Master Thesis

A Cost-Effectiveness Analysis Of Surgical Versus Organ-Preserving Treatment Modalities for Advanced Laryngeal Cancer.

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Master Health Sciences
Track: Optimization of Healthcare Processes

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Date: 25th of August 2018

Course code: 201600036

Preface

The following report gives insight into the project I worked on within the scope of my thesis assignment of the Master in Health Sciences at the University of Twente.
The research has been done at the Head and Neck Department of the Netherlands Cancer Institute in Amsterdam.
The topic for this assignment immediately caught my interest, as it is patient-related and close to clinical practice, hence provides the chance of having an actual impact on the decision-making of laryngeal cancer treatments.

For giving me the possibility to work on this project and to gain the knowledge to a level I did over the past months, I would like to thank my supervisors Prof. Dr. Wim van Harten, Dr. Valesca Rètel, Prof. Dr. Michiel W.M. van den Brekel and mostly Ann-Jean Beck. Not only have they guided me throughout the entire project, giving me input and feedback in our meetings but also supported me in every other way possible.
Working together with specialists, who helped me understanding the procedure of treatments and their consequences for the patient, guided me in the right direction and improved my work a lot. I do really appreciate the determination they had towards this topic and their willingness to support me with this study.

Besides, I would like to thank the closest people around me for their support during the entire study program.

Retrospectively I can say, that this project entirely matched my expectations, hence strengthened my desire to work in the clinical setting of a hospital in my future career.

Rosaly Meissner,
Amsterdam, August 2018

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List of Abbreviations

95%-CI	95% Confidence Interval
BRT	Bioradiotherapy
CE plane	Cost-Effectiveness Plane
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CRT	Chemoradiotherapy
DBC	Diagnosis Treatment Combination (Diagnose Behandeling Combinatie)
DFS	Disease-Free Survival
EORTC QLQ-C30	The European Organization for Research and Treatment of Cancer quality of life questionnaire
EQ-5D	European Quality of Life Five Dimensions
ICER	Incremental Cost-Effectiveness Ratio
LY	Life Year
NKI	Netherlands Cancer Institute (Nederlands Kanker Instituut)
NZA	Dutch Healthcare Authority (Nederlandse Zorg Authoriteit)
OS	Overall Survival
PFS	Progression-Free Survival
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Year
QLQ-H&N35	Quality of Life Questionnaire Head and Neck Cancer Module
QOL	Quality of Life
RT	Radiotherapy
SE	Standard Error
TL	Total Laryngectomy
WTP	Willingness to Pay
ZIN	Healthcare Institute Netherlands (Zorginstituut Nederland)

General Introduction

The aim of this study within the scope of my thesis was to perform a cost-effectiveness analysis (CEA) of surgical versus organ-preserving treatment modalities in advanced laryngeal cancer.
This general introduction of my thesis provides an insight of the steps I took from the research to the final report, beginning with an introduction of laryngeal cancer and its treatment modalities.
Subsequently to this introduction is the completed thesis titled *"A Cost-Effectiveness Analysis of Surgical versus Organ-Preserving Treatment Modalities in Advanced Laryngeal Cancer",* reporting the detailed results of my research.

Laryngeal cancer, as a kind of head and neck cancer, is most likely to occur in patients from the age of 65 and has a detrimental impact on a patient's life. Not only is it correlated with severe pain and swelling, but also issues such as problems with swallowing. The current standard treatment of advanced laryngeal cancer consists of total laryngectomy (TL) as a surgical option with or without postoperative radiotherapy and organ-preserving modalities. The preservation of the larynx can be achieved by radiotherapy (RT), chemoradiotherapy (CRT) or bioradiotherapy (BRT), the latter is a newer immunotherapy combining radiation with Cetuximab. However, survival outcomes are known to be similar among these treatment modalities, while intensity, duration and outcomes associated with rehabilitation and treatment differ, hence costs and quality of life (QoL) vary with treatment.

The primary aim of this study was to investigate the cost-effectiveness of surgical (TL) compared to organ preserving treatment modalities (RT/CRT/BRT) in order to support reimbursement decision-making in clinical practice to make care and rehabilitation accessible for patients. The secondary objective was to elicit the cost-effectiveness of CRT versus BRT for advanced laryngeal cancer.
Initially, the idea was, to additionally include more innovative radiation- combined treatments besides Cetuximab, such as Olaparib and Nivolumab. But as these treatments are barely used in clinical practice for laryngeal cancer yet, hence patient data is rather limited, the selection of included treatment modalities had to be reduced.

The first step of my study was an extensive research about advanced laryngeal cancer, especially focusing on costs and factors influencing QoL related to each treatment modality.
Thereafter, I distinguished all treatment-related costs that I assumed needed separate consideration, such as costs for personnel, intensive care unit stay, regular hospital admission day, material (e.g. tube feeding), operating room, radiation dose and rehabilitation interventions. In addition, I took a detailed look into complications, listing all of the potential relevant acute and long-term complications per treatment modality, that could affect the overall costs.
Simultaneously I got provided with a small selection of patient-ID numbers per treatment modality, which were used as a base to elaborate the actual treatment costs. In order to discuss my findings and obtain the cost data based on the patient-ID numbers, I reached out to the Financial Department of the NKI-AVL. The option of using healthcare products (DBCs) that were applied to each individual patient, which already included most of the treatment-related costs, particularly costs related to acute complications, became present. Therefore, I decided to create costs packages per treatment modality based on patients that have been treated from 2016 to 2018. For calculating the cost packages, I requested all patient-ID numbers with the DBCs that have been applied from the database of the Business Intelligence. The data needed to meet specific inclusion criteria of laryngeal cancer patients of stage III or IV who completed a treatment pathway of either TL, RT, CRT or BRT. For each patient-ID number, only DBCs were considered that referred to an initial treatment or rehabilitation, all others (i.e. salvage surgery) have been disregarded. Tariff prices of the selected DBCs were obtained through the tariff price list 2018 from the Dutch Healthcare Authority.
The long-term complications, meaning their probability of occurrence and their treatment or medication necessary, was discussed with head and neck surgeons as well as radiotherapists. After adjusting the data of complications and excluding or adding others, associated costs have as well been derived from the same tariff price list. Costs for regular hospital admission, as well as for voice prosthesis and tube feeding have been obtained from NKI-internal data.
After the data collection has been completed, a Markov model has been constructed in order to elaborate the cost-effectiveness of the treatment modalities. Within the model patients move between the pre-defined health states of disease-free survival,

progression (consisting of locoregional recurrence and distant metastasis) and death. The probability of moving between those health states was based on progression-free survival (PFS) and overall survival (OS) data from literature.
A Monte Carlo Simulation, modeling 1000 patients, has been performed, based on several input parameters, such as the above described treatment-related costs, costs of rehabilitation and long-term complications, as well as QoL data.
Eventually, outcomes were expressed by an incremental cost-effectiveness ratio (ICER), dividing additional costs by additional QALYs and illustrated in a cost-effectiveness (CE) plane. In addition, a cost-effectiveness acceptability curve (CEAC) was created to display the probability of a treatment modality to have a positive net-monetary benefit with a willingness-to-pay (WTP) threshold of €80.000. Furthermore, parameters that had the largest impact on the cost-effectiveness were identified through a sensitivity analysis of changing each parameter to ± 25 percent.

Working on this project for the past months was an interesting, educational experience that made me understand the importance of a detailed elicitation in clinical research. The topic of laryngeal cancer became more and more of interest throughout the past months, which made me enjoy my work even more.
Working with various sources made me realize that one has to be very cautious about the data used for such a model as the least deviations might lead to a completely different result. Hence, preparing the data for the model need patience and accuracy. Discussing the data with multiple specialists was in fact very helpful and pushed the project forward. Although compromises needed to be made in some cases as literature didn’t give any input regarding the treatment of specific complications and the opinions of experts were not always consistent.
When looking back at the time I had at the NKI-AVL, I can say that I am confident about my work and the progress I made. Working with inspirational people who are very passionate about their work and who taught me a lot for my future pathway, made it an unmissable experience.

Abstract

Background

The treatment of advanced laryngeal cancer consists of surgical and organ-preserving modalities which are similar in overall survival but differ in intensity, duration and outcomes associated with rehabilitation and treatment. Also, treatment-related costs associated and quality of life outcomes vary amongst modalities. Therefore, the purpose was to determine the cost-effectiveness of surgery versus radiotherapy (RT), chemoradiotherapy (CRT) and bioradiotherapy (BRT) with the second aim to evaluate cost-effectiveness of BRT versus CRT to support decision-making in clinical practice.

Methods

A Markov model has been constructed to compare surgery versus organ-preservation. A Monte Carlo Simulation of 1000 iterations was performed, based on costs and health outcomes. Treatment-related costs (including short term complications), costs of long-term occurring complications, rehabilitation, voice prosthesis and tube feeding were included. Outcomes were analyzed from a healthcare perspective, based on a lifetime horizon and were expressed by an incremental cost-effectiveness ratio (ICER) and illustrated by a cost-effectiveness (CE) plane and a cost-effectiveness acceptability curve (CEAC).

Results

Quality-adjusted life years (QALYs) gained were similar in TL (9,75) and RT (9,97). CRT and BRT gained QALYs of 7,75 and 8,76 respectively. BRT showed the largest amount of LYs gained with 13,7. The healthcare costs of TL were €73.612 versus €31.595 for RT. CRT and BRT resulted in costs of €55.971 and €61.058. The ICERs for TL versus RT, CRT and BRT were €-193.591, €8.816 and € 12.649. Comparing the cost-effectiveness of BRT to CRT resulted in an ICER of €5.044/QALY gained when treated with BRT.

