Cost-Effectiveness of Neck Treatment Strategies for Sentinel Node-Positive Oral Cavity Squamous Cell Cancer: A Microsimulation Study.

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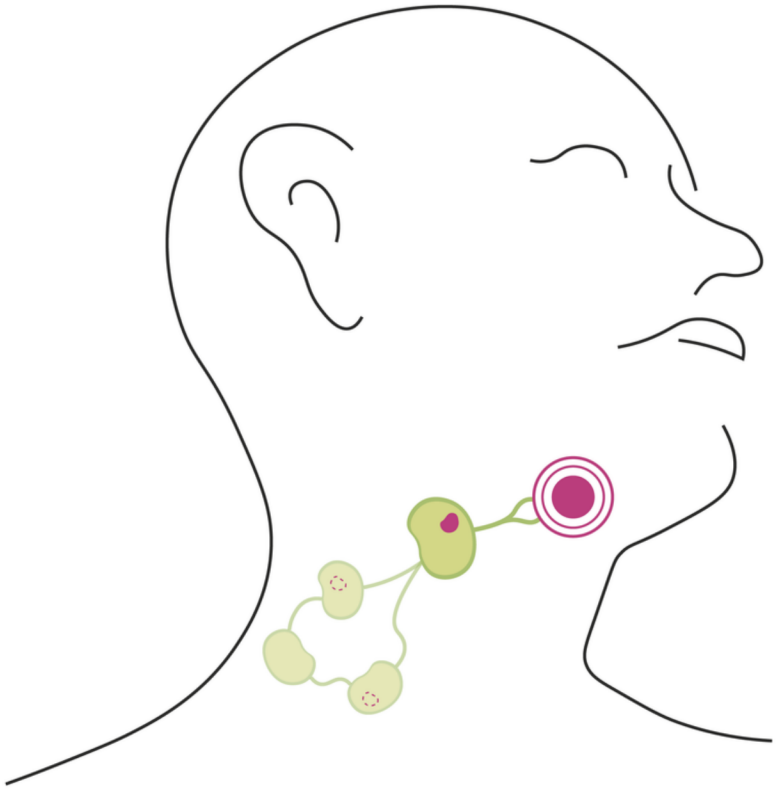

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Title
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I hope you enjoy reading my Master thesis.

Veerle Koeken
Utrecht, March 2023

Summary

Background: *This study aimed to evaluate the cost-effectiveness of neck treatment strategies for cT1-2 SN+ oral cavity squamous cell cancer. The research investigated the routine application of neck dissection, neck dissection with postoperative radiotherapy, radiotherapy, or watchful waiting to improve clinical decision-making and patient management and enhance health outcomes, given the available data. The most important uncertainty in data that influences the outcomes were assessed.*

Methods: *A microsimulation model was constructed to simulate primary and adjuvant neck treatment, regional disease recurrence, and salvage therapy in patients with T1/T2 sentinel node-positive oral cavity squamous cell carcinoma. This decision-analytic model was developed to study the cost-effectiveness of neck treatment strategies for isolated tumour cells, micrometastasis and macrometastasis-positive sentinel nodes separately. Survival, quality of life and costs associated with neck dissection, radiotherapy and observation were evaluated in these patient groups. Since individual patient data was not sufficiently available, literature was analysed, and clinical expertise was used to define input parameter values. A distribution was defined for each input parameter, describing the variation at the patient level. Uncertainty was addressed using deterministic and probabilistic sensitivity analyses. Value of information analyses described the value of additional research.*

Results: *Simulating patients' cost-effectiveness outcomes, it was estimated that radiotherapy I-V would give the highest number of QALY for the different dimensions of metastatic lymph node deposits in ITC, MiM and MaM size. In terms of cost-effectiveness, watchful waiting was the best treatment strategy for isolated tumour cells and micrometastasis and neck dissection I-III for macrometastasis. However, the PSA indicated a high degree of uncertainty in the cost-effectiveness of each strategy, with a probability of acceptable cost-effectiveness of 92%, 57%, and 58% given the Dutch threshold of €20,000/QALY. Uncertainty in the parameters* non-SN metastasis *(additional non-SN metastases after removal of the sentinel nodes) and* in surgery field recurrence *(recurrence in a neck level in which the nodes were dissected) had the most influence on the outcomes for isolated tumour cells and the micrometastasis model. For macrometastasis, uncertainty in the probability of non-SN in level IV and the probability of shoulder morbidity complications had the most influence on outcomes.*

Conclusion: *The quality and quantity of available observational and literature data resulted in a large uncertainty surrounding the parameter values used for simulation modelling, and therewith the outcomes. Therefore, no clear conclusion can be drawn. Gathering more data to reduce uncertainty and make informed decisions is essential. The study should increase awareness of the importance of data collection of sentinel node-positive OSCC patients and influence key choices in data sharing.*
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Keywords: Cost-effectiveness, oral cavity cancer, positive sentinel node, microsimulation

Contents

List of abbreviations.

CEAC	Cost-effectiveness acceptability curve.
DSA	Deterministic sensitivity analysis.
ENE	Extranodal extension.
EVPI	Expected value of perfect information.
EVPPI	Expected value of partially perfect information.
HR-QoL	Health-related quality of life.
ICER	Incremental cost-effectiveness ratio.
IMRT	Intensity-modulated radiotherapy.
ITC	Isolated tumour cells.
LVI	Lymphovascular invasion.
MaM	Macrometastasis.
MiM	Micrometastasis.
MRND	Modified radical neck dissection.
ND	Neck dissection.
NMB	Net monetary benefit.
non-SN+	Additional non-sentinel node metastases.
OCC	Oral cavity cancer.
OS	Overall survival.
OSCC	Oral squamous cell carcinoma.
PNI	Perineural invasion.
PORT	Post-operative radiotherapy.
PSA	Probabilistic sensitivity analysis.
QALY	Quality-adjusted life year.
RND	Radical neck dissection.
RT	Radiotherapy.
SCM	Sternocleidomastoid muscle.
SLNB	Sentinel lymph node biopsy.
SMGs	Submandibular glands.
SN	Sentinel node.
SN+	Positive sentinel node.
SND	Selective neck dissection.

VoI Value of Information.

WTP Willingness-to-pay.
WW Watchful waiting (No treatment).

1 Introduction

Oral squamous cell carcinoma (OSCC) arising from the oral cavity is one of the most common types of malignancy in the head and neck region. Oral cavity cancer accounts for approximately 3% of the total cancer incidence worldwide, with an estimated incidence of more than 370,000 new cases per year[1]. Oral cavity cancer develops in several anatomical subsites: the lip, oral tongue, the floor of mouth, buccal mucosa, upper and lower gum, retromolar trigone and hard palate. The neck lymph nodes are the first site of metastatic disease.

1.1 Regional oral cavity cancer

The average 5-year survival rate for patients with neck failure is 37%, a significantly poorer outcome than the 5-year overall survival of 74% for patients without neck failure[2]. Therefore, lymph node metastasis is a critical prognostic factor for head and neck cancers, which may reduce the 5-year survival rate by 50%[3]. Moreover, lymph node metastasis is observed in more than 50% of patients with oral cavity cancer[4]. Even patients with clinically node-negative (cN0) disease still have a high risk of occult nodal involvement, which can exceed 40% in selected patients[5]. Due to the high risk of occult nodal involvement of clinically negative nodes, sentinel lymph node biopsy (SLNB) is performed in standard clinical care in the Radboud UMC and most other Dutch centres to detect lymph node metastasis as a screening method and staging process[6].

1.2 Sentinel node procedure

The Sentinel Node (SN) procedure is an interoperative staging procedure for patients without clinically detectable lymph node metastases and is able to detect occult metastases in head and neck cancer[7]. In the procedure, a radioactive agent is injected into the primary tumour to identify the first draining lymph node, the sentinel lymph node most likely to harbour metastases. Uptake in lymph nodes of this agent can be visualised using a gamma probe or single photon emission computed tomography-computed tomography (SPECT/CT). The sentinel lymph nodes are removed and histologically examined to determine whether cancer cells are present and have started to spread from the primary tumour.

An SN is considered positive if at least one tumour cell is found during histological examination. The size of the positive SN is divided into Isolated tumour cells (ITC): defined as a tumour diameter smaller than 0.2 mm, micrometastasis (MIM); defined as between 0.2 and 2 mm, and macrometastasis (MAM); defined as greater than 2 mm. If the SLNB is positive, it may suggest that cancer has spread to the rest of the nodal basin. Regional failure is defined as having an ipsilateral regional recurrence in the lymph nodes after a positive sentinel node and accompanying therapeutic therapy.

1.3 Therapeutic therapy

The aim of therapeutic therapy after a positive sentinel node is to prevent regional failure in the clinically negative neck. A neck dissection is considered the golden standard for T1-2 SN+ M0 patients. Postoperative radiotherapy is commonly used as a comprehensive treatment for high-risk nodal metastasis. The care pathway for patients with a positive sentinel node, as described in the current protocol, can be seen in Figure 1 and is explained in the following paragraphs.

The TNM classification is a globally recognised standard for classifying the extent of the spread of cancer. The T refers to the size and extent of the primary tumour. T1 means the tumour is only in the inner layer of the bowel. T2 indicates the tumour has grown into the muscle layer of the bowel wall

but is no larger than 4 cm and not growing into the epiglottis (the base of the tongue). The N refers to the number of involved lymph nodes. Clinically node-negative (cN0) means no positive nodes following scans and examination. SN+ means the sentinel node is positive. The M refers to whether the tumour has metastasised. M0 means cancer has not spread to other parts of the body.

Figure 1: *Care-pathway cT1-2 SN+ M0 oral cavity cancer patients.*

1.3.1 Dissection of the cervical lymph nodes

The neck is divided into anatomical lymph node levels to assess head and neck cancer staging, as shown in Figure 3. Neck dissections are classified according to the extent of those levels[8].

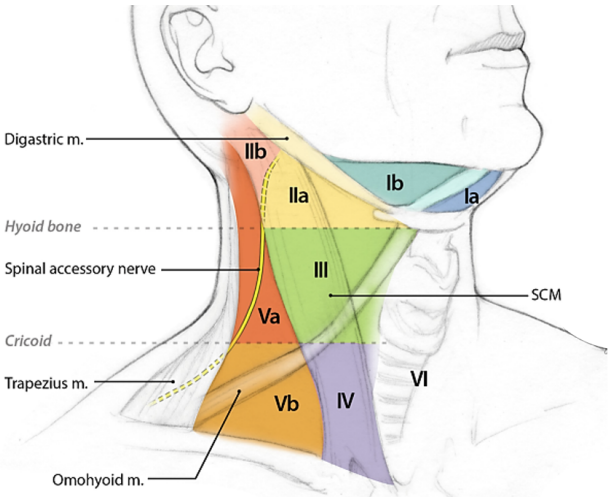

Figure 2: *Side view of the ipsilateral lymph node levels of the neck with important non-nodal cervical structures. SCM = sternocleidomastoid muscle. Adapted from*[9]

In 1994, Weiss et al. concluded that an oral cavity cancer patient with a cN0 neck should be treated with modified radical neck dissection (MRND) if the probability of occult lymph node metastasis is greater than 20%[10]. MRND refers to the removal of level I through V and key non-nodal structures, including the spinal accessory nerve, sternocleidomastoid muscle (SCM), and internal jugular vein and additional removal of other lymph node groups or non-lymphatic structures, such as arteries, muscles, and nerves. The primary focus at that time was the control of neck disease, and MRND was also an independent prognostic indicator. However, the removal of the spinal accessory nerve and dissection of lower neck levels is associated with higher shoulder morbidity. Therefore, the procedure has been modified over time to reduce morbidity while maintaining oncologic efficacy by only removing lymph node groups at greatest risk with preservation of key non-nodal structures[6].

Currently, the standard neck treatment for patients with early-stage oral cavity cancer and positive sentinel node includes selective neck dissection (SND)[11]. An SND preserves one or more lymph node groups and key structures routinely removed in MRND. Depending on the level of the positive sentinel node and the location of the primary tumour, the preserved groups are level V or level IV to V. However, even in a neck dissection involving level I-III or level I-IV with preservation of the spinal accessory nerve, there is always some devascularisation of a part of the nerve. SND may cause limited shoulder function disfigurement, pain in the shoulder region, loss of strength, reduced range of motion, loss of function of the shoulder, sensory disturbance, and restrictions in daily activities. Therefore, shoulder morbidity is still the most common complication of neck dissections[12].

1.3.2 Radiotherapy

Only a subset of SN+ patients is treated curatively with radiotherapy. Radiotherapy is usually reserved for patients with unresectable regional metastases (1), unsafe surgery due to the patient's medical condition (2), or patient refusal (3). Besides, medical guidelines state that neck dissection is replaced with radiotherapy for patients with micrometastasis or ITC SNs and an indication of local or regional postoperative radiotherapy.

Post-operative radiotherapy (PORT)
The absolute indications for postoperative radiotherapy for the primary tumour, because of the high risk of occult metastasis, are: non-radical resection edges (< 1mm), lymph node metastases with extranodal growth, or multiple lymph node metastases. Relative indications, giving an intermediate risk of occult metastasis, are dependent on multiple tumour characteristics. These relative risks are tight resection edges (1-5 mm), perineural growth, and sprawling growth. If PORT is used for primary tumour treatment, the treatment area is often extended to the neck region. In addition, PORT is commonly used as part of comprehensive treatment for patients with SN with macrometastases.

Xerostomia (dry mouth) is the most common and prominent complication after radiotherapy for head and neck cancers. It affects taste, speech, swallowing, and overall discomfort. It is caused by damage to the salivary glands, which alters the consistency and pH of secreted saliva and causes reduced salivary flow. The submandibular glands (SMGs) contribute up to 90% of the salivary in the non-stimulated state and contain mucins, which chiefly contribute to the patient's subjective sense of moisture. SMGs are located bilateral within level IB of the neck. In stimulated state, most of the saliva is produced by the parotid glands. The parotid is located in front and beneath the ear. The severity of radiation-induced salivary damage depends on the total radiation dose and volume reaching the irradiated tissue and saliva glands[13]. Currently, intensity-modulated radiotherapy (IMRT) is used as a radiotherapy technique and focuses on sparing the salivary glands from unnecessary irradiation. Besides, ipsilateral radiotherapy partially spares the functionality of the contralateral glands.

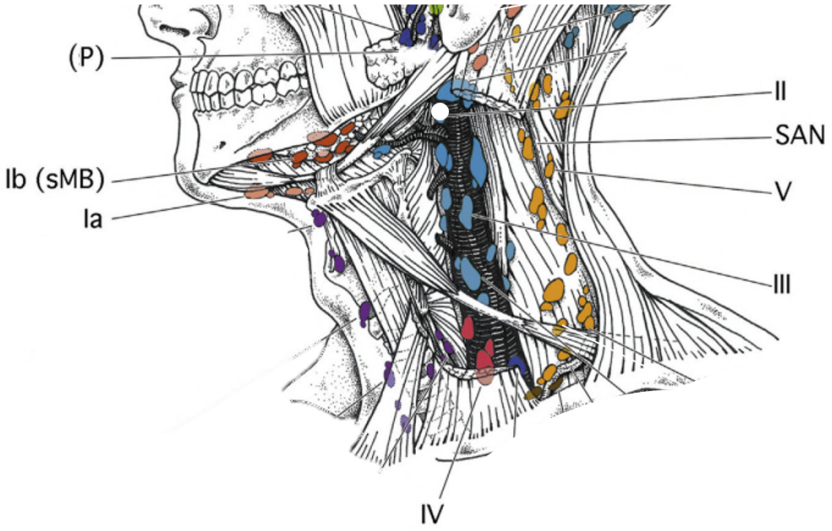

Figure 3: *Location of the lymph nodes, close to the submandibular and parotid glands. sMB = Submandibular gland, SAN = spinal accessory nerve. P= Parotid Adapted from*[14]*)*

1.3.3 Observation - Watchful waiting policy

The watchful waiting (WW) policy, also called the wait-and-see method or observation, is closely monitoring and not giving treatment unless symptoms appear or change. This method is examined in the literature and used from time to time for some other cancer types[15][16]. For oral cavity cancer, research shows that neck treatment could significantly reduce neck recurrence and improve disease-free survival and overall survival compared to watchful waiting for patients with cT1-T2N0 oral cavity cancer (without SN procedure)[17]. Therefore, WW never gained wide acceptance as a standard treatment method[18]. However, non-sentinel nodes rarely contain metastasis in the pathological examination of lymph nodes of the ND after SLNB. The possibility of overtreatment extends to 87% for some cases, and a significantly higher complication rate is found for patients after neck dissection compared to WW[5][6]. Accordingly, observation and closely monitoring of the lymph nodes could be a new strategy for low-risk SN+ patients.

1.3.4 Salvage therapy

In the case of curable regional recurrence, a patient receives salvage treatment. The type of salvage therapy depends on the location of the regional recurrence and the primary treatment of the neck if the regional failure inside the field[6]. The difference in salvage therapy after a regional failure between END, SND, radiotherapy and WW is the availability of more effective treatment options for regional failure. Radiotherapy is performed in case of previous neck dissection or neck dissection with PORT. After primary neck radiation, it is, in principle, possible to perform surgery or re-radiate. All treatment options are possible if the regional recurrence is outside the treated region. Accordingly, salvage after WW is more effective than after neck dissection or radiotherapy.

Salvage surgery has a high complication rate and diminished quality of life since difficulties include scarring from previous SLNB and treatment. Besides, a delay in diagnosis increases the chance of an increase in the number of positive nodes and extracapsular spread[?] .

1.4 Research problem

Despite the significant progress made with using SLNB, there remain some challenges in the treatment after a positive sentinel node biopsy for oral cavity cancer patients.

1.4.1 Problem formulation

There is a trade-off between an improved prognosis and the oncological effect of more invasive procedures (e.g. removing or depleting lymph nodes involved at risk for involvement by metastatic cancer) on one end and a negative impact on quality of life by complaints and complications as a result of removing or depleting lymph nodes on the other end. The core problem is the remaining unclarity of the added value of treatment strategies as the standard treatment of patients with a positive SLNB in oral cavity cancer, and if they outweigh their potential adverse effects and impact on quality of life. Current treatment can cause overtreatment, and patients consequently experience decreased quality of life. It is of great importance that lymph node removal is restricted to those patients who are expected to actually benefit. Since the optimum treatment of the SN+ neck is unresolved, there is no consistent agreement on neck management. So far, no extensive research has been conducted on the actual advantages and disadvantages of treatment after a positive sentinel node biopsy for head and neck oncology.

1.4.2 Study objective and research questions

The objective of this study is to develop a health economic model, to assess the cost-effectiveness of strategies to treat the neck of patients with T1/T2 SN+ m0 oral cavity cancer. Crucial is to compare the outcomes of the treatment strategies. Consequently, the aim of this study is to compare the cost-effectiveness of neck dissection, (post-operative) radiotherapy, and watchful policy in comparison to each other of regional oral cavity cancer after positive SLNB separately for macrometastasis, micrometastasis and ITC. Accordingly, the research question is: *'What is the cost-effectiveness of neck treatment strategies compared to watchful waiting strategy for cT1-2 SN+ oral cavity squamous cell cancer?'*. More specifically, the treatment strategies are a neck dissection of levels I to III, I to IV or I to V, adjuvant radiotherapy after a neck dissection of levels I to III, I to IV, or I to V, radiotherapy of levels I to III, I to IV or I to V, or a watchful policy (no surgery, no radiotherapy) when used as a modality to treat occult lymph node metastasis after positive SLNB compared to eachother.

What is the cost-effectiveness of neck treatment strategies for cT1-2 SN+ oral cavity squamous cell cancer, specifically evaluating neck dissection, neck dissection with postoperative radiotherapy, radiotherapy, and watchful waiting for isolated tumour cells, micrometastasis, and macrometastasis-positive sentinel nodes separately
Subsequently, to answer the main problem, the sub-questions are:

- Can the neck region of low-risk oral cavity cancer patients with a positive sentinel node be treated with less morbidity and higher quality of life (QALY) without an increase in costs higher than the willingness-to-pay?
- Does a watchful waiting strategy as standard neck management for SN+ prevent patients from harbouring complications or overtreatment of regional oral cavity cancer and prevent unnecessary surgery, compared to a neck dissection, radiotherapy, or a neck dissection with postoperative radiotherapy?
- How does uncertainty in parameters influence the outcomes and conclusions, and could further data collection and analysis diminish uncertainty in the results?

1.4.3 Contribution

To conclude, this modelling study contributes to a scientific foundation on how to reach an optimal follow-up care pathway for patients with oral cavity cancer and regional occult metastases. This study will provide insight into the benefits of the WW policy, (post-operative) radiotherapy and neck dissections in follow-up care under various scenarios without intervening in the real process.

2 Methods

2.1 Study population

The target population comprises patients diagnosed with low- or intermediate-risk oral cavity cancer with a positive SN, i.e. early-stage (T1/T2) clinically node-negative (cN0) sentinel node-positive oral cavity cancer. Three different subgroups are analysed separately according to the size of the positive SN: Isolated tumour cells (ITC), micrometastasis (MIM), and macrometastasis (MAM). An SN was considered positive if at least one tumour cell was found during histological examination.

2.2 Model design

A decision-analytic model was developed to study the cost-effectiveness of adopting a neck dissection, radiotherapy or a neck dissection with postoperative radiotherapy as a treatment strategy compared to watchful waiting. An integrated decision tree and microsimulation model have been constructed, visible in Figures 4 and 5, respectively. For the treatment and complications, patient pathways can be represented adequately by a decision tree model, suitable to model the direct outcomes of the treatment strategies and assign shares of the initial population to different health states. To model the transition between health states and costs, life-years and QALYs, a microsimulation model was designed to evaluate the cost-effectiveness of treatment strategies compared to neck dissection of levels I-III for each of the three subgroups.

For all simulation analyses and cost-effectiveness analyses, R version 4.0.3. with the Decision Analytic Modeling Package (dampack package) version 1.0.1 was used[19]. The TECH-VER verification checklist was used to reduce errors in the model and for validation[20].

