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Health economic impact of diagnostic information using CTCs in the early staging phase of primary breast cancer

Sofie Berghuis
(S1110373)
Master Programme Health Sciences
Health Technology Assessment and Innovation

Examination committee:
Prof. dr. M.J. Ijzerman
Dr. ir. H. Koffijberg

Summary

Blood biomarkers, such as circulating tumour cells (CTCs) can give important information about the prognosis and clinical management of cancer patients. The FDA approved CellSearch, but one problem to solve is that CTCs may not be sensitive enough because the blood samples are small (7,5 mL). Currently a technique is developed which can separate CTCs from the whole blood and is called the CTC Trap. This study addresses the potential impact of implementing the CTC Trap in addition to currently used imaging techniques in early staging of primary stage I-III breast cancer in women.

The early staging process has been identified using the Dutch breast cancer guideline. This process was finally displayed in a decision tree. Three points in this process have been identified as possible implementation options for the CTC Trap. A simulation model has been built in Excel to simulate the cost-effectiveness of implementing the CTC Trap at these three different points. Deterministic and probabilistic sensitivity analysis have been performed to get insight in the influence of uncertain parameters.

Potentially relevant points for implementing the CTC trap are: 1) following negative sentinel lymph node procedure to test for micro metastases, 2) following negative result of initial MRI to test for (micro-) metastases, 3) following negative results of further imaging. Usual care resulted in an average survival of 2,42 years, a 3-year survival of 93,71%, 1,51 QALYS and a cost of € 992,56. When implemented at all 3 implementation points simultaneously CTC Trap resulted in an average survival of 2,84 years, a 3-year survival of 97,46 %, 1,84 QALYS and a total cost of € 6.035,45. Survival and QALY gain are approximately the same If CTCs are implemented in option 1 compared to implementing CTCs at all options. Implementing CTCs in option 1 is most cost-effective with a cost per QALY of € 2.684,16.

CTCs clearly have the potential to improve overall survival. Use of CTCs can potentially improve survival with 0,42 years and improve QALYs with 0,34. Costs do increase at all options but from a health economic perspective it is most valuable to implement CTC Trap in option 1) following negative sentinel lymph node procedure to test for (micro-) metastases.

Preface

This research was done at the University of Twente. The report is the result of my research project which I did for the master track health technology assessment and innovation, which is in the master health sciences. This master track is part of the research department health technology and services research which again is part of the faculty behavioural management and social sciences.

Results of this research project aim to provide an estimation of the health economic impact of implementing the new diagnostic device (CTC Trap) in the early staging phase of breast cancer. The economic model that has been built to simulate this impact can be a valuable tool which can possibly assist decision making for decision makers in health care. This master assignment gave me the opportunity to combine knowledge from all the courses which were in the master track, but as well the courses which I have been following during my bachelor program 'Gezondheidswetenschappen' which I also did at the University of Twente.

I would like to thank my supervisors Erik Koffijberg and Maarten Ijzerman from the University of Twente for the great support during this project. Meetings really added some interesting new insights to the project by which I think it was possible to improve even more on the quality of this project. Besides my primary supervisors, I would also like to thank the PhD candidates Michelle Kip and Annemieke Witteveen from the university of Twente for their great support and help. At last I would like to thank dr. de Noo from the hospital in Deventer for her great feedback on the care pathway of the early staging process. It has been a really valuable meeting in which the whole process became clear.

At last I would like to thank my colleagues from the working room in which we have all been working during our research projects. I think we all have stimulated each other to make the best of our research projects and interesting discussions led to valuable insights sometimes. Besides, I would also like to thank my friends and family at home who really gave me the time and support to work on and motivate me even more for my research project.

I hope you enjoy reading the study as much as I enjoyed the writing of it.

Sofie Berghuis

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1. Introduction

Breast cancer is the second most common cancer in the world. Among women it is by far the most frequently diagnosed form of cancer with an estimation of 1,67 million new cases diagnosed in 2012, which counts for 25% of all cancers diagnosed. The incidence rate is 43,3 per 100.000. There are 522.000 deaths per year from breast cancer worldwide. Overall breast cancer is ranked as the fifth cause of death from cancer but in women it is the most common cause of cancer death (1). Besides the increasing burden of cancer, health expenditures for cancer treatment are rising which increase the demand for more evidence based and cost efficient medicine (2).

Breast cancer mortality has decreased over the past two decades as a result of earlier diagnosis and major treatment advances in the adjuvant and metastatic settings. Overall breast cancer has a 5-year survival of 89% (3). If breast cancer is localized the 5-year survival is even 99% (3). Despite progress in diagnostics and treatment advances, metastatic disease still largely is an incurable condition, with 5-year survival rates below 25% (4). The metastatic disease can be seen as the leading cause of breast cancer death. The median survival is only two years after detection of the metastasis (5). To start early treatment to reduce the development of distant metastases, it is important to detect metastases as early as possible (6).

Staging and detecting metastases is currently done by using several imaging techniques or combinations of these, like CT, MRI, bone scintigraphy, PET, PET/CT and FDG-PET/CT (7). Unfortunately, all standard imaging technologies are not able to detect small, distant- or micro metastases at the time of diagnosis due to their lack of resolution, and thereby sensitivity and specificity. Micro metastasis are metastasis smaller than 2 millimeters (8). This low resolution makes it hard for physicians to decide on further treatment and leads to high false-negative rates and hence under treatment (9,10).

To overcome the limitations of imaging modalities in the detection of metastases, the sentinel lymph node biopsy has become accepted as a reliable method of predicting the status of further axillary node metastasis in the early stages of breast cancer (7,11). Even though this procedure has become accepted as a reliable method, the lack of diagnostic markers

detectable in early breast cancer and the possibility of over diagnosis remain critical issues (12).

A possible solution for enabling earlier detection of metastases is using a blood biomarker, such as CTCs. Previous research has shown that CTCs in the blood can give important information about the prognosis and treatment options for cancer patients (13,14). The probability that metastases will be formed can be determined by counting the number of circulating tumor cells (9). The FDA approved CellSearch but methods like these are not sensitive enough in early stages because the blood samples are small (7,5 mL) (15). Therefore a new technique is needed that separates CTCs from the whole blood. Currently a technique is developed which meets this requirements and is called the CTC TheRapeuticApheresis (CTC Trap) (16).

Previous work has been done to provide an early estimation of the health economic value of using the CTC Trap in breast cancer care (17). Cost-effectiveness-gap analysis has been performed to identify the most valuable options for implementing the CTC Trap. It has been shown that it is most valuable to implement the CTC Trap in the early staging phase of breast cancer. In this early staging phase the diagnosis of breast cancer is confirmed and imaging modalities are used to check for metastasis (7). In this phase in the care pathway of breast cancer the QALY gain and the cost savings are relatively high compared to the other stages in the diagnostic pathway (17). As the previous project only roughly performed a CE-gap analysis, it is required to look into more detail using a modelling approach. The model study is performed to calculate the health economic impact of additionally determining CTCs in the early staging phase of primary breast cancer in women compared to currently used staging techniques.

2. Methods

2.1 The model and parameters

A simulation model has been built to simulate the health economic impact of implementing the CTC Trap additionally in the early staging phase of breast cancer. Simulating the health economic impact in a model is the only feasible option because in this stage of the technology no alternatives exist. Economic models are valuable tools which can assist decision makers in healthcare in their estimation of the value of new healthcare technologies (18). Before developing the model the early staging process has been identified using the diagnostics guidelines which are described in the Dutch Breast Cancer Guideline (7). This phase starts directly after the diagnosis of the primary tumor has been histologically confirmed. The care pathway was converted into a flowchart to further identify all possible implementation points for the CTC Trap in this phase. The flowchart and the added value of CTCs along the entire care pathway were evaluated with breast cancer experts.

Given the available evidence a decision tree of the early staging care pathway has been developed. More advanced modelling methods need a lot of data as input to the model (18). As this data does not exist for the CTC Trap, the decision tree is most feasible. More advanced methods like discrete event simulation can provide additional inside when additional evidence comes available. The simulation model which calculates the health economic impact is based on this decision tree and was built in Excel. As input to the model data was required on diagnostic test performance of CTC Trap, currently used imaging methods, treatments carried out, as well as consequences. These values were available from literature for the currently used imaging techniques. For the CTC Trap this data does not exist so these values were estimated. Sensitivity, specificity and incidence were used to calculate test outcomes (true positives, false positives, true negatives, false negatives).

2.2 Outcome measures and analysis

In the early staging process there are several points in the care pathway at which the CTC Trap can possibly be implemented. All these implementation points were evaluated using one single model. To be able to calculate the results for all possible implementation options using one single model, probabilities were built into the model by which the CTC Trap at the different implementation points can be switched on or off. Probabilities that have been used

are Bernouilli and so can have a value of 0 or 1, which simulates that the CTC Trap is implemented at one of the established implementation points (value of 1) or not (value of 0). Different outcome measures will be evaluated, which are the 3-year overall survival, the survival in years, quality adjusted life years (QALYs) and the cost of implementing the CTC Trap. Systematic literature research was performed to find information on these outcome measures. If historical costs were used these were updated to present costs by using historical exchange rates (19). Results of the model were generated using a base-case in which all most likely values for all parameters were used.

Because of the uncertainty around several parameters as well deterministic as probabilistic sensitivity analysis was performed. The results of the deterministic sensitivity analysis are calculated using lower- and upper-levels for the values of these parameters. In this initial analysis results from the CTC Trap were based on using CTCs in all possible implementation points. Related outcomes for these lower- and upper-level parameter values were presented in a tornado diagram in which the impact based on the outcome deviation from the base-case of each of these parameters became clearly visible. For the parameter which has most impact on QALYs, a more detailed sensitivity analysis was performed. In this parameter analysis multiple CTC implementation options were examined at different thresholds of the parameter. The deterministic sensitivity analysis gave insight in the values for each parameter at which they have an optimal effect on the results. Based on these values the possible results in the most pessimistic and most optimistic scenario of implementing the CTC Trap in all possible implementation points were calculated.

As last a probabilistic sensitivity analysis has been performed to find out what possible outcomes there are if the CTC Trap is implemented in all possible options. Because of the uncertainty around the different parameters it was not possible to base this analysis on distributions that exist in literature. Values that have been used as boundaries for each of the parameters are based on an estimation of the value which they at minimum or at maximum are expected to be able to have.