Conclusion

The analysis showed RT alone to be most cost-effective compared to surgery due to lowest costs. Although costs of BRT are higher than for RT, the ICER is far below the WTP threshold while a favorable outcome was shown in QALYs and LYs gained. This makes BRT relevant for clinical practice and supports the decision-making regarding reimbursement of organ-preserving modalities in advanced laryngeal cancer.

1. Introduction

Head and neck cancer (HNC) accounts for over 600.000 deaths per year worldwide (1). In the Netherlands, the incidence of HNC was 3.081 cases in 2017. Approximately 700 diagnoses are assigned to laryngeal cancer annually, of which approximately one third has advanced stage cancer (stage III or stage IV) (2).

Laryngeal cancer has a detrimental impact on a patient's life as the disease is accompanied by multiple problems, e.g. pain in the head and neck area, difficulties in swallowing and altered speech (2, 3).

Treatment modalities for advanced laryngeal cancer consist either of surgical approaches, mostly total laryngectomy (TL) with(out) postoperative radiotherapy (RT) or organ-preserving approaches, including RT solely or combined with Cisplatin (CRT) or Cetuximab (BRT) (4, 5).

According to Timmermans et al., the survival is shown to be similar, ranging from 45% after CRT and 47% after RT to 49% after total laryngectomy, which make both, surgical and non-surgical modalities, an option in clinical practice (4). Organ preservation however allows to maintain the larynx and the muscular tissue, facilitating the maintenance of swallowing and speech and therefore may be a favorable option over surgery for laryngeal cancer patients (2). Compared to RT alone, both BRT and CRT show a benefit in progression-free survival and overall survival, whereas CRT has more toxic effects and BRT is costlier (6-8) .

Surgical and organ-preserving treatment modalities vary in intensity, duration and outcomes associated with rehabilitation and treatment, including functioning (e.g. voice quality, swallowing function, complications) differ. In addition, also quality of life (QoL), as well as hospital- and societal-related costs show different outcomes (9).

However, to our knowledge, no current European study could have been found evaluating the cost-effectiveness of surgery versus organ-preservation. Present existing studies were limited to the comparison of RT and BRT, stating BRT to be more cost-effective, as it has beneficial effects on the health-related outcome even though it resulted in an increase of costs (8, 10, 11). A cost-effectiveness analysis (CEA) is necessary to strengthen reimbursement decision-making and support medical decision-making in clinical practice(12).

Therefore, the primary aim of this study was to investigate the cost-effectiveness of surgical compared to organ-preserving treatment modalities (TL versus RT/CRT/BRT), with the secondary objective to elicit the cost-effectiveness of CRT versus BRT for advanced laryngeal cancer in order to support decision-making in clinical practice.

2. Methods

In order to gain an overview on available data on laryngeal cancer treatments and outcomes, a literature research in the databases PubMed and Scopus has been conducted, finding relevant journal papers published between 2003 and 2018. Some of the articles were used for the basis of input parameters for the constructed model, when comprising relevant terms such as survival, progression, quality of life (QoL) and complications (*Appendix I)*.

2.1 Patient Population

This study focused on patients with advanced laryngeal cancer (TIII or TIV), treated with: 1) TL, including postoperative radiation, 2) RT, 3) CRT or 4) BRT. For the construction of a model, a sample of patients with a mean age of 65 years, the age group to most likely be diagnosed on average with laryngeal cancer, was included (4, 13).

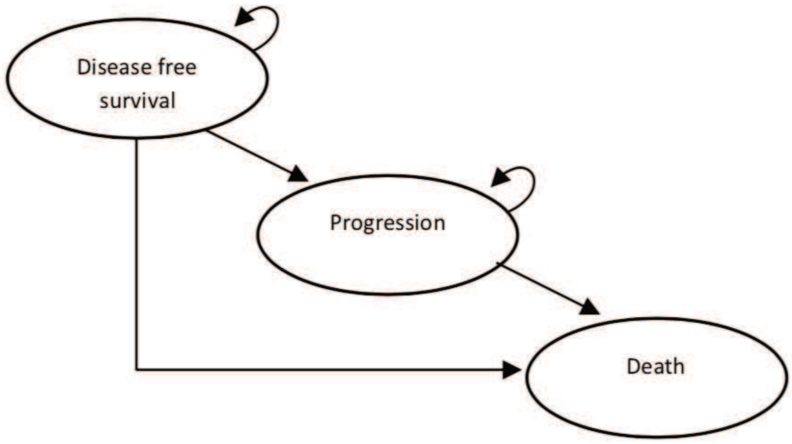
2.2 Economic Evaluation

A Markov model was created in Microsoft Excel version 2016 in order to conduct the CEA, simulating 1000 patients for each of the four treatment arms. The following three health states have been defined for the model: disease-free survival, progression and death (*Figure 1*). Within the disease-free survival state, patients with or without complications have been considered, taking into account the costs of the complications when they occur. The ratio of occurrence of complications in the surgery group to RT group was 6.7 to 1, whereas the ratio for surgery to CRT/BRT was 2.5 to 1.

The progression state consisted of patients with locoregional recurrence or distant metastasis.

Outcomes were analyzed from a healthcare perspective, using a lifetime horizon and a 1-year cycle length.

FIGURE I: *MARKOV MODEL HEALTH STATES*



2.2.1 Probabilities and state transfer

An overview of health state utilities and probabilities per treatment arm is provided in *Table I (5, 14, 15).*

TABLE I*: INPUT PARAMETERS MARKOV MODEL: PROBABILITIES AND UTILITIES*

TL	Mean	SE	Distribution	Source
Health State Utilities				
Disease-free survival	0,88	0,010	Beta	NKI
Progression	0,60	0,015	Beta	Assumption
Probabilities				
DFS to DFS	0,81	0,013	Beta	(16)
DFS to progression	0,07	0,008	Beta	(16)
DFS to death	0,12	0,010	Beta	(14)
Progression to progression	0,19	0,013	Beta	(16)
Progression to death	0,81	0,013	Beta	(16)
RT	Mean	SE	Distribution	Source
Health State Utilities				
Disease-free survival	0,85	0,011	Beta	(17)
Progression	0,60	0,015	Beta	Assumption
Probabilities				
DFS to DFS	0,81	0,012	Beta	(5)
DFS to progression	0,06	0,007	Beta	(5)
DFS to death	0,13	0,011	Beta	(14)

TABLE I continued

	Mean	SE	Distribution	Source
Progression to progression	0,19	0,012	Beta	(5)
Progression to death	0,81	0,012	Beta	(5)

CRT	Mean	SE	Distribution	Source
Health State Utilities				
Disease free survival	0,64	0,015	Beta	(18)
Progression	0,60	0,015	Beta	Assumption
Probabilities				
DFS to DFS	0,87	0,011	Beta	(15)
DFS to progression	0,05	0,007	Beta	(15)
DFS to death	0,08	0,008	Beta	(15)
Progression to progression	0,13	0,011	Beta	(15)
Progression to death	0,87	0,011	Beta	(15)

BRT	Mean	SE	Distribution	Source
Health State Utilities				
Disease-free survival	0.64	0,015	Beta	(18)
Progression	0.60	0,015	Beta	Assumption
Probabilities				
DFS to DFS	0,87	0,011	Beta	(15)
DFS to progression	0,02	0,005	Beta	(15)
DFS to death	0,11	0,010	Beta	(15)
Progression to progression	0,13	0,011	Beta	(15)
Progression to death	0,87	0,011	Beta	(15)

TL total laryngectomy, *RT* radiotherapy, *CRT* chemoradiotherapy, *BRT* bioradiotherapy, *DFS* disease-free survival

2.2.2 Cost data

The considered costs included treatment costs, as well as rehabilitation and follow-up costs which were based on tariff prices from 2018 per 'Diagnose Behandeling Combinatie' DBC from the Dutch Health Insurance Board (NZa) guideline (19). The DBCs per treatment modality had been identified based on the average application of DBCs per patients treated at the NKI from 2016 to 2018. For surgery, five patients met the inclusion criteria for the cost calculation of being in stage III or IV of laryngeal cancer and having completed the pathway of initial treatment. For RT alone, CRT and BRT, a total number of patients of n=12, n=4 and n=2 were used respectively.

The DBCs that had been applied during the treatment period had been summed up in an average cost package, whereas costs for dental hygienic care and high-dose medication, such as Cisplatin and Cetuximab were added separately. The same applied for costs that occurred outside the scope of treatment (>42 days after surgery/radiation cycle) such as follow-up consultations or additional treatment due to progression of disease. Furthermore, long-term complications for up to five years after treatment have been added separately (*Appendix II*). Acute complications (occurrence <42 days during and after surgery/radiation cycle) are included in the treatment cost package, thus didn't need separate consideration. In addition, costs for permanent feeding support, meaning the daily utilization of tube feeding material and dietary supplement and voice prosthesis placement were taken into account. For all added costs an activity-based costing method had been applied as stated in Lievens et al. 2003 (20). All costs that were taken into consideration are listed in *Table II.* The costs for complications are based on their probability of occurrence per treatment modality (*Appendix II).*

The discount rate for costs of 4% per year had been applied for all costs in accordance with the Zorginstituut Nederland (ZIN) cost manual 2015 (21).

