HEALTH ECONOMIC EVALUATION OF WATCH AND WAIT POLICY AFTER CLINICAL COMPLETE RESPONSE TO NEOADJUVANT CHEMORADIOTHERAPY IN LOCALLY ADVANCED RECTAL CANCER PATIENTS

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Background: Non-surgical Watch & Wait (W&W) policy has recently gained prominence in the treatment of patients with locally advanced rectal cancer with a clinical complete response after neoadjuvant chemoradiotherapy. By omitting surgery, peri and postoperative morbidity and mortality could be avoided.

Objective: The aim of this study is to estimate long-term clinical value of Watch & Wait strategy in terms of quality of life, life expectancy and costs.

Method: A Markov model was used with input parameters derived from demographics, literature and expert elicitation. A hypothetical population of 100,000 locally advanced rectal cancer patients was considered at the restaging phase after neoadjuvant therapy. The current golden standard of TME surgery was compared with W&W implementation, and a univariate sensitivity analysis was performed.

Results: The model indicates that an implementation of Watch & Wait policy leads to an increase of Quality-Adjusted Life Years (QALYs) of 0.089 and cost savings of €511 ($583) per patient.

Discussion: This study provides supportive evidence for the implementation W&W strategy. Furthermore, it shows an incentive for further research into increasing sensitivity and specificity rates for Watch & Wait inclusion.

INTRODUCTION

The current standard treatment option for patients with locally advanced rectal cancer (LARC) exists of neoadjuvant chemoradiotherapy (nCRT) prior to total mesorectal excision (TME).[1] However, TME is associated with 4% perioperative mortality rate,[2] severe adverse effects, such as a 3-11% anastomotic leakage rate,[3,4] and morbidity, such as permanent or temporary colostomy, and bowel, bladder and sexual dysfunction.[5] In 15-27% of treated LARC patients, no residual tumor or tumor positive lymph nodes are found in resection specimens after surgery, indicating a pathological complete response (pCR) to nCRT.[6-8]

By clinically predicting a pCR, the research group of Habr-Gama et al. have been the first to assess whether patients with a clinical complete response (cCR) could safely be treated non-surgically, with intensive clinical and imaging follow-up.[9] In their series of studies from Brazil, cCR rates varied from 26% to 38% and recurrence rates were 3-6% in the most recent studies and 27% in the first study.[9-13] Similar results were achieved by a small Dutch clinical cohort study reporting a recurrence rate of 5%.[14] Driven by these positive initial results, a large international collaborative was launched to investigate the non-surgical Watch & Wait (W&W) policy further.[15] Moreover, using clinical assessment (digital rectal examination and endoscopy) combined with MRI (T2W and DWI), sensitivity and specificity rates of 71% and 97% respectively can be reached for predicting pathologic complete responders.[16] The incentive for further investigation of W&W grows as excess mortality rate for false positively selected W&W patients seems to be low (<2-3%),[15] and long-term bowel function is expected to be significantly better in patients observed in a W&W program.[14]