2.2.1 Decision tree

The first part of the model consists of decision trees to model the direct effects of treatment for the ten strategies, namely:

- Neck dissection of levels I-III
- Neck dissection of levels I-IV
- Neck dissection of levels I-V
- Radiotherapy of levels I-III
- Radiotherapy of levels I-IV
- Radiotherapy of levels I-V
- Neck dissection of levels I-III and PORT
- Neck dissection of levels I-IV and PORT
- Neck dissection of levels I-V and PORT
- Watchful waiting (No treatment, e.g. no neck dissection, no radiotherapy, and extra observations)

Each treatment arm is followed by the outcome part of the tree. After treatment, patients can harbour positive tumour cells, have complications or experience regional failure. Shoulder morbidity and xerostomia (dry mouth) were defined as the most important causes of long-term morbidity for the patient for neck dissection and radiotherapy, respectively[21]. Regional failure was defined as having an ipsilateral regional recurrence. It can result from metastasis in lymph nodes (positive non-sentinel nodes) in areas not previously dissected or irradiated, missed lymph nodes during surgery or radiotherapy in the surgery field, or extracapsular nodal disease that recurs in soft tissues of the neck.

The decision tree for treatment strategies and outcomes is shown in Figure 4. There are three separate trees for ITC, MiM, and MaM in the SN. The squares represent decision nodes, the circles represent chance nodes, and the circles with an M are health states representing the microsimulation part of the model.

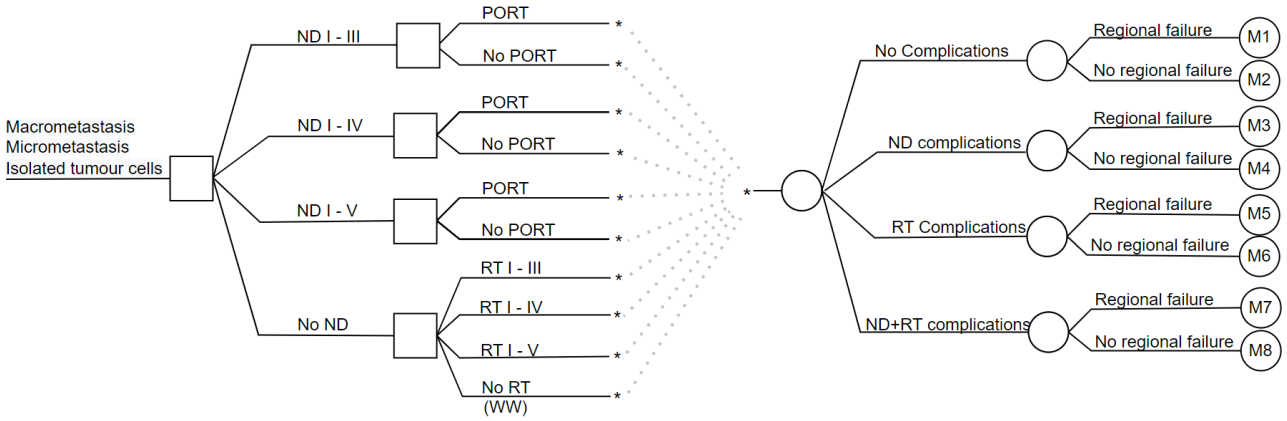

Figure 4: *Decision tree part of the model. Three separate trees for the patient subgroups: isolated tumour cells, micrometastases and macrometastases positive sentinel nodes. After treatment (left), positive non-sentinel nodes, complications and recurrence are possible (right). The chances are dependent on the treatment strategy. ND = neck dissection, RT= radiotherapy, Non-SN+ = Positive non-sentinel nodes, Non-SN- = absence of positive non-sentinel nodes.*

2.2.2 Introduction to microsimulations

Microsimulations are individual-based state transition models which can accurately reflect individual clinical pathways, incorporating the impact of history on future events (e.g. modelling interventions for diseases that involve recurrent events), and easily capture the variation in patients' characteristics[22]. Therefore, microsimulation models can provide a framework to represent the care pathway of SN+ patients and the impact of treatment decision-making on health and economic outcomes.

2.2.3 Microsimulation model

An individual-based state-transition microsimulation model was built to simulate the long-term consequences and involves patients transitioning between health states over time periods. The microsimulation part of the model is shown in Figure 5. Possible health states are 'Post-treatment', 'Detection and Salvage', 'Post-salvage therapy' and 'Dead'. Individual patients enter the microsimulation part of the model based on the decision tree. Therefore, the post-treatment health state is divided into eight subgroups based on long-term complications and regional failure.

Patients move through the model, and the future states of patients are determined based on the current state and the transition from one health state to another. In the model, transition probabilities were time-dependent, and other probabilities were used across model cycles. After each cycle, the patients could stay in their health state, regional recurrence could be discovered and treated with salvage therapy, or patients could die. Depending on the type of treatment initially received, patients with detected regional failure receive salvage treatment and move to the post-salvage therapy state. Death can be either cancer-related or due to mortality from other causes. Each health state was assigned an HR-QoL value and corresponding costs. These were then aggregated, per patient, across all health cycles, and discounting was applied. The model consists of fixed time-to-events intervals with a cycle length of 1 year, and a 10-year time horizon was used.

While longer time horizons could provide more comprehensive information, regional failure occurs within two years after neck treatment, and differences in survival tend to plateau after a certain point. Additionally, longer time horizons require more data and computational time. Therefore, a 10-year time horizon is assumed to be sufficient for capturing the most important outcomes and differences between treatment strategies.

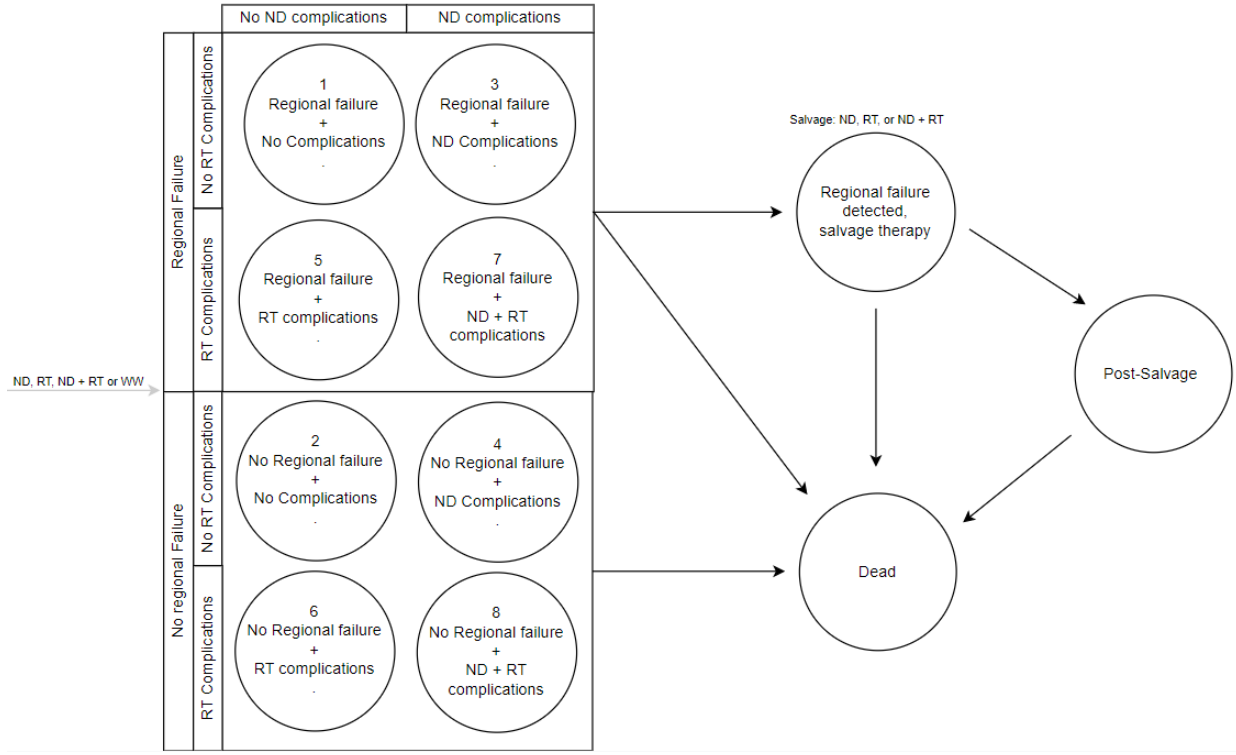

Figure 5: *Microsimulation part of the model. There are eight start health states: (undetected) regional failure and complications from surgery or radiation. Patients stay in their start health state until regional failure is detected and the patient is treated with salvage therapy, or the patient dies. ND = Neck dissection, RT= radiotherapy, WW= watchful waiting.*

3 Model parameters

The microsimulation model was populated using input parameter values. Patient data were collected from patients receiving an SLNB at Radboud University Medical Center (Radboud UMC) and patients with a positive SN from a Dutch retrospective study collected at University medical centre Utrecht (Utrecht UMC). In addition, a literature review was performed to collect complete and comprehensive model data on complication rates, recurrence rates, survival, and health outcomes, shown in E). Assumptions (visible in Appendix A) and expert opinions addressed missing data.

3.1 Cohort-level parameters

We assume all patients enter the model with early-stage sentinel node-positive oral cavity cancer. The probabilities of entering the start health states differ depending on the characteristics of the positive sentinel node and treatment strategies.

3.1.1 Regional failure

Regional recurrence rates are calculated from non-sentinel node metastasis, extranodal extension and tumour cells in the soft tissue of the neck, and the effectiveness of treatment strategies, which are explained below.

The prevalence of non-SLN metastases
Given the probability of lymph node metastases after a neck dissection in clinically node-negative oral cancer patients and the location of recurrences after observation in the clinically node-negative neck (cN0), the prevalence of non-SN metastases after a positive sentinel node was estimated. Concerning the size of the SN metastasis, additional non-sentinel node metastases (non-SN+) were detected in 13, 20, and 40% of patients with ITC, micro-, and macrometastasis in the SLN, respectively[5]. The distribution of positive non-SN in the specific levels of the ipsilateral cN0 neck after observation is visible in Figure 6 and assumed to be the same for ITC, MiM and MaM-positive SNs. The location of ipsilateral neck recurrence in patients in observation groups is 5% in level IV, and 5% in level V[2 23].

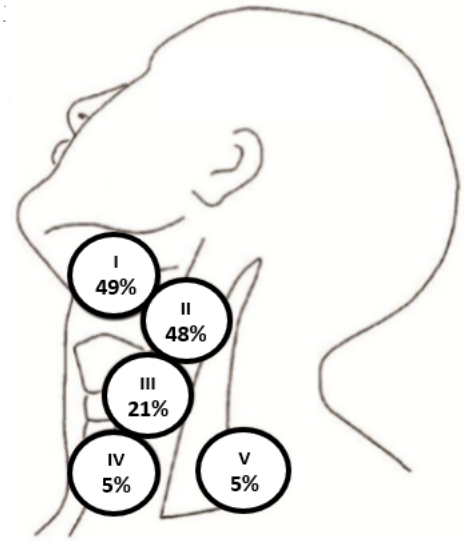

Figure 6: Ipsilateral neck recurrence rates after observation in the different neck levels. Adapted from[2]

In Figure 7, the estimated prevalence of additional non-SN metastases in levels I-III, IV and V is visible.

With an increase in the size of the SN, the prevalence of non-SN metastases is higher in each of the levels.

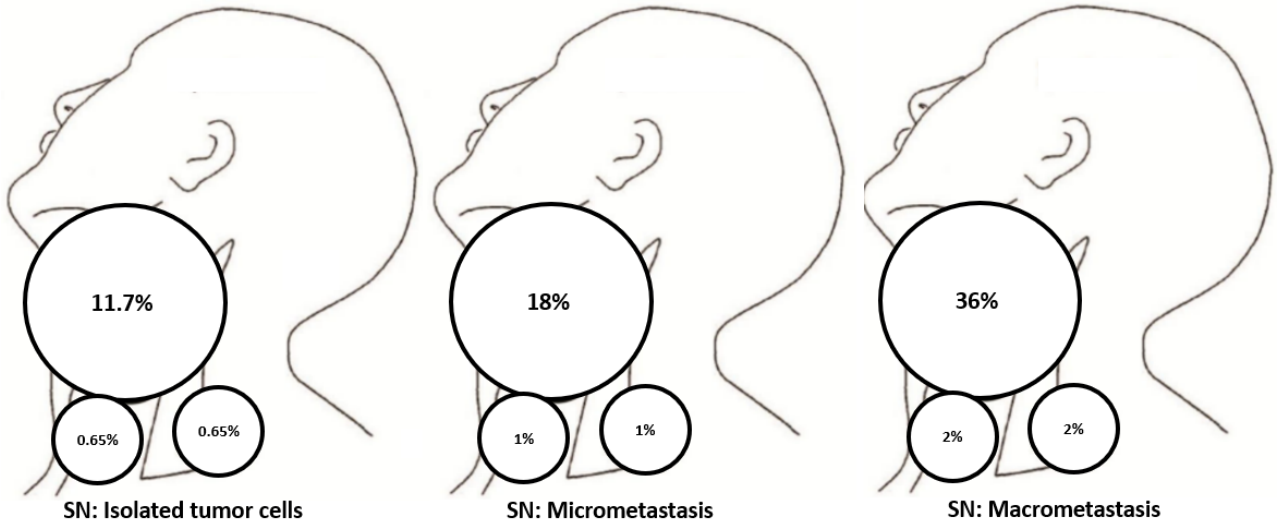

Figure 7: Additional non-SN metastasis in neck levels I-III, IV and V for isolated tumour cells (A), micrometastases (B) and macrometastases (C) SN. Adapted from[2]

In surgery field recurrence

Even if all non-sentinel nodes are removed during neck dissection, there is still a chance of regional recurrence. In general, one or more major adverse pathological features like positive surgical margins and extranodal extension (ENE), as well as minor risk factors, i.e. perineural invasion (PNI) and lymphovascular invasion (LVI), have been found to negatively impact recurrence outcomes[24 25]. It is assumed that in addition to non-sentinel node metastases, recurrence can occur due to missed lymph nodes in the dissected neck levels and extracapsular nodal disease extension that recurs in the neck's soft tissues, including extranodal extension, perineural invasion, and lymphovascular invasion. The recurrence rate within the surgery field is experienced by 2.4% of the patients[26]. Regional failure from missed tumour cells from the primary tumour is excluded.

Evaluation of treatment strategies

Depending on the extent of treatment, non-sentinel node metastases (Non-SN+) and the tumour cells in soft tissue are removed or irradiated. In Appendix B, a complete overview of regional failure for the size of the positive SN and treatment methods are given. Figure 8 shows the effects of neck dissection, radiotherapy and neck dissection with postoperative radiotherapy on neck levels I-III for an ITC SN. In the following paragraphs, the calculation of regional failure rates from untreated nodes, treated nodes, and the soft tissue per treatment strategy and size of the SN is given.

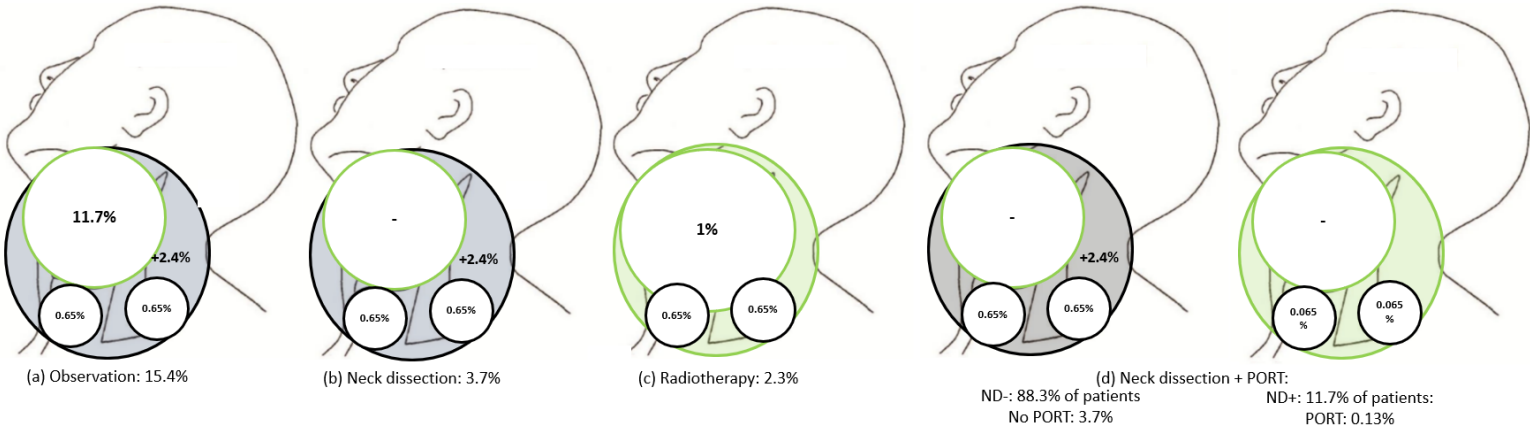

Figure 8: *Different regional recurrence rates for watchful waiting (no treatment) (a), neck dissection levels I-III (b), radiotherapy levels I-III (c) and neck dissection levels I-III + PORT when metastasis is found in the neck dissection(d) for isolated tumour cells positive SN. The neck dissection removes lymph nodes in levels I-III. Radiotherapy is effective in the nodes and extranodal extension. PORT is given after a neck dissection if metastases are found. Green = treated, black = untreated. PORT = Post-operative radiotherapy. Adapted from*[2]

Neck dissection

The extent of the neck dissection determines the probability that all positive lymph nodes are removed. Table 1 gives the probabilities of positive non-SN after the different neck dissections.

Table 1: Additional non-SN metastasis in the neck after dissection of levels I-III, I-IV and I-V, concerning size (isolated tumour cells, micro-metastasis and macro-metastasis) of the SN. Abbreviations: Non-SN+ = positive non-sentinel nodes, * Since all nodes are removed, there is no possibility of not removing a positive non-sentinel node

Neck dissection levels	ITC: % Non-SN+	MiM: % Non-SN+	MaM: % Non-SN+	Source
I-III	1.3%	2%	4%	5 2
I-IV	0.65%	1%	2%	5 2
I-V	0%	0%	0%	5

Regional recurrence is the probability of untreated positive non-sentinel nodes outside the area of treatment as given in Table 1, and the additional probability of in-surgery field recurrence of 2.4%. The in-surgery field recurrence is assumed to be independent of the removed neck levels. Table 2 shows the total regional failure rate after neck dissection.

Table 2: Regional failure in the neck after dissection of levels I-III, I-IV and I-V, concerning size (isolated tumour cells, micro-metastasis and macro-metastasis) of the SN.

Neck dissection levels	ITC: % RF	MiM: % RF	MaM: % RF	Source
No	15.4%	22.4%	42.4%	5
I-III	3.7%	4.4%	6.4%	5 2
I-IV	3.05%	3.4%	4.4%	5 2
I-V	2.4%	2.4%	2.4%	26

Watchful waiting

Without treatment, the regional failure rate is the total of non-SN metastases and in-field regional failure rate, visible in the first row of Table 2.

Radiotherapy

The regional failure rates for radiotherapy are visible in Table 3 and are assumed to depend on the treatment field and size of the positive SN. It is assumed that only targeted lymph node levels are irradiated, and metastases outside the radiation field are not controlled. No high-quality data can clearly describe the effectiveness of RT in the neck after positive SLNB of early-stage OSCC[27 28]. The effectiveness of RT was estimated to be 90% from clinical expertise, and therefore the regional failure rates were 1%, 2% and 4% for ITC, MiM and MaM, respectively[28]. This regional failure occurs in the treated lymph node levels of the neck. The total recurrence rate is the regional failure rate of the treated nodes in the radiation field (1) and the total of untreated nodes outside the treatment area (2).

Table 3: Regional failure in the neck after radiation of levels I-III, I-IV and I-V, concerning size (isolated tumour cells, micro-metastasis and macro-metastasis) of the SN.

Radiotherapy levels	ITC: % RF	MiM: % RF	MaM: % RF	Source
I-III	2.3%	4%	8%	[28]
I-IV	1.65%	3%	6%	[28]
I-V	1%	2%	4%	[28]

Neck dissection and postoperative radiotherapy

After a neck dissection, histological information about the metastases in dissected levels becomes available. Knowledge about the presence of metastasis is used to decide whether or not to perform postoperative radiotherapy (PORT). It is assumed that patients with pathologically positive non-sentinel nodes found during the neck dissection are high-risk patients and therefore recommended to receive PORT after neck dissection. Both regional failure rates of patients with metastasis in the dissected levels after the SLNB receiving PORT and patients without metastasis and no PORT are unknown in literature[27 28].

It is assumed postoperative radiotherapy is always given to levels I to V. The effectiveness of postoperative radiotherapy is estimated to be the same as for radiotherapy, i.e. 90%. Radiotherapy reaches the missed lymph nodes during surgery and tumour cells in the soft tissue of the neck (1) and undissected levels. Therefore, regional failure after PORT is 10% of the regional failure rate after a neck dissection, as shown in Table 4.

Table 4: Regional failure in the neck after neck dissection with postoperative radiotherapy of levels I-III, I-IV and I-V, concerning size (isolated tumour cells, micro-metastasis and macro-metastasis) of the SN.

Neck dissection levels	ITC: Non-SN+ dissected	MiM: Non-SN+ dissected	MaM: Non-SN+ dissected	Radiotherapy levels	ITC: % RF	MiM: % RF	MaM: % RF	Source
I-III	11.7%	18%	36%	I-V	0.37%	0.44%	0.64%	[28]
	88.3%	82%	64%	No	3.7%	4.4%	6.4%	[28]
I-IV	12.35%	19%	38%	I-V	0.305%	0.34%	0.44%	[28]
	82%	81%	62%	No	3.05%	3.4%	4.4%	[28]
I-V	13%	20%	40%	I-V	0.24%	0.24%	0.24%	[28]
	87%	80%	60%	No	2.4%	2.4%	2.4%	[28]

Overview regional failure

An overview of regional failure rates per treatment and size of the positive SN is given in Table 5. These estimates were discussed and validated with clinical experts.

Table 5: Overview of recurrence rates per treatment strategy and size of the sentinel node metastasis.