***TABLE II**: INPUT PARAMETERS MARKOV MODEL: COSTS IN EURO*

	Unit Costs	Units	Costs	SE	Total Costs	Distribution	Source
Costs TL							
Treatment			20.855,50	0,25		Gamma	NKI
Postoperative RT			13.327,20	0,25		Gamma	NKI
Reconstruction			2.644,30	0,25		Gamma	NKI
Voice prosthesis[a]	568,00	6,0	3.408,00	0,25		Gamma	NKI
Dental hygienist[b]	20,00	30,0	600,00			Fixed	NKI
Rehabilitation			2.821,20	0,25		Gamma	NKI
Complications							
Pharyngocutaneous Fistula			279,90	0,25		Gamma	NKI
Tracheoesophageal Puncture			240,80	0,25		Gamma	NKI
Stenosis			1.557,00	0,25		Gamma	NKI
Pneumonia			538,00	0,25		Gamma	NKI
Tube feeding			1.341,60	0,25		Gamma	NKI
					€ 47.613,00		

TABLE II continued

	Unit Costs	Units	Costs	SE	Total Costs	Distribution	Source
Costs RT							
Treatment			17.133,40	0,25		Gamma	NKI
Dental hygienist[b]	20,00	30,0	600,00			Fixed	NKI
Rehabilitation			553,30	0,25		Gamma	NKI
Complications							
Dysphagia			292,00	0,25		Gamma	NKI
Pneumonia			78,90	0.25		Gamma	NKI
Tube feeding			838,50	0.25		Gamma	NKI
					€ 19.496,00		

	Unit Costs	Units	Costs	SE	Total Costs	Distribution	Source
Costs CRT							
Treatment			32.133,20	0,25		Gamma	NKI
Cisplatin[c]			45,05			Fixed	(22)
Dental hygienist[b]	20,00	30,0	600,00			Fixed	NKI
Rehabilitation			2.701,60	0,25		Gamma	NKI
Complications							
Dysphagia			834,40	0,25		Gamma	NKI
Pneumonia			322,80	0,25		Gamma	NKI
Tube feeding			2.180,00	0,25		Gamma	NKI
					€ 38.817,00		
Costs BRT							
Treatment			30.392,60	0.25		Gamma	NKI
Cetuximab[d]			7.247,50			Fixed	(22)
Dental hygienist[b]	20,00	30,0	600,00			Fixed	NKI
Rehabilitation			3.419,70	0,25		Gamma	NKI
Complications							
Dysphagia			834,40	0.25		Gamma	NKI
Pneumonia			322,80	0.25		Gamma	NKI
Tube feeding			2.180,00	0.25		Gamma	NKI
					€ 44.997,00		

[a] Costs for voice prosthesis including material costs of €330 and €238 per placement consultation

[b] Assuming 30 sessions of dental hygiene care due to radiation

[c] Dose of Cisplatin of 100ml per 1,7m^2 body volume, resulting in a total of 510mg

[d] Dose of Cetuximab of 650ml per 1,7m^2 body volume, resulting in a total of 3230mg

TL total laryngectomy, *RT* radiotherapy, *CRT* chemoradiotherapy, *BRT* bioradiotherapy, *SE* standard error, *NKI* The Netherlands Cancer Institute

2.3 Patient Related Outcomes

Quality of Life

For conducting the cost-effectiveness analysis (CEA), utilities were necessary to calculate the quality-adjusted life years (QALYs) per treatment arm. The utilities for patients treated with TL have been derived from European Quality of Life Five Dimensions (EQ-5D-5L) data, obtained through a database from a prospective study at the NKI for a group of 10 advanced stage laryngeal cancer patients. For QoL data of laryngeal cancer patients in the organ-preservation group, overall head and neck EQ-5D scores have been derived from literature (8, 17, 18).

Complications

Complications that are most likely to occur when being treated with surgery or organ-preserving modalities were included for the CEA as they impact QoL and costs. Initially, relevant treatment-related complications were identified through literature. Subsequently, the relevance as well as the incidence of complications for each treatment have been confirmed through expert elicitation of head and neck surgeons (n=2) and radiotherapists (n=2). The complications that were found to be most relevant in regard to each treatment modality have been included.

We assumed no complications leading to death, even though they might decrease QALYs.

For taking into account changes regarding patient-related outcome parameters throughout development over time, a discount of 1,5% has been applied (21).

2.4 Outcome- and uncertainty analysis

The outcomes of this study were constituted in incremental costs, life years (LYs), QALYs, survival differences, and the incremental cost-effectiveness ratio (ICER). The latter showing the difference in costs divided by the difference in QALYs.

A cost-effectiveness (CE) plane, which illustrates differences in costs and effects between the modalities had been created based on a Monte Carlo Simulation simulating 1000 patients per treatment modality in terms of a probabilistic sensitivity analysis (PSA). Thereafter, a cost-effectiveness acceptability curve (CEAC) with a willingness-to-pay (WTP) threshold of €80.000 per QALY, being the standard threshold in the Netherlands per QALY, had been created. It summarizes the impact of uncertainty on the result and finally determining the cost-effectiveness of surgical and organ-preserving treatment modalities.

2.5 Sensitivity analysis

To test the robustness of the model a one-way sensitivity analysis had been performed, pointing out the rate of uncertainty of specific parameters. This was achieved by changing selected variable input parameters to an extend of ± 25 percent. The uncertainty of parameters has been visualized through tornado diagrams (*Figure Iva-c*). Cost packages per patient group, meaning tariff prices included and outcomes of activity-based costing, might differ due to the heterogeneity of patients included. With regard to this uncertainty, the maximum costs have been calculated to determine the cost-effectiveness with a WTP threshold of €80.000.

3. Results

3.1 Main results

The main results of the analysis, such as QALYs, LYs, costs and ICERs are displayed in *Table III.*

Surgery treated patients gained 9,75 QALY's (95%-CI 9,07-10,48) whereas RT treated patients gained 9,97 QALY's (95%-CI 9,31-10,60). With CRT, 7,75 QALYs (95%-CI 7,21-8,27) were gained, while BRT resulted in a gain of 8,76 QALYs (95%-CI 9,12-11,27).

The gained LY for surgery, RT and CRT were respectively 11,23, 11,82 and 12,13, while BRT showed the most LYs gained with 13,70.

The overall healthcare costs for surgery were €73.612 (95%-CI €62.874-€84.984) compared to €31.595 (95%-CI €27.184-€36.263) for RT. Overall costs for CRT and BRT treated patients were €55.971 (95%-CI €47.752-€65.665) and €61.058 (95%-CI €81.920-€111.866).

The ICERs per QALY gained of surgery versus RT, CRT and BRT were €-193.591, €8.816 and € 12.649. Comparing the cost-effectiveness of BRT to CRT resulted in an ICER of €5.044/QALY gained when treated with BRT.

***TABLE III**: MAIN RESULTS OF COST-EFFECTIVENESS ANALYSIS*

	Costs	QALY	LY	ICER/QALY Surgery vs. OP	ICER/LY Surgery vs. OP
TL	€73.612	9,75	11,23		
RT	€31.595	9,97	11,82	-€193.591	-€71.586
BRT	€61.058	8,76	13,70	€12.649 €5.044*	-€5.092 €3.245*
CRT	€55.971	7,75	12,13	€8.816	-€19.635

*ICERs based on BRT versus CRT

TL total laryngectomy, *RT* radiotherapy, *BRT* bioradiotherapy, *CRT* chemoradiotherapy, *QALY* quality-adjusted life year, *LY* life year, *ICER* incremental cost-effectiveness ratio, *OP* organ-preservation, *CI* confidence-interval of 95%

3.2 Probabilistic sensitivity analysis

A cost-effectiveness (CE) plane has been illustrated for each treatment modality in *Figures IIa-c,* showing the distribution of 1000 iterations. RT is shown to be placed in the lower right quadrant, thus indicating RT being dominant compared to surgery in 63,7 percent of cases (less costly, more effective) (*Figure IIa*).

The CE-plane of surgery versus CRT shows CRT to be situated in the lower left quadrant, initiating to be less costly while appearing to have decrements in effectiveness (*Figure IIb*).

