questionnaires to patients treated with brachytherapy in Arnhem. After building the model could be validated. This was done by comparing the survival of patients simulated through the model with the survival of a comparable group of real bladder cancer in the Netherlands provided by the Dutch Cancer Registration. Other strength of this study is that many sensitivity analyses have been performed. These analyses indicate certain aspects of brachytherapy that require additional observations during the implementation of brachytherapy because when their values turn out to be worse in reality than the value used in this study, this will have a negative influence on the cost-effectiveness of brachytherapy. Though, unless these points of attention all analyses still showed that brachytherapy is the preferred treatment strategy for these patients.

On the other hand this study also has some limitations. First limitation is brachytherapy is only applicable for a limited part of all bladder cancer patients. The treatment would be even a better if it would also be applicable for other patients that now need to have their bladder removed. Another limitation is that brachytherapy is a difficult treatment to perform and so far not many surgeons are capable of doing it. Therefore first more surgeons should learn how to perform the treatment. The fact the hospital requires a surgical robot is also a limitation. If a hospital does not own such a device or if they own one that is already maximal utilized first a new robot system has to be bought to be able to perform the surgery. It is not likely that a hospital will buy a new robot especially for this treatment. A solution would be to centralize bladder cancer treatment with brachytherapy in a few hospitals. In this study experience with robot-surgery was not taken into account. However, it is scientifically proofed that performance with robot surgery is associated with a learning curve [41]. Also no distinction in data between hospitals with different patient volumes was made unless the fact that a patient volume often influences the quality of care.

The fact that this study indicates a positive health economic impact if a selected group of bladder cancer patients is treated with brachytherapy makes it interesting to continue with researching this subject. For example more research can be done to the input parameters, especially the health-related quality of life of both treatments should be determined with a bladder specific tool, and define more accurate values for the standard errors which were now most often estimated. Also the Markov model could maybe still be improved by defining health-state for each type of complication (each with its own disutility, costs and time to recovery) because right now all complications were taken together into one health-state in the model. Another improvement would be to make the age dependent mortality time-dependent, which was not done in current model. Last improvement would be to study whether there are more patients that can benefit from brachytherapy instead of cystectomy to treat their bladder cancer to increase the potential of brachytherapy.

Conclusion

After performing this research, an answer can be given to the research question of this study:

What is the health economic impact of brachytherapy as a new standard treatment for muscle-invasive bladder cancer compared to the current standard radical cystectomy?

Cost-effectiveness analysis has shown that robot-assisted brachytherapy is a more expensive treatment but also has a better effectiveness compared to open radical cystectomy and robot-assisted radical cystectomy. The incremental cost-effectiveness ratio is €15.578,96 per QALY which is below a willingness-to-pay threshold of €25.000,-. Therefore it is most likely that robot-assisted brachytherapy is the most cost-effective treatment strategy for a selected group of muscle-invasive bladder cancer patients. Deterministic sensitivity analysis showed that long term utilities after both treatments had the biggest impact on the cost-effectiveness of brachytherapy. They also were the only input parameters for which accounted that a change in the base value could lead to a change in decision for treatment strategy from brachytherapy to cystectomy. Other input parameters showed to have less influence on the outcome and as long as only one of these parameters was changed at a time, robot-assisted brachytherapy always would be the preferred treatment strategy. Threshold analysis showed that costs of initial treatment of brachytherapy should not be higher than €32.000,- or, according to a two-way sensitivity analysis, even less expensive if also the probability of developing a distant recurrence after brachytherapy is higher than expected. Probabilistic sensitivity analysis showed that, if uncertainties of all input parameters are taken into account, the chance is 67,3% that brachytherapy is the preferred treatment. However, this is at a willingness-to-pay threshold of €25.000,- which is estimated quite low. The higher this threshold, the higher the chance that robot-assisted brachytherapy is more cost-effective than robot-assisted radical cystectomy for a selected group of muscle-invasive bladder cancer patients. Additional research should be performed to find more accurate values for the input parameters of the model so it becomes more certain that brachytherapy is indeed the best treatment strategy for these patients.