ND	RT	ITC: % RF	MiM: % RF	MaM: % RF	Source*
No	No	15.4%	22.4%	42.4%	[5 26]
I-III	No	3.7%	4.4%	6.4%	[2 26]
I-IV	No	3.05%	3.4%	4.4%	[2 26]
I-V	No	2.4%	2.4%	2.4%	[2 26]
No	I-III	2.3%	4%	8 %	[28]
No	I-IV	1.65%	3%	6%	[28]
No	I-V	1%	2%	4%	[28]
I-III	I-V	0.13%	0.2%	0.4%	[28]
	No	3.7%	4.4%	6.4%	[2 26]
I-IV	I-V	0.065%	0.1%	0.2%	[28]
	No	3.05%	3.4%	4.4%	[2 26]
I-V	I-V	0.24%	0.24%	0.24%	[28]
	No	2.4%	2.4%	2.4%	[2 26]

* Assumptions based on source and validated with clinical expertise.

Variations in the effect of (postoperative) radiotherapy

The effectiveness of (postoperative) radiotherapy in preventing recurrence in the primary tumour and negative neck or single positive node of oral cavity cancer is much debated in the literature [27 29 30 31 32]. However, evidence on the effectiveness of (postoperative) radiotherapy in low and intermediate-risk squamous cell carcinoma of the oral cavity (OSCC) and nodes remains inconclusive. In this study, the effectiveness of (postoperative) radiotherapy is estimated with clinical expertise and is highly uncertain. Therefore, a range of effectiveness is analysed besides the base case effectiveness in a scenario analysis.

3.1.2 Survival

Transition probabilities were included in the model to move patients between model health states. Probabilities of overall survival (OS) were derived from the literature. OS was assumed to be the same for each treatment strategy[33 34 35]. The OS differed between patients experiencing regional failure and those without regional failure[36]. In these survival rates, patients receiving salvage therapy are included. An overview of the conditional probabilities per year used in the model is shown in Table 6. Beta distributions were assigned to the survival probabilities.

Table 6: *Survival probabilities*

Parameter	Point estimate (SD)	Distribution	Source
Survival probability without regional failure		Beta	[36]
Year 1	0.88 (0.01)		[36]
Year 2	0.89 (0.01)		[36]
Year 3	0.94 (0.01)		[36]
Year 4	0.92 (0.01)		[36]
Year 5	0.92 (0.01)		[36]
Year 6	0.94 (0.01)		[36]
Year 7	0.94 (0.01)		[36]
Year 8	0.90 (0.01)		[36]
Year 9	0.92 (0.01)		[36]
Year 10	0.93 (0.01)		[36]
Survival probability with regional failure		Beta	
Year 1	0.80 (0.01)		[36]
Year 2	0.82 (0.01)		[36]
Year 3	0.89 (0.01)		[36]
Year 4	0.87 (0.01)		[36]
Year 5	0.86 (0.01)		[36]
Year 6	0.89 (0.01)		[36]
Year 7	0.89 (0.01)		[36]
Year 8	0.83 (0.01)		[36]
Year 9	0.86 (0.01)		[36]
Year 10	0.88 (0.01)		[36]

Regional failure

The mean time to regional failure was derived from 65 patients from a Dutch database. 78% of the patients with a regional failure encounter this recurrence one year after initial neck treatment and all other patients two years after initial neck treatment[6]. Literature confirms the median time to recurrence is less than one year, with no isolated neck recurrence seen after two years.

3.1.3 Salvage therapy for regional failure

Salvage therapy was assumed to vary depending on the primary treatment strategy, as illustrated in Figure 9. If a neck dissection or neck dissection with PORT was the primary treatment, then salvage therapy was assumed to be radiotherapy. If radiotherapy is used as the primary neck treatment

strategy, neck dissection was assumed to be the standard salvage therapy. For watchful waiting as treatment strategy, a neck dissection with PORT was considered standard salvage therapy.

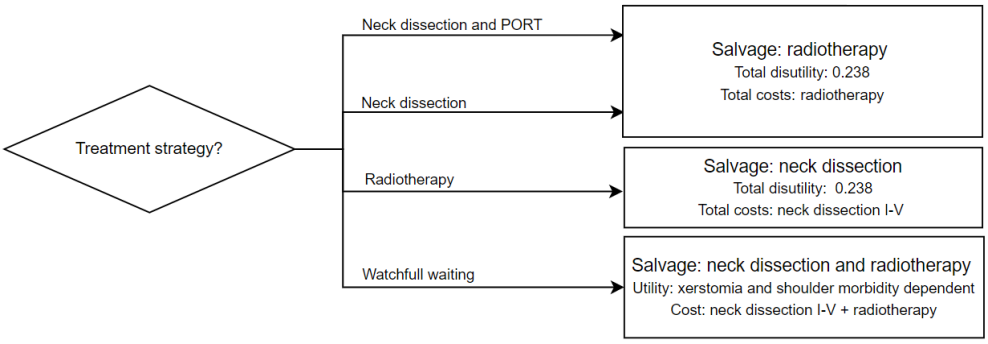

Figure 9: *Salvage treatment, quality of life and costs after regional recurrence*

3.1.4 Complications

In the treatment strategies, patients had a chance of suffering from shoulder morbidity, xerostomia, both shoulder morbidity and xerostomia, or no shoulder complications or xerostomia after treatment. These complication rates are based on the literature, visible in Table 7. The shoulder morbidity chance depends on the extent of the neck dissection. The chance of xerostomia is independent of the extent of the radiotherapy since the dose and volume reaching the parotid glands is the same for radiation of levels I-III, I-IV and I-V. Patients who suffered from shoulder morbidity after a neck dissection or from xerostomia after (postoperative) radiotherapy were assumed to experience these complications after treatment and experienced these complications for each following year, permanently until death. It is assumed (Postoperative) radiotherapy does not increase shoulder morbidity, and neck dissection does not increase the xerostomia rate[37 38].

Table 7: *Complication rate per treatment strategy.*

Treatment	Complication	Complication rate	Source
Neck dissection level I-III	Shoulder morbidity	7%	39
Neck dissection level I-IV	Shoulder morbidity	14%	39 6*
Neck dissection level I-V	Shoulder morbidity	41%	39
Radiotherapy	Xerostomia	8.6% **	40

*assumption based on reference and clinical expertise. ** The long-term probability of xerostomia after intensity-modulated radiotherapy (IMRT) of primary tumour and neck.

3.2 Patient-level parameters

Each patient experiences health effects and incurs costs depending on the care pathway. Patient-level parameters and variation were reflected as it was relevant to address the differences in parameter values.

3.2.1 Health effects

Given the long-term adverse quality-of-life impact of shoulder morbidity and xerostomia, a utility score is assigned to an individual based on the long-term adverse events of a patient. These utilities represent the valuation of health-related quality of life (HR-QoL) over time on a scale from zero (death) to one (perfect health after SLNB). All patients had a similar baseline health utility score after primary tumour resection and SLNB. Disutilities were assigned to each patient that experienced treatment-related complications that appeared or in the event of regional recurrence, followed by salvage therapy. The health-related utility scores were derived from literature[41 42 43]. Table 8 includes health utility and disutility values. From the mean utility values, it was clear that the recurrence-free group experienced a better quality of life than the group with recurrent neck metastasis. Distributions were assigned to the (dis)utilities.

Table 8: Disutility value per event.

Event	Utility	Disutility (SD)	Distribution	Source
No regional failure after SLNB	1		Fixed	[10]
Shoulder morbidity		0.12 (0.259)	Beta	[41]
Xerostomia		0.059 (0.010)	Beta	[42 44]
Salvage therapy after primary treatment (WW excluded)		0.238 (0.0477)	Beta	[45 43]
Death	0		Fixed	

By assigning utility scores to each patient over time, the effectiveness of the treatment strategies was measured in QALYs and costs per QALY. Following the Dutch guidelines for health economic evaluations, annual discount rates of 1.5% were applied to all future health outcomes[46].

3.2.2 Costs

Costs per patient were determined from a healthcare perspective. Treatment costs and length of surgery for the three types of neck dissection and treatment costs for radiotherapy were obtained from the Radboud University Medical Centre[47 6 48]. Note that pricing agreements may differ per hospital. Standard unit costs were used for hospital days, consultation and physiotherapy following the Dutch guidelines for health economic evaluations[46].

Every patient who underwent a neck dissection was assumed to have received a preoperative and postoperative consult by a physical therapist to examine shoulder function. The costs for surgery were based on the length of surgery with a variance valued as 20% of the total length. After surgery, a patient is assumed to stay in the hospital until a drain in the neck can be removed. The total cost for neck dissection consists of these general costs and costs for surgery. Costs for complications after treatment were expressed in physiotherapy sessions for all patients suffering from shoulder morbidity. It was assumed that patients suffering from xerostomia did not undergo treatment or receive any medicines. We assumed an ultrasound as an examination method in the evaluation of recurrent nodes

in the neck for the WW strategy every 3-4 months for two years based on clinical expertise[6]. Salvage therapy costs depend on the primary treatment, as stated in section 3.1.3.

Costs are given in Table 9. Following the Dutch guidelines for health economic evaluations, annual discount rates of 4.0% were applied to all future costs[46].

Table 9: Costs

Event	Resource use	Unit price* (€)	Uncertainty**	Distribution	Cost (€)
Neck dissection general					
- Pre-consultation	1	163[49]		Fixed	163
- Post-consultation	1	163[49]		Fixed	163
- Hospital days	3 days	405[49]		Fixed	1,215
Total					1,541
+ Neck Dissection I-III					
- OR time + materials	3 hr[47]	650[49]		Gamma	1,950
- Medical specialist	3 hr[47]	116[49]		Gamma	348
Total I-III specific			shape=91.92,scale=25		2,298
Total I-III (incl. general)					3,839
Neck Dissection I-IV					
- OR time + materials	3.25 hr[47]	650[49]		Gamma	2,112.50
- Medical specialist	3.25 hr[47]	116[49]		Gamma	377
Total I-IV specific			shape=99.58, scale=25		2,489.5
Total I-IV (incl. general)					4,030.50
Neck Dissection I-V					
- OR time + materials	4 hr[47]	650[49]		Gamma	2,600
- Medical specialist	4 hr[47]	116[49]		Gamma	464
Total I-V specific			shape=122.56, scale=25		3,064
Total I-V (incl. general)					4,605
Shoulder morbidity					
- Physiotherapy	14[50]	33[49]		Fixed	462
Radiotherapy					
- Neck levels				Fixed	6,832[48]
- If RT for primary					0[48]
Watchful policy					
- Ultrasounds per year	4[6]	84,11[51]		Fixed	336.44
Salvage therapy					
- After ND or ND+RT: RT				Fixed	6,832[48]
- After RT: ND (4hr)			shape=122.56, scale=25	Gamma	3,670.50
- After WW: ND (4hr) + RT			shape= 35.83,scale=292.47	Gamma	11,077

*Base-case values, i.e., no parameter uncertainty incorporated; ** Distribution parameters are presented as scale- and shape parameters for gamma distributions

Variations in values

A four-step approach was applied for using parametric probability distributions, which consisted of inspecting the data and fitting multiple distributions by calculating two parameters (e.g., shape and scale) from mean and variance (1), checking the distribution density histogram (2), replacing the extreme values (disutility > 1) (test for n=10,000) (3), and drawing values from the distributions in the simulation model (4).

4 Analysis

First, preparation runs were performed to determine the number of patients to simulate. The analyses were based on Monte Carlo simulations with 5,000 patients. This number of patients was sufficiently large to limit the impact of patient-level variation in cost-effectiveness outcomes (see Appendix C). Next, independent analyses were performed: Base case analyses, probabilistic sensitivity analyses, and deterministic sensitivity analyses, each for ITC, MiM and MaM separately.

4.1 Cost-effectiveness analysis

The cost-effectiveness analyses were performed regarding QALY, costs, incremental cost-effectiveness ratios (ICERs) and net monetary benefit (NMB). The model's base case presented average outcomes without variations in cohort-level parameters. A strategy was dominated if it was more costly but yielded fewer QALYs than any other strategy or if the ICER exceeded the willingness-to-pay threshold (WTP) or if the ICER of another strategy was found to be more effective. A strategy was considered "cost-effective" compared to another if the costs of gaining one additional QALY were less than the WTP.[52]. According to the Dutch Council for Public Health and Care, a WTP threshold of €20,000/QALY was recommended, the lowest reference value for the WTP per QALY[53]. The WTP was determined based on the burden of disease, where a higher burden of disease leads to a higher WTP for health gains. The burden of disease was assessed using a proportional shortfall method, which compares the lost quality of life and life years of patients with regional failure to those of patients who have undergone an SLNB. This method takes into account the proportional loss of life years and quality of life. Primary oral cavity cancer already involves a shorter life expectancy than 'healthy' people. Therefore, the burden of disease is the lowest category with a WTP of €20,000/QALY.

4.2 Uncertainty

For the simulation model to support decision-making, uncertainty was included. The impact of uncertainty was established by quantifying the uncertainty of the output due to the uncertainty in model parameter values.

Probabilistic analyses
A probabilistic sensitivity analysis was performed to assess the impact of uncertainty over all parameter values on the outcomes. All input parameters (probability of regional failure, the effectiveness of treatment methods, survival, complications rates, costs, and utilities) were varied simultaneously using Monte Carlo simulation. An overview of reflected variations in the cohort-level data for the corresponding model parameters is given in Table 10.

Additionally, the cost-effectiveness acceptability curve (CEAC) was plotted. The CEAC indicated the chance that a strategy is cost-effective compared to all alternative strategies for a range of WTP threshold values.

Table 10: Variations in cohort level data

Parameter	Value base case	95% CI (in PSA)	Distribution parameters	Distribution
Probability of additional non-SN for ITC SN	0.13	0.035-0.26	α= 4, β=28	Beta
Probability of additional non-SN for MiM SN	0.20	0.11 - 0.32	α= 11, β=44	Beta
Probability of additional non-SN for MaM SN	0.40	0.26 - 0.52	α= 19, β=30	Beta
Probability of additional non-SN metastasis in level IV	0.05	0.015 - 0.11	α= 4, β=72	Beta
Probability of additional non-SN metastasis in level V	0.05	0.015 - 0.11	α= 4, β=72	Beta
Probability of recurrence in surgery field	0.024	0.0051 - 0.057	α= 3, β=122	Beta
Effectiveness radiotherapy	0.90	0.70 - 1	α= 7.2, β= 0.8	Beta
Effectiveness postoperative radiotherapy	0.90	0.70 - 1	α= 7.2, β= 0.8	Beta
Probability shoulder morbidity ND levels I-III	0.07	0.028 - 0.13	α= 11, β=44	Beta
Relative risk shoulder morbidity ND level I-IV	2	1.44 - 2.81	meanlog=0.69, sdlog=0.172	Lognorm
Relative risk shoulder morbidity ND of levels I-V	5.6667	4.06 - 7.92	meanlog=1.73, sdlog=0.172	Lognorm
Probability xerostomia	0.086	0.025 – 0.19	α= 4, β=42	Beta

*Distribution parameters are presented as α- and β-parameters for beta distributions, minimum and maximum for uniform distributions and as the mean of the log and standard deviation of the log for lognormal distributions. ** If the total probability of shoulder morbidity exceeds 1 due to probability after ND I-III multiplied by relative risk, a maximum probability of 1 is maintained.

Deterministic sensitivity analysis

Deterministic analyses were performed to assess the robustness of results to changes in individual parameters. The most important parameters influencing the effect (QALY), costs (€) or NMB (€) were identified. Parameter values for the percentage of non-SN metastases, in surgery field recurrence, the effectiveness of (post-operative)radiotherapy values, and chances of complications were varied over a range of values of extreme values to detect the tipping points of best strategy methods in terms of QALY and NMB.

The effectiveness of (post-operative) radiotherapy was estimated based on clinical expertise. Due to high uncertainty in the effectiveness of radiotherapy, a range of regional failure rates after radiotherapy were analysed to determine the impact of this parameter. The tipping points when different strategy exceeds each other as the best strategy in terms of QALY and NMB were studied.

The probability of additional non-SN metastases after an SLNB depends only on the SN's size (ITC, MiM and MaM) in the model. Other parameters influencing the additional non-SN metastases after an SN, e.g. the number of positive SNs, are excluded. Therefore, a range of probabilities of *additional*

non-SN metastases after an SN was analysed to determine the impact of different values for this parameter on the outcome in terms of QALY and NMB.

All other above-mentioned parameters from the DSA were likewise analysed to give insights into the consequences of variations in these input values on the outcomes(1) and for model validation (2).

Value of information

Value of information (VoI) analyses were performed to quantify how additional information on the input parameters may improve decision-making and patient management outcomes. It is helpful to know the expected monetary gain from reducing uncertainty in the input parameters of a decision. One metric reflecting the value of information analysis (VOI) is the expected value of Perfect Information (EVPI). The EVPI reflects the expected costs of uncertainty relating to all input parameters in the model based on the probability of making an incorrect decision and its consequences. The EVPI is based on the cost-effectiveness of the treatment strategies that appear given the current information, the uncertainty surrounding the estimates of cost- effectiveness and the consequences of decision error based on current information (i.e. the opportunity loss) based on the WTP threshold. The EVPI represents the maximum amount that should be invested to eliminate all of the uncertainty in the decision model.[46].

Once the EVPI is known for an individual patient, the total EVPI is calculated, guiding the treatment of other current and future patients. The total EVPI requires an assessment of the effective lifetime of the technology, the estimate of disease incidence over this period and the discounted EVPI to provide the total EVPI for the population of current and future patients. If the population EVPI is higher than the cost of additional research, it is potentially cost-effective to do further research[54 55]. Last, the expected value of partially perfect information (EVPPI) is calculated as a measure of the expected reduction in uncertainty that results from obtaining partial information. The EVPPI considers that the information obtained will lead to the best treatment choice and thus provides the maximum potential benefit of obtaining additional information.

For all VOI analyses, the Sheffield Accelerated Value of Information (SAVI) tool was used[56].

5 Results

The developed microsimulation study consisted of multiple sensitivity analyses. First, we provide the cost-effectiveness outcomes for the base case. Afterwards, we show sensitivity cost-effectiveness estimates through PSA, DSA and VoI outcomes.

Base case

The baseline results of the ten strategies are presented in Figure 10. Note that the differences in QALY between strategies are small. Radiotherapy of level I-V resulted in the highest number of QALYs over a 10-year time horizon for both ITC, MiM and MaM. The costs of radiotherapy are higher than for neck dissections. The costs and effects for neck dissections+PORT depend on the percentage of patients with resected non-SN metastasis receiving PORT. Hence, the costs increase, and the effects decrease as the size of the SN increases. The effects of watchful waiting (NoTrt) decrease as the size of the SN increases since more patients experience a regional failure and accessory salvage treatment.

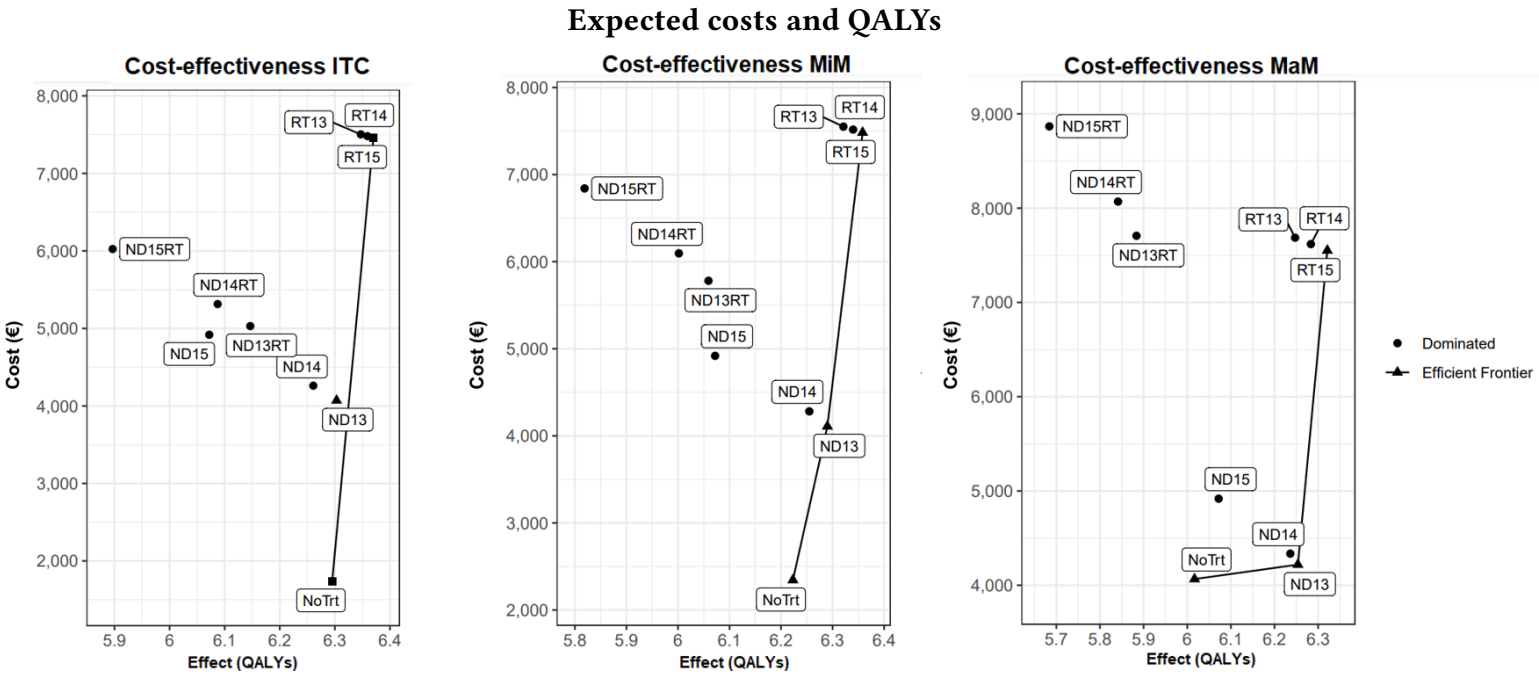

Figure 10: Baseline results of the ten strategies for ITC, MiM and MaM. Expected mean costs and QALYs 10 years.

The strategies expected total life years, QALYs and costs per patient are given in Tables 11, 12, and 13 for ITC, MiM and MaM, respectively. First, the comparator strategy WW is given. The first strategy listed is the comparator strategy WW, followed by all other strategies listed in ascending order based on their QALY values. Each strategy is compared to the no-treatment comparator WW in the fifth column until the strategy is dominated by another strategy. The strategy that dominates becomes the new comparator for the subsequent strategy listed. The last column in the tables provides an outcome for each strategy, indicating whether it is dominated by another strategy or whether it dominates some or all other strategies listed. The strategy dominating all other strategies is considered the most cost-effective option.