FIGURE IIa: CE-PLANE OF SURGERY VERSUS RT

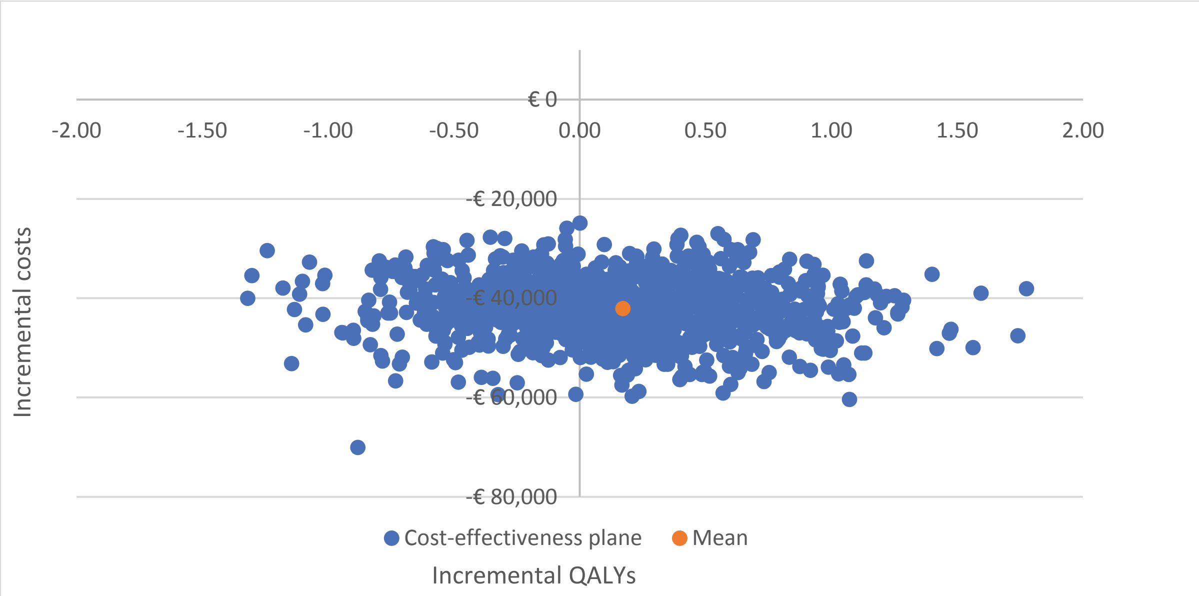
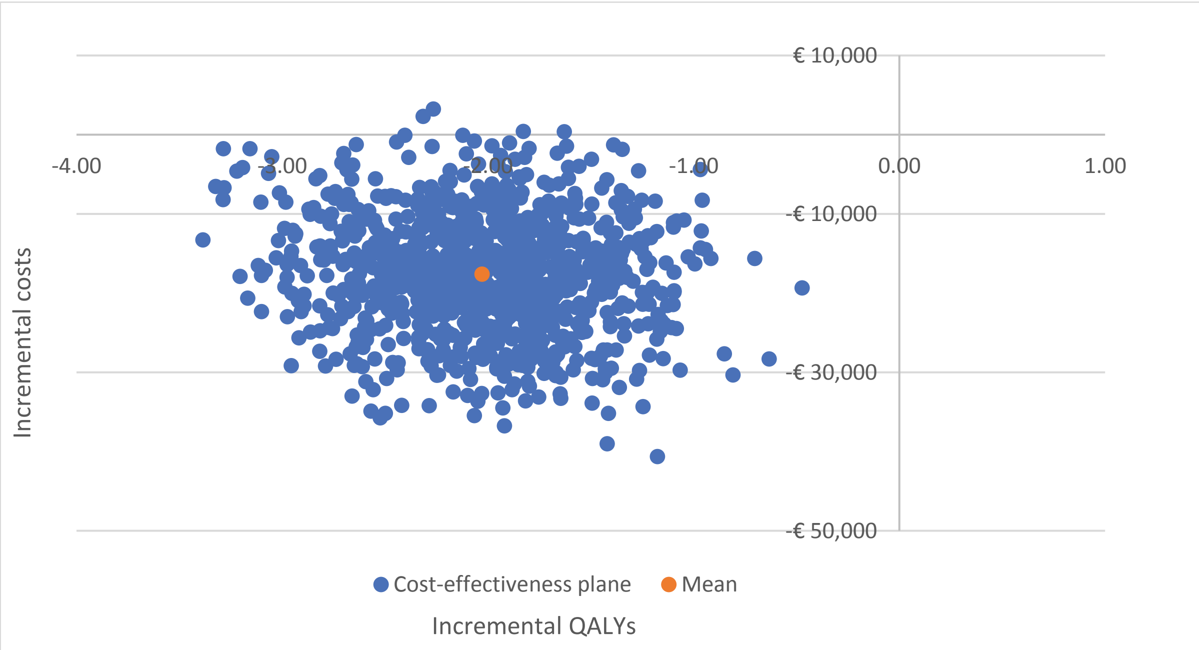
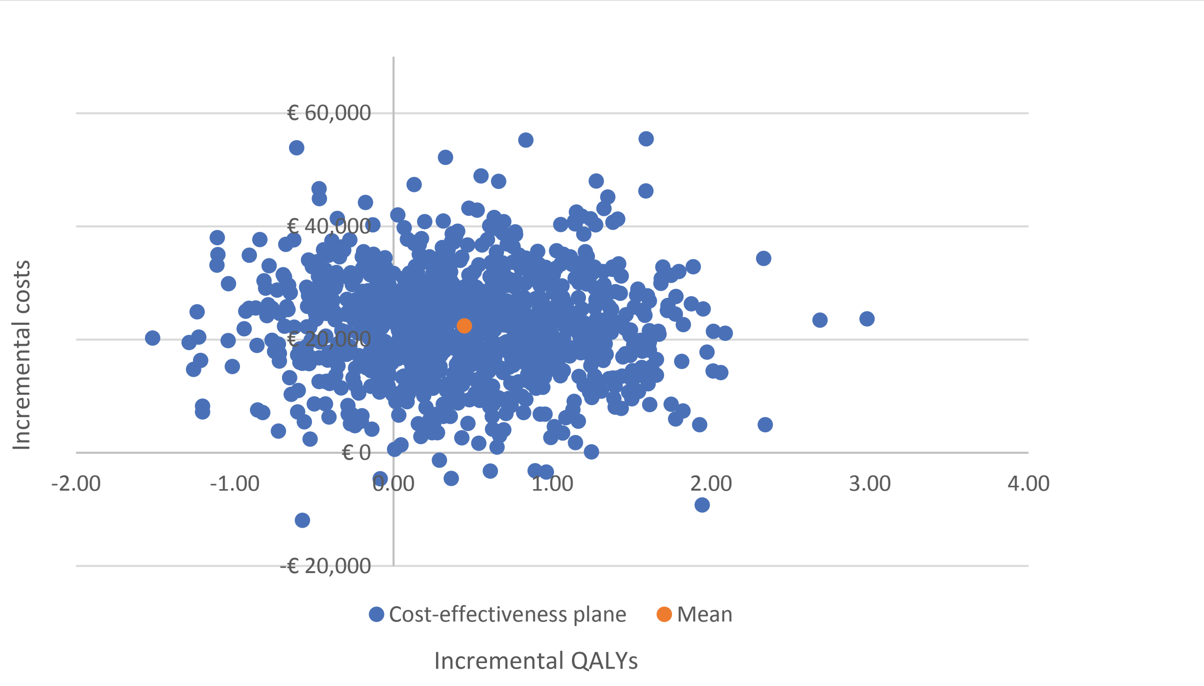


FIGURE IIb: CE-PLANE OF SURGERY VERSUS CRT



While RT and CRT happen to be less costly than surgery, BRT is shown to be costlier but also more effective, as well demonstrating a higher effectiveness than RT (*Figure IIc*).

FIGURE IIc: CE-PLANE OF SURGERY VERSUS BRT



When comparing BRT to CRT, BRT is found to be costlier while being more effective than CRT. The ICER is displayed in *Appendix III.*

The CEACs in *Figure IIIa-c* are representing the probability of the net monetary benefit to be positive, thus showing the effectiveness for several WTP thresholds per treatment modality.

Figure IIIa outlines RT to be cost-effective with 0,91 percent before reaching the WTP threshold of €80.000/QALY, whereas surgery is shown to be 100 percent cost-effective compared to CRT in accordance with the given threshold (*Figure IIIb*). Regarding surgery versus BRT, BRT shows a higher probability of being cost-effective with 0,58 percent (*Figure IIIc*).