3. The simulation model and parameters

3.1 The early staging process

The flowchart that has been developed according to the Dutch Breast Cancer Guideline is presented in appendix 1. A simplified version of this flowchart is presented in figure 1. TNM classifications with a status T3, T4 and/or ≥N2 in stage I-III breast cancer currently get an MRI to test for metastases because the probability that metastases in this stage will develop is relatively high (30%) (7). For each T or N classification which is lower than these, no further testing for metastases is needed due to the small (3-5%) probability that metastases will develop in this carcinoma (7).

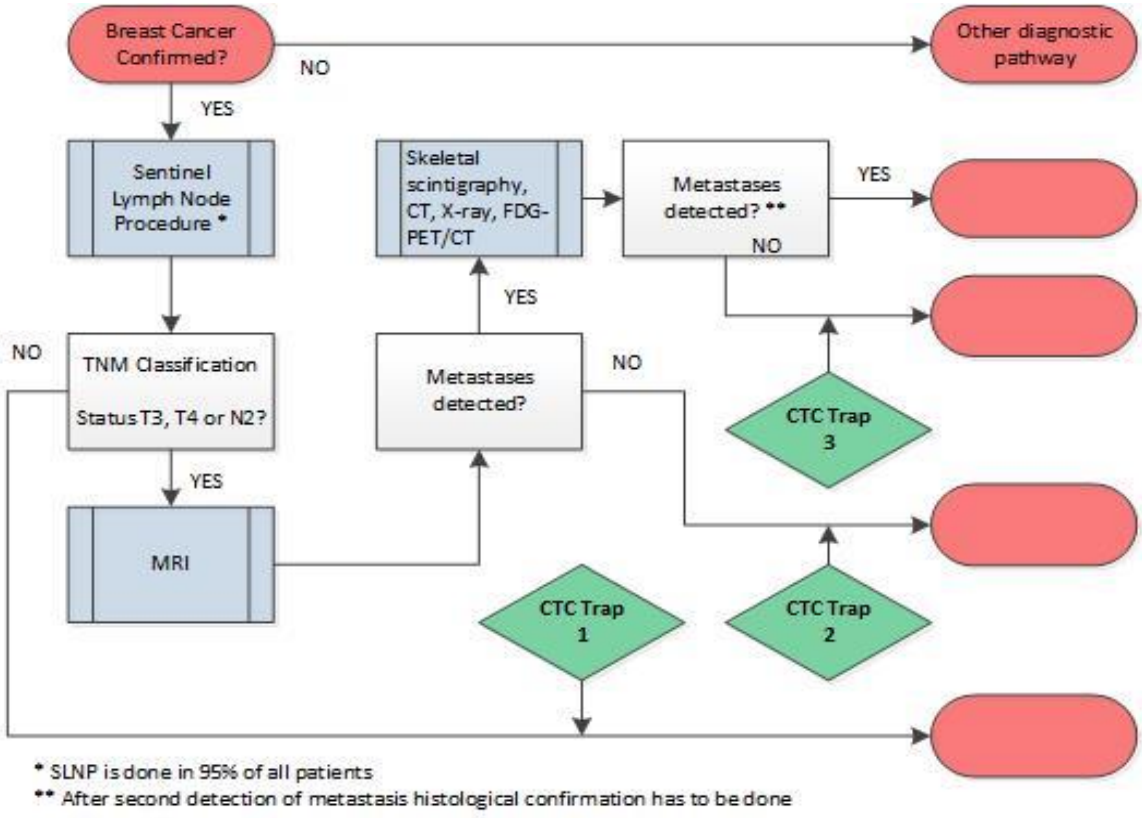


Figure 1: Simplified flowchart for early staging with CTC Trap options

Different values for T, N or M are classified as different stages (Stage 0-IV). Several stages together form a specific type of carcinoma. Carcinomas that can be distinguished for breast cancer are carcinomas in situ, operable infiltrating carcinomas, locally advanced carcinomas and metastasized carcinomas. A more comprehensive overview of the TNM stages and carcinoma classifications can be found in table 11 in appendix 2. The flowchart is based on patients who have an operable infiltrating- or a locally advanced mamma carcinoma. Stages

that are included in these two types of carcinomas are stage I till stage IIIC. The locally advanced mamma carcinoma includes all patients who do have a TNM classification with a T3, T4 and/or ≥N2 value which is the group of patients that usually gets an MRI after the sentinel lymph node procedure. Stages that include these values for T and N are stage IIB till stage IIIC. However, stage IIB is usually divided in two parts which are split up over the operable infiltrating- and the locally advanced mamma carcinoma. The first part of stage IIB, which has a TNM classification of T2-N1 is usually classified as an operable infiltrating mamma carcinoma. The second part of stage IIB, which has a TNM classification of T3-N0, is usually classified as a locally advanced mamma carcinoma. Because available literature only presents outcome measures according to full stages (stage I, IIA, IIB etc.), it has been assumed in this model that whole stage IIB, including the first group, is classified as a locally advanced mamma carcinoma.

In the flowchart in figure 1 several points were identified in which it is possible to implement the CTC Trap. These points are:

1. Following negative sentinel lymph node procedure to test for (micro-) metastases
2. Following negative result of an initial MRI to test for (micro-) metastases
3. Following negative results of further imaging to test for (micro-) metastases

These three possible points of implementing the CTC Trap lead to 8 different combinations of implementation options. These options are:

Reference (Do not implement the CTC Trap)

1. Implement the CTC Trap in point 1
2. Implement the CTC Trap in point 2
3. Implement the CTC Trap in point 3
4. Implement the CTC Trap in point 1 and 2
5. Implement the CTC Trap in point 1 and 3
6. Implement the CTC Trap in point 2 and 3
7. Implement the CTC Trap in all 3 possible points

The flowchart has been used to develop the decision tree, which is presented in figure 2. An enlarged version of the decision tree can be found in appendix 3. The decision tree is a more

comprehensive version of the flowchart because the endpoints have been extended. In these endpoints probabilities for adjuvant treatment were added because survival depends on which, and if treatment is given (20).

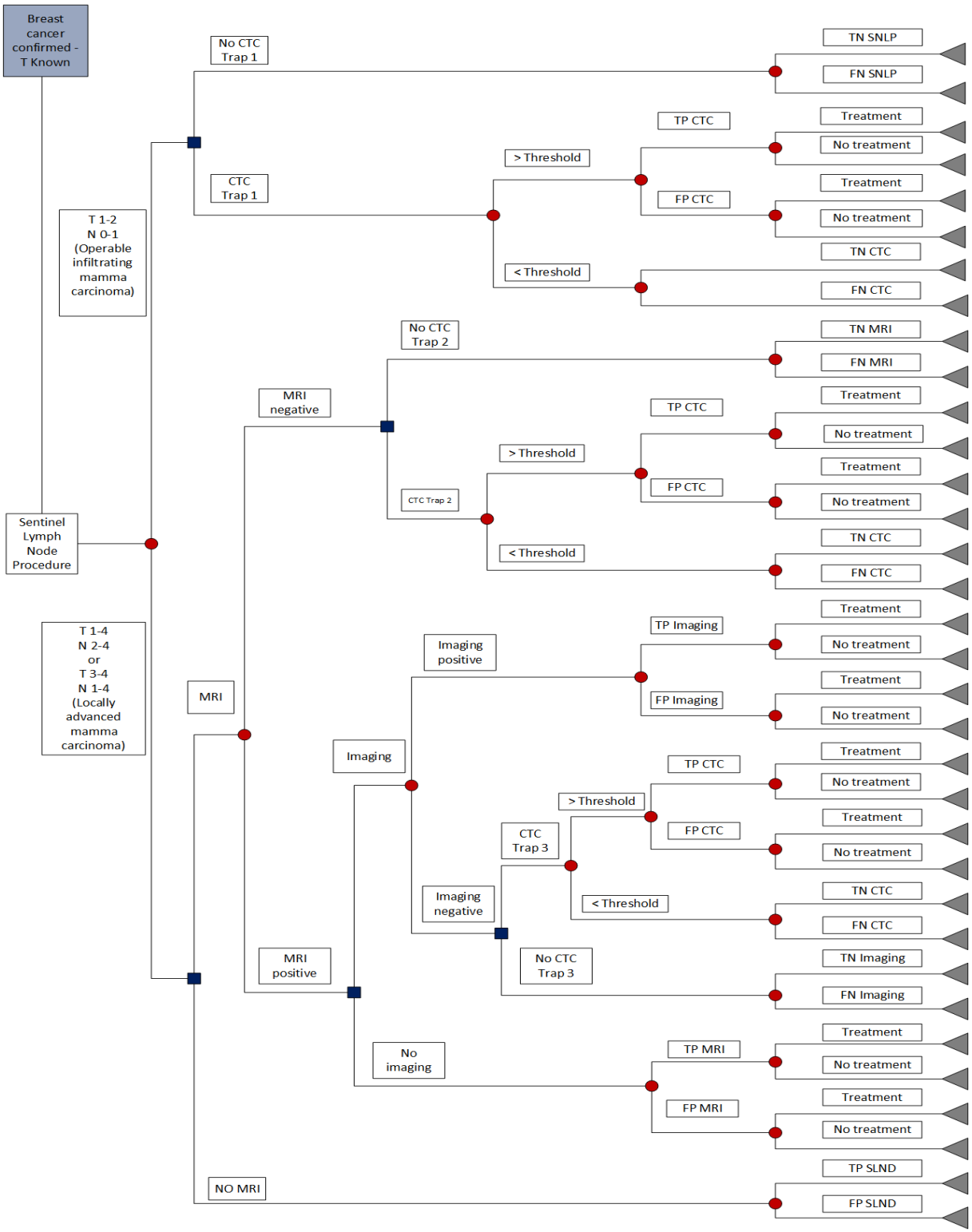


Figure 2: Decision tree of the early staging process including CTC Trap implementation options

3.2 Base-case parameter values

For the base-case analysis the values for all parameters were gathered from literature or IKNL data. The first probabilities that should be known are the probabilities that patients have a locally advanced or operable infiltrating mamma carcinoma. In table 1 the probabilities that patients will have a locally advanced- or an operable infiltrating mamma carcinoma and the probabilities that these patients do or do not get adjuvant treatment are shown. These percentages are based on data that was received from IKNL. Weights have been used to calculate summary percentages for receiving adjuvant treatment or not for each type of carcinoma. An overview of further calculations on IKNL data and the use of weights can be found in appendix 4. Base-case analysis is for all information that could be extracted from the IKNL data based on this data. However, previous studies showed different percentages of patients which are classified as stage I-IIA (operable infiltrating mamma carcinoma) (20). Therefore the percentage of patients having an operable infiltrating mamma carcinoma will be varied in sensitivity analysis.