Table 11: Costs and QALYs per strategy resulting in the base case ICER for ITC. The comparator of each strategy is given in the fifth column and is WW until a strategy dominates WW. For ITC, no strategy dominates WW, so each strategy is compared to WW. Abbreviations: ND = Neck dissection, (PO)RT = (Postoperative) Radiotherapy, QALY = Quality-adjusted life years, ICER = Incremental Cost-Effectiveness Ratio.

Nr	Strategy	Cost (€)	Effect (QALY)	Comparator	Incremental Cost (€)	Incremental effect (QALY)	ICER (€/QALY)	Outcome
1	WW	1741	6.295	-	-	-	-	Dominates all strategies
2	ND I-V + PORT	6025	5.900	WW	4284	-0.395	-	Dominated by WW
3	ND I-V	4918	6.072	WW	3207	-0.223	-	Dominated by WW
4	ND I-IV + PORT	5314	6.087	WW	3603	-0.208	-	Dominated by WW
5	ND I-III + PORT	5030	6.146	WW	3319	-0.149	-	Dominated by WW
6	ND I-IV	4261	6.261	WW	2520	-0.034	-	Dominated by WW
7	ND I-III	4071	6.303	WW	2330	0.008	291250	Dominated by WW
8	RT I-III	7503	6.347	WW	5762	0.052	110808	Dominated by WW
9	RT I-IV	7481	6.359	WW	5740	0.064	89688	Dominated by WW
10	RT I-V	7460	6.370	WW	5719	0.075	76253	Dominated by WW

Table 12: Costs and QALYs per strategy resulting in the base case ICER for MiM. The comparator of each strategy is given in the fifth column and is WW until a strategy dominates WW. For MiM, no strategy dominates WW, so each strategy is compared to WW. Abbreviations: ND = Neck dissection, (PO)RT = (Postoperative) Radiotherapy, QALY = Quality-adjusted life years, ICER = Incremental Cost-Effectiveness Ratio.

Nr	Strategy	Cost (€)	Effect (QALY)	Comparator	Incremental Cost (€)	Incremental effect (QALY)	ICER (€/QALY)	Outcome
1	WW	2344	6.223	-	-	-	-	Dominates all strategies
2	ND I-V + PORT	6840	5.819	WW	4497	-0.404	-	Dominated by WW
3	ND I-IV + PORT	6095	6.002	WW	3751	-0.221	-	Dominated by WW
4	ND I-III + PORT	5781	6.059	WW	3437	-0.164	-	Dominated by WW
5	ND I-V	4918	6.072	WW	2574	-0.151	-	Dominated by WW
6	ND I-IV	4281	6.255	WW	1937	0.032	60531	Dominated by WW
8	ND I-III	4109	6.290	WW	1765	0.067	26343	Dominated by WW
7	RT I-III	7550	6.321	WW	5206	0.098	53122	Dominated by WW
9	RT I-IV	7517	6.340	WW	5173	0.117	44214	Dominated by WW
10	RT I-V	7483	6.358	WW	5139	0.135	38067	Dominated by WW

Table 13: Costs and QALYs per strategy resulting in the base case ICER for MaM. The comparator of each strategy is given in the fifth column and is WW until a strategy dominates the original comparator. For MaM, ND I-V dominates WW, ND I-IV dominates ND I-V, and ND I-III dominates ND I-IV. Abbreviations: ND = Neck dissection, (PO)RT = (Postoperative) Radiotherapy, QALY = Quality-adjusted life years, ICER = Incremental Cost-Effectiveness Ratio.

Nr.	Strategy	Cost (€)	Effect (QALY)	Comparator	Incremental Cost (€)	Incremental effect (QALY)	ICER (€/QALY)	Outcome (compared to strategies)
1	WW	4066	6.017	-	-	-	-	-
2	ND I-V + PORT	8867	5.684	WW	4801	-0.333	-	Dominated by WW
3	ND I-IV + PORT	8069	5.841	WW	4003	-0.176	-	Dominated by WW
4	ND I-III + PORT	7707	5.884	WW	3641	-0.133	-	Dominated by WW
5	ND I-V	4918	6.072	WW	852	0.055	15.491	Dominates strategies 1-4
7	ND I-IV	4335	6.236	ND I-V	-583	0.164	-3.555	Dominates strategies 1-5
6	RT I-III	7686	6.247	ND I-IV	3351	0.011	304.636	Dominated by ND I-IV
8	ND I-III	4219	6.254	ND I-IV	-116	0.018	-6.444	Dominates all strategies
9	RT I-IV	7618	6.283	ND I-III	3399	0.029	117.207	Dominated by ND I-III
10	RT I-V	7550	6.321	ND I-III	3331	0.038	87.658	Dominated by ND I-III

The radiotherapy I-V strategy was expected to provide the highest number of QALYs, 0.075, 0.135 and 0.304 QALY more than the comparator treatment WW. However, costs associated with the treatment strategy were estimated to be higher for the radiotherapy group than the comparator group. In the base case scenario for ITC and MiM, the ICERs for treatment strategies showed that watchful waiting could be considered cost-effective compared to other strategies with ICERs above the WTP threshold of €20,000. For MaM, neck dissection I-III was the most cost-effective compared to all other strategies.

Probabilistic sensitivity analysis

Probabilistic sensitivity analyses were performed using of Monte Carlo simulations to demonstrate the effect of joint uncertainty in the input parameters on the outcomes of the model. Scatter plots with the joint distribution of costs and effects of 5000 iterations for each strategy are shown in Appendix D.1. The scatter plots reveal that the differences between several strategies are small compared to the uncertainty around the ICER point estimates.

The incremental cost-effectiveness planes for strategies compared to WW (no treatment) after a positive ITC, MiM and MaM SN are shown in figures 11, 12, and 13. Each dot represents a simulation with random parameter values from the corresponding distributions. The dashed lines are the Dutch WTP thresholds of € 20,000 and €50,000 as the threshold value for one QALY. Incremental cost-effectiveness point estimates to the right of the vertical indicated improved health outcomes, and point estimates below the horizontal indicated cost savings. Point estimates to the right of the WTP diagonal represent simulations in which the strategy group was cost-effective compared to the WW (no treatment) group. The mean of each strategy compared to WW is given with a coloured dot with a white outline. The shape of the joint distribution depicts the uncertainty surrounding the cost-effectiveness results. In these figures, the ellipsoids indicate the 95% confidence regions for incremental cost and effects, for the different strategies in each figure, based on the results from the probabilistic sensitivity analysis. To some extent, the ellipsoids cover the north-western quadrant, indicating increased costs and worse health outcomes for the treatment strategy compared to WW. With an increase in the size of the SN, the ellipses shift to a higher incremental effect, resulting in a higher probability for the treatment strategies to be cost-effective. However, uncertainty also increases with an increase in size.

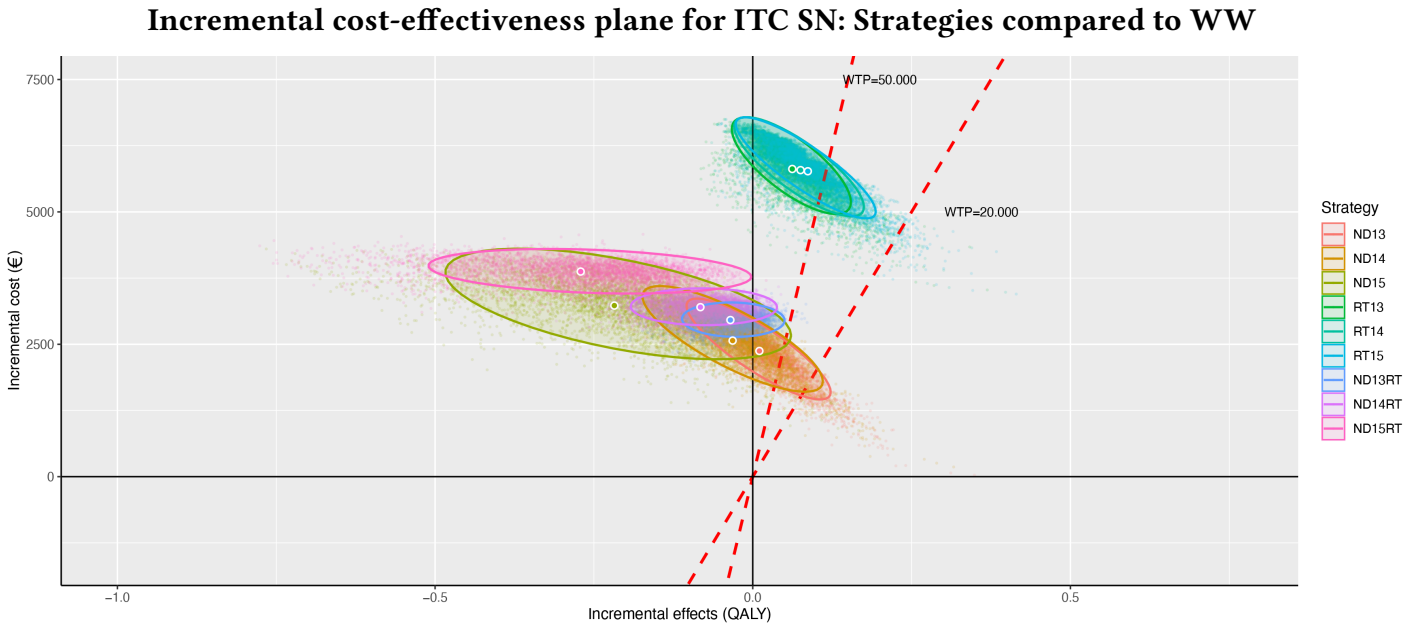

Figure 11: Incremental cost-effectiveness plane for isolated tumour cells SN. Strategies compared to WW. Coloured dots with a white outline represent the mean. Ellipse = 95% confidence incidence.

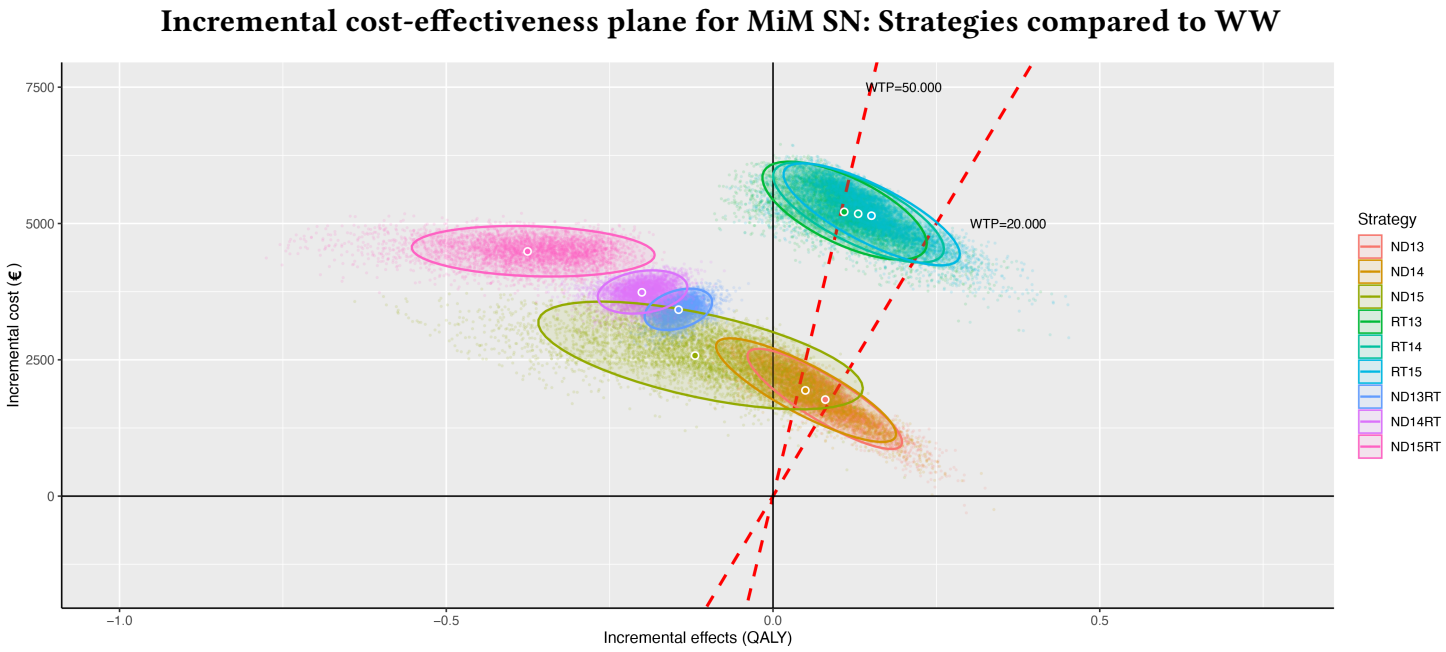

Figure 12: Incremental cost-effectiveness plane micrometastasis SN. Strategies compared to WW. Coloured dots with a white outline represent the mean. Ellipse = 95% confidence incidence.

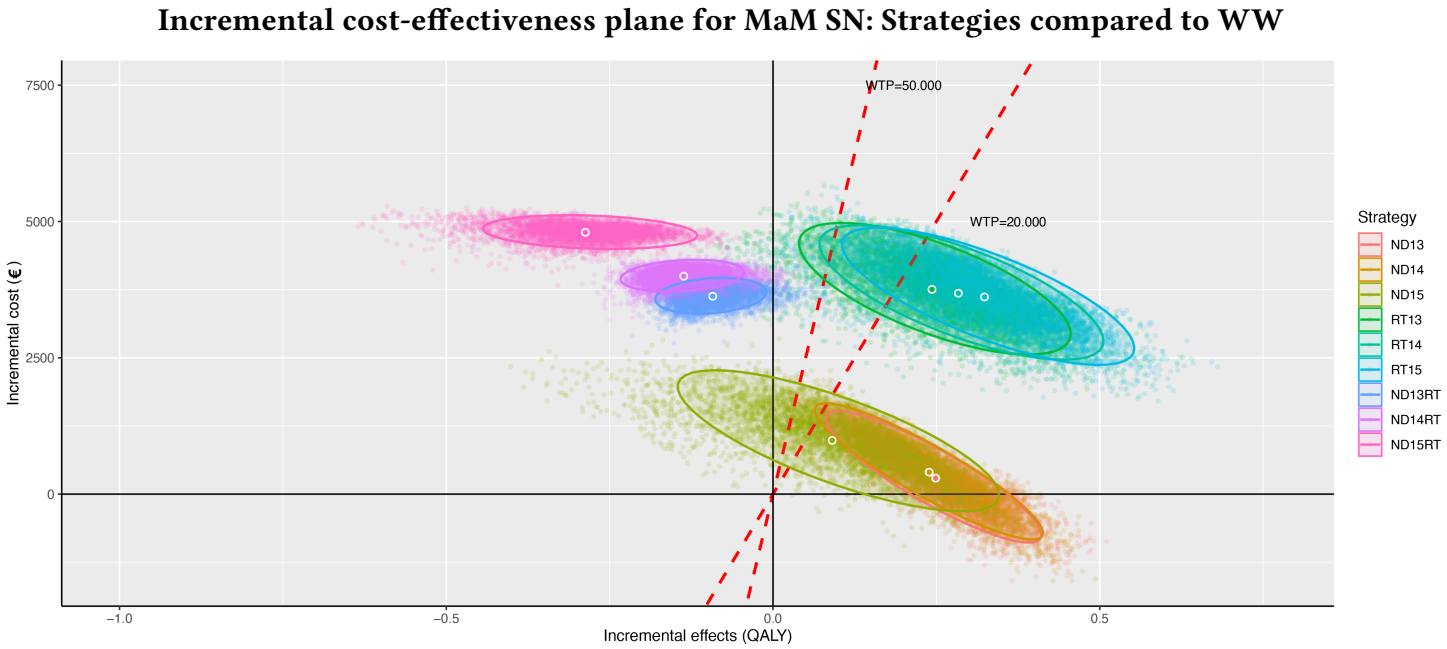

Figure 13: Incremental cost-effectiveness plane macrometastasis SN. Strategies compared to WW. Coloured dots with a white outline represent the mean. Ellipse = 95% confidence incidence.

CEAC

Figures 14, 15 and 16 present the cost-effectiveness acceptability curves (CEACs) for all treatment strategies for ITC, MiM and MaM, respectively. The CEAC was used to evaluate the cost-effectiveness of different strategies at different WTP thresholds. For ITC and MiM, it shows that the WW (no treatment) group was cost-effective at WTP thresholds of €20,000/QALY in 92% and 57 % of the simulations, respectively. For the MaM intervention, the neck dissection I-III strategy was cost-effective in 58% of the simulations at the same WTP threshold of €20,000/QALY. In 30% of the simulations, the neck dissection I-IV strategy was cost-effective. Besides the probability of being cost-effective, the efficacy frontiers are visible. The frontier shows the strategy expected to be most cost-effective at each WTP threshold value.

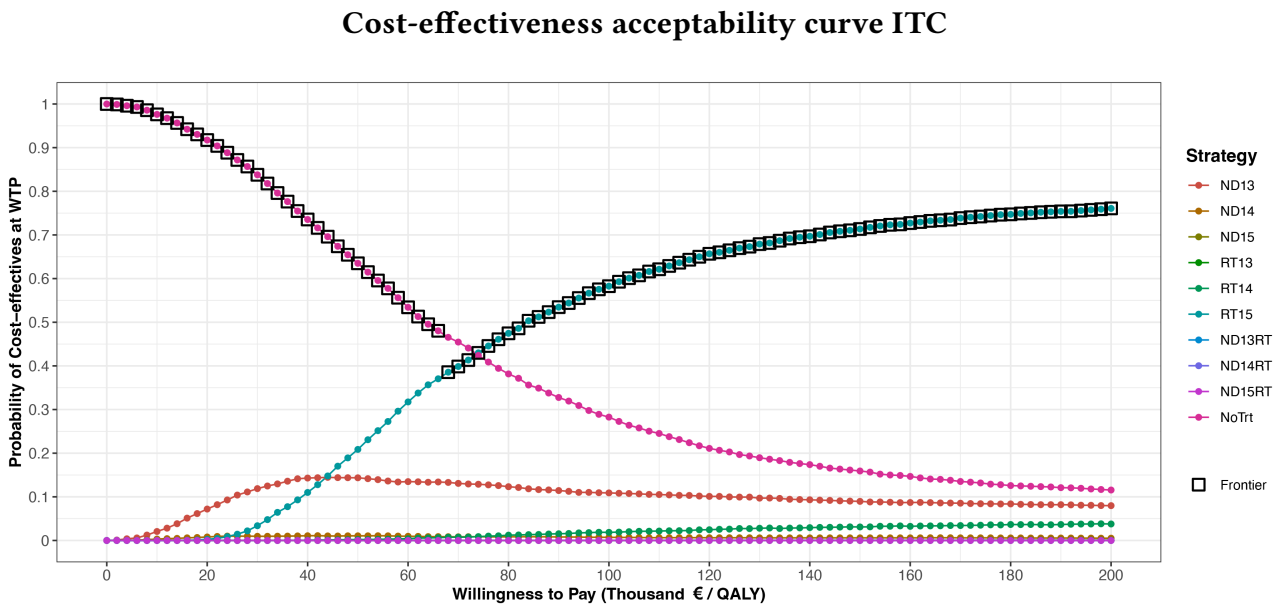

Figure 14: Cost-effectiveness acceptability curve and frontier for ITC SN. WW (No treatment) has the greatest probability of being cost-effective at a WTP of €20,000.

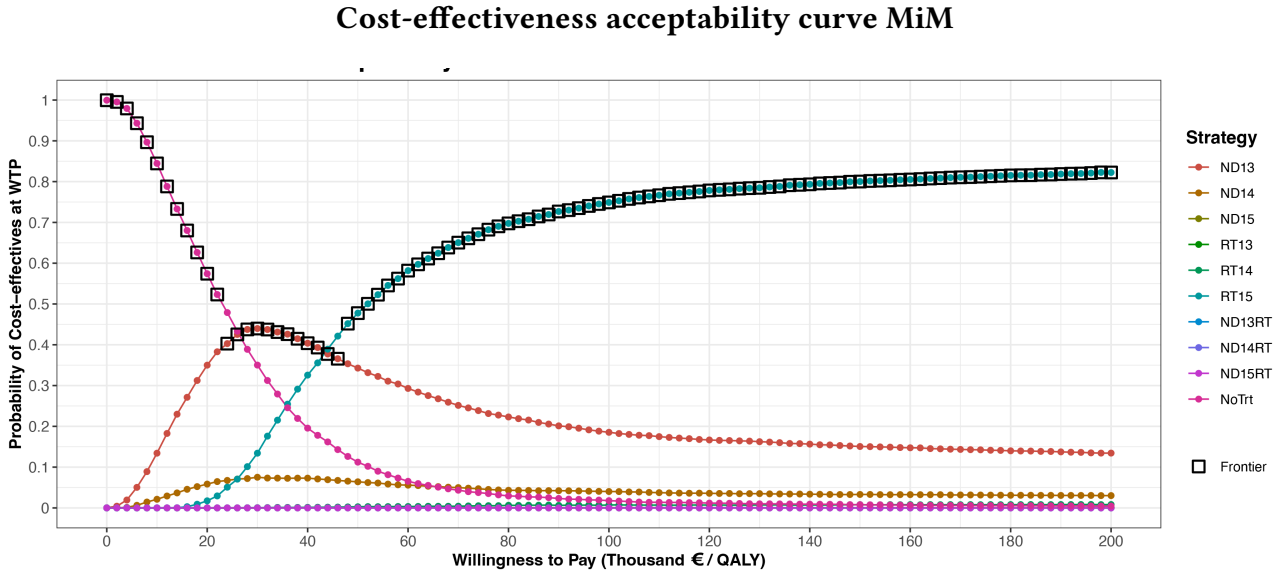

Figure 15: Cost-effectiveness acceptability curve and frontier for MiM SN. WW (No treatment) has the greatest probability of being cost-effective at a WTP of €20,000.