FIGURE IIIa: *CEAC SURGERY VERSUS RT SHOWING THE PROBABILITY OF COST-EFFECTIVENESS GIVEN A CERTAIN WTP THRESHOLD*

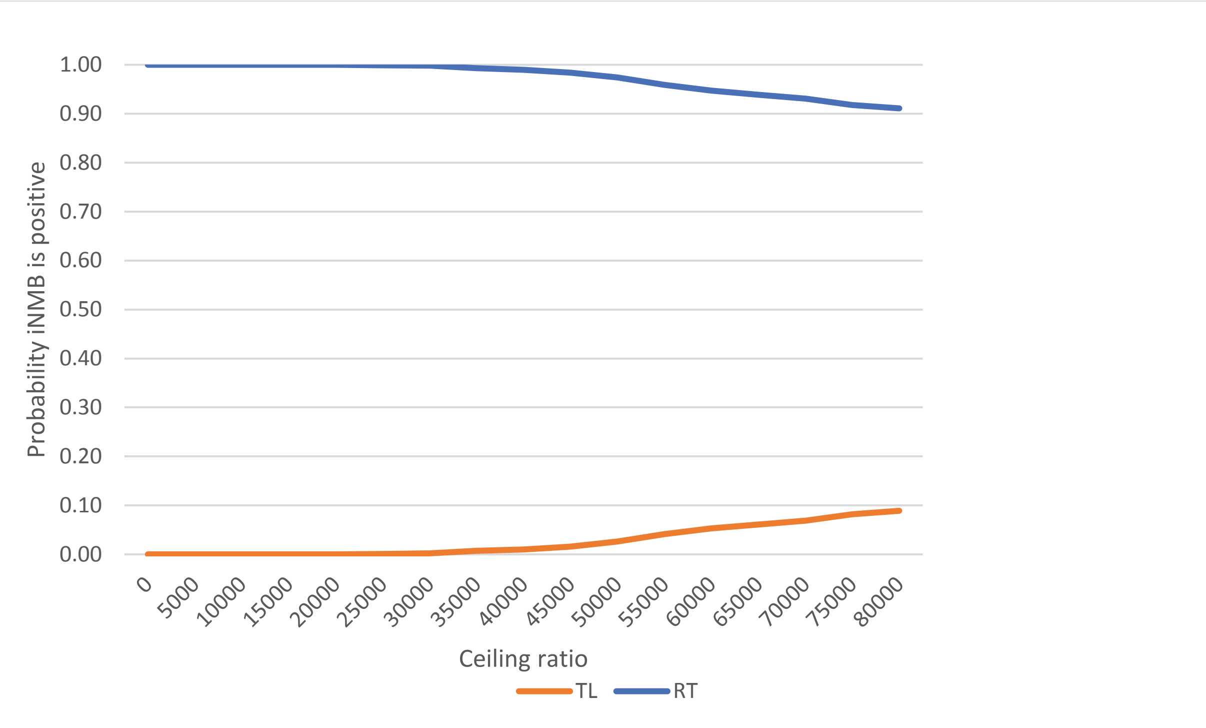


FIGURE IIIb: *CEAC SURGERY VERSUS CRT SHOWING THE PROBABILITY OF COST-EFFECTIVENESS GIVEN A CERTAIN WTP THRESHOLD*

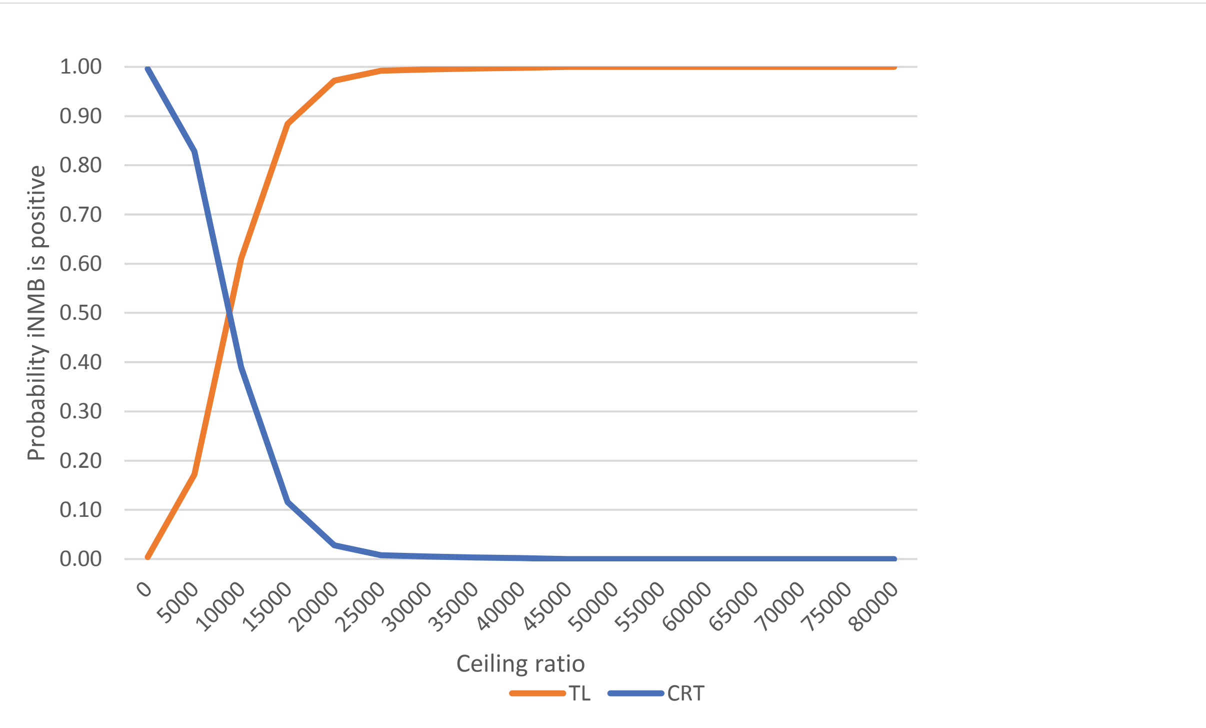
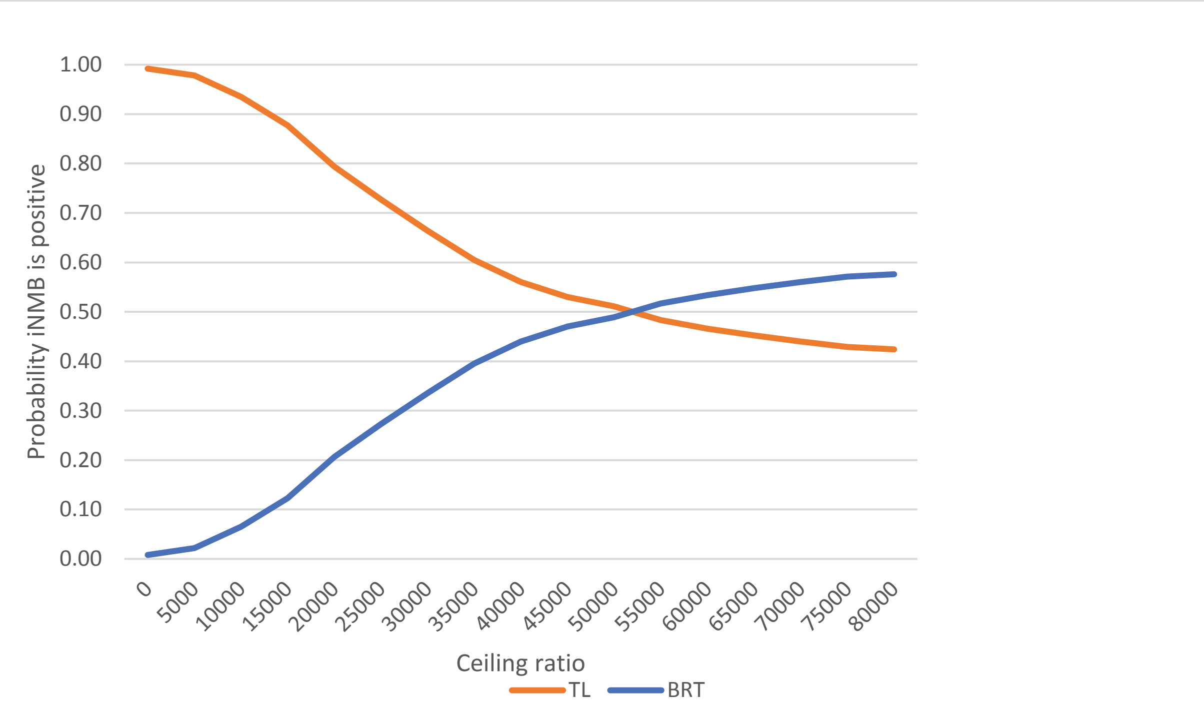


***FIGURE IIIc**: CEAC SURGERY VERSUS BRT SHOWING THE PROBABILITY OF COST-EFFECTIVENESS GIVEN A CERTAIN WTP THRESHOLD*



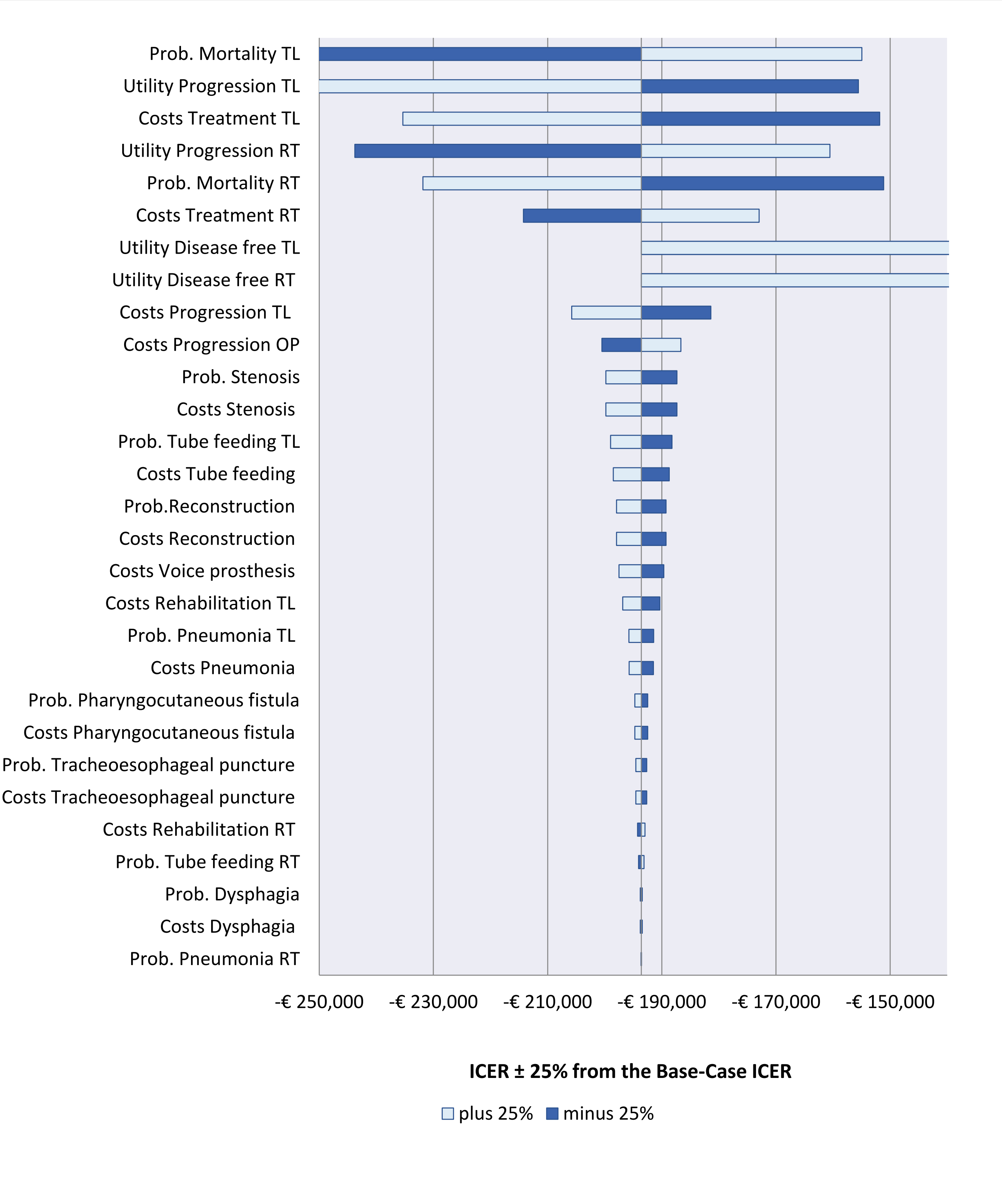
The CEAC of BRT versus CRT outlines BRT to be cost-effective when reaching a threshold of €20.000 and finally at a WTP threshold of €80.000 with a probability of 100 percent (*Appendix IIII)*.