Table 1: Weighted percentages of patients receiving adjuvant treatment for all carcinomas in stage I-III

Type carcinoma	# patients	Adjuvant treatment	No adjuvant treatment
Operable infiltrating mamma carcinoma	16702 (90,01 %)	60,90 %	39,10 %
Locally advanced mamma carcinoma	1853 (9,99 %)	97,99 %	2,01 %

Probabilities that patients do get an MRI or additional conventional imaging do not exist in literature. According to breast cancer experts all patients with a locally advanced mamma carcinoma should get an MRI so this probability has been estimated to be 1. If the MRI shows a positive test result additional imaging is recommended to locate possible metastases and get insight in the size of these. It is therefore assumed that the probability for further imaging is 1 if an the MRI shows positive test results. Values of test characteristics for the MRI and conventional imaging are known and are presented in table 2. For the CTC Trap these values are unknown so these were estimated based on the best available literature. Previous research has shown that the CTC Trap should have a sensitivity and specificity which is at least as high as these of conventional imaging (9). For base-case analysis it was therefore assumed that these parameter values are equal to those of conventional imaging. To be able to

calculate the probabilities for positive or negative test results, the sensitivity, specificity and incidence rates for micro metastases in the different stage groups were used. For the operable infiltrating mamma carcinoma the incidence rate for metastases is 3 %, for locally advanced mamma carcinomas the incidence rate is 30 % (21).

Table 2: Base case values for all procedures

Procedure	Sensitivity	Specificity
Sentinel lymph node procedure	93,0 % (7)	78,6 % (22)
MRI	93 % (7)	86 % (7)
Conventional imaging	79 % (23)	83 % (23)
CTC Trap	79 % (9)	83 % (9)

3.3 Outcome measures and model assumptions

Outcome measures that were used in the model are the 3-year survival percentage, survival in years, QALYs and costs. Regarding the 3-year survival outcome different assumptions have been made. The following assumptions hold for the outcomes for usual care in which MRI and conventional imaging are used:

- If the test results are positive it is assumed that macro metastases are detected because these test are not able to detect micro metastases. Outcomes for these patients are assumed to have the value of the outcomes for patients with a metastasized mamma carcinoma (stage IV).
- If the test results are negative it is assumed that macro metastases were not detected. Outcomes for these patients are assumed to be the average outcomes which were extracted from IKNL data for patients with a locally advanced mamma carcinoma (stage IIB-IIIC) because only these patients receive these both tests.

The survival in years and QALYs were calculated for each endpoint in the decision tree using IKNL data. Out of the IKNL data only survival from stage 0-III could be extracted. The survival for stage IV therefore had to be estimated. In this model the survival for stage IV is assumed to be half of the survival of the operable infiltrating carcinoma. This assumption is based on the 3-year survival which can be found in table 3 and is less than half of the 3-year survival of the locally advanced carcinoma. Weights that were used in the calculations for adjuvant treatment that have been used in table 1 were also used for this calculation.

Table 3: weighted years of survival for carcinomas in stage I-III

		Survival in years			
		No micrometastasis		**Micrometastasis**	
	Utility	No adjuvant therapy	Adjuvant therapy	No adjuvant therapy	Adjuvant therapy
Operable infiltrating mamma carcinoma (**I-IIA**)	0,65	2,97	3,08	1,91	2,01
Locally advanced mamma carcinoma **(IIB-IIIC)**	0,59	1,88	2,42	1,20	1,75
Metastasized mamma carcinoma (**IV**)	0,42	0,9	1,4	0,58	1,08

IKNL data shows survival results for all patients in each stage group. In this data no difference between patients with micro metastases exists. Outcomes for micro metastases therefore were estimated and are also presented in table 3. These were based on previous research in which was shown that survival outcomes for patients with micro metastases are worse than for patients without (hazard ratio of 1,56 (95% CI 1,20-1,90)) (24). For these outcomes it is assumed that survival for patients with micro metastases increases at least as much as survival increases when treatment is given in the group without micro metastases. Further calculations of survival can be found in appendix 4. The survival in years has been combined with the utilities for the different stage groups to calculate QALYs for each type of carcinoma (17).

Costs for all currently used procedures were derived from literature and are presented in table table 4 (25). As these costs are not known for the CTC Trap these were assumed to be approximately the same as costs for leukapheresis because this technique seems to be comparable with the CTC Trap. These costs were found to be $ 2.990,- (26). Recalculation of this amount with the historical exchange rate gave that this amount is equal to € 3.030,96 (historical exchange rate January 2000: 1,0137 (27)). Besides these costs, costs for conventional imaging were also estimated. Usually a chest X-ray or CT, skeletal scintigraphy and ultrasound of the liver are recommended for patients with a locally advanced mamma carcinoma (7). If these imaging techniques are all used cost are calculated to be € 836,18. Because it is unknown which (combination of) tests exactly are performed, costs of conventional imaging will be varied in sensitivity analysis between a lower level and an upper

level of which the exact values are presented in table 4 (25). More comprehensive calculations on the estimation of the costs of conventional imaging and the ranges which are used in sensitivity analysis are presented in appendix 5.

Table 4: Costs of different procedures and treatment

Procedure	Base-case	Lower Level	Upper Level
Sentinel lymph node procedure	€ 371,94 (25)	-	-
MRI	€ 283,87 (25)	-	-
Conventional imaging	€ 836,18 (25)	€ 200,-	€ 2.100,-
CTC Trap	€ 2.990,- (26)	€ 800,-	€ 3.700,-
Treatment for stage 0	€ 189,68 (28)	-	-
Treatment for stage I-IIA	€ 18.278,79 (28)	-	-
Treatment for stage IIB-IIIC	€ 28.686,54 (28)	-	-

*** Procedures with no values given for lower or upper level are not taken in sensitivity analysis**

3.4 Parameter values for sensitivity analysis

In the analysis the base-case has been set at all above mentioned most relevant values for each parameter. This base-case was compared to the worst outcomes and the best outcomes for CTC Trap. Table 5 shows all uncertain parameters and their ranges which were used in sensitivity analysis. It should be noted that these values are based on assumptions and not on existing distributions.

Parameter	Base-case value	Lower-level value	Upper-level value
Sensitivity	79	50	100
Specificity	83	50	100
Cost CTC Trap	€ 3.030,96	€ 800,-	€ 3.700,-
Cost conventional imaging	€ 836,18	€ 200,-	€ 2.100,-
Probability conventional imaging	1	0,75	1
Probability MRI	1	0,75	1
Survival outcome in years stage IV	0,9	0,4	1,4
% Patients with a locally advanced mamma carcinoma	90,0 %	50,0 %	100,0%

4. Results

4.1 Model results

Potentially relevant points for the CTC trap were: 1) following negative sentinel lymph node procedure to test for micro metastases, 2) following negative result of initial MRI to test for (micro-) metastases, 3) following negative results of further imaging. Usual care resulted in average survival of 2,420 years, 93,71 % 3-year survival, 1,513 QALYs, a cost of € 992,56 and a cost per QALY of € 656,-. Base-case results for implementing the CTC Trap at different points are presented in table 5. The highest survival is derived when the CTC Trap is implemented in all points simultaneously with an average survival of 2,839 years, 97,46 % 3-year survival, 1,836 QALYs and a total cost of € 6.035,45. However, this survival is approximately the same as the possible increase in survival when the CTC Trap is only implemented at option 1 (2,836 in option 1 vs. 2,839 in option 7) while costs are increasing relatively much (€ 4.920,97 in option 1 vs. € 6.035,45 in option 7).

Table 5: Results of base case CTC Trap implementation

	CTCs on/off	Survival in years	3-year survival	QALYs	Cost	Cost/QALY
Reference	All off	2,420	93,71 %	1,513	€ 992,56	€ 656,-
Option 1	CTC 1 on	2,836	97,35 %	1,833	€ 4.920,97	€ 2.684,16
Option 2	CTC 2 on	2,421	93,74 %	1,514	€ 1.794,51	€ 1.185,29
Option 3	CTC 3 on	2,422	93,80 %	1,515	€ 1.305,09	€ 861,70
Option 4	CTC 1 and 2 on	2,837	97,38 %	1,834	€ 5.722,92	€ 3.119,98
Option 5	CTC 1 and 3 on	2,838	97,43 %	1,835	€ 5.233,49	€ 2.852,30
Option 6	CTC 2 and 3 on	2,423	93,83 %	1,515	€ 2.107,04	€ 1.390,34
Option 7	All CTCs on	2,839	97,46 %	1,836	€ 6.035,45	€3.287,68

Additional survival and QALYs gained from implementing the CTC Trap in option 2 and 3 are low as can be found in table 5. Costs at these options, however, do increase relatively much compared to the relatively small amount of QALYs gained. By implementing the CTC Trap at all points simultaneously (option 7) costs are high compared to option 2 and option 3.

4.1 Deterministic sensitivity analysis

In the results section was presented that survival and QALY outcomes are the highest when the CTC Trap is implemented in all points (option 7). Because of the high uncertainty around some of the parameters deterministic sensitivity analysis was performed. Table 6 shows the results of this analysis. In this initial analysis results are presented based on implementing the CTC Trap in all implementation points.