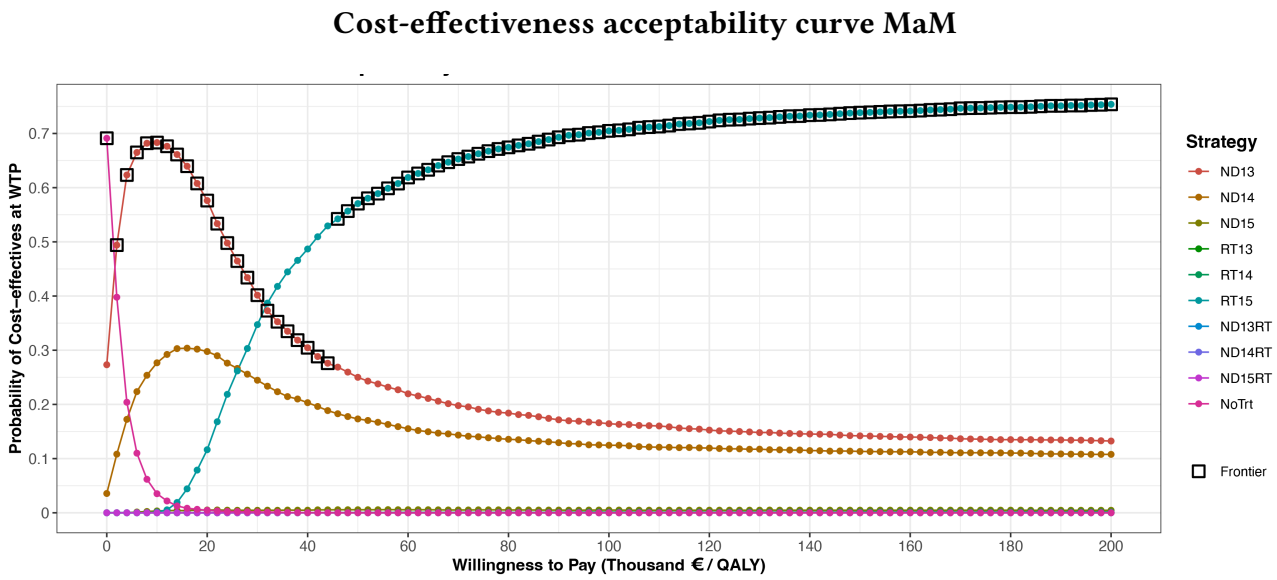

Figure 16: Cost-effectiveness acceptability curve and frontier for MaM SN. Neck dissection I-III has the greatest probability of being cost-effective at a WTP of €20,000.

In appendix D.3, the tornado diagrams for changes greater than 5% in QALY, costs and net monetary benefit is given for the most promising treatment strategies; ND13, RT15, and WW. The model was sensitive to variations in the probability of non-SN metastasis, the probability of positive non-SN in level IV and positive non-SN in level V, and the probability of in-surgery field recurrence after neck dissections, as only these parameters did result in a difference of 5% in model outcomes QALY, costs or NMB. Other parameters did not influence the effect, costs or NMB more than 5%.

Deterministic sensitivity analyses

Extreme parameter variations were analysed to provide further insight into the effect of each parameter on the outcomes. The best strategies in terms of the highest QALY and NMB were given.

The probability of additional non-SN metastases after an SN influences the best treatment strategy, as shown in Figure 17. Watchful waiting (NoTrt) provides the highest number of QALYS compared to all other strategies until a non-SN metastasis percentage of 2%, at a higher risk radiotherapy I-V gives the highest number of QALYs. Watchful waiting (NoTrt) remains cost-effective until a percentage of 22% and neck dissection I-III between 22% and 50% for the lowest willingness-to-pay threshold of €20,000/QALY.

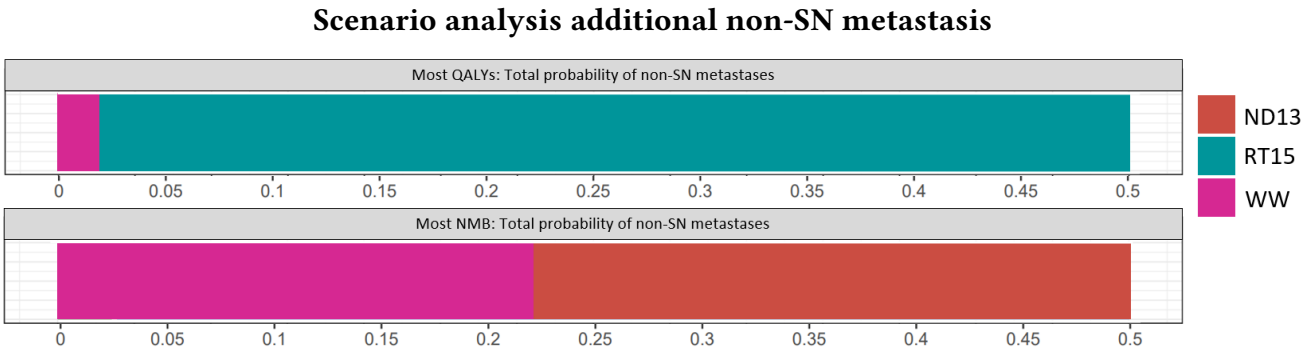

Figure 17: The best strategy in terms of QALY depends on the probability of additional non-SN with a WTP threshold of 20,000.

In addition to the probability of non-SN metastases, we evaluated the effectiveness of radiotherapy in a broader range to determine the tipping point of the optimal strategy. Figure 18 presents scenario analyses to examine the impact of alternative parametric assumptions for the regional failure rate after radiotherapy on the estimated best strategy for ITC, MiM and MaM. An increase in the regional failure rate after radiotherapy treatment makes neck dissections more favourable. Improving the effectiveness of radiotherapy to a value of 66%, 74%, and 82% makes radiotherapy I-V the strategy with the highest QALY for ITC, MiM and MaM respectively. Parameter variation showed that variations did not alter watchful waiting (NoTrt) for ITC and MiM and neck dissection I-III for MaM to give the highest net monetary benefit.

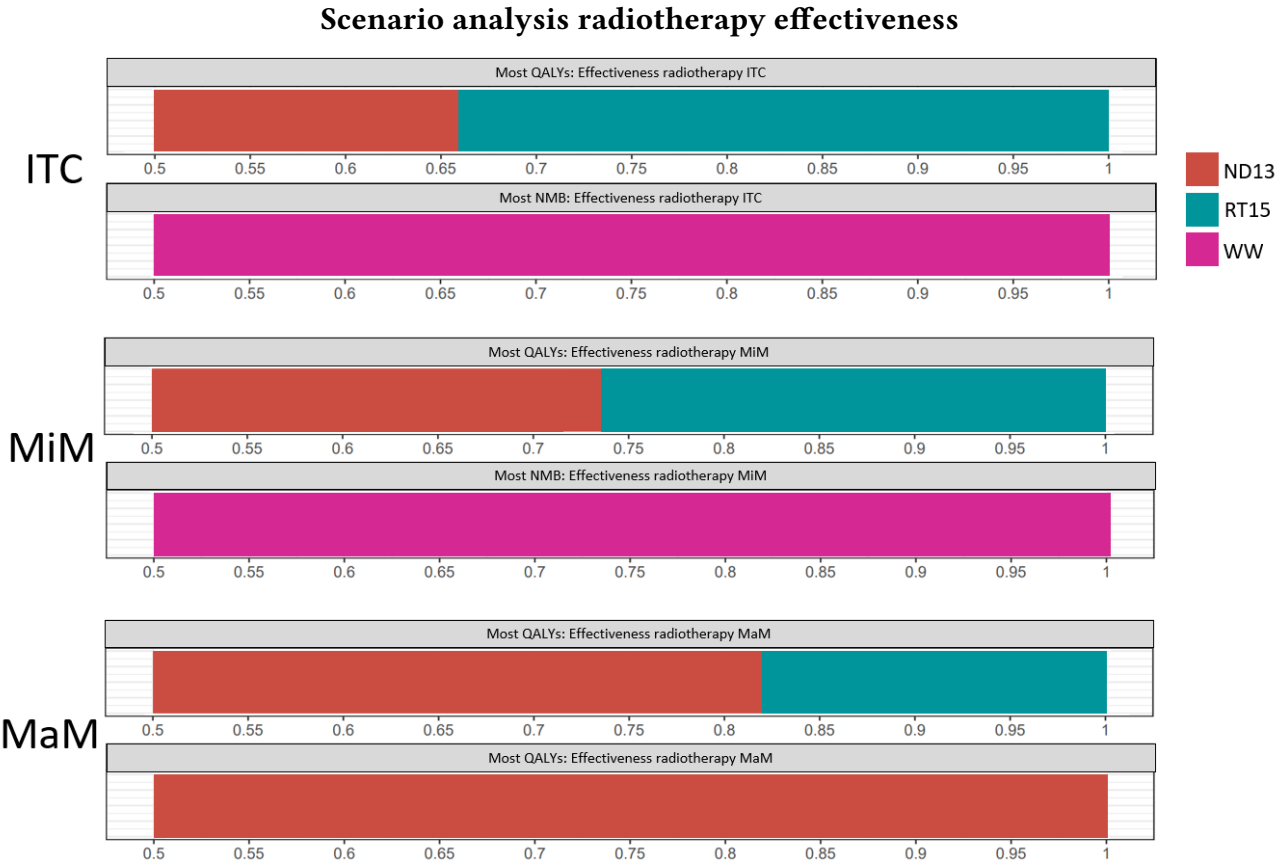

Figure 18: The best strategy in terms of QALY depends on the effectiveness of radiotherapy with a WTP threshold of 20,000.

For all other parameters, the best strategies in terms of the highest QALY and best NMB at a WTP threshold of €20,000 for extreme values of input parameters are given in Appendix D.2.

Value of Information

The value of information (VoI) graphs the EVPIs at different WTP thresholds are given in figures 19, 20, and 21 for ITC, MiM and MaM, respectively. The EVPI increases as the threshold increases since uncertainty surrounding the adoption decision increases. The probability that a different treatment strategy was cost-effective increased for larger WTP thresholds, and therefore the EVPIs decreased. The EVPIs at a WTP threshold of 20,000/QALY are €83,36, €543,86, and €254,13 for ITC, MiM and MaM, respectively.

The estimated total EVPIs over 5 years if each year 50 persons are affected in the Netherlands, €20,840 €136,000 and €63,530 for ITC, MiM and MaM, respectively.

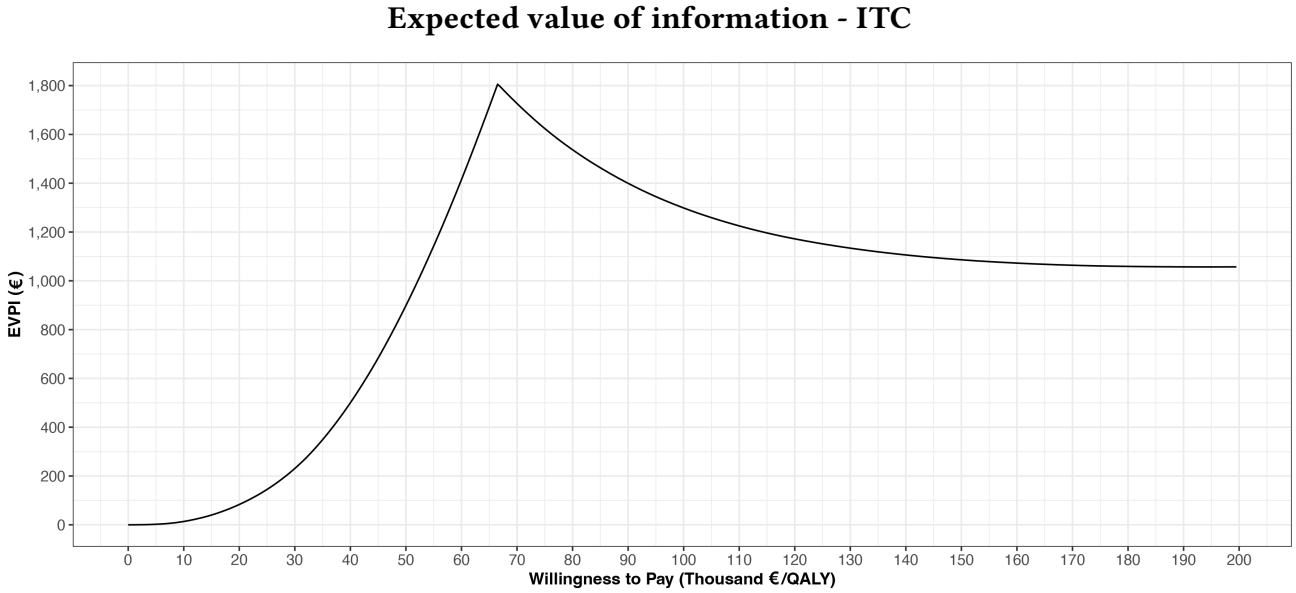

Figure 19: The EVPI for an individual patient with ITC.

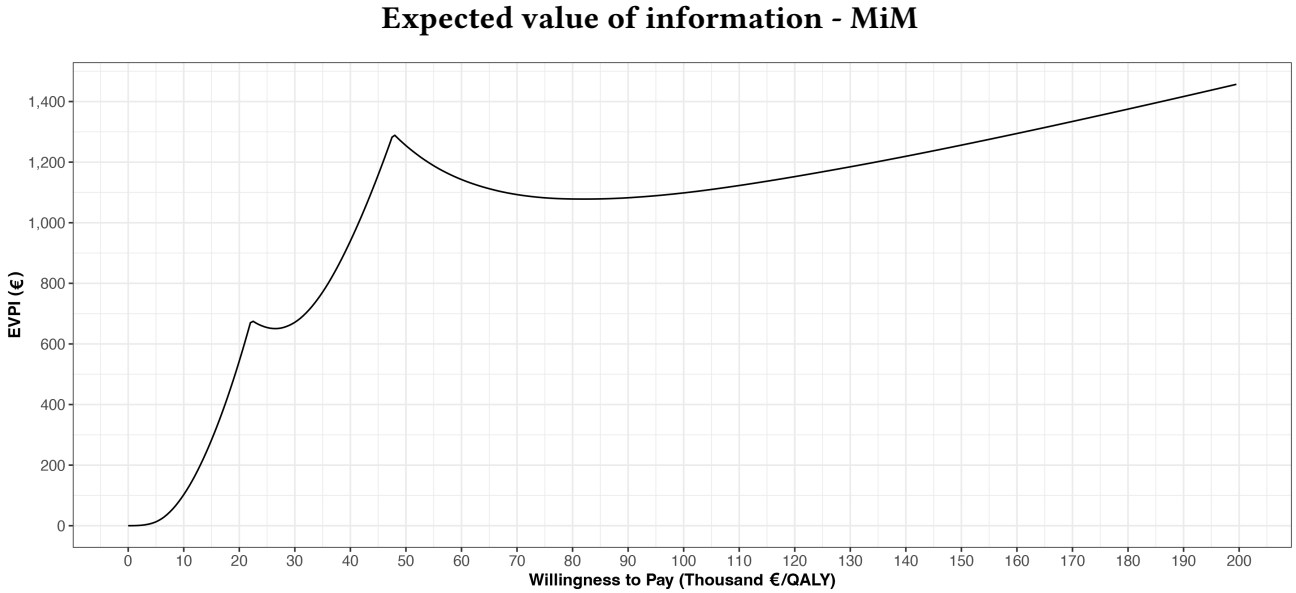

Figure 20: The EVPI for an individual patient with MiM.

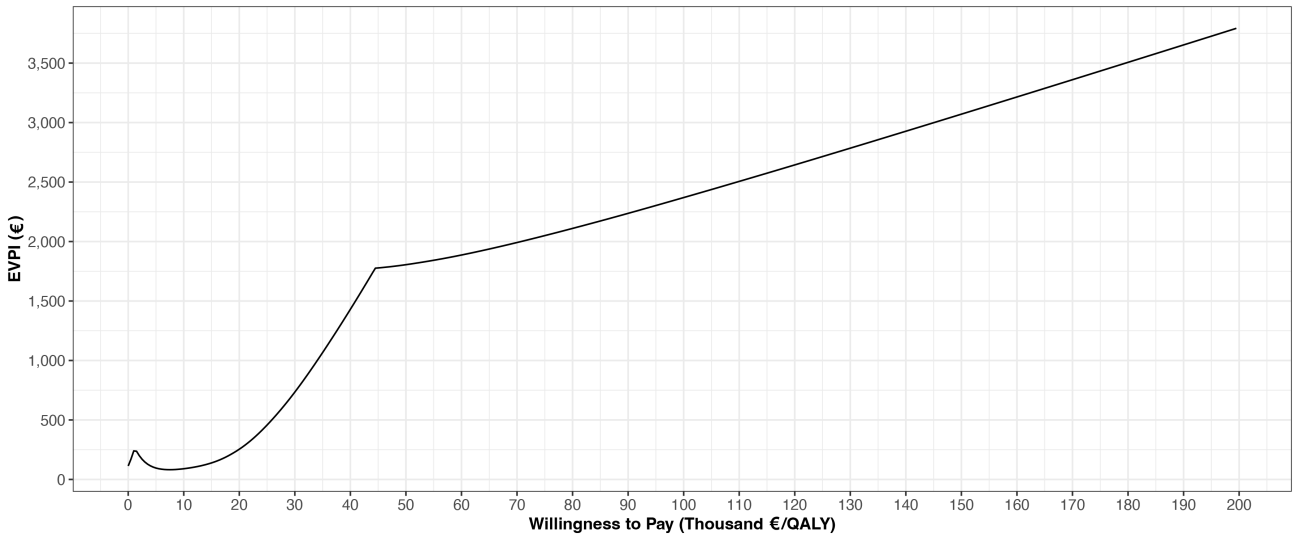

Figure 21: The EVPI for an individual patient with MaM.

Partial EVPI

The results of the EVPPI analysis are given in supplementary document A - SAVI tool VoI report. The parameters that cause the most decision uncertainty and have the highest potential value of reducing uncertainty by collecting more data were calculated. For ITC, the EVPPI was only non-zero for the parameter *probability of non-SN metastasis*. For MiM, EVPPI per person was the highest for the parameters *probability of non-SN metastasis*, followed *probability of in-surgery field recurrence*. For MaM, the EVPPI for the parameters *the probability of non-SN metastases in level 4*, followed by *shoulder morbidity complications*, was the highest. The grouped EVPPIs showed that regional failure rates were the parameters associated with the most uncertainty across each of the ITC, MiM, and MaM-positive sentinel node sizes."

6 Conclusion

This study demonstrated the value of a comprehensive decision-analytic approach in a specific case study on the neck treatment of T1-2 SN+ oral cavity cancer patients using different treatment options. This economic evaluation estimated the cost-effectiveness of treatment strategies for the neck of T1-2 SN+ oral cavity cancer patients compared to watchful waiting. To our knowledge, literature on the cost-effectiveness of treatment strategies after positive SN for oral cavity cancer patients is lacking. Here we find that the cost-effectiveness of the treatment strategies compared with a watchful waiting strategy, given the current data, is uncertain. Nevertheless, the treatment strategies' cost-effectiveness varies with the positive SN size. In low-risk OSCC patients, radiotherapy I-V is expected to result in small health benefits at relatively high incremental costs at Dutch WTP thresholds. Watchful waiting for ITC and MiM and Neck dissection I-III for MaM were expected to improve QALY with a smaller cost increase, with a probability of acceptable cost-effectiveness of 92%, 57%, 58% given the Dutch threshold of €20,000/QALY. Besides the implication of the best treatment method or health outcome, the value of this model-based analysis lies in the systematic examination of uncertainty and the potential to update the cost-effectiveness analysis when new data becomes available. The model outcomes were most influenced by the uncertainty in regional failure rates.

7 Discussion

Due to the potential for multiple treatment options, including surgery, radiotherapy, surgery with PORT and watchful waiting in the neck area for OSCC patients, the overall best treatment strategy is hard to establish. The SLNB is a relatively new diagnostic method and this causes data on patients with T1-2cN0SN+ oral cavity cancer to be limited. Additionally, standard statistical analyses of randomised controlled trials with partially missing outcome data often exclude valuable information from individuals due to short follow-ups about the long-term consequences of treatment strategies. This complexity implies an opportunity for simulation modelling, so different scenarios can be simulated and insights can be gained about treatment strategies that may not be obtainable through traditional clinical trials alone[22 57].

Microsimulation and available data

The microsimulation model is a commonly used tool in cost-effectiveness analysis. However, microsimulation models have several limitations that should be considered when using them for cost-effectiveness analysis[58]. Microsimulation models are highly flexible, and patient characteristics can be added or adjusted. The flexibility may make them harder to interpret and understand and may lead to over-fitting or over-specification. Because of the requirement of specialised knowledge and expertise to develop and interpret, it can be challenging to understand and use the model for decision-making by non-experts[54].

Furthermore, biases can significantly affect the accuracy of the health economic outcome estimates and should therefore be minimised[20]. To accurately simulate healthcare interventions using microsimulation models, it is crucial to have access to high-quality data to calibrate and validate the model and to prevent data input bias resulting from incomplete, inaccurate, or non-representative data used to populate the model.—besides transparent and robust modelling assumptions and an unbiased approach to model interpretation to counter model development biases. However, in this study, the model was limited by the availability of representative data in literature and a small nationwide dutch dataset. Some limitations in the data quality were inevitable and described in the following paragraphs. It should be noted that despite these limitations, microsimulation models can provide valuable insights

into the costs and outcomes of healthcare interventions and can be useful tools for decision-making and policy development.