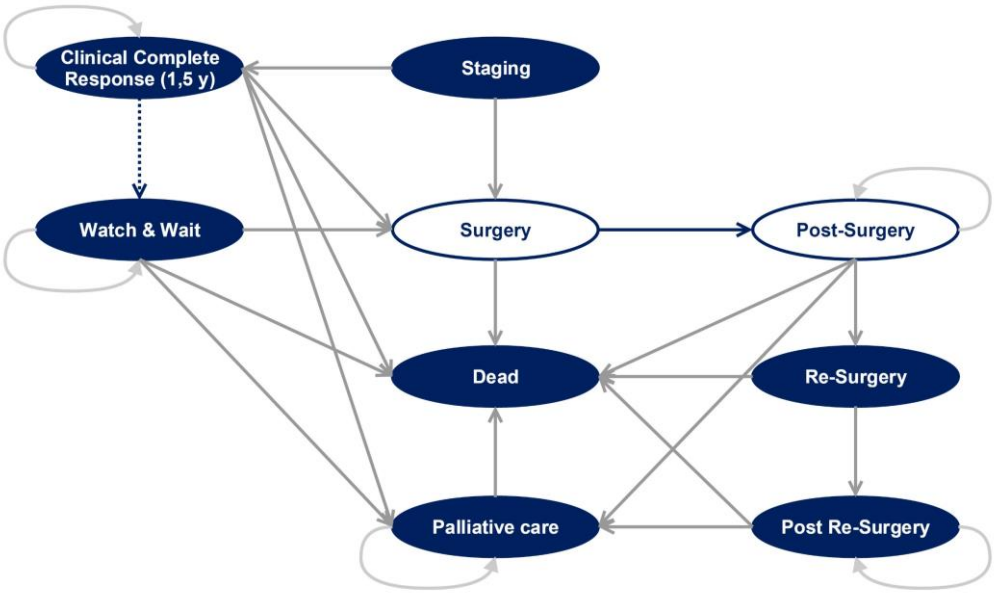

Figure 1: Diagrammatic representation of Markov Model. Ovals represent health states and straight arrows represent possible transition between health states. The dotted arrow is a time dependent state transition (after 1,5 years, all patients with a cCR transfer from clinical complete response to watch & wait). The pathway of white health states is divided into two separate tracks for patients with and without pCR.

Despite the successes booked so far, current clinical evidence is insufficient for adapting W&W as treatment option instead of TME surgery in patients with a clinical complete response after nCRT due to inconsistent results, small sample sizes and a lack of consensus on the best way to identify patients eligible for W&W.[17] Previously conducted clinical studies focused on patient-level health outcome parameters, such as safety and disease-free survival. By performing a health economic evaluation, this study is distinctive by looking at cohort level outcome measures of W&W implementation, in a comparison to the standard treatment of TME surgery. This model-based study also supports the identification of key aspects for future research by analyzing the effects of different parameters on the model's outcome.

PATIENTS AND METHODS

Structure of the Decision Model

A decision analytic Markov Model was made to assess cost-effectiveness of the W&W treatment in locally advanced rectal cancer.[18, 19] The model is based on current Dutch clinical practice guidelines and W&W study design.[14, 20] Figure 1 shows a diagrammatic representation of the Markov model. In the model, a hypothetical cohort of 100,000 patients is considered first at restaging after nCRT. At this inclusion moment, based on incidence of pCR, and sensitivity and specificity of available imaging modalities used for W&W inclusion, the patients transfer to either surgery or cCR in the first Markov cycle. Patients with an initial cCR who develop a recurrent malignancy in the first 18 months are considered to be falsely included for W&W, without pCR. Persistent complete responses, lasting longer than 18 months, are assumed to be identical to a pCR, associated with lower rates of recurrences and metastasis.[21] Post-surgical perspectives are better for patients who experienced a pCR after nCRT.[21] Therefore, the red track in Figure 1 is divided into two sub-tracks with different post-surgical transition chances. Patients developing incurable metastatic cancer are all assigned for palliative treatment. Each Markov cycle lasts 1 month. The model is terminated when all patients are in the end-state (death), with the risk of death set to 100% for patients reaching the age of 100 years. The model was created in Microsoft Excel 2016 with use of Microsoft Visual Basic.

Population

In the model, the hypothetical cohort was diagnosed with locally advanced rectal cancer and entered the Markov model at the moment of restaging after nCRT. Demographic statistics of Dutch rectal cancer patients were derived from the IKNL (Netherlands comprehensive cancer organization) database. By using the age and gender specific chance of developing rectal cancer combined with general population characteristics, the average age of rectal cancer patients was 68 years old.[22, 23] Of all rectal cancer patients, 61% were male and 39%

Table 1: Model Parameters for Base Case

Parameter	*Value*	*Reference*
Inclusion parameters:		
Incidence pCR	0.20	21
Sensitivity	0.71	16
Specificity	0.97	16
Complete responders:		
Early regrowth (1.5Y)	FP*	
Early Metastasis (1Y)	0.025	15
Recurrence (4Y)	0.14	12
Metastasis (4Y)	0.01	12
(Re-) Surgery:		
Mortality rate	0.04	2
Post-surgery:		
Recurrence no pCR (5Y)	0.097	21
Recurrence pCR (5Y)	0.028	21
Chance non-curable recurrence	0.57	24
Post Re-surgery:		
Mean survival (in months)	35.3	25
Palliative Care:		
Mean survival (in months)	6.1	24
Health-related Quality of Life		
Average Dutch Population	0.78	26
Initial cCR	0.55	
Watch & Wait	0.67	
Postsurgical	0.60	
Perisurgical	0.36	
Palliative	0.25	27
Costs (in €) *		28-30
Re-Staging	612	
Initial cCR (annual)	2448	
W&W (annual)	1224	
Surgery	10,306	
Post-Surgery (annual)	578	
Post Re-Surgery (annual)	578	
Palliative Care (monthly)	967	

*FP = False positively included patients for W&W.
Time frame of chance is placed in brackets. Y= years.
Costs derived from Dutch Diagnosis-treatment costs (DBC):
Additional details are provided in Appendix 1.

were female.[22, 23] Potential demographical differences between locally advanced rectal cancer patients and the cohort including all stages of rectal cancer were not adjusted for.