3.3 Uncertainty Analysis

Tornado diagrams (*Figure IVa-c*) for surgery versus all organ-preserving modalities have been created to outline the effect on incremental costs per QALY when each of the input parameters are changed to ± 25 percent of the baseline.

The illustration of the parameters for surgery versus RT (*Figure IVa*) indicated the mortality rate due to cancer in the TL and RT group (-€301.944 to -€154.945; -€231.831 to -€151.137), the utility of progression health state in the TL and RT group (-€256.271 to -€151.827; -€243.780 to -€160.540), as well as the treatment costs for TL (-€235.355 to -€151.827) to have the greatest impact on the cost-effectiveness. Other parameters that influence the ICER are the treatment costs of RT, the utilities for disease-free health state in both groups, as well as the costs for progression. Minimal effects were recognized when setting the parameters of the probability and costs of dysphagia, the probability of pneumonia, the probability of tube feeding in the RT group and the costs for disease-free health state (not displayed) to a minimum or maximum.

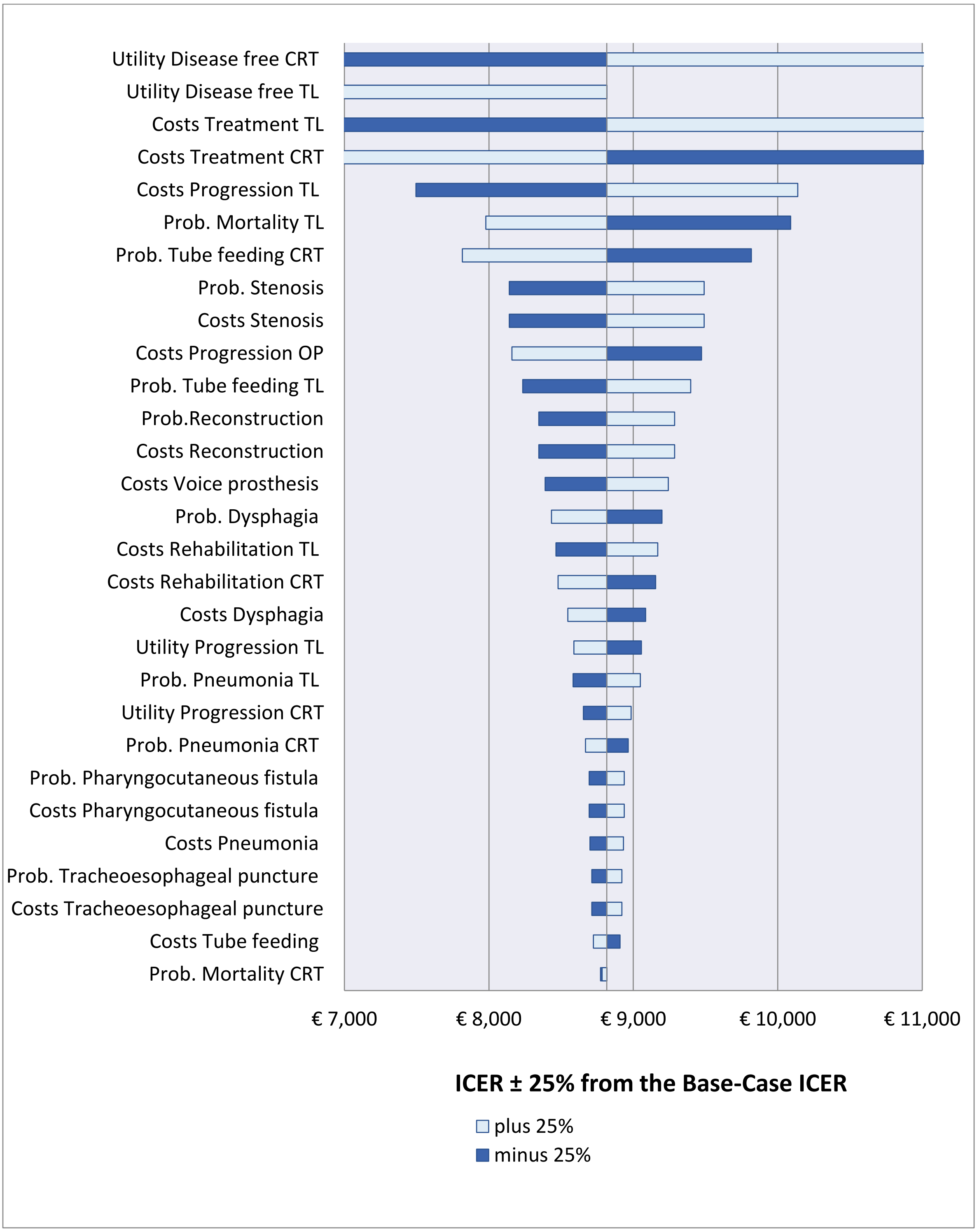
***FIGURE IVa**: TORNADO DIAGRAM, ONE-WAY DETERMINISTIC SENSITIVITY ANALYSIS, SURGERY VERSUS RT*



Probability of Mortality TL with minus 25% resulted in an ICER of -€301.944 (not fully displayed)
Utility of Progression TL with plus 25% resulted in an ICER of -€256.271 (not fully displayed)
Utility Disease free TL with plus 25% resulted in an ICER of -€19.377 (not fully displayed)
Utility Disease free RT with plus 25% resulted in an ICER of -€15.766 (not fully displayed)

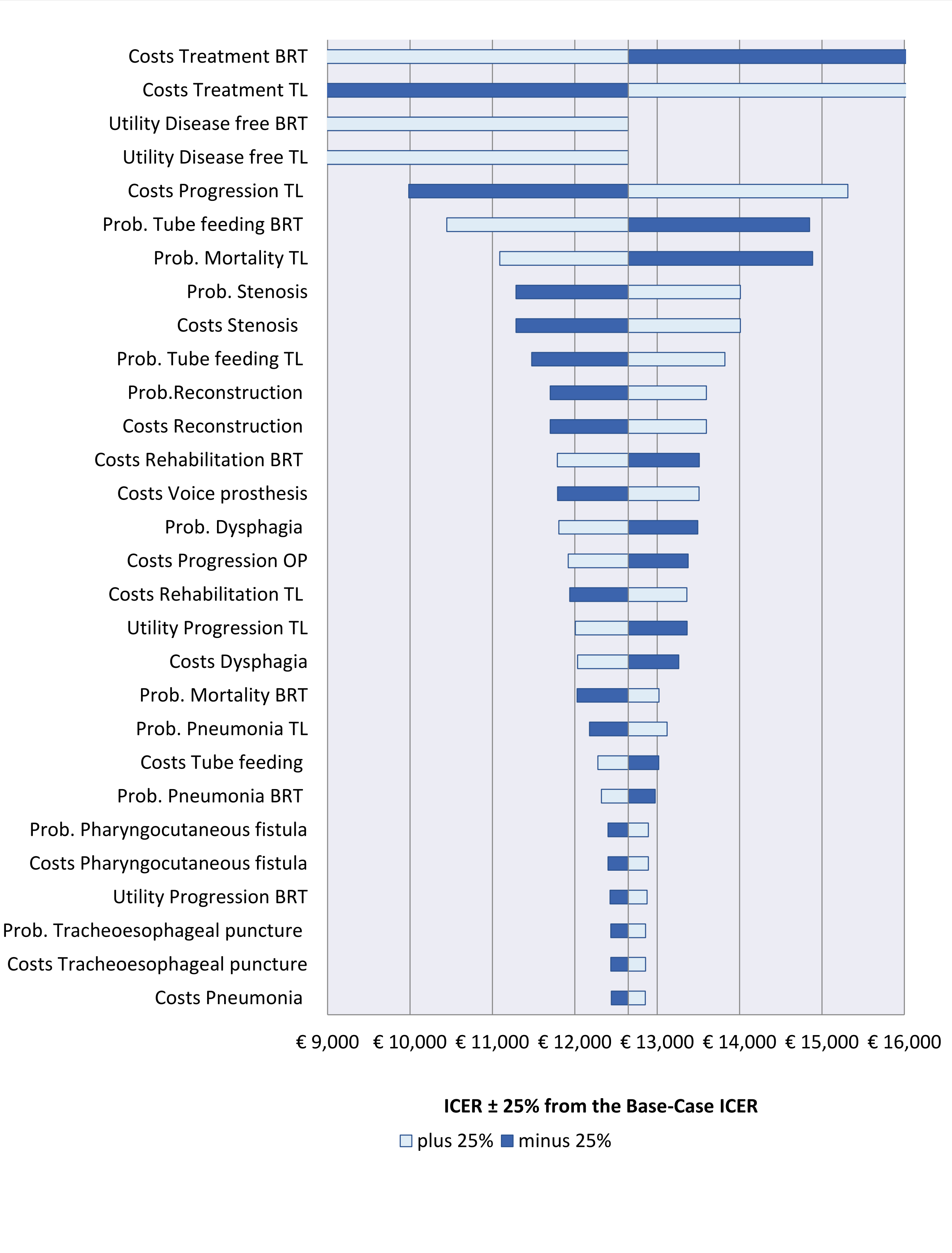
Comparing surgery and CRT (*Figure IVb*), parameters that influence the ICER/QALY the most are the utilities of disease-free health state in CRT and TL group (€4.521 to €175.928; -€45.886 to €4.022), as well as treatment costs for TL and CRT (€4.286 to €13.346; €4.696 to €12.937). In addition, costs for progression, the mortality probability in the TL group and tube feeding appear to have an effect on the ICER/QALY. Parameters such as costs in the disease-free health state (not displayed), the probability and costs of pharyngocutaneous fistula, the probability and costs of tracheoesophageal puncture, the mortality probability in the CRT group, as well as costs of pneumonia and tube feeding then again do not have a significant effect or no effect at all.