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Appendix

Appendix A: Literature Study

This section contains the literature study that was performed to answer the first two sub questions. These questions will identify the entire treatment process of the current situation and the situation in which the brachytherapy is used as initial treatment. With this knowledge a model can be built that simulates these processes.

Bladder cancer and its treatment

As already mentioned in the introduction of this research, bladder cancer is an often occurring type of cancer and its treatment can be accompanied with huge costs. Therefore it is important that each specific case of bladder cancer is treated optimal. This section of the research is about indentifying which different types of bladder cancer there are and how they are currently treated. Of each of these treatments will be looked at the advantages and disadvantages and which improvements that already have been established.

Bladder cancer in general

Transitional-cell carcinoma comprises nearly 90% of all primary bladder tumors. These tumors originate in the bladder mucosa, then progressively invade the lamina propria and move sequentially into the muscularis propria and the perivesical fat. Later on it might even invade into adjacent pelvic structures. All with increasing incidence and progression of lymph node involvement and metastasis[5]. These different degrees of disease progression require different treatments. This treatment planning is mainly based on standardized tumor gradation and is performed with TNM classification[22]. The extent of tumor tissue invasion is used to define tumor stage, from stages Ta-T4 of whom T2-T2 is called muscle-invasive bladder cancer.

The specific cellular morphology is used to assign a tumor grade from grade I (well differentiated) to grade III (poorly differentiated). In general, for the diagnostics of bladder cancer it is most important to make a divide between non muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) because both require totally different treatments. Of all bladder cancers about 30% are found as invasive bladder cancer because the tumors have invaded the smooth muscle or beyond (Stage T2-T4). [21]

Then how is bladder cancer diagnosed? Most common symptom of bladder cancer is painless haematuria. Sometimes this goes together with urgency, dysuria, increased frequency and in advanced tumors pelvic pain and symptoms related to urinary tract obstruction[21]. When a patient with painless haematuria is presented, this is an indication to perform a transurethral resection (TUR). The goal of TUR is to make the correct diagnosis and remove all visible lesions[21]. It is a critical procedure for the treatment of bladder cancer because it is very important to determine to which extent the tumor has invaded the bladder wall. When the pathological report of the TUR has been completed and the tumor has been graded, further treatment can be planned.

In treating non-muscle invasive bladder cancer TUR often suffices[44]. However, because of a high recurrence rate and progression to muscle-invasive bladder cancer adjuvant therapy has to be considered in all patients. This adjuvant therapy can for example be intravesical chemotherapy (e.g. mitomycin c) or intravesical immunotherapy (e.g. bacillus Calmette-Guérin)[26][43]. Current standard treatment for muscle invasive bladder cancer is radical cystectomy. Next part of this chapter will further elaborate on this treatment. About half of all patients that have had radical cystectomy develop metastases. There is no curative treatment to metastases as a result of bladder cancer. Therefore the only possibility is to prolong the patient's life expectancy and the associated quality of life which is done with systemic chemotherapy. Guidelines suggest that Cisplatin combinated chemotherapy should be provided as first-line treatment. A choice can be made between MVAV and gemcitabine/cisplatin though gemcitabine/cisplatin is most often chosen since it is less toxic. Median survival of this palliative treatment varies between twelve and fourteen months[5].

Radical cystectomy

Radical cystectomy includes en bloc cystectomy (bladder removal), bilateral pelvic iliac lymph node dissection and some form of lower urinary tract reconstruction[45]. In case of micrometastates, chemotherapy is given before surgery to improve overall survival[8]. Radical cystectomy has become the golden standard in high grade invasive bladder tumors because it provides the highest survival as well as the lowest recurrence rate in these patients[7]. When radical cystectomy is performed an accurate evaluation of the primary bladder tumor as well as the regional lymph nodes can be done which allows for adjuvant treatment strategies to be based on pathologies rather than on clinical staging[8]. After the surgery the patients will have be monitored to check if the cancer has recurred. Therefore the patient gets a consult with the physician, physical examination, blood test and some form of imaging every three months in the first three years after surgery, every six months in the fourth and fifth year and after that the patient will be seen only once a year. Overall-survival of all patients that were registered by the IKNL to have had radical cystectomy in the Netherlands from 1995-2013 is shown below[46].