Table 6: Results of primary deterministic sensitivity analysis

Parameter	Input levels			Lower Level outcomes		Upper level outcomes	
	Current	LL	UL	QALY	Cost	QALY	Cost
Sensitivity	79	50	100	1,83	€ 5.771,84	1,84	€ 6.226,34
Specificity	83	50	100	1,85	€ 8.625,95	1,83	€ 4.700,95
Cost CTC Trap	€ 3.030,96	€ 800,-	€ 3.700,-	1,84	€ 3.834,43	1,84	€ 6.695,51
Cost conventional imaging	€ 836,18	€ 200,-	€ 2.100,-	1,84	€ 6.011,47	1,84	€ 6.083,10
Probability imaging	1,00	0,75	1	1,83	€ 6.117,23	1,84	€ 6.035,45
Probability MRI	1,00	0,75	1	1,84	€ 5.649,10	1,84	€ 6.035,45
QALY stage IV	0,90	0,4	1,4	1,83	€ 6.035,45	1,84	€ 6.035,45
% patients	0,90	0,5	1	1,49	€ 10.471,19	1,92	€ 4.926,52

One of the remarkable things for these results is that specificity has a negative effect on QALYs gained at the upper-level value (100), while it at this value has a positive effect on costs. This is due to some of the assumptions on survival outcomes in the model. As can be seen in the table 3, the outcomes for patients who do receive treatment are better than for patients who do not for both stage groups (I-IIA and IIB-IIIC). When specificity is high, then the number of negative patients who are in this model assumed to have no treatment, increase. In each of the stage groups (I-IIA and IIB-IIIC) and in both categories (with or without micro metastases) the outcomes for patients who do not get treatment are worse than if they do get treatment. This assumptions in the model cause that the survival and QALY outcomes for CTC Trap decrease when specificity is high. Costs are however less for patients with a negative outcome because in the model it is assumed that patients with a negative test result do not receive adjuvant treatment which is very expensive.

Based on the results of this initial sensitivity analysis a tornado diagram has been created which is presented in figure 2. This diagram shows that the percentage of patients in stage I-IIA and the specificity of the CTC Trap have relatively high influence on the QALYs. Cost of the CTC Trap and of conventional imaging have no influence on QALYs so these were not presented in this figure.

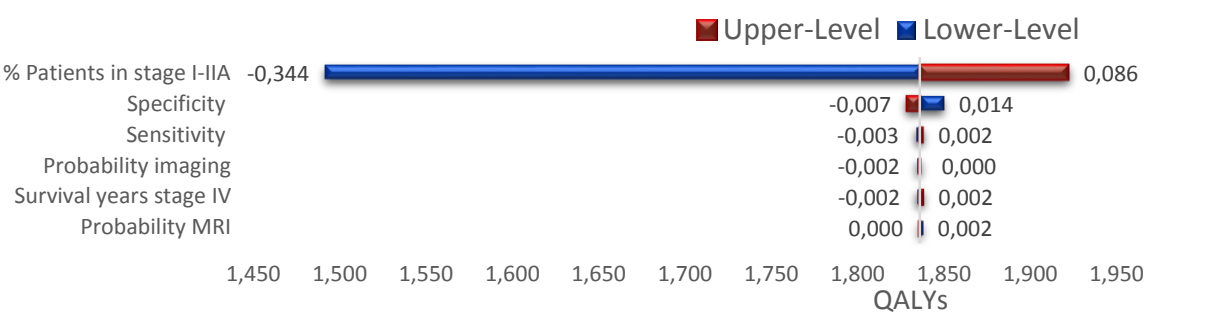


Figure 3: Tornado diagram of all uncertain parameters and their influence on QALYs

The percentage of patients in stage I-IIA (operable infiltrating mamma carcinoma) has most influence on the total QALY result when CTC Trap is implemented at all possible options. Therefore a second analysis has been made which shows the results for different CTC Trap implementation options at different percentages of patients in stage I-IIA.

Table 7: Additional QALYs at different percentages of patients in stage I-IIA

	Additional QALYs compared to reference			
% Patients in stage I-IIA	**Option 1**	**Option 2**	**Option 3**	**Option 7**
0 %	0,00	0,01	0,01	0,02
10 %	0,00	0,01	0,01	0,02
20 %	0,00	0,01	0,01	0,02
30 %	0,00	0,01	0,01	0,02
40 %	0,01	0,01	0,01	0,03
50 %	0,03	0,00	0,01	0,04
60 %	0,05	0,00	0,01	0,06
70 %	0,09	0,00	0,00	0,10
80 %	0,16	0,00	0,00	0,17
90 %	0,32	0,00	0,00	0,32
100 %	0,82	0,00	0,00	0,82

A part of the results are presented in table 8. Like the base-case results this analysis has shown that CTC Trap has almost no influence on the QALYs if implemented in option 2 or 3. The full table is presented in appendix 6.

4.2 Scenario analysis

The base-case results present the most realistic scenario. Based on the results of the deterministic sensitivity analysis it was determined which values the parameters should have for a pessimistic and optimistic scenario. Table 8 gives an overview of parameter values which have been used for this analysis.

Table 8: Values for different parameters different scenarios for cost/QALY

		Costs per QALY	
Parameter	**Base case value**	**Pessimistic value**	**Optimistic value**
Sensitivity	79	100	50
Specificity	83	50	100
Cost CTC Trap	€ 3.030,96	€ 3.700,-	€ 800,-
Cost conventional imaging	€ 836,18	€ 2.100,-	€ 200,-
Probability conventional imaging	1,00	0,75	1
Probability MRI	1,00	1	0,75
Survival years stage IV	0,90	0,4	1,4
% Patients in stage I-IIA (operable infiltrating mamma carcinoma)	0,90	0,5	1

In table 9 the results of the scenario analysis are presented. In the most optimal scenario a QALY gain of 0,41 can be realized at an additional cost per QALY of € 109,55. In none of these scenarios a decrease in costs is realizable.

Table 9: Results of scenario analysis

	QALYs	**Costs**	**Costs per QALY**
Usual care result	1,51	€ 992,56	€ 656,-
Base case result	1,84	€ 6.035,45	€ 3.287,68
Pessimistic result	1,51	€ 16.088,62	€ 10.668,66
Optimistic result	1,92	€ 1.467,71	€ 765,55

4.3 Probabilistic sensitivity analysis

Because multiple parameters are still very uncertain, it was decided to make an estimation of the variation of costs and QALYs by doing a probabilistic sensitivity analysis. Because of the uncertainty in the parameters no distribution does exist in literature. The limits of the values of each parameter are therefore chosen based on the assumptions that have been made in this model. Limits that were presented in table 6 have been used as boundaries for this analysis. Results are summarized in the cost/effectiveness plane which is shown figure 5. A part of the full results are shown in appendix 7. This plot is based on 10.000 repetitions of calculating the cost-effectiveness with different values for all uncertain parameters.

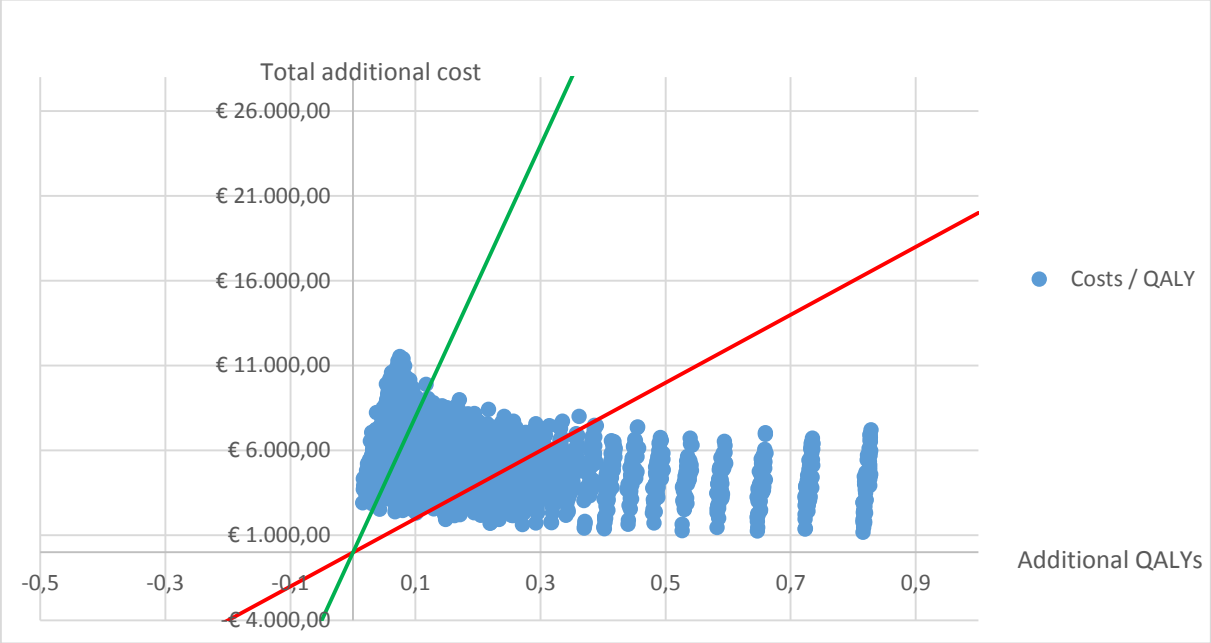


Figure 4: Cost-effectiveness plane of additional cost per QALY gained for implementation option 7

Both lines in the figure represent borders for willingness to pay. When € 20.000,- per QALY (red line) is considered as the upper limit for the willingness to pay it is still very uncertain if the CTC Trap meets this requirement. When € 80.000,- per QALY (green line) is considered as the upper limit for the willingness to pay the probability that the CTC Trap meets this requirement increases. Because of the uncertainty around the parameters and the assumptions around the limits of the values for these parameters which have been made for this analysis, no further valid conclusions can be drawn from this figure.

5. Discussion

This model has been built based on the assumption that the CTC Trap will be additionally implemented because it was assumed that it is not relevant that the CTC Trap in this phase of development can or will replace the existing imaging techniques. If it appears that the CTC Trap is that good at predicting whether there are metastases, the impact on survival can potentially be higher as it shows to be in this model.

The locally advanced mamma carcinoma is assumed to consist of stages IIB till IIIC. Usually this mamma carcinoma only includes a part of stage IIB. The lower part of stage IIB is usually classified as an operable infiltrating mamma carcinoma. It has been chosen to add this part of the stage to a locally advanced mamma carcinoma because outcome measures are reported for complete stages and could otherwise not have been used. It therefore was assumed that the complete stage IIB is classified as a locally advanced mamma carcinoma. It is possible that results were significantly different if the lower IIB part was classified as an operable infiltrating mamma carcinoma.