***FIGURE IVb**: TORNADO DIAGRAM, ONE-WAY DETERMINISTIC SENSITIVITY ANALYSIS, SURGERY VERSUS CRT*



Utility Disease free CRT with minus 25% resulted in an ICER of €4.521 (not fully displayed)
Utility Disease free CRT with plus 25% resulted in an ICER of €175.928 (not fully displayed)
Costs Treatment TL with minus 25% resulted in an ICER of €4.286 (not fully displayed)
Costs Treatment TL with plus 25% resulted in an ICER of €13.346 (not fully displayed)
Costs Treatment CRT with minus 25% resulted in an ICER of €12.937 (not fully displayed)
Costs Treatment CRT with plus 25% resulted in an ICER of €4.696 (not fully displayed)

***FIGURE IVc**: TORNADO DIAGRAM, ONE-WAY DETERMINISTIC SENSITIVITY ANALYSIS, SURGERY VERSUS BRT*



Costs Treatment BRT with minus 25% resulted in an ICER of €22.332 (not fully displayed)
Costs Treatment BRT with plus 25% resulted in an ICER of €2.966 (not fully displayed)
Costs Treatment TL with minus 25% resulted in an ICER of €3.516 (not fully displayed)
Costs Treatment TL with plus 25% resulted in an ICER of €21.782 (not fully displayed)
Utility Disease free BRT with plus 25% resulted in an ICER of -€10.637 (not fully displayed)
Utility Disease free TL with plus 25% resulted in an ICER of €3.717 (not fully displayed)

Likewise, the tornado diagram for surgery versus BRT (*Figure IVc*) outlined similar parameters to be affecting the cost-effectiveness as illustrated for other modalities. Treatment costs for BRT and TL (€2.966 to €22.332; €3.516 to €21.782) and the utilities of the disease-free health state in the BRT and TL group (-€10.637 to €3.966; -€9.013 to €3.717), as well as the progression costs in the TL group (€9.985 to €15.313) appear to have the greatest impact. The least affecting parameters, including the probability and costs of pharyngocutaneous fistula, the probability and costs of tracheoesophageal puncture along with the utility for progression health state in the BRT group, costs of pneumonia appear to result in similar ICER/QALY, ranging from €12.405 to €12.894.

When setting all cost input parameters to a maximum of +25 percent, RT still remained cost-effective compared to surgery with an ICER/QALY of -€246.966, whereas costs for TL exceeded the WTP threshold of €80.000 with €92.409.

4. Discussion

Within this study findings outlined RT of all considered organ-preserving modalities to be cost-effective compared to surgery with an ICER of -€193.591. This is to be explained due to RT having the lowest costs, whereas the difference in effectiveness between RT and TL is rather limited (9,97 QALY vs 9,75 QALY). CRT, being less costly than surgery, had the least favorable outcome in QALYs. BRT however, as the innovative organ-preserving treatment, is costlier than RT and less effective regarding QALYs gained compared to surgery but shows an increase of LYs compared to surgery (13.70 vs. 11,23) and other organ-preserving modalities. Moreover, costs of BRT do not exceed the WTP threshold of €80.000 which makes it relevant for clinical practice nonetheless.

Focusing on the cost-effectiveness of BRT versus CRT, BRT showed an increase in QALYs while showing higher costs. However, the effectiveness of BRT and CRT is similar regarding QALYs gained, whereas LYs are shown to be increased with BRT.

While observing which parameters had an impact on the overall outcome for all treatment modalities, utilities for the disease-free health state, treatment costs, as well as costs of progression health state were found to be of interest. Additionally, for the TL and RT group, the probability of mortality has been observed to have an impact other than the aforementioned parameters.

Costs for pharyngocutaneous fistula, tracheoesophageal puncture, pneumonia and their associated probabilities, as well as the probability of mortality for CRT and rehabilitation costs for RT barely had any effect on the cost-effectiveness.

Changing cost input parameters to +25 percent within the scope of the one-way sensitivity analysis, still lead to RT being cost-effective, while costs of TL exceeded the WTP threshold.

Comparing the treatment costs of the different modalities stated in literature to this study, costs were shown to be less in existing literature while similarly showing surgery and combined RT to be costlier than RT alone. The study of Morton was the only one to be found to have determined the cost-effectiveness of TL versus RT, resulting in costs of TL and RT to be NZ$15.840 and NZ$6.473 (€9.173 and €3.749, 1 NZ$ = €0.579, 15/06/2018) (23). Brown et al. stated costs for RT alone and BRT to be €9.037 and €19.052 (11). Differences in costs found in literature compared to this study are to be justified mainly due to a decrease in intensity and duration of treatment based on a patient sample consisting mainly of stage TI and TII laryngeal cancer. Furthermore, rather than applying DBC cost-packages, treatment-related costs, such as patient imaging, outpatient visits routine monitoring costs and nursing care were considered separately. Moreover, country-specific, trial-based costs differ and long-term complications were disregarded.

Considering the finding of RT being significantly cost-effective compared to surgery, one has to be aware that those results might most likely differ in other healthcare settings. In this study 90 percent of the patients who received surgery, additionally received postoperative RT which lead to a significant difference in costs. Furthermore, costs of treatments might vary among (Dutch) hospitals due to patient groups being heterogeneous, leading to the average costs based on DBCs per treatment modality being rather specific.

A limiting factor to mention regarding the costs of complications, is the extensive range of occurring costs related to diagnosis and treatment of complications, compounding the precise determination of costs. The same applies to rehabilitation costs as those are primarily a burden for primary care, which was not taken into account within this study.

Regarding the input parameters, several sources have been used which need to be critically observed as study conditions might vary and thus lead to different results. This especially applies to survival data found in literature as OS for TL for instance ranges from 47,5% to 87,7% (14, 24, 25). Furthermore, the EQ-5D data of organ-preserving modalities used in the model have been obtained from literature stating quality of life scores based on head and neck cancer patients in general, not specifically focusing on laryngeal cancer only (17, 18). Hence, it would be desirable for future research to elicit first-hand, carcinoma-specific QoL scores in order to achieve the outcome to be more representative for each modality. The same applies to the NKI-based EQ-5D-5L measurement of patients who received surgery, as a larger sample would most likely emphasize the validity of the QoL score. The limitation of the EQ-5D obtained data however, needs to be considered, as for patients who received surgery, the loss of the larynx is not reflected in the utility score. In addition, head and neck specific symptoms are not displayed, which could be achieved through mapping EORTC QLQ-C30 and QLQ-H&N35 questionnaires to the EQ-5D (26).

This study appears to be the first, to have compared surgery versus RT, CRT and BRT. To our knowledge existing literature either solely examined the cost-effectiveness of surgery versus RT by not exclusively focusing on advanced laryngeal cancer and disregarding other combined modalities such as BRT. Results showed no significant differences in cost-effectiveness between surgery and RT (23), which is not in accordance with this study. Furthermore, existing studies were limited to the comparison of RT and BRT, showing a probability of 0,76 for BRT to be cost-effective with a WTP threshold of €80.000 per QALY (8).
Therefore, this study functions as a theoretical framework for improvement and a guideline to further elaborate research in that field, especially in regard to newer innovative treatments.
A strength to be outlined, giving this study an added value, is its focus on a detailed elicitation by combining data from literature with data obtained from clinical practice of the AVL-NKI as a primary source and expert opinion of surgeons and radiotherapists. Several relevant complications affecting QoL and costs were precisely considered, primarily based on literature and eventually elicited by radiologists and head and neck surgeons.
Apart from that, treatment costs were based on patients from the AVL-NKI, ensuring a realistic basis for the cost-effectiveness, specifically compatible to advanced laryngeal cancer in clinical practice.