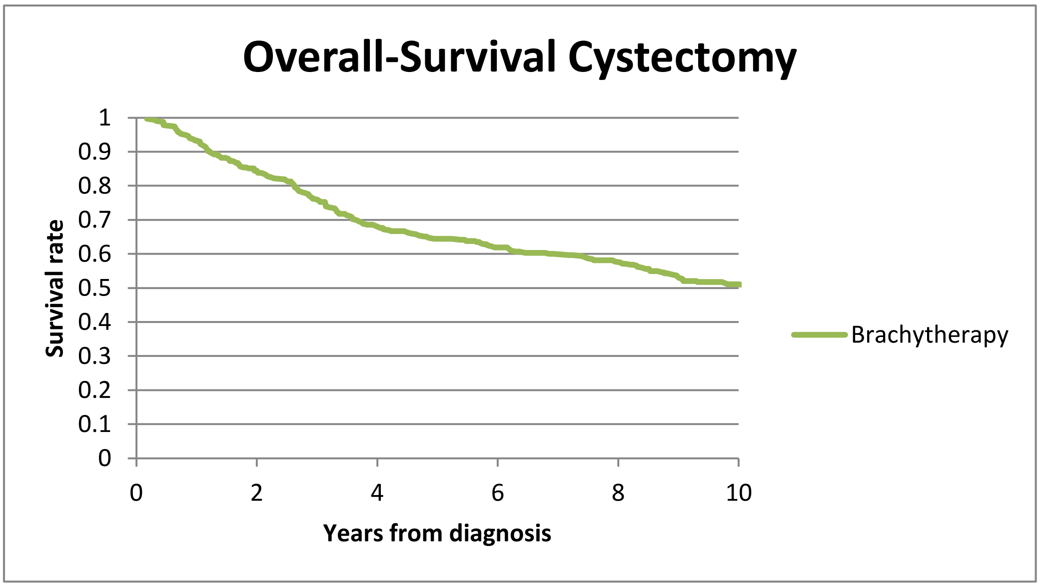

Figure 1 Overall survival of all patients with a radical cystectomy in the Netherlands (1995-2013)

One of the main aspects of radical cystectomy is that it requires some form of urinary diversion because the patient no longer has a bladder. Urinary diversion is a surgical procedure that reroutes the normal flow of urine out of the body, which off course is necessary after radical cystectomy. This flow of urine can end either in a stoma or a surgically created internal reservoir. Ureterosigmoidostomy was the first widely used surgical technique providing permanent urinary diversion. The ureters were anastomosed to the sigmoid so the anal sphincter could be used for continence. Though, decline in renal function over time, an increased risk for secondary malignancies and metabolic complications were the reasons that it was not very useful[47]. Urinary diversion techniques that are nowadays used are ileal conduits, continent cutaneous diversions and orthotopic neobladders. An ileal conduit uses a section of the bowel to serve as a passage for urine from the ureters to a stoma. This technique, which is most cost-effective of all diversion techniques[7], has become the 'golden standard' because it has as main advantage that the bowel tissue still has a peristaltic function which drives the urine to the stoma and prevents it from flowing back to the kidney. If an ileal conduit is not possible, for example when the bowel has had too much exposure to high doses of radiation, a continent cutaneous diversion is an alternative. With this technique an internal reservoir is created from a section of the bowel from which the urine has to be drained by the patient. A final optional technique uses the creation of a bladder substitute, a so-called neobladder. An internal reservoir is created and connected to the ureters on the one hand and to the urethra on the other. The urine leaves the body in a more natural way; however in some cases a catheter must be inserted through the urethra to completely empty the reservoir. Patients with this type of permanent diversion also have a higher chance of urinary incontinence. [47][48]

Figure **X** below shows the urinary diversion techniques that were used in the Netherlands in the year 2013[46]:

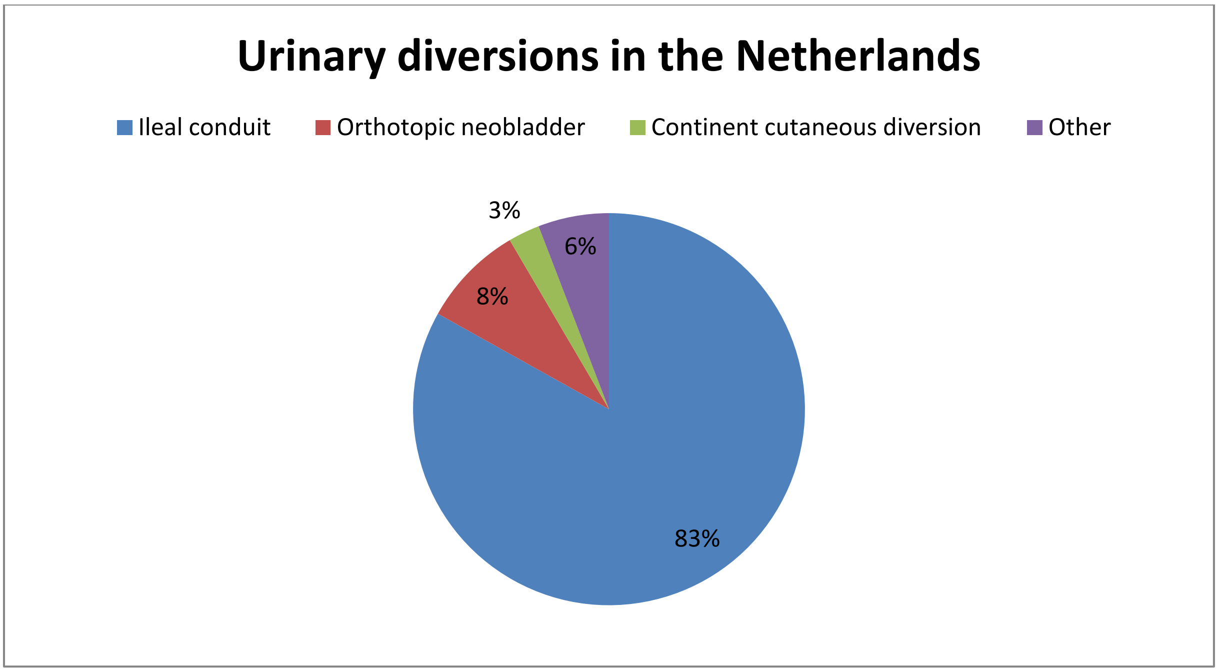

Figure 2 Urinary diversions in the Netherlands in 2013

Although the quality of urinary diversion techniques after radical cystectomy has improved in recent years it still is one of the most traumatic cancer operations in terms of alteration in life-style and psychological stress[18]. For example patients have to learn how to live with their stomas. A continent stoma requires daily care aimed at maintaining a clean and healthy stoma. If this cleaning is not done properly a symptomatic urinary tract infection will occur. Another problem could be that patients worry that people have negative reactions to their urinary diversion. Although most people will never know patients are wearing a stoma it still has a bad influence on the patient's body image[50]. Urinary leakage is another result of radical cystectomy with a negative impact on the patient's quality of life. Finally sexual dysfunction is an important quality of life issue after radical cystectomy since 90% of the men suffers from erectile dysfunction after the surgery[20].

Problems with the urinary diversion are not the only disadvantage of radical cystectomy. Another major disadvantage of this treatment is that the surgery has potential for serious complication, most of which develop in early postoperative period. For example the article of *Novotny et al.*[10] found that 27,3% of the patients developed at least one perioperative complication. At last, radical cystectomy also leads to pain, large scars and it has a long recovery time.

Improvements to current treatment

In order to reduce the high perioperative complication rate, minimally invasive techniques for radical cystectomy have been explored[13]. Examples of minimally invasive techniques are laparoscopic and robot-assisted radical cystectomy. The techniques might require more operation time, it also leads to a significant reduction in early postoperative morbidity and fewer postoperative complications. In particular major complications occur less frequent after a robot-assisted surgery[14]. Examples of improvements by minimally invasive surgery are decreased blood loss, lower transfusion rates, quicker recovery of bowel function, decreased hospital stay, a more rapid recovery, reduced pain medication and reduced scarring[15][16]. At the same time minimally invasive techniques show recurrence free survival and cancer-specific survival estimates similar to those reported in literature for open radical cystectomy[17]. For these reasons these techniques are a huge improvement in bladder cancer treatment. Later in this chapter more information will follow on how robot-assisted surgical techniques can be an improvement on the current treatment.