For simplicity reasons the flowchart has been simplified in two parts. It is only focusing on patients who have had a sentinel lymph node procedure (which is 95%). For this evaluation the other part (which directly gets MRI) has been let out of this diagram. Results could have been different if the last 5% of patients would also have been considered in this analysis.

In the model is assumed that there are only 3 points in which the CTC Trap can be implemented. The model is based on the decision tree which is developed based on the flowchart of the early staging process. In the flowchart has been let out that after metastasis are detected by as well MRI as other conventional imaging techniques, this diagnosis still has to be histologically confirmed. A possible fourth option could have been to use the CTC Trap to check whether histological confirmation has to be done. In this case we assumed that when metastasis are found by as well MRI as other conventional imaging techniques that it is not valuable to do another test because this one is assumed to be probably unnecessary.

In this model the rates for micro metastases in the different stages have been used to calculate the number of positive and negative tests of the CTC Trap. No threshold for CTC amount was taken into account. Preliminary research for CTC Trap showed that the threshold for CTCs is 9

CTCs in the whole blood (9). Incidence rates for micro metastases might be different if it will become possible to trace micro metastases with the CTC Trap. When these incidence rates change then the percentages of patients with positive or negative test results do also change by which results might be significantly different as those presented.

The model shows that costs are probably high if the CTC Trap will be additionally implemented. This is due to the fact that in this model it is assumed that adjuvant treatment, which is very expensive, is given to every patient with a positive test result. These treatment costs would also exist if another device shows that patients might benefit from treatment. Results might therefore be a bit biased, these costs do also exist in usual care but they appear in a later stadium.

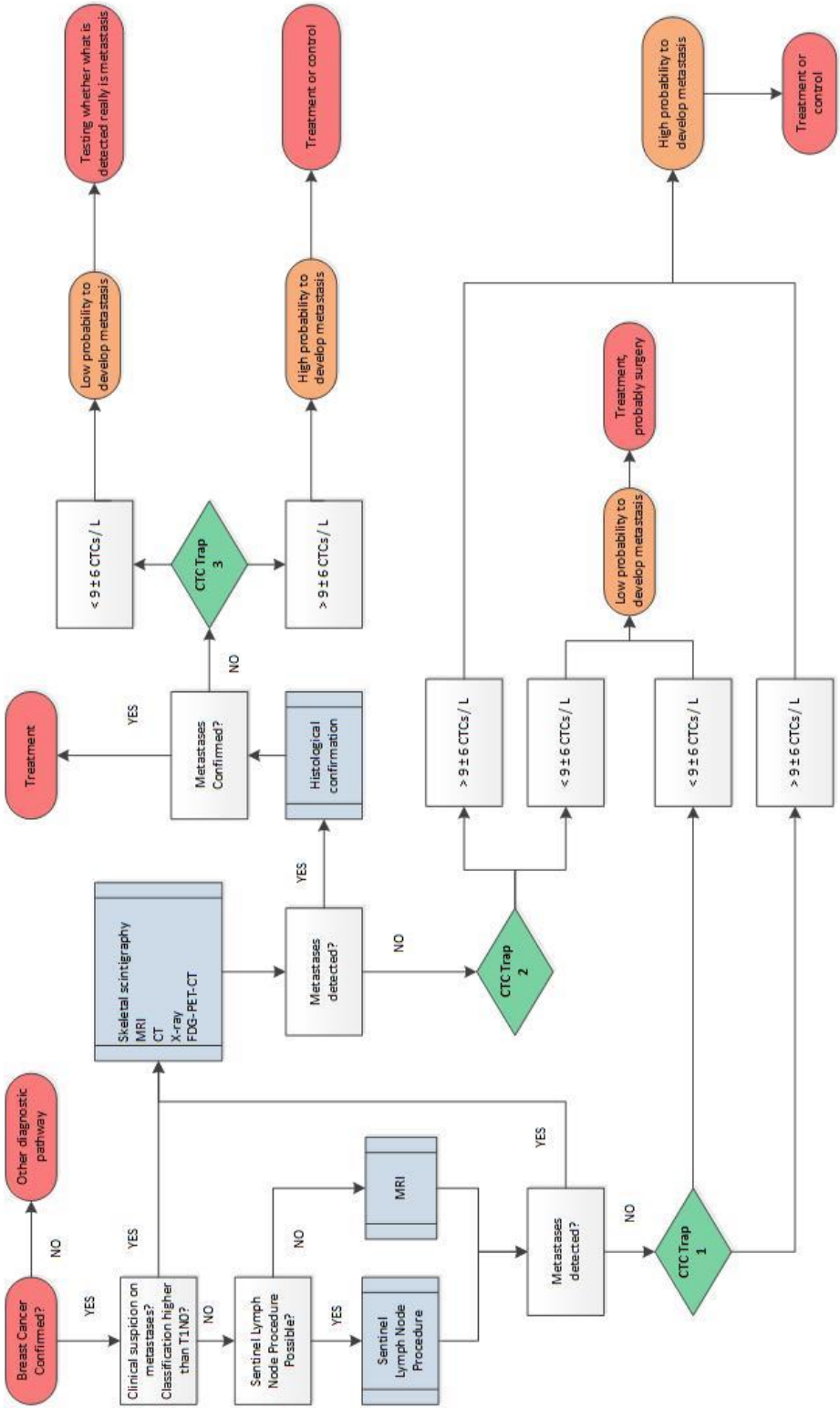
Future research should focus on the probability of the CTC Trap being implemented as a possible replacement of one of the currently used imaging tests. In this research should become clear if the CTC Trap might probably be useful as a companion diagnostic to improve the quality of treatment decisions. At last it is important to gather data on the amount of CTCs presented in the blood. Based on this data new estimations can be made on the amount of patients who probably would have a positive CTC Trap test result.

6. Conclusion

CTCs clearly have the potential to improve the overall survival of breast cancer. Use of CTCs can potentially improve the survival in years with 0,42 years, 3-year survival with 3,75% and QALYs with 0,33 if the CTC trap is implemented at all 3 identified implementation points. Costs however increase with € 5.042,89 which is relatively high compared to the costs of usual care at the moment. From a health economic perspective it would be most valuable to implement the CTC Trap only at implementation option 1) following negative result of sentinel lymph node procedure to check for micro metastases, with a cost per QALY of € 2.684,16. Results show that the QALY gain remains limited. This is due to the fact that QALY measures are a combination of survival and utilities. Survival which was derived from IKNL data in both of the analysed groups (stage I-IIA and stage IIB-IIIC) is relatively low. The probability that the CTC Trap can be cost-effective seems to increase if the threshold for costs per QALY increases from € 20.000,- to € 80.000,- per QALY.

Appendices

Appendix 1: Flowchart of the early staging process



* SLNP is done in 95% of all patients

** After second detection of metastasis histological confirmation has to be done

Appendix 2: TNM Classification

Table 10: TNM Classification and utilities

Stage	T	N	M	Description	Utility (all ages)
0	Tis	N0	M0	DCIS or LCIS	0,70
IA	T1*	N0	M0	Operable infiltrating mamma carcinoma	0,68
IB	T0-1*	N1mi	M0		0,68
IIA	T0-1*	N1	M0		0,61
	T2	N0	M0		0,61
IIB	T2	N1	M0	Locally Advanced Mamma Carcinoma	0,61
	T3	N0	M0		0,61
IIIA	T0-2*	N2	M0		0,56
	T3	N1-2	M0		0,56
IIIB	T4	N0-2	M0		0,56
IIIC	Any T	N3	M0		0,56
IV	Any T	Any N	M1	Metastasized mamma carcinoma	0,42

Usually T2N1M0 in stage IIB is an operable infiltrating mamma carcinoma. In this model it has been assumed that whole stage IIB can be classified as a locally advanced mamma carcinoma.

For the utilities per carcinoma weights from IKNL data were used to weigh utilities according to the percentage of patients that is in each group.

The survival from IKNL in years has been multiplied with the average utility per carcinoma to gather the QALYs in each group, with or without micro metastasis and with or without adjuvant treatment