All patients had a chance to die from other causes from any health state, except from states with a clearly described mortality rate in literature. The chances of death due to other causes were obtained from Statistics Netherlands and were averaged over the period of 2010-2014, adjusted for the ratio men/women in the target population and calculated for each year of age.[31] Nevertheless, estimated mortality was too low compared to observational data from comprehensive cancer organization Netherlands (IKNL).[32] The model was recalibrated to meet a more realistic mortality curve by adjusting the general mortality rates for the first three years.

Model Parameters

The model was built based on available Dutch data, supplemented by data from other (foreign) studies. Input parameters for the health economic evaluation are given in Table 1.

Quality of Life

Expressing health outcomes in terms of quality adjusted life-years (QALYs) requires an adjustment of the life years gained by the health-related quality of life corresponding to each health state. The incremental costs per QALYs gained is the primary outcome of this health economic evaluation.

As W&W has only been implemented clinically in research settings, no data is currently available on the quality of life of W&W patients. Therefore, expert elicitation was used to estimate missing data on quality of life, supported by a Multi-Criteria Decision Analysis (MCDA) using Measuring Attractiveness by a Categorical Based Evaluation Technique (MACBETH) methodology.[33] Quality of life was compared between health states: average quality of life of the general Dutch population, long-term post-operative, W&W regimen, perioperative condition (up to 30 days) and palliative care. A nine-point ordinal scale was used, ranging from an equal quality of life to an extremely higher quality of life. The multidisciplinary expert panel included a professor in surgical oncology (specialized in colorectal cancer), professor in radiology (specialized in oncologic diagnostics of the abdominal region), professor in oncology, professor in nuclear medicine, and stoma consultant. Most clinical experts are involved in clinical W&W research. Pairwise comparisons between the quality of life of different health states were judged individually after group discussions. The quality of life of all health states were estimated based on the relative quality of life of all health states and the known quality of life values of the average Dutch population and end-stage rectal cancer patients.[26, 27] Furthermore, an annual 1,5% discounting rate was applied in the calculation of QALYs, in line with Dutch guidelines for health economic evaluations.[34]

Costs

Health care costs were approximated by using price agreements between health insurance companies and hospitals. Average tariffs of three health insurance companies with all Dutch hospitals were used as input parameter for the Markov model.

Furthermore, Dutch clinical guidelines were used to determine diagnostic methods, treatments and follow-up schedule. The schedule of Maas et al. (2011) was used to determine the W&W follow-up costs.[14] Follow-up costs were applied by defining separate health states for every first five years after intervention or inclusion in W&W, using the tunnel states in the model.[18] A specification of all estimated costs can be found in Appendix 1. An annual discounting rate of 4% was used in determining overall costs, which is in line with Dutch guidelines for health economic evaluations.[34]

The currency conversion factor used is €1 = $1,14 (June, 2016).

Base Case and Scenario Analysis

In the base case analysis, patients were included for W&W, and parameters as stated in Table 1 were used. Different populations and situations were evaluated by altering the input parameters: sensitivity, specificity and incidence. Evaluations were performed in which only pCR patients were observed with different inclusion parameter. Besides, a health economic evaluation was performed with the result of two clinical trials as input parameters for the model. The diagnostic values (sensitivity and specificity) for cCR inclusion, pCR incidence and early and late (metastatic) regrowths were used from the Dutch study performed by Maas et al. and a Brazilian study performed by Habr-Gama et al. (2014) in two separate analyzes.

Sensitivity Analysis

The influence of input alteration on the incremental costs and effects was tested with a sensitivity analysis. A univariate sensitivity analysis was conducted in which all input variables are altered by 20% (both upwards and downwards). By adjusting all input variables similarly, their influence on incremental costs and effects could be compared.

RESULTS

Table 2 shows the outcomes of TME surgery and the implementation of W&W. With base case input parameters, 16,600 patients were included with an initial cCR, of which 11,840 had a sustained response for 18 months. Averaging over the entire cohort of 100,000 patients, 0.089 QALY was gained and €511 ($583) was saved per patient. The incremental cost-effectiveness rate (ICER) is €-5,742 ($-6,546) per QALY, indicating that W&W treatment dominates TME surgery.