Even with improvement of quality of both urinary diversion and minimally invasive surgical techniques the effects of radical cystectomy can still be so severe that some patients are willing to give up the possibility of maximal survival in favor of a better quality of life[18]. Especially for young patients the loss of potency and the social handicap of a stoma heavily influence their quality of life[21]. Conservative treatments like bladder preserving therapy may offer an alternative to radical cystectomy with a possible reduction of side effects[21].

One of such bladder preserving therapies is partial cystectomy preceded by neoadjuvant chemotherapy. When compared with radical cystectomy it is perceived to be less morbid and from a technical perspective easier procedure[22]. However, the treatment lost a lot of popularity over the years because many patients treated with partial cystectomy experienced intravesical tumor recurrence. Currently partial cystectomy is only performed in highly selected patients with invasive bladder cancer[23].

Other treatment strategies are aimed at complete bladder preservation. For example the surgeon can choose to treat a bladder cancer patient with only a transurethral resection (TUR), external beam radio-therapy (EBRT), chemotherapy or a combination of those techniques. In recent years a new treatment strategy has been developed for a specific group of bladder cancer patients. This treatment consists of a combination of TUR, EBRT and interstitial brachytherapy. This treatment is currently already often used as an alternative for radical cystectomy[24]. In the next part of this chapter all important aspects of brachytherapy as a treatment for muscle-invasive bladder cancer will be discussed. How robot-assisted surgery can contribute to an improved treatment for both radical cystectomy and brachytherapy will also be discussed.

When summarizing this section of the research can be concluded that muscle-invasive bladder cancer is transitional-cell carcinoma invaded to at least the muscle layer of the bladder wall. As long as there is no distant metastases the disease can be treated with radical cystectomy consisting of en bloc bladder resection combined with some form of urinary diversion. This treatment has the best survival rate but is also accompanied with many complications and has a negative impact on quality of life. Technological advances have improved treatment with radical cystectomy though a bladder preserving treatment would be preferred.

Brachytherapy

As was already mentioned in the previous section of this research, treatment of muscle-invasive bladder cancer could be improved when brachytherapy is used as an alternative for radical cystectomy. This section will gives more background on brachytherapy and how it is performed. Also the addition of robot-assisted surgical techniques will be evaluated.

History of brachytherapy

Interstitial radiotherapy, also called brachytherapy, was first introduced in oncologic practice almost 100 years ago. The principle of interstitial radiotherapy is that a radioactive source is implanted close to the tumor and radioactive irradiation damages DNA of the cells around. This will ultimately lead to cell dead. Unfortunately also healthy cells of the patient and the surgeon also receive high dose if he has to implant such a radioactive source. For this reason and because improvements were made with external beam radiotherapy, brachytherapy was not used for a long time.

However, the development of remote afterloading techniques led to a revival of brachytherapy. With this technique empty catheters are implanted to the bladder wall. After the patient has returned to her room, the radioactive sources are introduced through the tubes. Also development of high-dose-rate (1960) and pulsed-dose-rate (1970) afterloading techniques led to even more improvements of the technique[21]. Brachytherapy as treatment for solitary bladder cancer was introduced by Breur and De Waard in 1951 in Rotterdam and continued by van der Werf-Messing[58]. Their researches led to some important improvement of which most important was the introduction of a short course of EBRT to kill micrometastases in regional lymph nodes, initially postoperatively and later preoperatively[59]. Thereafter, poor prognostic factors were identified which resulted in an approach that has been used up to the present[60]. Worldwide agreement has been made about following indications for interstitial brachytherapy preceded by a short course of EBRT: a solitary T1G3, T2 or T3a bladder tumor, with a diameter <5 cm, in a patient fit enough to undergo a surgical procedure[21]. However, there are some national differences. In the Netherlands lymphadenectomy is not included in the standard procedure and partial cystectomy is performed only exceptionally whereas both are the case in France[61].