Appendix 3: Decision tree

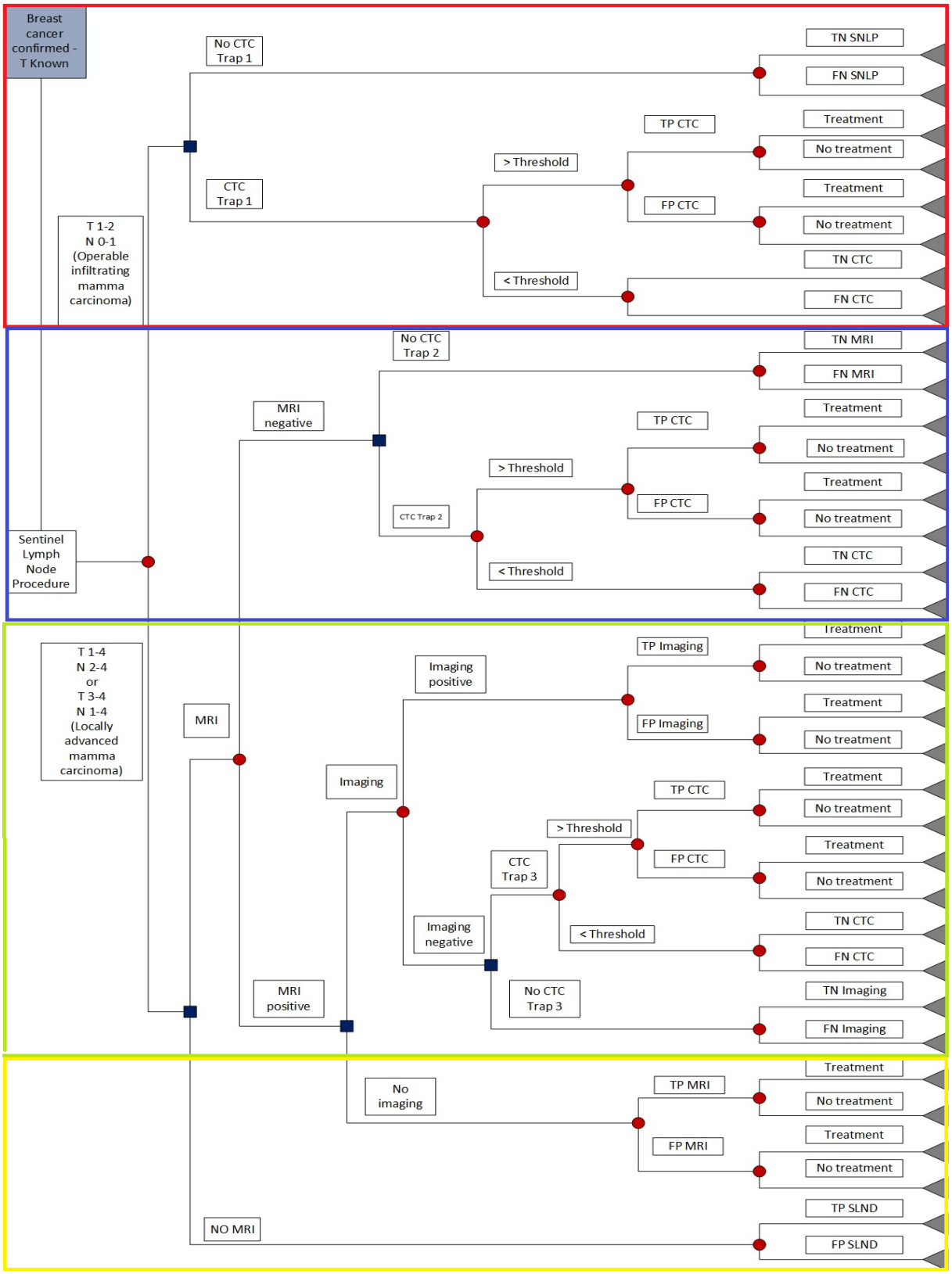


Figure 5: Decision tree of the early staging process

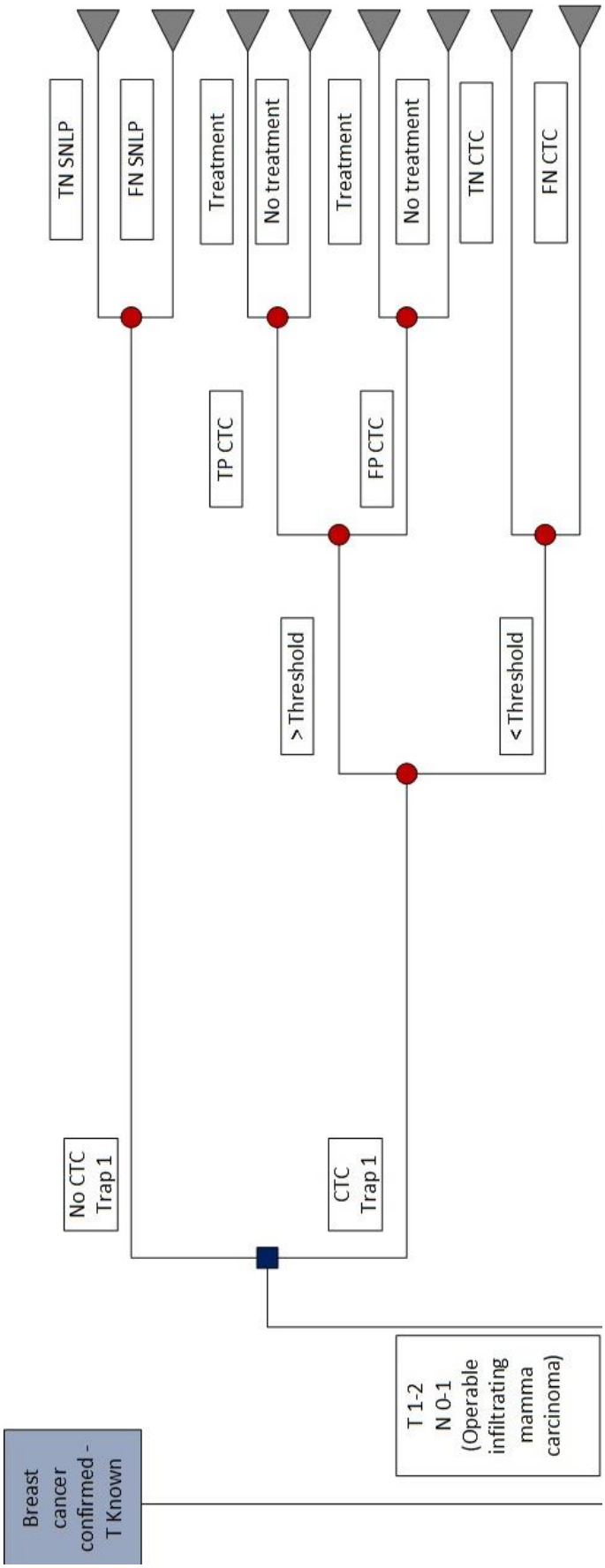


Figure 6: Enlargment 1 of the decision tree (red part)

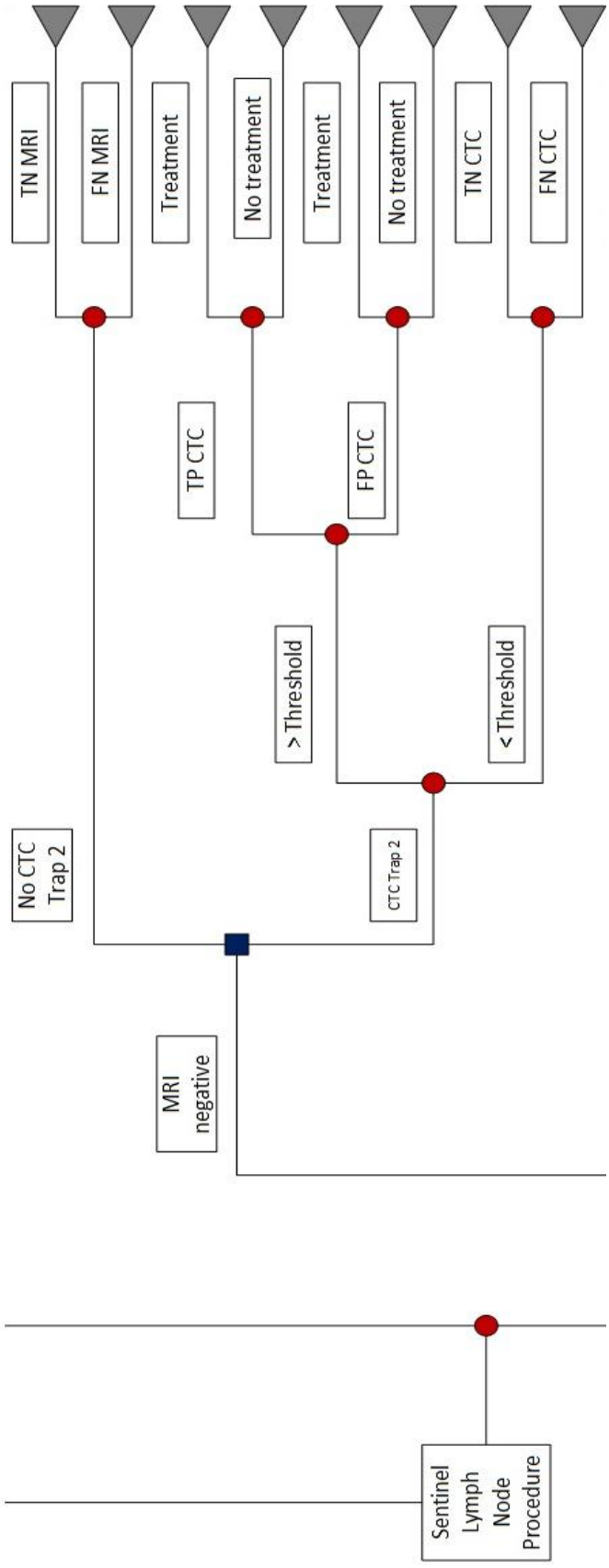


Figure 7: Enlargement 2 of the decision tree (green part)