Table 2: Expected health outcomes, costs, and incremental cost effectiveness ratios

	TME Surgery	Watch & Wait
Effectiveness (QALY)	6,302	6.391
Costs (€)	17,048	16,537
Incremental costs (€)	-	-511
Incremental effectiveness (QALY)	-	0.089
ICER (€ per QALY gained)	-	-5,742

Numbers are averaged over entire cohort of 100,000 patients.
QALY = Quality Adjusted Life-Years;
ICER = Incremental Cost-Effectiveness Rate

Scenario Analysis

Table 3 shows the cost-effectiveness of W&W for pCR patients only, and the influence of the inclusion parameters for identifying pCR. Incremental effects reach up to 0.630 QALY for perfect diagnostic values, when comparing to TME surgery. The money saved when applying base case inclusion parameters is €2,591 ($2,954). This could further be increased to a maximum of €3,650 ($4,161) with perfect inclusion parameters.

Table 4 shows the outcome of a health economic evaluation of earlier performed clinical trials, based on the Markov Model as presented in this study. Both considered studies show higher incremental effectiveness and savings than the outcome of this study.

Sensitivity Analysis

Figure 2 shows two tornado diagrams of deviated incremental costs and QALYs as result of the univariate sensitivity analysis. The six parameters that lead to the highest outcome deviation as result of 20% input variation are shown in the diagrams. Full results of the sensitivity analysis can be found in Appendix 2 Most influencing parameters include the quality of life of postsurgical and W&W patients, and costs of surgery and postsurgical follow-up. The sensitivity analysis of all state transition chances cause fewer effects on incremental costs and QALYs. The quality of life of postsurgical and W&W patients were the only parameters to cross the red line in Figure 2. This means that these are the only parameters to potentially cause TME surgery to be

Table 3: Cost-effectiveness of Watch & Wait procedure for pCR population at varying sensitivity and specificity for cCR inclusion

Sensitivity	0.71	1.0	TME
Specificity	0.97	1.0	Surgery
Effectiveness (QALY)	7.269	7.451	6.821
Costs (€)	11,947	10,888	14,538
Incremental costs (€)	-2,591	-3,650	-
Incremental effectiveness (QALY)	0.448	0.630	-

Numbers are averaged over entire cohort of 100,000 patients.
QALY = Quality Adjusted Life-Years

Table 4: Health economic evaluation of previously performed clinical studies, compared to current outcomes

	Clinical Studies		*Model based outcome*	
	Maas et al.	Habr-Gama et al.	Watch & Wait	TME Surgery
Effectiveness (QALY)	6.458	6.713	6.391	6,302
Costs (€)	16,297	14,895	16,537	17,048
Incremental costs (€)	-751	-2,153	-511	-
Incremental effectiveness (QALY)	0.156	0.411	0.089	-

Numbers are averaged over entire cohort of 100,000 patients. QALY = Quality Adjusted Life-Years;
ICER = Incremental Cost-Effectiveness Rate

beneficial over W&W implementation, within their sensitivity range.

DISCUSSION

In this study, a Markov model is used for early health economic evaluation purpose. Most model parameters are derived from available clinical evidence and missing data was complemented using expert elicitation. The combination of these methodologies allows for a judgement in an early stage on the effect of altering clinical practice

The results of this study indicate that W&W dominates TME surgery, as €511 ($583) is saves per patient at with incremental effect of 0.089 QALY. To assess the robustness of these results, different aspects of uncertainty are being addressed on first, followed by considerations for implementation.

Uncertainty

Figure 2 shows that the incremental costs and effects are robust to the artificial variation induced in the input parameters. Nevertheless, additional evidence is likely to be valuable for increasing the outcome stability. All state transition chances are based on best available clinical evidence, which is sometimes of rather poor quality due to the number of studies and their sample sizes. The sensitivity analysis suggests that each parameter alone may have limited influence. However, in reality more parameters may turn out unfavorable. Besides, actual values may deviate more than 20% from the model parameters used.