Brachytherapy provides to opportunity to treat muscle-invasive bladder while preserving the bladder. This will most likely result in an improved quality-of-life. On the other hand it is important that the conservative treatment does not lead to a much higher recurrence rate compared to radical cystectomy. Due to a lack of consistent scientific proof that brachytherapy should always be performed in selected cases, brachytherapy is not (yet) included into the national guidelines regarding the treatment muscle-invasive bladder cancer[5]. However, in some Dutch hospitals EBRT followed by brachytherapy is already standard treatment in selected patients[44]. Some of these hospitals have published their results of patients they have treated with brachytherapy and results are promising [62][63][16][17][18]. Each hospital performs the operation in slightly different ways, depending on their own preferences and experiences. Therefore the review of *Koning et al.*[25] provides a good overview of the results of brachytherapy as treatment for early-stage muscle-invasive bladder cancer. For a period of five years the review shows a recurrence-free probability of 75%, a metastasis-free probability of 74% and an overall survival probability of 62%. A survival curve made of the data of IKNL of all Dutch patients treated with EBRT followed by brachytherapy within the period 1995-2013 is shown below. This figure shows a 5-year overall survival of 64% which is comparable to the 62% found by *Koning et al*[25]. The 10-year overall survival according to the IKNL is 51%.

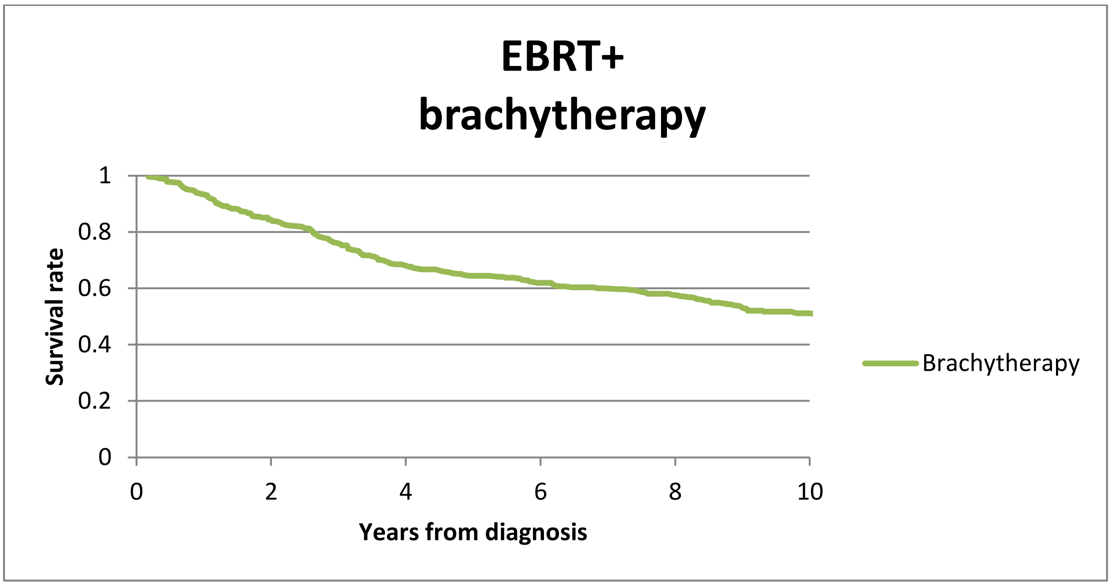

Figure 3 Overall survival of all patients with a EBRT followed by brachytherapy for muscle-invasive bladder cancer in the Netherlands (1993-2013)