Nonetheless, recommendations for further research on the matter are to improve the reliability of health state utilities, with a keen eye on prospective utilities for all treatment modalities with a more extensive sample size. Furthermore, more detailed costs, especially within the scope of primary care, should be taken in consideration. This is said as these expenses take a significant part in the overall costs regarding post treatment care.
However, as costs in this study are based on Dutch tariffs and guidelines, costs need to be converted to country-specific healthcare systems in order to generalize the results of this study on an international level.

This study functions as a tool to support clinical practice, however it does not incorporate the burden that comes along with different treatments. The pathway of surgical treatment is completed with one operation and results in the loss of the larynx, while organ-preserving modalities include a longer treatment pathway. Despite that, patients in stage IV laryngeal cancer show a better outcome in survival and QALYs gained when treated with surgery according to Timmermans et al. (27). Consequently, not only the patient's preference is decisive but also each case requires individual evaluation.

5. Conclusion

This study evaluated the cost-effectiveness of surgical versus organ-preserving treatment modalities in laryngeal cancer. Among all considered organ-preserving modalities, RT was found to be cost-effective compared to surgery (ICER of -€193.591) with a probability of 0,91 given the WTP threshold of €80.000 per QALY in. The difference in QALYs was +0,22. BRT after all, had the largest increase in LYs with 13,7 compared to all other modalities, while being less costly than surgery. Besides the initial purpose of this study, BRT was found to be cost-effective compared to CRT accordingly to the WTP threshold of €80.000/QALY. Although costs were higher with BRT (+€5.087), a slight better effectiveness was to be found (+1,01 QALYs; +1,57 LY). The analysis identified organ-preservation to be a reliable option to surgery, leading to lower costs and an increase of QALYs with RT and BRT and a positive effect on PFS duration with BRT and CRT.

This paper is meant to inform specialist and patients about the treatment modalities in advanced laryngeal cancer and their outcomes, while the decision of which modality to choose eventually is as well an issue of affordability and the patient's preference.

In order to strengthen and eventually improve the results of this study, it is recommended to gain more reliable health state utilities, take into consideration rehabilitation costs that appear in the scope of primary care, as well as including each individual burden of treatments, such as the loss of the larynx, through mapping EORTC QLQ-C30 and QLQ-H&N35 questionnaires.

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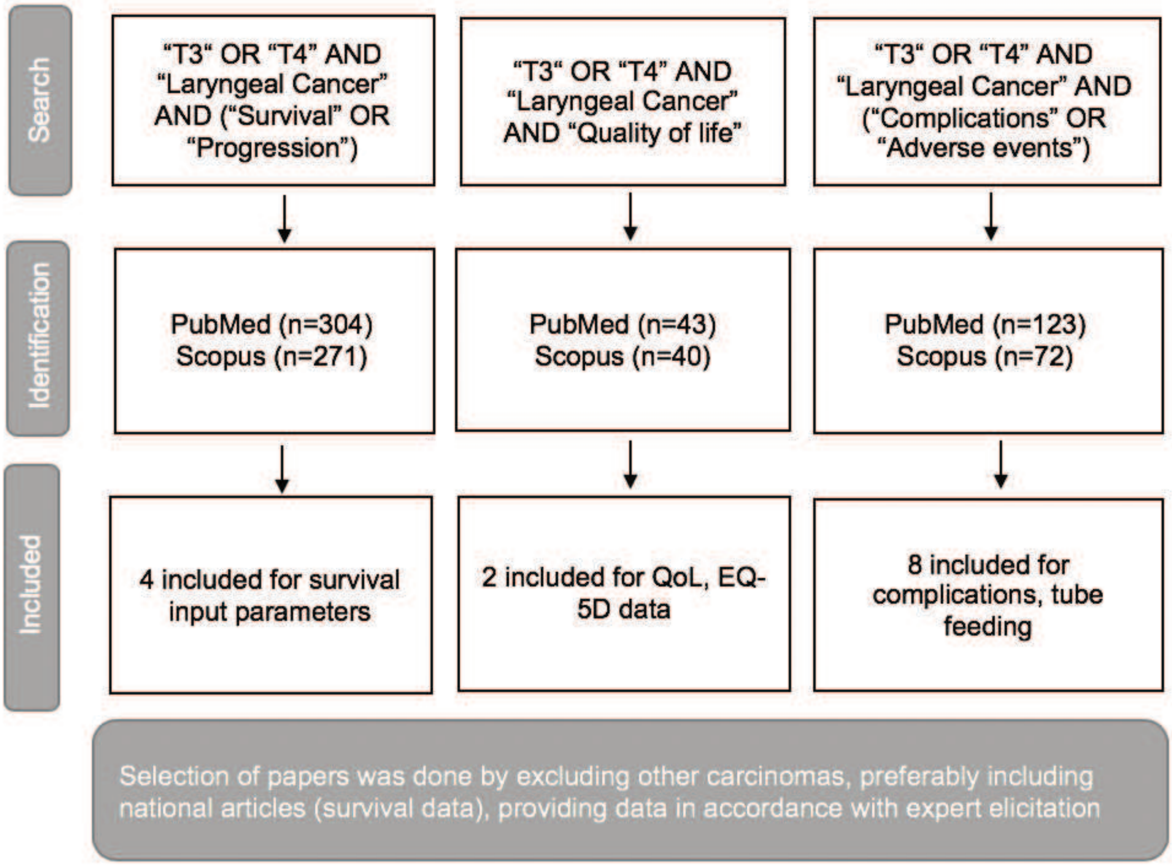
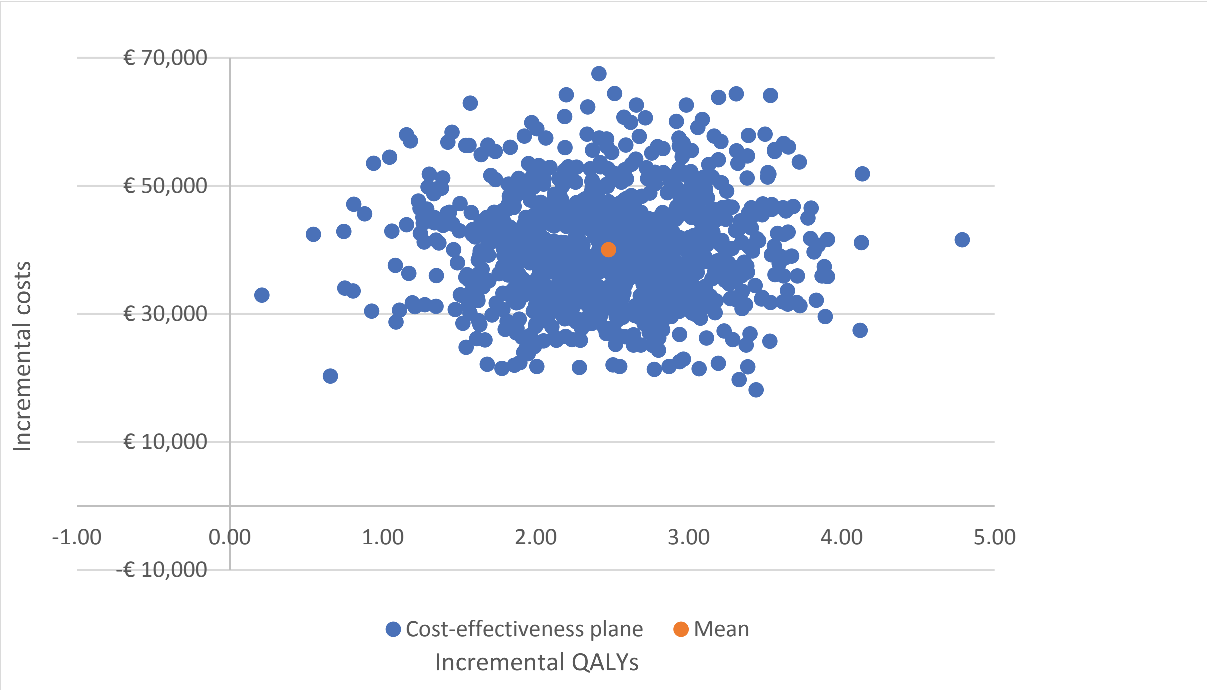
APPENDIX I: *SEARCH STRINGS IN PUBMED AND SCOPUS FOR INPUT PARAMETERS*



APPENDIX II: *PROBABILITY OF COMPLICATIONS PER TREATMENT MODALITY*

Treatment	Probability	Standard Error	Distribution	Source
TL				
Reconstruction	0,410	0,016	Beta	(14)
Pharyngocutaneous Fistula	0,171	0,012	Beta	(14)
Tracheoesophageal Fistula	0,116	0,010	Beta	(28)
Stenosis	0,750	0,014	Beta	(29)
Pneumonia	0,150	0,011	Beta	NKI
Tube feeding	0,080	0,009		(30)
RT				
Dysphagia	0,140	0,011	Beta	(31)
Pneumonia	0,022	0,005	Beta	(2)
Tube feeding	0,050	0,007	Beta	NKI
CRT				
Dysphagia	0,400	0,015	Beta	NKI
Pneumonia	0,090	0,009	Beta	(7)
Tube feeding	0,130	0,011	Beta	(32)
BRT				
Dysphagia	0,400	0,015	Beta	NKI
Pneumonia	0,090	0,009	Beta	(7)
Tube feeding	0,130	0,011	Beta	(32)

APPENDIX III: *CE-PLANE OF BRT VERSUS CRT*



APPENDIX IIII: *CEAC CRT VERSUS BRT*