In particular, the quantity of data on SN+ patients is currently limited. This causes the evidence of the effectiveness of treatment strategies to be nonexistent. Therefore, the model is specifically limited by some of the underlying assumptions used to formulate our model. As a result of the lack of evidence regarding regional failure probabilities, we had to formulate and estimate these probabilities using several intermediary steps and assumptions. First, the number of non-SN metastasis after a positive sentinel node is only based on the size of the positive SN. This assumption was necessary because accurate evidence of the risk of regional failure for the number of positive SNs and the ratio of positive SLNs to total SLNs is lacking. The number of non-SN metastasis might be overestimated because the cN0 OSCC patients in the studies were treated from 1985 to 2012. Since then, diagnostic methods have been improved significantly, and the patients did not undergo an SLNB[2]. The levels of recurrence are estimated from the same source. Second, there are no clear estimates of the prevalence of extranodal extensions of nodal disease or other risk factors increasing the risk of regional failure in patients undergoing treatment. Currently, the number of patients is too low to perform reliable statistical analyses on the risk of non-SLN metastases in these different tumour deposits in SLNs[5]. Consequently, the model is appropriate for patients with a low-risk probability of experiencing extranodal extension. Regional recurrence from the primary tumour is therefore also neglected. However, a rate of in-surgery field recurrence has been incorporated to mitigate the potential impact of extranodal growth and any missed lymph nodes during the surgical procedure for these low-risk patients. Third, the effectiveness of radiotherapy in the neck after SLNB is based on clinical expertise due to lacking literature[28]. The regional failure rates after postoperative radiotherapy may be overestimated since patients receiving PORT are at higher risk because they have multiple metastases. However, the probability of occult metastasis after neck dissection is so small that the possible effectiveness rates of PORT have little influence on regional failure rates. This is also seen in our sensitivity analyses' on effect, costs and NMB outcomes. Clear is that there is little evidence available on the recurrence rate of a patient after treatment, and therefore much uncertainty surrounding the individual probability of positive non-SN and regional failure.

Furthermore, the impact of salvage therapy is unknown. The severity and the location (e.g. in- or out-surgery field) of regional failure after treatment are not documented in the dutch database or literature, and therefore neglected. Consequently, some model structure assumptions were made, like ND I-V with PORT as salvage therapy for WW, which is a model estimate possibly underestimating the watchful waiting strategy.

Additionally, there is a lack of HR-QoL data for regional recurrence, treatment after the sentinel node procedure, and the utilities of reoperation and reirradiation following salvage surgery in patients primarily treated that remains questionable[59]. The limited availability of methodologically robust studies also does not provide a full range of values for all health states of interest with regard to xerostomia. As a result, the literature reported HR-QoLs might not completely correspond with reality. Therefore, HR-QoL from the literature was consulted and confirmed with clinical experts[6,28]. This adds to the uncertainty regarding our cost-effectiveness estimates.

Besides, due to the absence of QoL of patients after neck treatment in combination with the SLNB, only the most essential complications are taken into account. While several publications examine the health-related quality of life (HR-QoL) impacts of neck dissection and radiotherapy, these studies agree that shoulder morbidity and xerostomia are the most critical complications associated with

neck dissection and radiotherapy, respectively[39 40 6 28]. The likelihood of shoulder morbidity following neck dissection remains uncertain. According to clinical expertise, it is possible that the incidence of this complication may be lower than what is currently reported in the literature[6]. However, there is also a probability of underestimation since the probabilities follow from primary neck dissections. Neck dissection after SLNB causes reoperation with higher chances of complications and morbidity. Fourth, in patients undergoing unilateral neck dissection or radiotherapy, one submandibular gland is typically preserved, reducing the risk of xerostomia. The severity of xerostomia is thus determined by the level of radiation that reaches the parotid gland[28]. According to clinical expertise, it is possible that the reduction in QoL of xerostomia may be higher than what is currently reported in the literature (e.g. 0.59)[6]. Furthermore, radiotherapy can cause fibrosis, a build-up of excess fibrous connective tissue, leading to shoulder joint stiffness and reduced mobility, resulting in shoulder morbidity. The severity of shoulder morbidity due to fibrosis depends on the dose and duration of radiation exposure. The currently used Intensity-modulated radiation therapy with simultaneous integrated boost (IMRT-SIB) technique has shown low long-term toxicity. Therefore, shoulder morbidity due to radiotherapy is neglected in the model.[60].

Lastly, input cost parameters, including surgery time and radiotherapy, were based on the Dutch situation using costs in one centre, the Radboud UMC. Further, the model was built from a healthcare perspective. A societal perspective would consider a broader range of costs and benefits. However, focusing on a healthcare perspective allows for a more targeted analysis of the most relevant costs and benefits rather than trying to account for all possible costs and benefits that may be relevant from a societal perspective. Besides, it is assumed that productivity, absenteeism from work, number of hospital visits, and travel expenses are comparable between the strategies. However, future studies may wish to explore the potential impact of a societal perspective in more detail.

Hence, the data causes the microsimulation model to rely on assumptions about the population and interventions being studied, which may not always hold true, affecting the accuracy of the model results. Therefore, it is important to acknowledge that the microsimulation model is a simplified reflection of clinical practice. For decision analytic models, there is often a discrepancy between theoretical study results and real-world observations due to biases and confounding factors. However, this limitation is not unique to this particular model and applies to all model-based cost-effectiveness analyses.

Uncertainty

Because the microsimulation model is subjected to a degree of uncertainty from all the mentioned parameters, the model results were interpreted in light of this uncertainty. This uncertainty allows for a more transparent and comprehensive assessment of different treatment strategies' potential risks and benefits and can support more responsible and evidence-based policy decisions. The structural uncertainty of the model implied the cost-effectiveness of treatment strategies remained highly uncertain. However, the probabilistic and deterministic sensitivity analysis strengthened the base case cost-effectiveness outcomes for parameter uncertainty. Sensitivity analyses gave insight into which input parameters cause the greatest uncertainty in the outcomes and which data is needed to improve the reliability and accuracy of this health economic evaluation[22 57].

Results VoI

Furthermore, value of information analyses are useful in decision-making, particularly in this health economics situation where data availability and quality may be limited[61]. It is crucial to highlight that the estimated EVPI represents the maximum value that can be gained from additional research for an

individual. The interpretation of the EVPI value should be considered in conjunction with the cost of acquiring the perfect information. If the cost of obtaining the additional information is lower than the population EVPI, it may be cost-effective to collect more data. However, data are lacking to calculate population EVPI, including the number of patients with an ITC, MiM and MaM positive SN and an estimation of the time the information would be beneficial. Nonetheless, it becomes clear from the results that accurate information can significantly impact clinical and policy decisions.

Further research was found to be most valuable for the probability of regional failure values; the EVPPI showed that most of the decision uncertainty was caused by the probability of non-SN metastasis for ITC, probability of non-SN metastasis and regional recurrence for MiM, and the distribution of these non-SNs in level IV and shoulder morbidity for MaM. Therefore, measuring regional failure rates in patients who underwent ND, RT, and WW after an SLN procedure is worthwhile.

Validation

Because of the lack of model validation with previous research(1), model assumptions (2) and possible parameter variation (3), the exact cost-effectiveness of adopting a certain treatment as routine follow-up remains highly uncertain. Further research could improve validity. Nevertheless, input data(1), model structure(2), code(3) and output(4) verification is (partly) done to validate the model[20]. The validity was also tested by consultations with clinical experts in the field.

Exclusions from scope

Last, it is important to acknowledge that some relevant topics were excluded from the scope of this study. The analysis did not account for the patient's demographics, patient preference and adherence to treatment protocols, any secondary primary tumour occurrences or comorbidities in the patient care pathway. To extend the model, more complications could be included. However, the decrease in QoL in a small period of time of short-term complications and the low incidence of other long-term complications would result in a negligible decrease in QoL. Furthermore, we did not record the time between diagnoses and treatment in the model. Additionally, we did not examine potential patient waiting lists for surgery or radiotherapy.

Moreover, a 10-year time horizon was used in our decision-analytic model, while a lifetime time horizon is generally preferred for health economic evaluations if the effects of treatment strategies occur over the entirety of a patient's life[62]. However, with no regional failures 2 years after the SLNB, unknown mortality risk differences after 10 years, and the majority of the patients not surviving beyond 10 years, it is expected that a longer time horizon in this model would not have extremely altered the conclusions, and would unnecessarily increase the running time. However, we acknowledge that using a shorter time horizon may result in underestimating the long-term benefits of the different treatment strategies. Future studies could consider using a longer time horizon to capture the full range of outcomes associated with a subset of the treatment strategies. Important to note that collecting data over a lifetime can be resource-intensive and time-consuming, and there may be limitations in the availability and quality of data for longer time horizons.

Theoretical contribution

This research contributes to the literature by providing a modelling approach and first impression of possible cost-effectiveness outcomes, which to the best of our knowledge, the literature does not discuss. This research combines extensive literature research and comprehensive discussions with clinical experts, allowing for the development of a microsimulation model based on the work of Krijkamp et al., with adjustments for OCSS patients made accordingly[19]. Finally, this research extends

the model using the SAVI tool to calculate and focus on the value of missing data for a microsimulation model[56].

Implications for practice and further research

From the results of this study, the best treatment strategy was not proven to be the most cost-effective alternative to current treatment methods. Specifically, multiple assumptions were made to build the microsimulation. Additionally, the uncertainty especially surrounding the effectiveness estimates, was inevitable, as demonstrated in the incremental cost-effectiveness planes in Figures 11, 12, and 13. Furthermore, the results of the scenario analyses did not prove to be quite robust, and QALY and NMB estimates fluctuated with different input parameters. Caution should be exercised when drawing conclusions about our findings on lifetime health and economic consequences. The results of a cost-effectiveness study may not be generalisable for all patients with different characteristics and settings. Knowledge of these parameters and results without aggregation would shift the result from general cohort outcomes to more patient-level outcomes. Also, the model could be extended to higher-risk patients if data becomes available in the future on risk factors such as tumour size, histologic grade, perineural invasion, and vascular invasion[63 5]. Nonetheless, additional research and collection of data could improve model assumptions and input parameter distributions to adjust and complement the model to draw valid conclusions in the future. This study could be the first step towards research regarding the added value of neck dissection, radiotherapy, and watchful waiting for sentinel node-positive oral cavity cancer patients. Further investigation should be performed to determine the cost-effectiveness while incorporating patient-specific characteristics and, in combination with incorporating true regional failure rates with regard to these characteristics for treatment strategies, to influence clinical practice.

The first step in further research should focus on enhancing the evidence regarding true regional failure rates following treatment strategies for sentinel node-positive oral cavity cancer and improve both model structure and model input accordingly. From the results, a starting point could be a clinical study among patients with micrometastasis-positive SNs to compare the effectiveness of neck dissection I-III against watchful waiting to gain a more thorough understanding of regional recurrence rates. Given that the probability of WW being cost-effective is also highest for isolated tumour cells, this trial could potentially inform decisions regarding the most beneficial approach to managing both MiM and ITC SN-positive patients. Although the follow-up duration of 2 years is relatively long for detecting regional failure, there is no documentation of outcomes parameters for salvage therapy (or quality of life) after neck treatment. This is a significant limitation that could be improved upon in future studies. It is essential to extensively document the clinical effects of watchful waiting in future studies. This will help provide a more comprehensive understanding of the effectiveness of different treatment strategies and enable clinicians to make more informed decisions regarding patient care.

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8 Appendix

A Assumptions

- All patients enter the model with early-stage sentinel node-positive oral cavity cancer.
- Regional failure rates depend on the size of the positive SN and treatment strategy. Patient-, tumour- and (other than size) sentinel node characteristics (e.g. risk factors such as smoking and use of alcohol, the location in the oral cavity of the primary tumour and the neck level of the positive sentinel node) are not taken into account. See Table 18 for lacking extensions. Patients experience regional failure in the model after one year or two years.
- In case of watchful waiting, the regional failure rate is equal to the probability of non-sentinel node metastases.
- For neck dissections, it is assumed that in addition to non-sentinel node metastases, recurrence can occur due to in-surgery field recurrence. In-surgery field recurrence evolves from (1) missed lymph nodes in the dissected neck levels and (2) extracapsular nodal disease extension that recurs in the neck's soft tissues, including extranodal extension, perineural invasion, and lymphovascular invasion. In the surgery field recurrence is the same for all types of neck dissection. i.e. independent of the removed neck levels (I-III, I-IV and I-V).
- The effectiveness of radiotherapy is the same for ITC, MiM and MaM. The size of additional non-SN could influence the effectiveness, but it is unknown[28]. Therefore, regional failure after radiotherapy only depends on the size of the positive SN and irradiated levels. The effectiveness of RT is based on clinical expertise[28 40].
- PORT is always given to levels I-V[28]. PORT has the same effectiveness as radiotherapy. Since regional failure rates after a neck dissection is already small, different effectiveness of PORT does not influence region failure rates to a large extent after PORT.
- Short-term complications are excluded from the model since differences in QALYs between the different strategies are small and in a short time period. Only the most important long-term complications are taken into account. These are shoulder morbidity and xerostomia for neck dissection and radiotherapy, respectively. It is assumed that a neck dissection does not cause xerostomia, and radiotherapy does not cause shoulder morbidity. So, it is assumed that no shoulder complications can occur due to radiation-induced fibrosis. Only severe shoulder or xerostomia complications (grade 2/3) cause a reduction in QoL. Note that not all literature does use the same standards for these grades. Because radiotherapy in the upper neck levels affects the salivary glands more directly, it is assumed that there are no differences in xerostomia complications between radiation of levels I-III, I-IV, and I-V.
- It is assumed that salvage depends on the primary neck treatment strategy. The level of the neck where the recurrence is located (if the recurrence is in- or out-surgery field) is excluded from the model. E.g. it is not considered that a regional failure in level IV or V after a neck dissection of level I-III could still be dissected. The disutility distribution is the same for all patients receiving salvage treatment (WW salvage therapy excluded), independent of the primary and salvage treatment strategy. When recurrence occurs after WW, the assumed salvage therapy is a neck dissection + PORT, with complication rates the same as for primary neck dissection + PORT treatment.
- OS and time till regional failure were the same for each treatment strategy. The OS differed between patients experiencing regional failure and those who had no regional failure.

- Regional failure does occur in year one or two years after initial neck treatment.
- To calculate the total EVPI, the annual patient volume and the time over which the information would be beneficial are needed. The precise annual patient volumes of patients with T1-2 ITC, MiM and MaM SN+ OSCC are unknown[64]. To give an indication, the patient volume is roughly estimated to be 50 in the results, but could also be estimated to be a multiple of 10 and less than 100. The time over which the information would be beneficial is set to 5 years.

B Regional failure

The calculation of regional failure rates per treatment strategy and the size of the positive SN is explained. Neck dissection removes one or more positive non-sentinel lymph nodes during surgery in the area of treatment. In-field failures are caused by missed tumour cells during surgery, extranodal extension, perineural invasion, and lymphovascular invasion. Radiotherapy controls regional failure with effectiveness of 90% in the area of treatment. PORT controls positive non-sentinel lymph nodes with the same effectiveness of 90% and also controls the in-surgery field failures with this effectiveness.

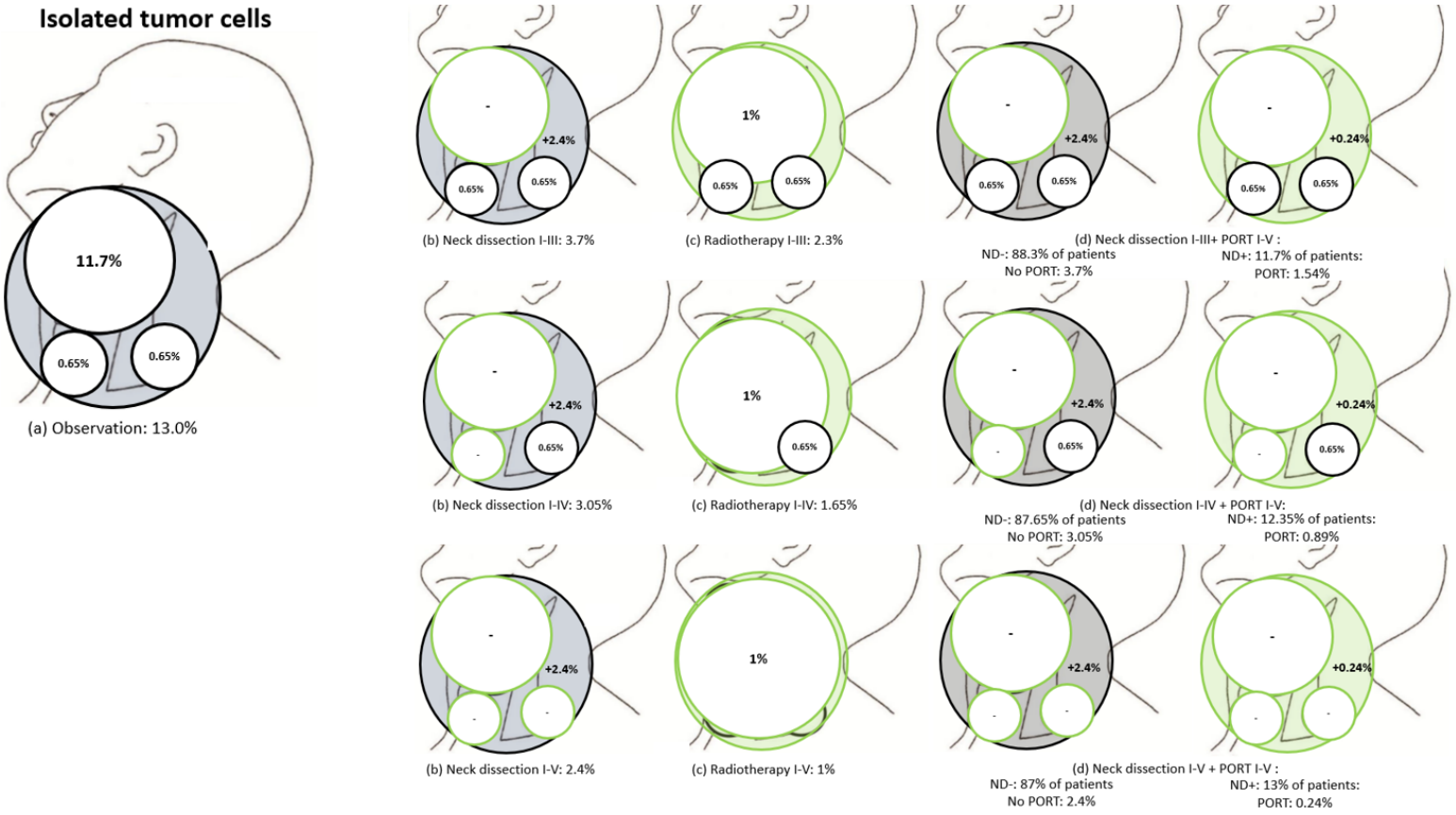

Figure 22: Regional failure rates after treatment of positive SN with isolated tumour cells. From left to right: Observation (watchful waiting), neck dissection, radiotherapy, neck dissection+PORT (PORT in case of positive-SN in neck dissection. From top to bottom: treatment to levels I-III, levels I-IV and levels I-V.

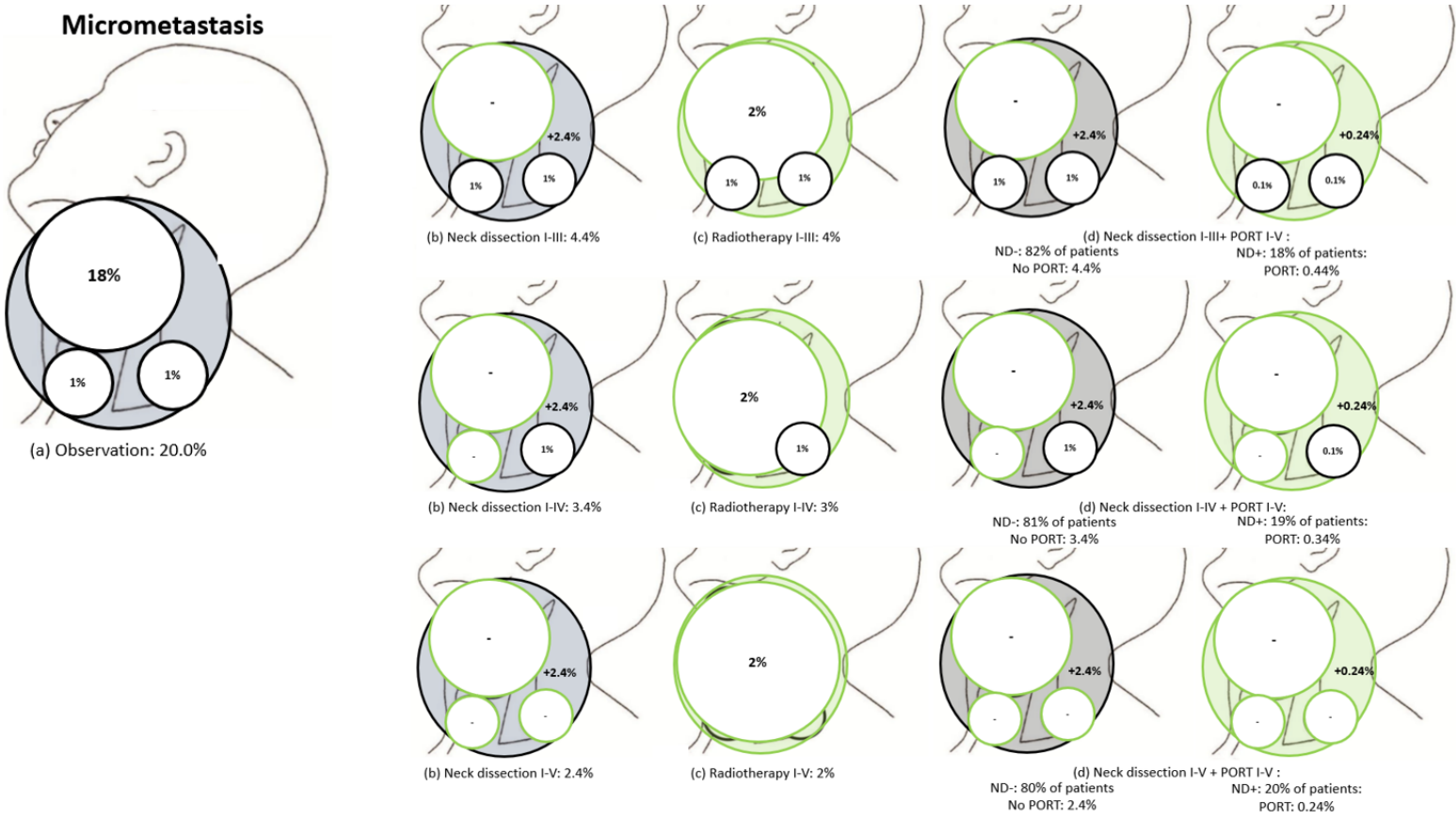

Figure 23: Regional failure rates after treatment of positive SN with micrometastasis. From left to right: Observation (watchful waiting), neck dissection, radiotherapy, neck dissection+PORT (PORT in case of positive-SN in neck dissection. From top to bottom: treatment to levels I-III, levels I-IV and level I-V.