Two quality of life parameters may potentially impact the conclusions drawn from the model within their sensitivity range. These parameters are the quality of life of W&W and postsurgical patients. Both utility values were compared during the expert elicitation session and all but one expert valued the quality of life of long-term W&W patients higher than the quality of life of postsurgical patients. In the initial phase of a clinical complete response (the first 18 months) the quality of life was however valued lower than postsurgical patients. The emotional burden of W&W was considered decreasing in the first few years due to the declining

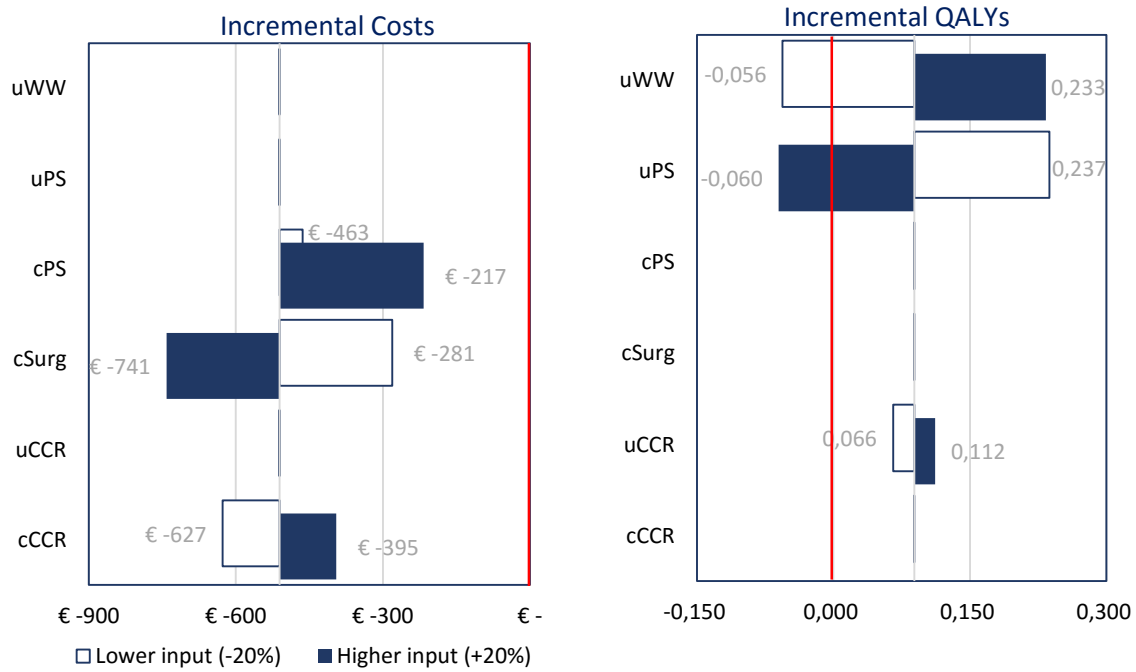

Figure 2: Tornado diagram which shows the effect of altering input parameters with 20% on the incremental costs and effects of the implementation of W&W policy. QALY = Quality-Adjusted Life Year; c= costs; u = utility (Quality of Life); WW = Watch & Wait; PS = Postsurgery; Surg= Surgery; CCR= Clinical Complete Response.

chance of recurrent malignancy. Further research into the quality of life of both health states is necessary to clarify the actual benefit of W&W strategy further.

The costs used are based on Dutch diagnosis-and-treatment costs. Most costs could be adopted with high certainty. However, some assumptions are necessary. First, costs of surgery and re-surgery are considered equal. Secondly, in this model the costs of surgery equal the tariff of TME surgery followed by a maximum of 28 in-hospital nursing days. In the Netherlands, the average number of nursing days after TME surgery is 6 (range: 2-32).[2] In the rare case of longer hospital-stay, costs are approximately three times as high.[28-30]

Implementation Considerations

This study suggests that the implementation of W&W has the potential to improve the number of QALYs and reduce health care costs. Although these results may not resolve the ongoing discussion on individual oncologic safety, they do contribute to medical decision making, as potential (health) benefit is demonstrated.

In Denmark, research on high dose nCRT has resulted into a high number (40/51 patients) of initial clinical complete responders.[35] If this level of complete response can be achieved in practice, potential benefits may turn out more favorable than shown in this study. However, as high dose radiotherapy is associated with late toxicity, its effect on long-term quality of life is uncertain.[36]

This model shows the benefit of W&W implementation to be dependent on the diagnostic values and that increasing sensitivity and specificity values will contribute to better health outcomes and lower costs. In the base case analysis, the sensitivity and specificity used are derived from Dutch literature. Although these values are based on clinical evidence, these high values are not confirmed in international literature yet.[37] Higher accuracy in identifying patients eligible for W&W may reduce the overall risk on falsely included patients for W&W policy and therefore, the oncologic risk is likely to reduce. A recommendation that can be derived from this study therefore is to keep searching for ways of improving sensitivity and specificity for the identification of a complete response after nCRT.