Treatment process of brachytherapy

As mentioned earlier this paper, a patient that is presented with common bladder cancer symptoms like haematuria will undergo a TUR. Based on the pathological findings of this operation the further treatment can be planned. If a patient satisfies to the also earlier mentioned indications the physician can choose to treat this patient with EBRT followed by brachytherapy. Within a mean time of three weeks after TUR external beam irradiation will be performed. This is done in 3-4 fractions of 3,5 Gy in one week for cT1 tumors or 20 fractions of 2 Gy in four weeks for cT2 tumors. Within a week after the last fraction of EBRT the surgical procedure for brachytherapy follows. During this procedure approximately three afterloading catheters are inserted into the bladder wall through the consecutive tissue layers and finally detached to the skin surface. Also for some indications the physician chooses to perform a partial cystectomy. As soon as possible after the operation a CT scan has to be made. This CT scan is used to make a reconstruction of the implantation and a computer planning for the dose delivery. When this is all done delivery of the internal dose can be started. The total dose will be either 60 or 30 Gy, depending on a short or long course of EBRT. This dose is delivered with a low dose rate over a period of six or three days. When the irradiation is completed the catheters are withdrawn without anesthesia.

In the period after the operation it is important to often check whether the cancer has returned or not. Therefore follow-up is needed. This consists of a consult with the physician, blood tests, cytoscopy and urine cytology and is performed every three months for the first three years after surgery, every six months in the fourth and fifth year and afterwards only once a year. If there is a suspected area within the bladder, a TUR will be performed. Result of the pathological findings of the treatment determines further treatment. If it turns out that the suspected area was no recurrence, the patient will continue will his follow-up schedule. If the suspected area turns out to be a non-invasive local recurrence the physician should consider adjuvant therapy for which can be chosen between intravesical chemotherapy or intravesical immunotherapy. Regardless of this adjuvant therapy the tumor can progress to either a muscle-invasive local recurrence or a distant recurrence. When a muscle-invasive local recurrence is detected the patient will have to undergo radical cystectomy since it is for radiation related reasons not safe to perform a new brachytherapy. This is called a salvage cystectomy. If a distant recurrence is detected, curative treatment is not longer possible. As discussed earlier this chapter the patient will then receive cisplatin combinated chemotherapy as a first-line treatment.

(dis)advantages of brachytherapy

Main advantage of brachytherapy as initial treatment for MIBC compared to radical cystectomy is that patients remain normal bladder function. Also all morbidities related to a urinary diversion are prevented. On the other hand brachytherapy is a much less invasive operation compared to cystectomy, resulting in fewer complications. According to *van der Steen et al.* [18] only 17% of the patients develops a perioperative complication. These complications are mostly surgical complications and sometimes radiation related complications. Normally, if there are no complications, patients do not experience physical complaints. Only bladder spasms might occur if the catheters are located uncomfortable. The patient should not move for the period of brachytherapy, which might also be quite uncomfortable.

Main disadvantage of brachytherapy is the risk that the treatment will lead to higher recurrence rates and lower cancer-specific survival. However, if the right patients are selected it seems that recurrence rates are not extremely higher for brachytherapy. Another disadvantage is that if a patient gets a muscle-invasive local recurrence the patient still has to perform a radial cystectomy with all the costs and morbidities that are accompanied. What can also be a problem is that there is a large difference in experience with brachytherapy between hospitals which might lead to quality of care differences. Last point of discussion is that it is quite difficult to place the catheters in the optimal position during surgery. In fact this can only be obtained if the surgery is performed with robot-assistance. Robot-assistance has the advantage that the surgery can be performed much more precisely, leading to less complications and a more effective treatment. On the other hand it can be very expensive and not all hospitals have a robot available. For these reasons there will not only be looked at the effectiveness of brachytherapy compared to cystectomy but also to the average costs of the entire treatment process.

When summarizing this section can be concluded that brachytherapy is a bladder preserving treatment for muscle-invasive bladder cancer based on eliminating tumor cells by administering a local radioactive dose through catheters that are surgically implanted in the bladder wall. Health-related quality-of-life is expected to be better if treated after brachytherapy, complication rates are lower and recurrence rates comparable. Due to the complexity of the surgery it is recommended to perform the operation with robot assistance, though this can also lead to higher cost.

Appendix B: Model assumptions

During development of the model, sometimes assumptions had to be made. Some of these assumptions have already been discussed in the previous section. This section contains some other assumptions that were made during modeling. It is also explained why it is possible to make the assumption.