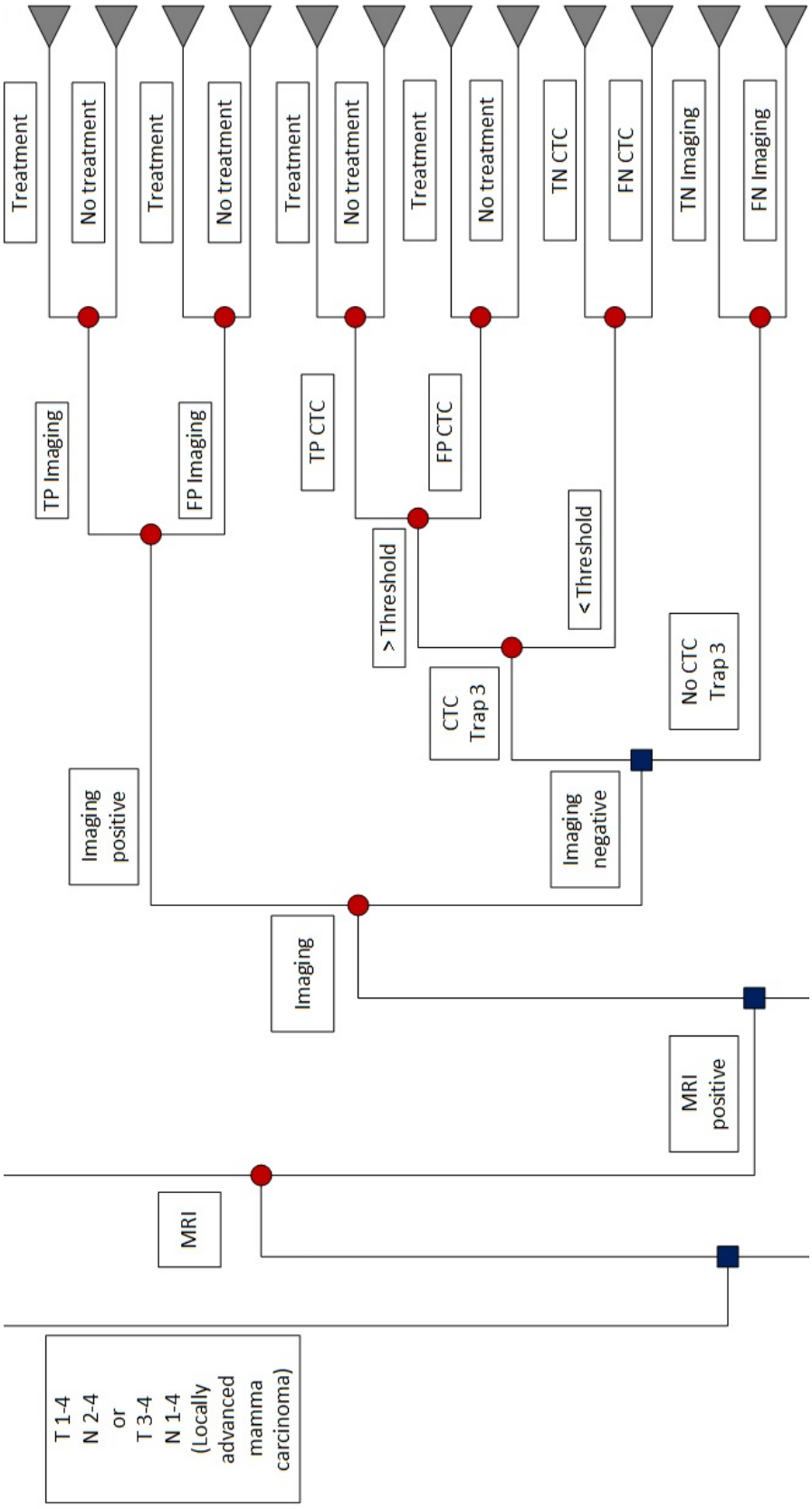


Figure 8: Enlargement 3 of the decision tree (blue part)

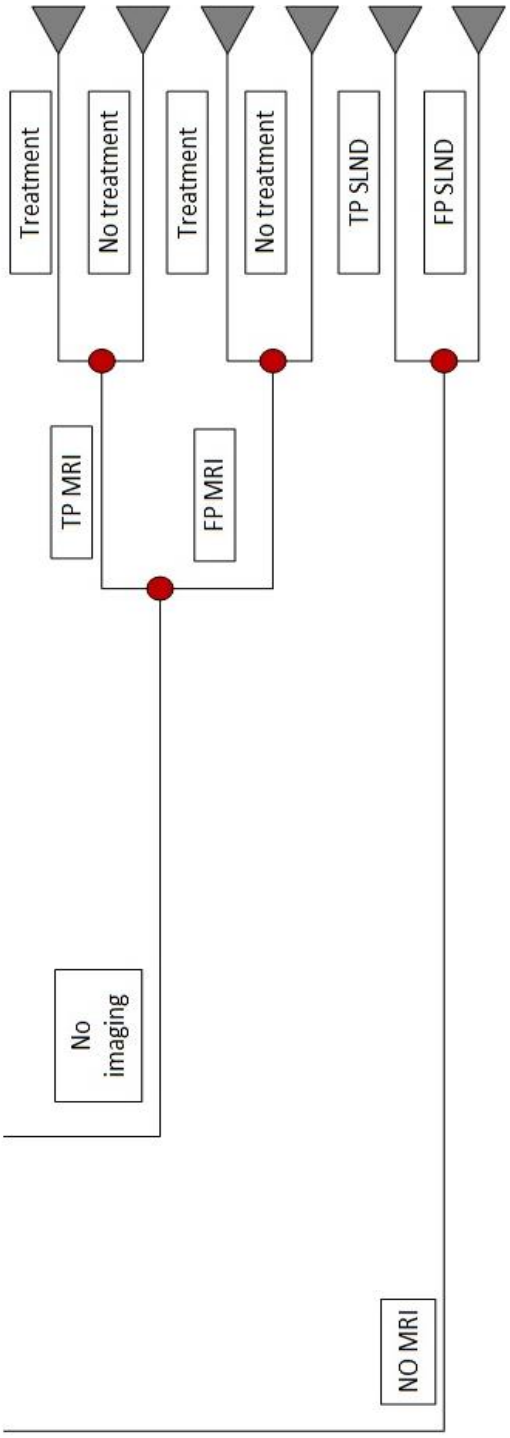


Figure 9: Enlargement 4 of the decision tree (yellow part)

Appendix 4: Survival calculations

Table 11: Example calculation of weights for stage O

PTNM Stage	Weight no adjuvant therapy	Weight adjuvant therapy	Calculation no adjuvant	Calculation adjuvant
O	0,211	0,203	5008/23769	1327/6536
OI	0,018	0,027	431/23769	176/6536
OIS	0,024	0,033	571/23769	217/6536
OS	0,747	0,737	17759/23769	4816/6536

Table 12: Treatment data IKNL including weighted averages per carcinoma

PTNM Stage	No adjuvant treatment	Adjuvant treatment	Total	Sort carcinoma	Weighted averages
O	5008	1327	6335	DCIS OR LCIS (Total n=30305 adjuvant n = 23769 no adjuvant n= 6536)	Adjuvant treatment 21,57% No adjuvant treatment 78,43%
OI	431	176	607		
OIS	571	217	788		
OS	17759	4816	22575		
1				Operable infiltrating mamma carcinoma (Total n= 16702)	Adjuvant treatment 60,90% No adjuvant treatment 39,10%
1A	3656	5967	9623		
1AS	190	183	373		
1B	33	52	85		
1BS	14	18	32		
1C	52	91	143		
1M	1366	1127	2493		
1MS	372	133	505		
2					
2A	847	2601	3448		
2B	7	18	25	Locally advanced mamma carcinoma (n=1853)	Adjuvant treatment 74,96%% No adjuvant treatment 25,04%
3					
3A	440	1283	1723		
3B	11	51	62		
3C	6	37	43		
Total	30763 62,96%	18097 37,04%	48860 100%		

Table 13: Survival data IKNL including weighted survival per carcinoma

	Survivaltime in years			**Survivaltime in years**	
pTNM stage	No adjuvant therapy	Adjuvant therapy	Sort Carcinoma	No adjuvant therapy	Adjuvant therapy
O	4,0796	3,754	DCIS or LCIS	3,90	3,32
OI	4,251	2,907			
OIS	3,353	3,4596			
OS	3,861	3,203			
1	7,932	0	Operable infiltrating mamma carcinoma	2,97	3,08
1A	2,692	3,017			
1AS	4,253	5,505			
1B	4,71	3,698			
1BS	5,2799	3,002			
1C	3,375	5,5195			
1M	4,258	3,249			
1MS	4,153	2,533			
2	0				
2A	1,183	2,904			
2B	0	7,507	Locally advanced mamma carcinoma	1,88	2,42
3	0				
3A	1,939	2,265			
3B	1,728	3,793			
3C	0	3,444			
$\mathbf{4}^{*\mathbf{2}}$	0,9	1,4	Metastasized mamma carcinoma	0,9	1,4

*** 1: Assumed is that the higher stages have a higher increase in survival if they get adjuvant therapy. Because it is unknown what increase this is for stage 4 (because they are never withhold from treatment) it is estimated that the increase is about the same as the average increase for the locally advanced mamma carcinoma.**

Table 14: Percentages of 3-year survival derived from IKNL website

	3-year survival
Operable infiltrating mamma carcinoma(**I-IIA**)	98,69%
Locally advanced mamma carcinoma **(IIB-IIIC)**	89,19%
Metastasized mamma carcinoma (**IV**)	42,0%

Appendix 5: Cost information

Costs which were derived from the Dutch health authority are presented in table 15.

Table 15: Costs of different tests and operation (25)

Ingreep	**Kosten**	**Diagnostiek borstkanker**
Operatieve verwijdering van grote benigne tumoren en cysten in kaak of weke delen (excl. Kaakcysten groter dan ¼ van het kaakvolume, zie 234012)	€ 189,68	
PET (whole body)	€ 1176,53	
Diagnostische puncties van niet palpabele afwijkingen of organen, onder CT controle	€ 200,11	
Diagnostische puncties van niet palpabele afwijkingen onder röntgencontrole	€ 113,94	x
Inbrengen röntgencontrastvloeistof	€ 97,08	x
CT onderzoek van het abdomen, retroperitoneum, inclusief inbegrepen orale en/of rectale contraststof, met of onder toediening van een intraveneus contrastmiddel	€ 234,57	x
Echografie van de buikorganen	€ 105,23	x
Schildklierscintigrafie	€ 213,33	
Volledig botdensitometrisch onderzoek met dexa apparatuur, ongeacht het aantal onderzochte anatomische gebieden en ongeacht het aantal zittingen	€ 109,09	
Statisch skeletonderzoek	€ 285,36	X
		Total: € 836,18

Usually a chest X-ray or CT, skeletal scintigraphy and ultrasound of the liver are indicated for patients with T3-4 N>2 breast cancer. If these imaging techniques are all combined then the total cost are € 836,18. If only a chest X-ray is made instead of a chest X-ray and a CT, costs are € 601,61. If besides the conventional imaging techniques a PET scan is made, then the total costs are € 2.012,71

The cost of conventional imaging will be varied from a lower level of € 200,- till an upper level of € 2.100,-. The range of values over which the CTC trap will be tested will be from a lower level of € 800,- until an upper level of € 3.700,-. This upper level has been chosen to be at € 3.700,-. A more detailed schedule of all costs which were derived can be found in appendix 5.The numerical results of the sensitivity analysis are presented in table 5.

If only a chest X-ray is made instead of a chest X-ray and a CT in combination with the skeletal scintigraphy and the ultrasound, costs are € 601,61. If only a CT scan is done then costs are € 234,57. If besides the conventional imaging techniques a PET scan is made, then the total costs are € 2.012,71. Because it is unknown which combination of techniques is currently used, a range of costs will be implemented in sensitivity analysis based on this cost estimation

Literature research showed that the costs for breast cancer treatment according to TNM stage are as presented in table 15. If adjuvant treatment is not given the operation only consists of an operation to remove the tumor (20).

Table 16: Costs of breast cancer treatment according to stage

Stage	**Cost** (28)
I	€ 17.273,-
II	€ 22.145,-
III	€ 28.776,-
Annual cost stage IV	€ 17.879,-

For these treatment costs weights were used which are based on the percentages of patients in each stage for each carcinoma. These percentages and weights have been extracted from IKNL data. These weights are presented in table 16.