CONCLUSION

Although on patient-safety level, further research on W&W implementation is necessary, this model suggests that on cohort level, €511 ($583) can be saved per patient whilst improving effectiveness for locally advanced rectal cancer patients. Cost-effectiveness may further be increased by improving diagnostic values for identifying complete responders after nCRT.

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APPENDIX 1: COSTS FOR EACH HEALTH-STATE

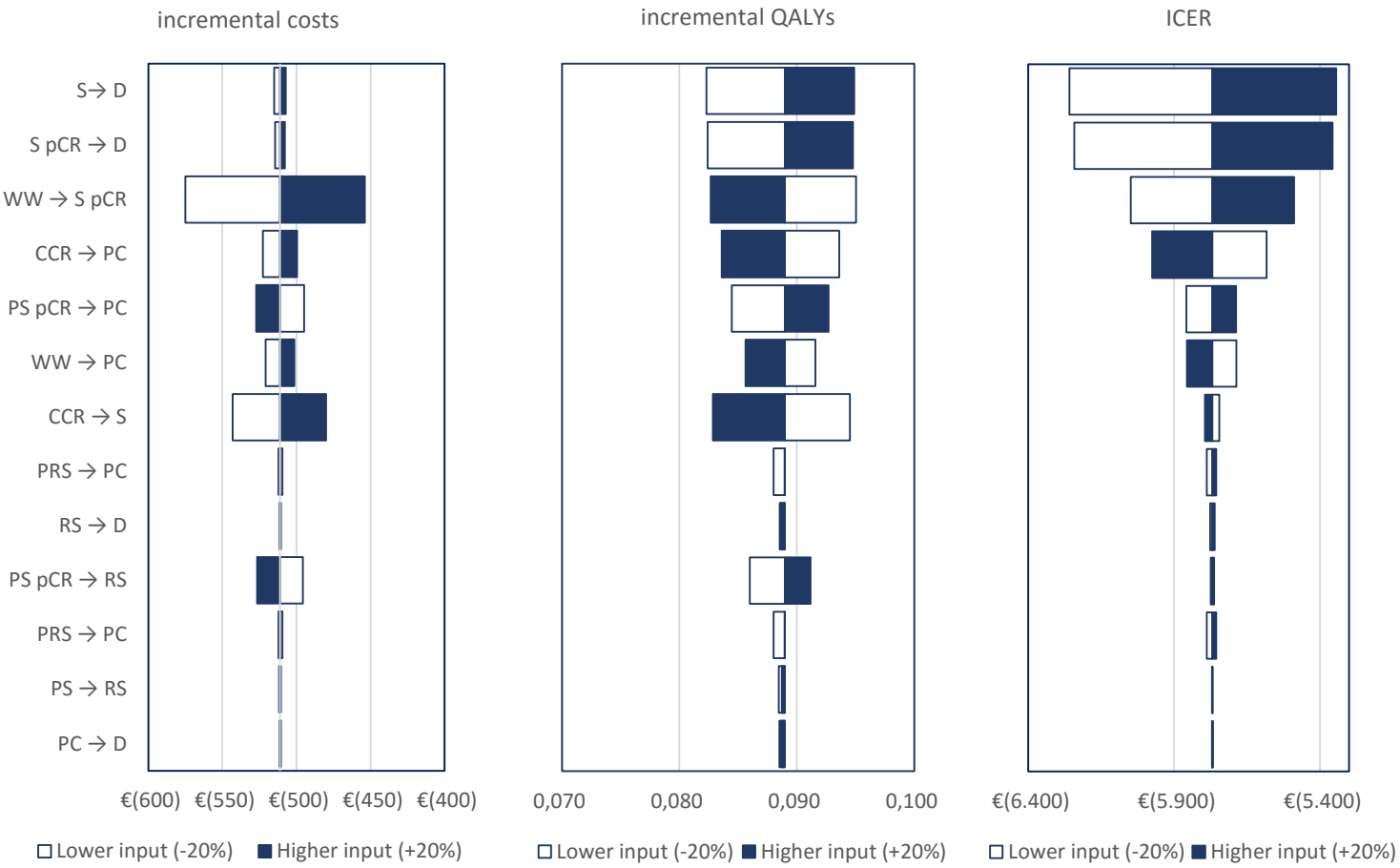
Yearly Costs			
	DTC	Number	Costs
Staging			
DWI-MRI	87096	1	€ 297,95
Consult	234003	1	€ 63,76
endoscopy (sigmoid)	34690	1	€ 250,40
Total			***€ 612,11***
Clinical Complete Response (1,5 year)			
endoscopy (sigmoid)	34690	4	€ 250,40
DWI-MRI	87096	4	€ 297,95
Consult	234003	4	€ 63,76
Total	***Year 1 &2:***	***€ 2.448,44***	***€ 204,04***
Watch & Wait (per year)			
endoscopy (sigmoid)	34690	2	€ 250,40
DWI-MRI	87096	2	€ 297,95
Consult	234003	2	€ 63,76
Total	***Year 3-5:***	***€ 1.224,22***	***€ 102,02***
Surgery			
TME + nursing	15B517	1	€ 10.305,63
Total			***€ 10.305,63***
Surgery pCR			
TME + nursing	15B517	1	€ 10.305,63
Total			***€ 10.305,63***