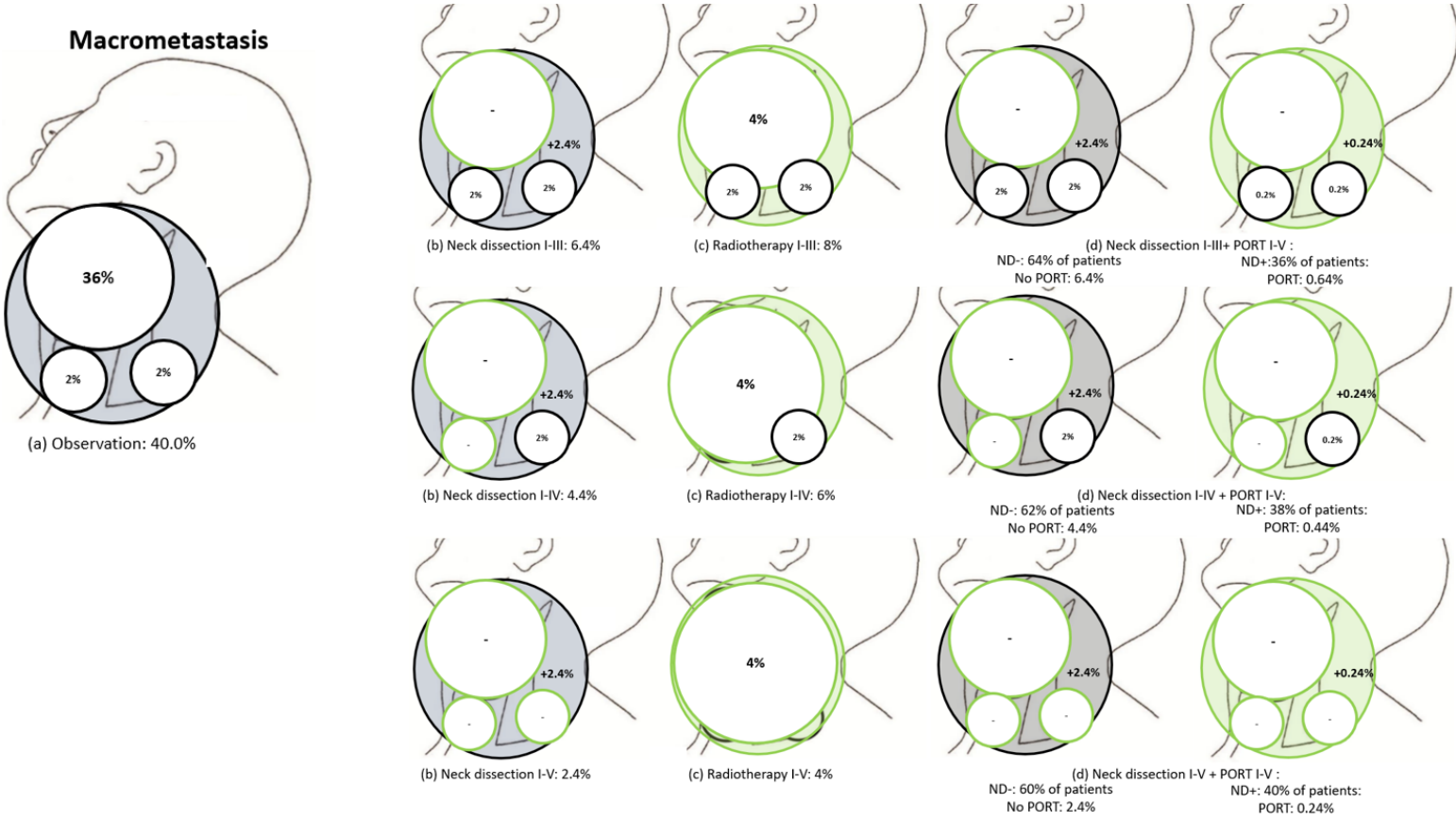

Figure 24: Regional failure rates after treatment of positive SN with macrometastasis. From left to right: Observation (watchful waiting), neck dissection, radiotherapy, neck dissection+PORT (PORT in case of positive-SN in neck dissection. From top to bottom: treatment to levels I-III, levels I-IV and level I-V.

C Number of patients to simulate

The number of samples (patients) to simulate needed to remove the impact of patient-level variation was determined. The sample size should be sufficiently large to remove the impact of variation at the patient's level on cost-effectiveness outcomes, e.g. cost and QALY for each treatment strategy. For the low regional failure after treatment, a base case analysis (BCA) is provided to determine the number of patients to simulate, and cohort-level parameter uncertainty is not incorporated. Table 15 shows the calculated mean cost and effect, standard deviation and standard error of the mean for the base case while increasing the number of patients from 1000 to 10000 for a fixed number of 100 runs. Table 16 shows the calculated ICERs of ND I-III compared to RT I-V while increasing the number of simulated patients. It was essential to assess stability for effects, costs and QALY while only accepting a decent computation time. It was decided to simulate a minimum of 5000 patients per run.

Sample size	n=1000		n=2.500		n=5,000		n=10,000	
Outcome	Cost (€)	QALY	Cost(€)	QALY	Cost(€)	QALY	Cost(€)	QALY
Mean	4071.60	6.31	4070.17	6.31	4072.05	6.31	4073.14	6.30
Sd	20.08	0.0888	11.23	0.0541	8.19	0.0395	5.00	0.0307
SEM	0.635	0.00281	0.225	0.00108	0.116	0.000559	0.0500	0.00031

Table 14: Mean, standard deviation and standard error of the costs and QALYs for ND I-III treatment while increasing the number of simulated patients.

Sample size	n=1000		n=2.500		n=5,000		n=10,000	
Outcome	Cost (€)	QALY	Cost(€)	QALY	Cost(€)	QALY	Cost(€)	QALY
Mean	7458.96	6.370	7459.77	6.377	7460.02	6.370	7459.61	6.369
Sd	5.97	0.0863	4.04	0.0539	2.75	0.0398	1.91	0.0311
SEM	0.188	0.00273	0.0808	0.00108	0.0389	0.000563	0.0191	0.000311

Table 15: Mean, standard deviation and standard error of the costs and QALYs for RT I-V treatment while increasing the number of simulated patients .

Number of patients	ICER (€/QALY)
n=1000 (x100 runs)	68373.00
n=2500 (x100 runs)	168477.49
n=5000 (x100 runs)	40478.14
n=10000 (x100 runs)	41832.01

Table 16: ICER estimates while increasing the number of simulated patients

D Sensitivity Analysis

D.1 Scatter plots from sensitivity analyses

The PSA results are given in Figures 25, 26, and 27 for ITC, MiM and MaM respectively. This analysis shows the effect of jointly varying model parameters on the model's outcomes. 5000 simulations were performed randomly selecting model parameters from the distributions shown in Table 10. The X-axis represents the discounted quality-adjusted life-years, and the Y-axis represents the discounted costs.

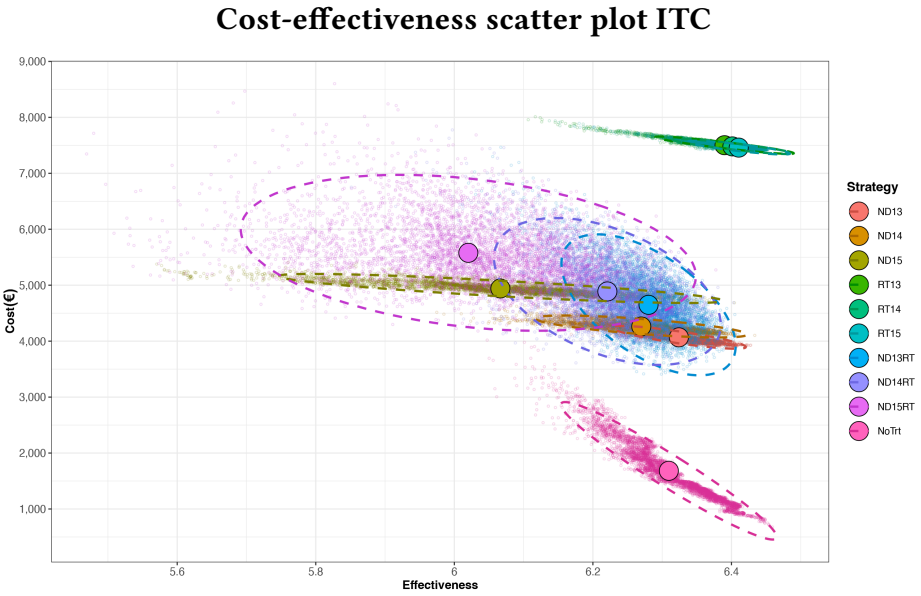

Figure 25: Probabilistic sensitivity analysis scatter plot for isolated tumour cells SN.

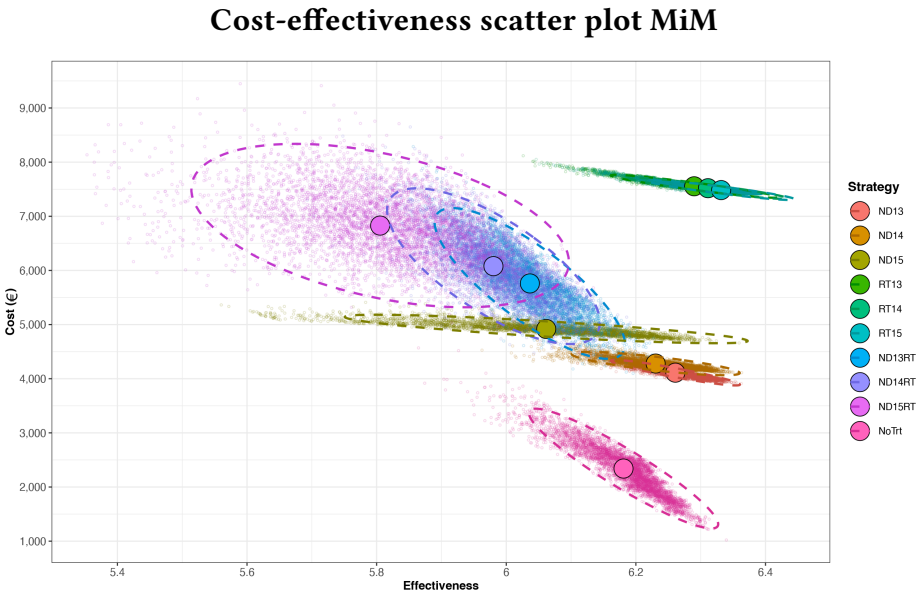

Figure 26: Probabilistic sensitivity analysis scatter plot for micrometastasis SN.

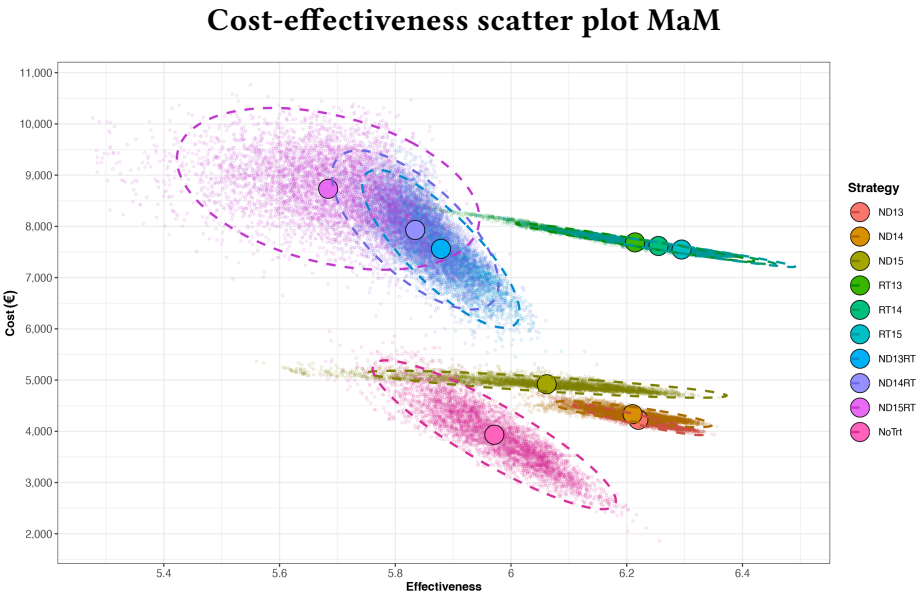

Figure 27: Probabilistic sensitivity analysis scatter plot for macrometastasis SN.

D.2 Determinisitic sensitivity analysis

The influence of input parameters on the outcomes in QALY and NMB is analyzed using DSA. The best treatment strategy in terms of QALY and NMB for a range of extreme values for multiple input parameters are given in Figures 28 and 29 for ITC, Figures 30 and 31 for MiM, and Figures 32 and 33 for MaM. The influence of the parameter values is also discussed below.

- **The probability of non-SN in level IV**: For all probabilities of non-SN in level IV in a range of 0% to 20% is RT I-V the strategy with the highest number of QALYS. ND I-IV becomes the strategy with the highest NMB instead of ND I-III for MaM if the probability of non-SN in level IV increases to higher levels. This is the consequence of removing level IV in strategy ND I-IV; level IV is not removed in an ND I-III. So, the increased likelihood of non-sentinel lymph nodes in level IV causes an elevated regional failure rate in ND I-III compared to ND I-IV.
- **The probability of non-SN in level V**: For probabilities of non-SN in level V in a range of 0% to 10%, RT I-V is the treatment strategy with the highest expected QALYs for ITC, MiM and MaM. For ITC, the WW strategy is expected to provide the highest NMB for the probabilities 0% to 10%. For MiM, ND I-III is predicted to give the highest number of NMB for a low probability of non-SN in level V, and if the probability increases, WW gives a higher NMB. This is because the number of positive non-SN in levels I-III, which are resected with an ND I-III, decreases if the number of positive non-SN in level V increases. For MaM, ND I-III is the strategy with the highest NMB for all probabilities in the given range.
- **The probability of in-surgery field recurrence**: The probability of in-surgery field recurrence influences the best strategy in terms of NMB for MiM and MaM. An increase in the probability of in-surgery field recurrence after a neck dissection causes a higher NMB for WW for MiM and RT I-V for MaM compared to ND I-III. Surgical treatment becomes less beneficial with increased recurrence after neck dissections.
- **The effectiveness of PORT**: The effectiveness of PORT does not influence the best treatment strategy. This is most likely caused by the fact that the recurrence rate is already low after neck dissection. A change of 10% in the effectiveness of PORT is causing minimal changes in regional failure rates after neck dissection.
- **The probability of xerostomia**: If the probability of xerostomia after radiotherapy increases, radiotherapy becomes less beneficial. Also, WW becomes less beneficial because salvage therapy includes radiotherapy.
- **The probability of shoulder morbidity**: As the probability of shoulder morbidity increases, a neck dissection becomes less beneficial.

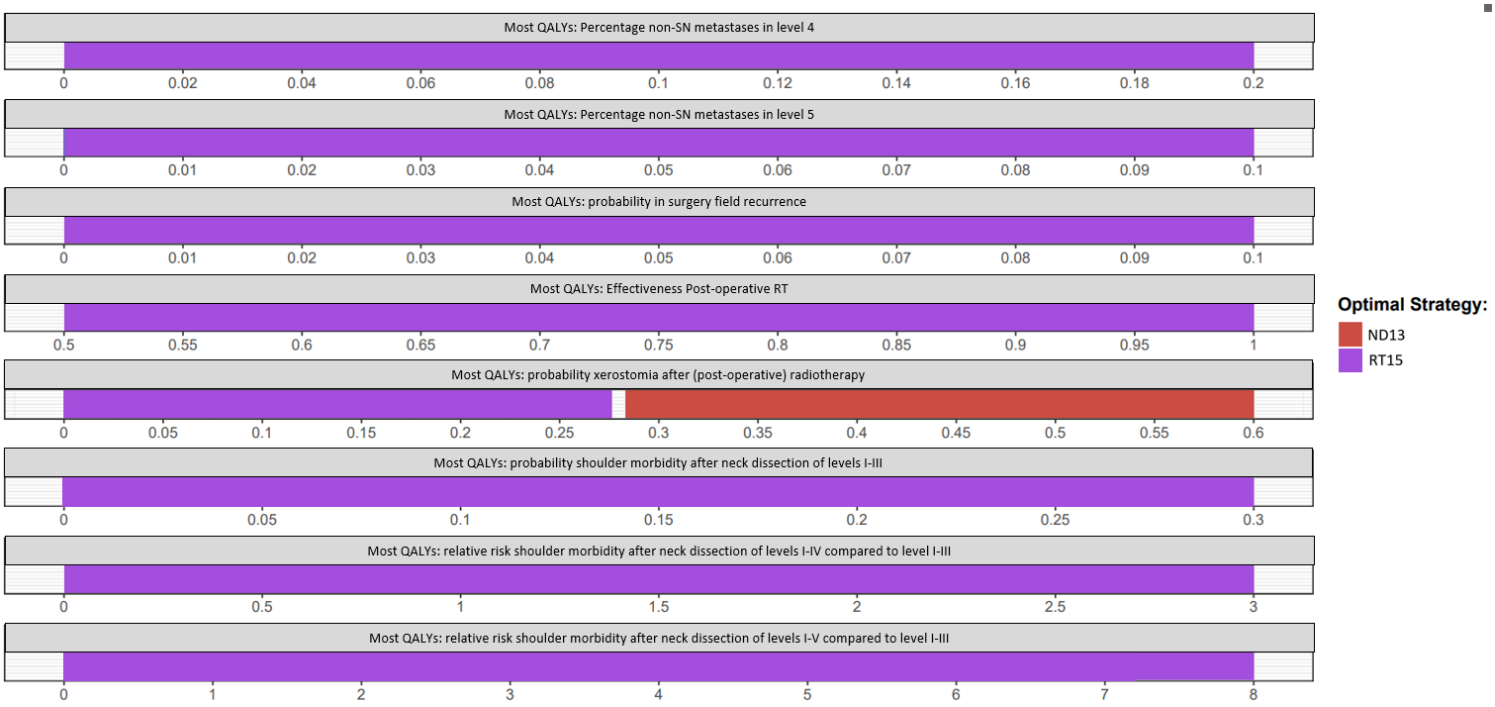

Figure 28: Best strategy for ITC in terms of QALY per parameter value.

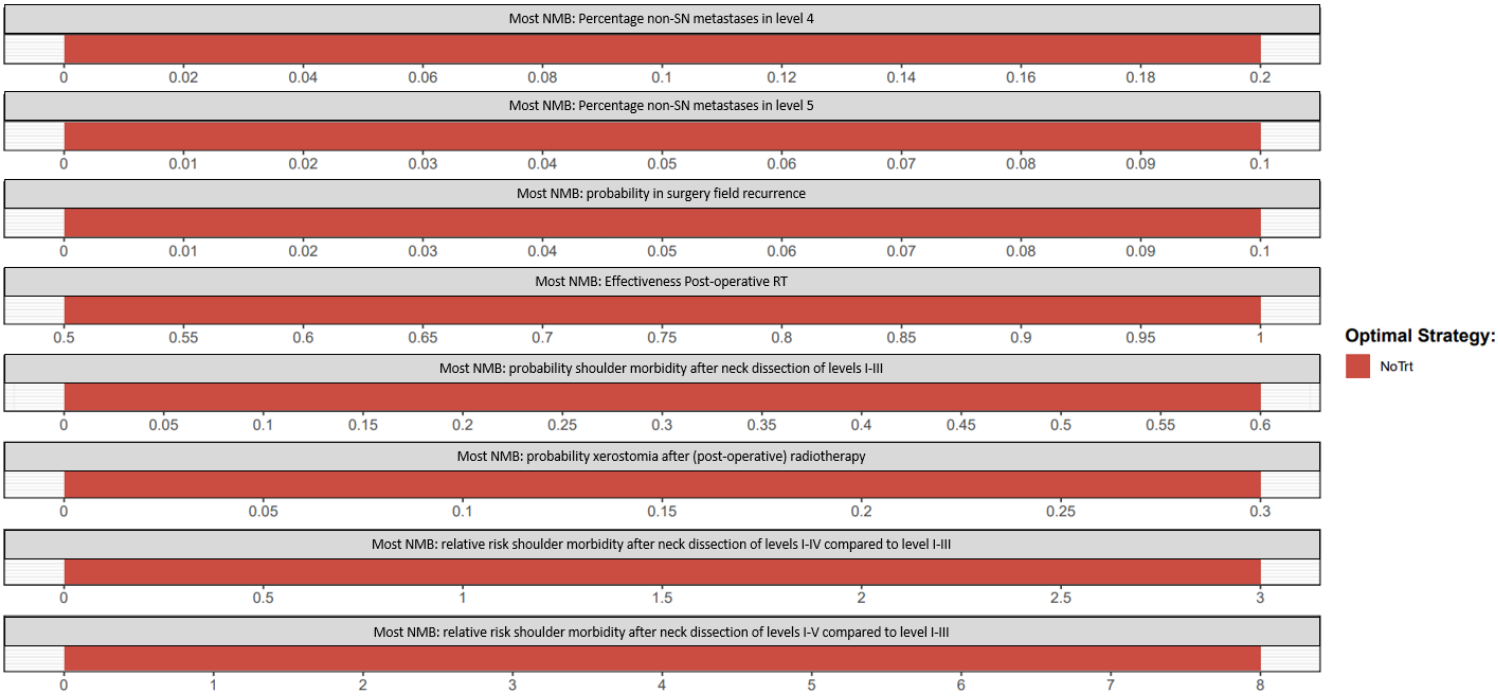

Figure 29: Best strategy for ITC in terms of NMB per parameter value.