General assumptions:

- The model is divided in cycles of three months, which is equal to the time between follow-up moments. This are also the moment on which in practice the most important treatment decisions are made. In the period between these follow-up moments it was assumed that the situation stays stable.
- Probabilities do not change over time. In practice it might for example be that chances for local recurrence are higher in the first few months after treatment. Also the probability of dying from other causes will get higher when patients get older during simulation. An exception is made for the first cycle. The initial values for the transition probabilities, utilities and costs will differ from the values in next Markov cycles. This is something that is actually not possible in Markov simulation because transition probabilities should be equal over time. However it also simplifies the model because fewer health-states are needed and therefore fewer assumptions have to be made.
- A Markov model has no memory. This means that the chance of developing a complication is the same for a person that has had a complication before when compared with a person that has not had a complication. In practice it might be that someone that has already had a complication has a higher chance of getting another one.
- To simplify the model it was assumed that each complication is solved at the start of the next cycle. For most complications this will be an overestimation since the complications are often solved shortly after they occur. Other symptoms on the other hand might lead to problems to the patient for the rest of his life. So this assumption can be made.
- Within the model was assumed that development of complication has no consequences on the probabilities of having recurrences. On the other hand, having an invasive local recurrence after brachytherapy increases the chance of getting a distant recurrence.
- No distinction has been made between hospitals. Though for example experience with robot surgery and high volumes of patients with bladder cancer might influence the results of the treatment.
- It was assumed that the initial treatment has no influence on the further process after having metastases. Issues like tumor progression during chemotherapy for metastases and chemotherapy related complications are not modeled. Since these values will be the same for both treatments they will not result in an advantage for either cystectomy or brachytherapy this can be assumed. On the other hand cystectomy and brachytherapy related complications during the metastatic phase are still modeled since this does lead to a difference in results for both treatments.
- When complications after a cystectomy are severe, it might be needed to perform a reoperation. Off course the bladder cannot be removed again but this still remains a significant operation. For brachytherapy it is assumed that the treatment can only be performed once since this would lead to irradiation related health problems.

Cystectomy related assumptions:

- Sometimes patients first get a partial cystectomy and afterwards they get a complete cystectomy. This is registered in the model as a complete cystectomy as initial treatment. The same accounts for the surgical technique. If the operation is started with robot-assistance but during surgery the surgeon switches to an open surgery than the latter is registered.
- In the model there has been made no distinction between a local and distant recurrence after cystectomy since both are not curative. There will not be a large difference in results of their treatments.

Brachytherapy related assumptions:

- Within the model there has been made no distinction between potentially different brachytherapy doses. It was assumed that all patients received 10x 2,5 according to the guidelines.
- In literature nowhere is mentioned that treatment of non-invasive bladder cancer is accompanied with a higher mortality rate. Therefore the assumption is made that this rate is equal to the complete remission state.
- For the health-state in the brachytherapy strategy where the patient develops an invasive local recurrence a constant value for utility, costs and mortality is modeled based on the findings of the cystectomy strategy because this patient will get a salvage cystectomy. Initial values are different because of the initial surgery. This patient is assumed to have the same survival and utility compared to patients that receive cystectomy as initial treatment.

Appendix C: Specification of cost EBRT + brachytherapy

Brachytherapy	Cost (€)	Reference
Surgeon fee	3500.00	[37]2011
Per-case cost of robot	2779.552	
investment robot per case	617.0518	[64] 2015
maintenance robot per case	312.5	[64] 2015
sterilization material	250	[64] 2015
disposable instruments	1600	[64] 2015
Utilization	3025.00	
cost per minute	24.20	[37]2011
median utilization time	125.00	[64] 2015
Anesthesia cost	171	
cost per minute	1.71	[37]2011
median anesthesia time	100.00	[64] 2015
LOS cost	3094.00	
cost per day	476.00	[65]2015
median days LOS	6.50	[64] 2015
Blood transfusion	216.00	[65]2015
Brachythepy catheters	1000	[64] 2015
Radiotherapist	2500.00	[64] 2015
Laborants	2000.00	[64] 2015
CT scan	140	[65]2015
Total direct cost	22997.47	