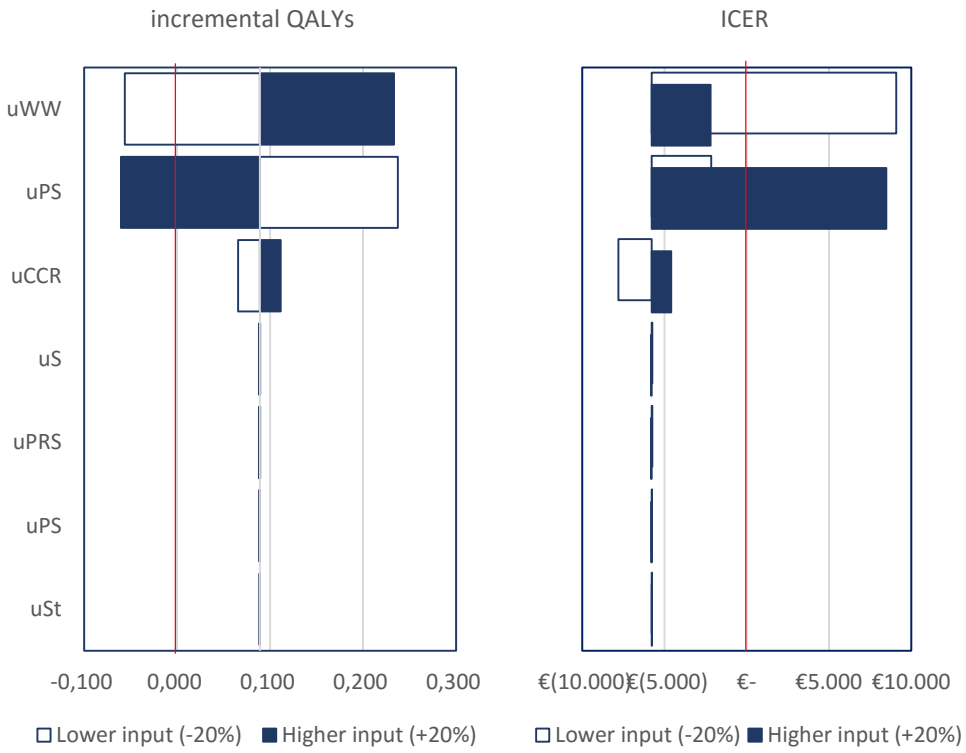
Post-surgery (Time Dependent)				**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Consult	234003		€ 63,76	3	3	1	1	1
Echo Lever	39492		€ 77,35	2	2	1	1	1
Order tariff small chemical investigation	799991		€ 12,16	3	3	3	2	2
Lab (CEA)	72630		€ 11,06	3	3	3	2	2
X-thorax	85000		€ 103,05	2	2	1	1	1
Colonoscopy	34686		€ 375,16	1			1	
		€ 2.888,82		*€ 996,90*	*€ 621,74*	*€ 313,82*	*€ 665,76*	*€ 290,60*
Average annual		€ 577,76		***€ 83,08***	***€ 51,81***	***€ 26,15***	***€ 55,48***	***€ 24,22***