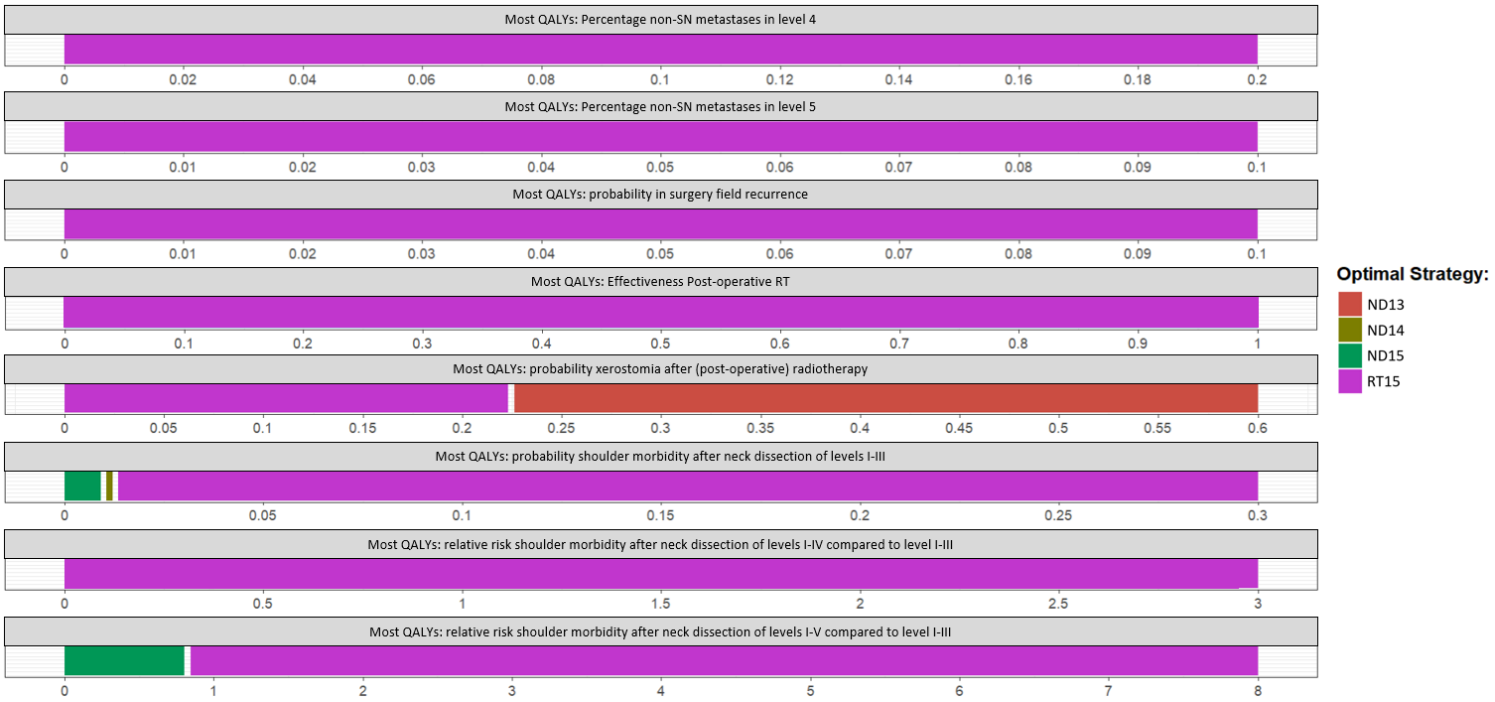

Figure 30: Best strategy for MiM in terms of QALY per parameter value.

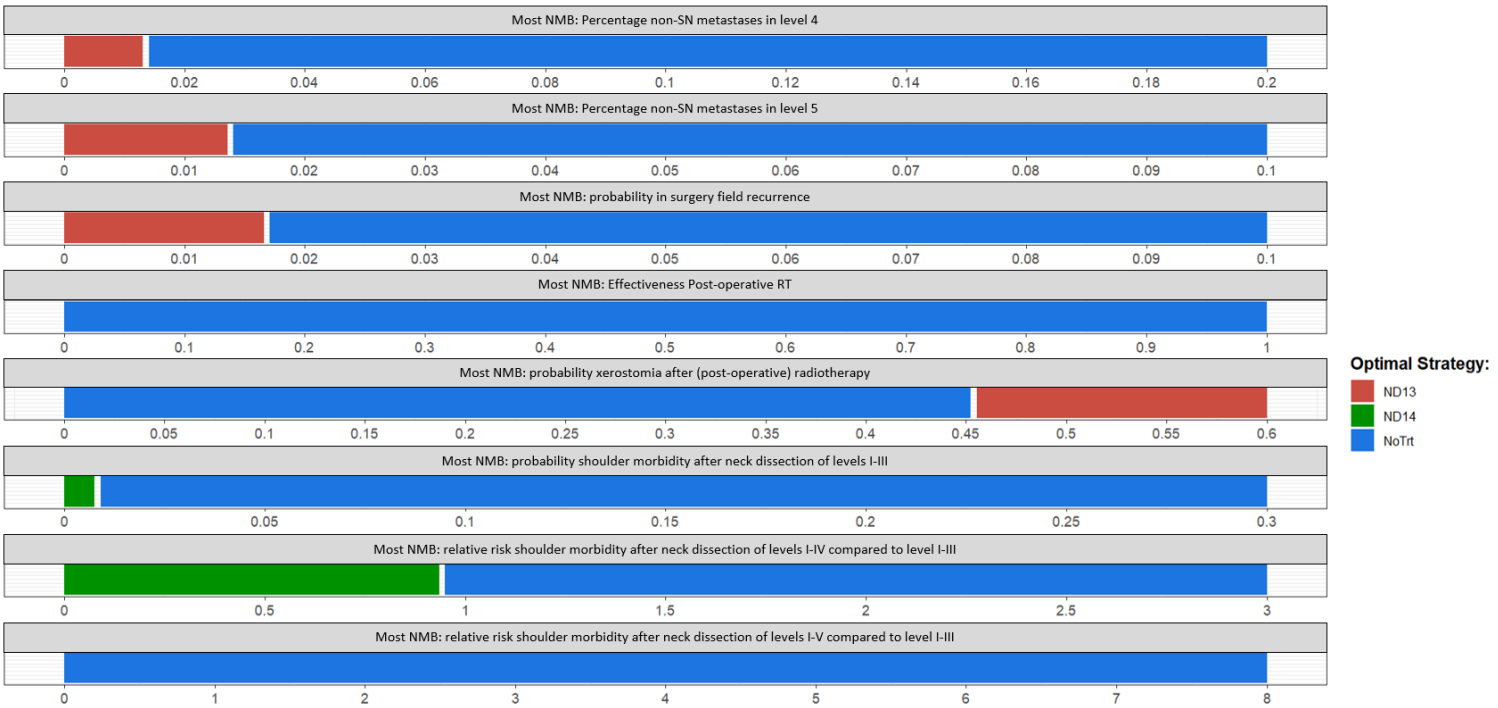

Figure 31: Best strategy for MiM in NMB per parameter value.

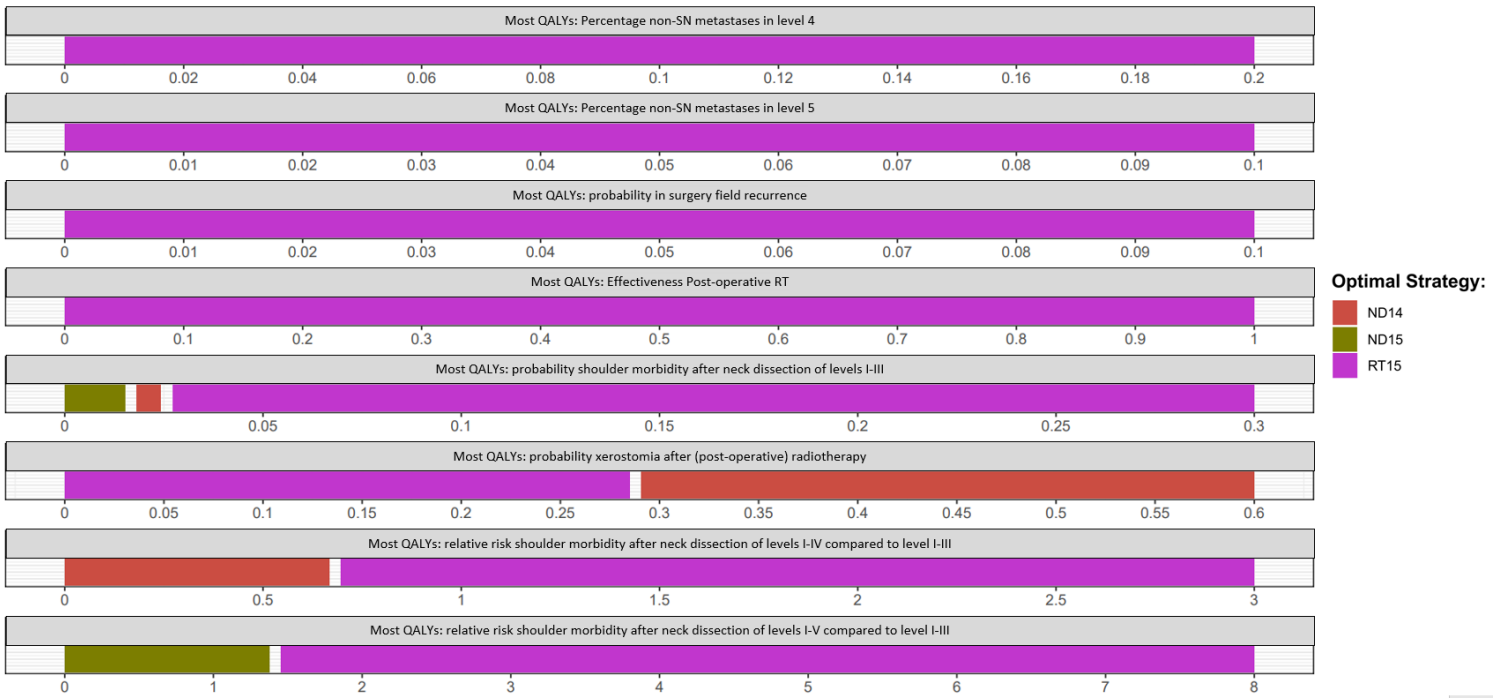

Figure 32: Best strategy for MaM in terms of QALY per parameter value.

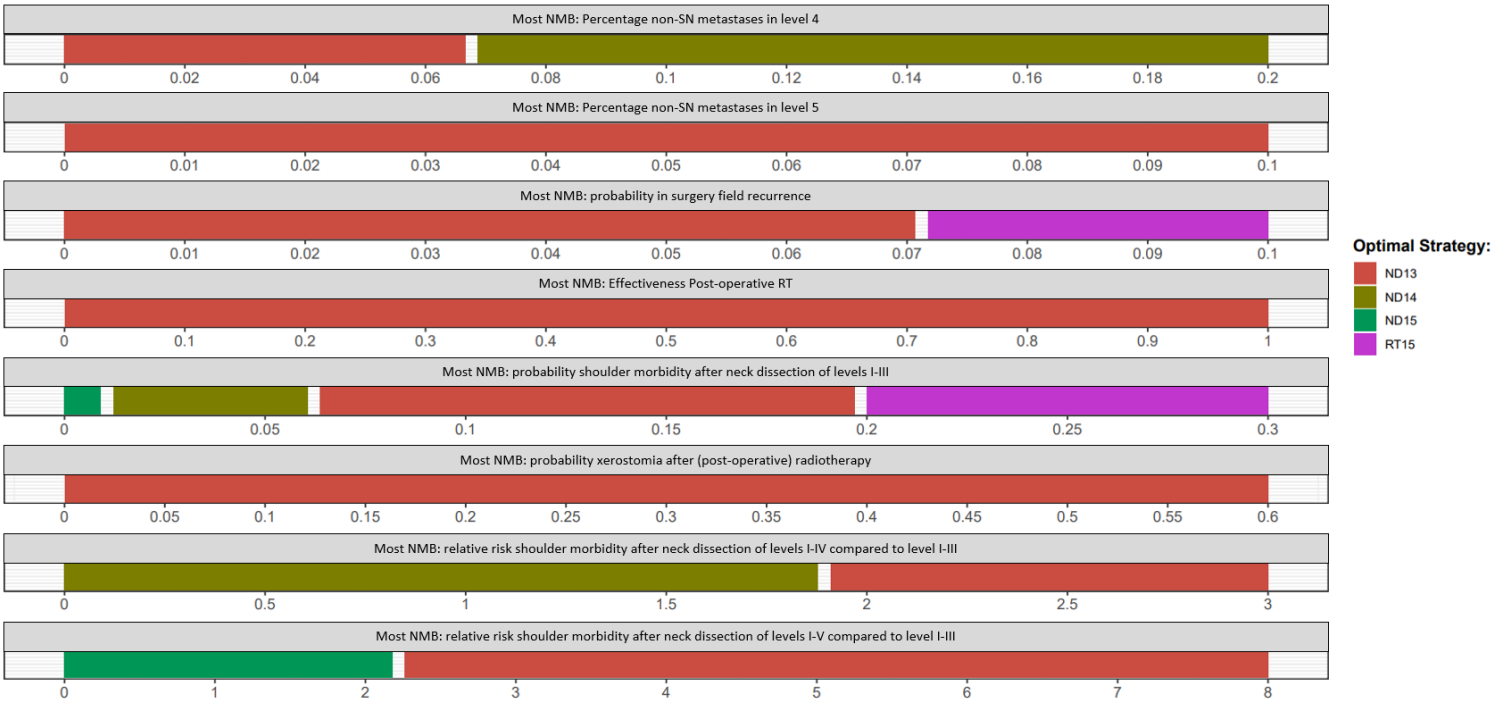

Figure 33: Best strategy for MaM in terms of NMB per parameter value.

D.3 Tornado diagrams

Sensitivity analysis of strategies neck dissection I-III, radiotherapy I-V and watchful waiting (no treatment) is shown. The graphic shows the impact of varying individual model inputs on the effectiveness (QALYs), costs (€) and net monetary benefit (€, incremental effect multiplied by the threshold minus the incremental cost) for the best treatment strategies for ITC, MiM and MaM. The factors are listed in descending order of influence on effect with various input values. Only parameters with a relative change greater than 5% are shown. If no graph is given for a strategy, no parameter varied more than 5%. For ITC, MiM and MaM, QALY, and MNB do not change more than 5% if one parameter is varied.

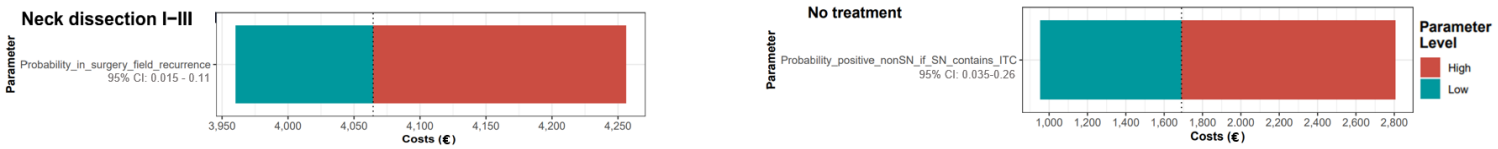

Figure 34: Tornado diagrams isolated tumour cells.

For ITC, the *probability of in-surgery field recurrence* altered the costs for the ND I-III strategy and *probability of positive non-SN* the costs for the WW strategy. Other parameters did not alter the outcomes more than 5% for ND I-III, RT I-V and WW.

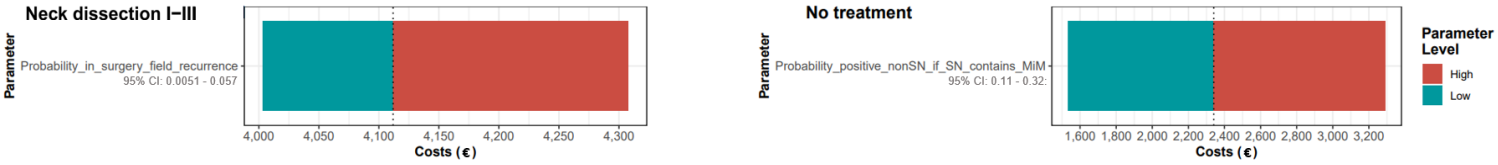

Figure 35: Tornado diagrams micrometastasis.

For MiM, the parameter *In surgery field recurrence* changed costs more than 5% in ND I-III strategy. For WW strategy, parameter *probability non-SN metastasis* changed the costs more than 5%.

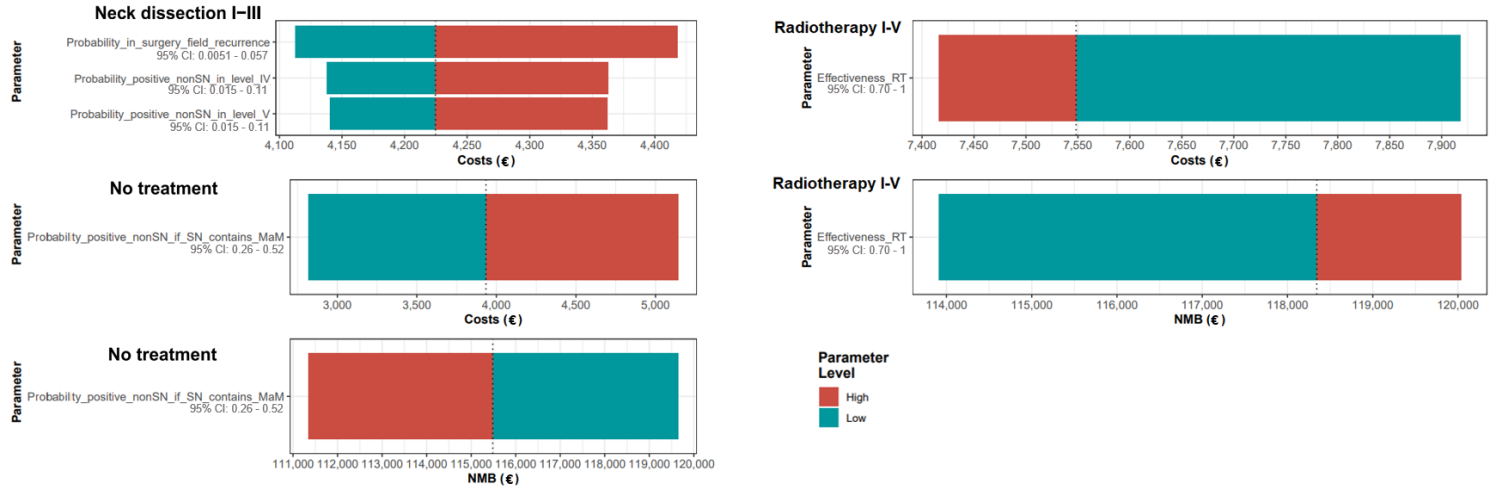

Figure 36: Tornado diagrams macrometastasis.

For MaM, the costs of ND I-III strategy changed more than 5% when varying the *In surgery field recurrence*, *Probability of positive non-SN in level IV*, and *Probability of positive non-SN in level V*. The

Probability non-SN metastasis changed costs and NMB more than 5% for WW strategy. The *effectiveness of radiotherapy* changes costs and NMB more than 5% for RT I-V strategy.

E Systematic literature review

A systematic literature review was performed to retrieve data on sentinel node research for oral cavity cancer patients. Search terms used were a combination of ("oral cavity cancer" OR "oral squamous cell carcinoma" OR OSCC) AND ("sentinel node" OR SLNB OR "Sentinel lymph node" OR SLN). SN was excluded due to many unrelated articles.

In the main search of ("oral cavity cancer" OR "oral squamous cell carcinoma" OR OSCC) AND (Sentinel OR "sentinel node" OR SLNB OR "Sentinel lymph node" OR SLN) on Pubmed, 192 articles were found (last accessed: October 2022). After screening the titles and abstracts of these articles, the results from positive sentinel node biopsies in oral cavity cancer patients were retrieved. In all other cases, it was evident from the abstract that it did not concern data for further use in this article. Screening the selected articles, most articles for regional failure rates were excluded for the following reasons: no information on the size of the positive SN, no information on the levels of the positive non-sentinel nodes, and extreme sample sizes (<5 patients). Several articles provided useful information and data and were used as literature or discussed with experts.

PICO

Since data after SLNB was limited, the scope was extended. Inclusion criteria were determined according to the PICO method, as shown in Table 17. Finally, only English and Dutch articles were included.

Table 17: PICO for regional failure rates

Population	The target population consists of patients with clinical early-stage T1-T2 oral cavity cancer and no clinical evidence of node metastasis in the neck (cN0) and no metastases (M0), and positive sentinel node biopsy. *If an article included patients outside this specific population, e.g. cN0 without SLNB, data from the literature source was consulted with clinical experts.
Intervention	Neck treatment strategies. This includes neck dissection of levels I-III, I-IV or I-V, such as selective neck dissection, radiotherapy or postoperative radiotherapy. For radiotherapy-related data, the intervention should be intensity-modulated radiotherapy, preferably with a simultaneous integrated boost (IMRT-SIB).
Comparator	The comparator is watchful waiting (observation, no treatment or no intervention) or any other treatment strategy. Since there are multiple treatment strategies, multiple intervention-comparator combinations are possible.
Outcome	The outcome must include pathological factors, level of positive non-sentinel node and size of metastasis, or other data needed for a full economic evaluation, meaning effects of treatment, i.e. (disease-free) survival and (dis)utilities. For regional failure rates, studies must include the pathological examination or a follow-up of at least 12 months after a positive sentinel node biopsy.

Complete data overview

The data from Table 18 was intended to gather from the hospital's patient database and the nationwide database as a starting point. Due to lacking evidence of relations between the parameters or outcomes,

only a subset of the input parameters is included in this study. The influence on outcomes of the following data could be analysed to improve the model to improve the current input parameters or extend the current model and study. Preferred from a diverse and large dataset.

Category	**Characteristic**
Patient demographics	Age, gender, race, smoking, alcohol usage
Medical history	Previous cancer treatments, comorbidities
Characteristics of the tumour	Size, grade (1-4),stage (TNM), location (subsites of the oral cavity)
Characteristics of the sentinel nodes	Number of positive nodes, ratio of positive/negative nodes, size of the positive node, level of invasion, location of the positive node (neck level)
Treatment	Type of surgery, levels treated, adjuvant therapy, salvage therapy
Outcomes	Recurrence rate, location (neck level) of regional failure, survival rate, regional failure-free survival, degree of metastasis, complications, quality of life

Table 18: Input parameters to improve current input data or extend the model.