Table 17; weighted treatment cost

		Weighted treatment cost
% IIA in stage I-IIA	0,206442342	0,21*€17.273,- + 0,79*€22.145,- = €18.278,79
% I in stage I-IIA	0,793557658	
% IIB in stage IIB-IIIC	0,013491635	0,01*€22.145,- + 0,99*28.776,- = €28.686,54
% stage III in stage IIB - IIIC	0,986508365	

Appendix 6: Result single parameter sensitivity analysis

Table 18: Full results sensitivity analysis for different CTC implementation points at different percentages of patients in stage I-IIA

	Additional QALYs compared to reference			
Percentage stage I-IIA	Option 1	Option 2	Option 3	Option 7
0%	0,00	0,01	0,01	0,02
1%	0,00	0,01	0,01	0,02
2%	0,00	0,01	0,01	0,02
3%	0,00	0,01	0,01	0,02
4%	0,00	0,01	0,01	0,02
5%	0,00	0,01	0,01	0,02
6%	0,00	0,01	0,01	0,02
7%	0,00	0,01	0,01	0,02
8%	0,00	0,01	0,01	0,02
9%	0,00	0,01	0,01	0,02
10%	0,00	0,01	0,01	0,02
11%	0,00	0,01	0,01	0,02
12%	0,00	0,01	0,01	0,02
13%	0,00	0,01	0,01	0,02
14%	0,00	0,01	0,01	0,02
15%	0,00	0,01	0,01	0,02
16%	0,00	0,01	0,01	0,02
17%	0,00	0,01	0,01	0,02
18%	0,00	0,01	0,01	0,02
19%	0,00	0,01	0,01	0,02
20%	0,00	0,01	0,01	0,02
21%	0,00	0,01	0,01	0,02
22%	0,00	0,01	0,01	0,02
23%	0,00	0,01	0,01	0,02
24%	0,00	0,01	0,01	0,02
25%	0,00	0,01	0,01	0,02
26%	0,00	0,01	0,01	0,02
27%	0,00	0,01	0,01	0,02
28%	0,00	0,01	0,01	0,02
29%	0,00	0,01	0,01	0,02
30%	0,00	0,01	0,01	0,02
31%	0,01	0,01	0,01	0,02
32%	0,01	0,01	0,01	0,02
33%	0,01	0,01	0,01	0,02
34%	0,01	0,01	0,01	0,02
35%	0,01	0,01	0,01	0,02

36%	0,01	0,01	0,01	0,02
37%	0,01	0,01	0,01	0,02
38%	0,01	0,01	0,01	0,03
39%	0,01	0,01	0,01	0,03
40%	0,01	0,01	0,01	0,03
41%	0,01	0,01	0,01	0,03
42%	0,01	0,01	0,01	0,03
43%	0,02	0,01	0,01	0,03
44%	0,02	0,01	0,01	0,03
45%	0,02	0,01	0,01	0,03
46%	0,02	0,01	0,01	0,03
47%	0,02	0,01	0,01	0,03
48%	0,02	0,00	0,01	0,04
49%	0,02	0,00	0,01	0,04
50%	0,03	0,00	0,01	0,04
51%	0,03	0,00	0,01	0,04
52%	0,03	0,00	0,01	0,04
53%	0,03	0,00	0,01	0,04
54%	0,03	0,00	0,01	0,05
55%	0,04	0,00	0,01	0,05
56%	0,04	0,00	0,01	0,05
57%	0,04	0,00	0,01	0,05
58%	0,04	0,00	0,01	0,05
59%	0,05	0,00	0,01	0,06
60%	0,05	0,00	0,01	0,06
61%	0,05	0,00	0,01	0,06
62%	0,06	0,00	0,01	0,07
63%	0,06	0,00	0,01	0,07
64%	0,06	0,00	0,01	0,07
65%	0,07	0,00	0,01	0,08
66%	0,07	0,00	0,01	0,08
67%	0,08	0,00	0,00	0,08
68%	0,08	0,00	0,00	0,09
69%	0,08	0,00	0,00	0,09
70%	0,09	0,00	0,00	0,10
71%	0,09	0,00	0,00	0,10
72%	0,10	0,00	0,00	0,11
73%	0,11	0,00	0,00	0,11
74%	0,11	0,00	0,00	0,12
75%	0,12	0,00	0,00	0,13
76%	0,13	0,00	0,00	0,13
77%	0,14	0,00	0,00	0,14

78%	0,14	0,00	0,00	0,15
79%	0,15	0,00	0,00	0,16
80%	0,16	0,00	0,00	0,17
81%	0,17	0,00	0,00	0,18
82%	0,18	0,00	0,00	0,19
83%	0,20	0,00	0,00	0,20
84%	0,21	0,00	0,00	0,21
85%	0,22	0,00	0,00	0,23
86%	0,24	0,00	0,00	0,24
87%	0,26	0,00	0,00	0,26
88%	0,28	0,00	0,00	0,28
89%	0,30	0,00	0,00	0,30
90%	0,32	0,00	0,00	0,32
91%	0,35	0,00	0,00	0,35
92%	0,37	0,00	0,00	0,38
93%	0,41	0,00	0,00	0,41
94%	0,44	0,00	0,00	0,44
95%	0,48	0,00	0,00	0,49
96%	0,53	0,00	0,00	0,53
97%	0,59	0,00	0,00	0,59
98%	0,65	0,00	0,00	0,65
99%	0,73	0,00	0,00	0,73
100%	0,82	0,00	0,00	0,82

Appendix 7: Data for PSA plot

Outcome measures		Uncertain parameter values							
Additional QALY	Additional cost	Sensitivity	Specificity	Cost CTC	Cost imaging	probability Imaging	Probability MRI	Survival outcome	% patients stage I-IIA
0,103	€ 10.502,21	81	52	€ 3.410,00	€ 1824,-	0,84	0,88	1,05	0,5
0,299	€ 6.519,59	98	51	€ 1.674,00	€ 1.156,00	0,93	0,92	1,33	0,87
0,151	€ 6.445,72	55	50	€ 1.116,00	€ 468,00	0,83	0,91	1,13	0,74
0,498	€ 4.177,41	60	71	€ 1.820,00	€ 1.971,00	0,85	0,85	1,23	0,95
0,316	€ 7.318,42	98	54	€ 2.794,00	€ 1.949,00	0,86	0,96	1,14	0,88
0,743	€ 4.707,27	61	57	€ 1.576,00	€ 1.397,00	0,95	0,77	0,56	0,99
0,131	€ 6.332,94	83	59	€ 850,00	€ 1.049,00	0,87	0,89	1,37	0,68
0,541	€ 4.861,65	50	79	€ 3.119,00	€ 843,00	0,91	1	1,09	0,96
0,261	€ 5.406,38	94	65	€ 1.530,00	€ 1.689,00	0,91	0,93	1,19	0,85
0,079	€ 5.898,72	55	79	€ 2.987,00	€ 768,00	0,86	0,83	0,67	0,61
0,067	€ 5.792,18	51	66	€ 1.564,00	€ 1.831,00	0,89	0,76	1,15	0,54
0,059	€ 4.685,56	68	93	€ 2.716,00	€ 1.489,00	0,79	0,8	1,16	0,55
0,213	€ 6.727,76	61	56	€ 2.763,00	€ 502,00	0,9	0,76	0,82	0,82
0,327	€ 2.656,55	57	97	€ 2.093,00	€ 1.611,00	0,85	0,78	0,73	0,9
0,11	€ 4.899,31	65	87	€ 2.505,00	€ 258,00	0,81	0,93	0,59	0,69
0,194	€ 7.560,74	94	51	€ 2.126,00	€ 950,00	0,86	0,88	1,25	0,78
0,655	€ 3.822,47	55	95	€ 3.315,00	€ 1.076,00	0,85	0,84	0,6	0,98
0,069	€ 3.039,60	65	96	€ 1.375,00	€ 1.520,00	0,98	0,77	1,3	0,61
0,833	€ 4.173,60	52	60	€ 1.319,00	€ 262,00	0,99	0,84	0,91	1
0,196	€ 4.149,01	55	88	€ 2.634,00	€ 1.596,00	0,84	0,86	1,27	0,82
0,102	€ 9.619,33	87	68	€ 3.597,00	€ 428,00	0,78	0,96	0,47	0,5
0,136	€ 5.456,95	78	74	€ 1.776,00	€ 2.064,00	0,85	0,9	1,29	0,72
0,087	€ 5.735,94	60	86	€ 3.395,00	€ 593,00	0,84	0,88	1,39	0,65
0,068	€ 6.602,74	62	83	€ 3.380,00	€ 300,00	0,83	0,91	0,76	0,54
0,061	€ 5.111,73	77	91	€ 2.378,00	€ 432,00	0,94	0,79	1,21	0,5
0,542	€ 5.209,82	62	82	€ 3.652,00	€ 2.015,00	0,97	0,93	0,81	0,96
0,262	€ 3.854,44	76	79	€ 1.524,00	€ 1.258,00	0,91	0,83	0,75	0,86
0,144	€ 8.277,69	74	54	€ 2.387,00	€ 471,00	0,99	0,95	0,86	0,7
0,29	€ 3.575,53	57	85	€ 1.915,00	€ 616,00	0,83	0,93	0,53	0,88
0,427	€ 6.917,65	57	54	€ 3.160,00	€ 531,00	0,87	0,95	1,37	0,93
0,277	€ 6.924,07	88	51	€ 2.475,00	€ 2.002,00	0,85	0,78	0,72	0,86
0,271	€ 3.853,91	65	90	€ 2.413,00	€ 2.026,00	0,81	1	0,93	0,87
0,323	€ 6.322,87	71	60	€ 2.749,00	€ 1.432,00	0,93	0,85	1,2	0,89
0,233	€ 3.586,22	82	89	€ 1.717,00	€ 710,00	0,98	0,93	0,66	0,84
0,13	€ 9.400,78	99	65	€ 3.597,00	€ 956,00	0,79	0,98	0,69	0,63
0,402	€ 7.340,83	77	53	€ 3.390,00	€ 1.763,00	0,94	0,86	0,61	0,92

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