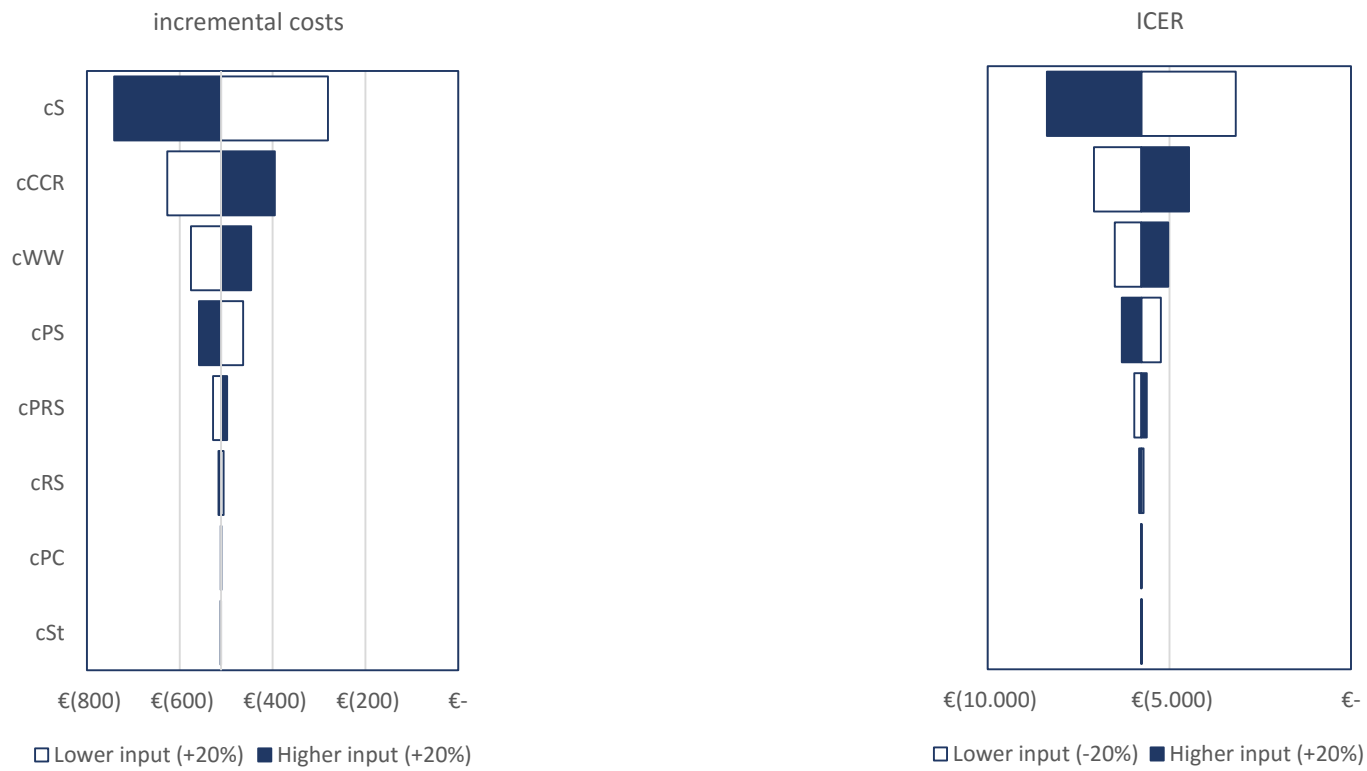
Re-surgery			
re-TME + nursing	15B517	1	€ 10.305,63
Total			***€ 10.305,63***
Palliative Care			
Chemotherapy	15E113	2	€ 3.249,99
Radiotherapy	15D261	2	€ 865,11
Palliative consultation	15E118	2	€ 972,44
Hormone Therapy	15D503	2	€ 716,63
Total		*€ 11.608,35*	***€ 967,36***

DTC = Diagnosis-treatment combination costs

APPENDIX 2: FULL SENSITIVITY ANALYSIS







Upper row: sensitivity analysis of health state transition chances, middle row: sensitivity analysis of quality of life values and bottom row: sensitivity analysis of costs. The effect of artificially induced 20% parameter variation is expressed in incremental costs (left column), incremental effects in QALYs (middle column) and incremental cost-effectiveness rate (ICER).

→ = health state transition chance; u = utility (quality of life); c = costs, S= Surgery; D= Dead; pCR = pathologic Complete Response; WW = Watch & Wait; CCR = clinical Complete Response; PC = Palliative Care, PS = Post-surgery; PRS = Post Re-surgery; RS = Re-surgery; St = Staging.

A bar crossing the 0-axis in incremental costs or effects means a possible shift of the final outcome. This happens at the utility values of W&W and postsurgical patients. In these cases, the sensitivity analysis results in a low, negative number. These properties cause the ICER to shift to a positive, high number, since the denominator approaches zero. Because of this exaggerated outcome measure, the ICER graphs are not included in the original article.