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Cost-effectiveness of proton radiotherapy versus photon radiotherapy for non-small cell lung cancer patients: Exploring the model-based approach

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Abstract

Introduction: Proton radiotherapy (PT) is a promising but more expensive strategy than photon radiotherapy (XRT) for the treatment of non-small cell lung cancer (NSCLC). PT is probably not cost-effective for all patients. Therefore, patients can be selected using normal tissue complication probability (NTCP) models with predefined criteria. This study aimed to explore the cost-effectiveness of three treatment strategies for patients with stage III NSCLC: 1. photon radiotherapy for all patients (XRT_all); 2. PT for all patients (PT_all); 3. PT for selected patients (PT_individualized).

Methods: A decision-analytical model was constructed to estimate and compare costs and QALYs of all strategies. Three radiation-related toxicities were included: dyspnea, dysphagia and cardiotoxicity. Costs and QALYs were incorporated for grade 2 and ≥3 toxicities separately. Incremental Cost-Effectiveness Ratios (ICERs) were calculated and compared to a threshold value of €80,000. Additionally, scenario, sensitivity and value of information analyses were performed.

Results: PT_all yielded most QALYs, but was also most expensive. XRT_all was the least effective and least expensive strategy, and the most cost-effective strategy. For thresholds higher than €163,467 per QALY gained, PT_individualized was cost-effective. When assuming equal minutes per fraction (15 minutes) for PT and XRT, PT_individualized was considered the most cost-effective strategy (ICER: €76,299).

Conclusion: Currently, PT is not cost-effective for all patients, nor for patient selected on the current NTCP models used in the Dutch indication protocol. However, with improved clinical experience, personnel and treatment costs of PT can decrease over time, which potentially leads to PT_individualized with optimal patient selection, will becoming a cost-effective strategy.

Key words: Proton radiotherapy, non-small cell lung cancer, cost-effectiveness, NTCP models, model-based approach.
**Introduction**

Proton radiotherapy (PT) is a potentially beneficial (e.g. reduced toxicities) but significantly more expensive treatment strategy for patients with stage I-III non-small cell lung cancer (NSCLC) compared to photon-based radiotherapy (XRT). Furthermore, treatment capacity is limited.

Considering the limited treatment capacity, costs and the substantial number of patients with NSCLC, great attention should be paid to optimal patient selection, since not all patients will benefit from PT. Hence, using PT instead of XRT without optimal patient selection would lead to unnecessary high costs, inefficient and unfair healthcare provision.

Currently, XRT with or without chemotherapy is the main treatment modality for the management of stage III NSCLC. Considering the proximity of the target volume to the lungs, esophagus and the heart, XRT causes dyspnea in 10% of the lung cancer patients and grade ≥3 dysphagia in approximately 5% of the patients. A larger group of patients experience grade 2 symptoms of dysphagia (18%) and dysphagia (22%). Cardiotoxicity is a less investigated toxicity but has since recently been recognized as a matter of concern, also for lung cancer patients. Cardiac events occurs in 33% of the patients within five years after diagnosis. An advantage of PT is its favorable in-depth dose distribution, reducing treatment toxicity by minimizing the exposure of radiation to surrounding normal tissues relative to the target dose. A reduction of toxicities could limit the impact on health related quality of life and could pose decreased costs of toxicity management, which could potentially reduce the overall costs for PT. However, despite the clinical benefits, effects are not likely to outweigh the costs for the total lung cancer population receiving radiotherapy. Optimal patient selection is therefore of great importance to use PT in a cost-effective way. At present, patient selection is based on normal tissue complication probability (NTCP) models which estimate the risk reduction in toxicity of healthy tissue by using PT compared to XRT (ΔNTCP). Using predefined ΔNTCP criteria as described, for example, in the Dutch indication protocol, patients can be selected for PT. This “model-based” approach for patient selection as described by the Dutch Healthcare Institute uses fixed thresholds per grade of toxicity and can be incorporated in a decision-analytical model to explore the cost-effectiveness of PT for selected patients, compared to XRT.

The cost-effectiveness of PT versus XRT for patients with early stage NSCLC has been explored in 2010 using a decision-analytical model. However, no studies have been performed yet on cost-effectiveness of PT versus XRT for patients with stage III NSCLC using the “model-based” approach to select patients. Patients with Stage III NSCLC are currently being considered as potentially eligible patients for PT based on planning studies. Hence, a decision-analytical state-transition model was developed to investigate whether the additional effects of PT for all patients or PT for selected patients are worth the extra costs for patients with NSCLC stage III, compared to XRT. With this decision-analytical modeling technique,
evidence of various sources for probabilities, costs and utilities can be synthesized in order to inform
decisions and to reflect the posed decision uncertainty. Therefore, the aim of the study was to explore
the cost-effectiveness of the model-based approach for selecting patients with NSCLC for PT and XRT.
Although Dutch indication protocols are used, PT capacity is limited globally, patient selection remains
fundamental. Therefore, this study is likely to be relevant to other countries and can serve as a
methodological approach to overcome unnecessary high costs, inefficient and unfair healthcare provision.

Methods

State-transition model approach and structure

A probabilistic decision-analytical state-transition model was used to assess the cost-effectiveness of
three treatment strategies for patients with NSCLC stage III: 1. XRT for all patients (XRT_all); 2. PT for all
patients (PT_all); 3. PT for selected patients (PT_individualized). In the third treatment strategy, eligibility of
patients was based on the model-based approach. Currently, models for dyspnea, pneumonitis, dysphagia and mortality related to heart dose have been published. For this exploratory analysis, three
out of the four models (pneumonitis, dysphagia and mortality related to heart dose) from the Dutch
indication protocol were used. Accordingly, patients were eligible for PT according to ΔNTCP criteria
and ineligible patients received XRT. Patient are eligible for PT with a clinical relevant ΔNTCP of ≥10% for
grade 2 toxicities, ≥5% for grade 3 and ≥2% for grade 4-5 toxicities. In case of multiple complications, the
sum of ΔNTCP should be minimal 15%, 7.5% and 3%, respectively. While the Dutch indication criteria
are determined by the models to predict pneumonitis, dysphagia and mortality related to heart dose, in
this exploratory analysis the model to predict pneumonitis was replaced by the model predicting dyspnea.
The latter model incorporated baseline dyspnea, which is considered as an important for the face validity
of the model.

The state-transition model was constructed using cohort simulation and adopted a cycle length of three
months. According to the Dutch health economic guidelines, a life-time time horizon, a societal
perspective and a discount rate of 4.0% for costs and 1.5% for effects was applied.

The model was divided in two timeframes. Within six months, health states were based on whether
patients experienced acute toxicities (dyspnea or dysphagia) with or without disease progression. From
six-months onwards, patients could be free of toxicities, but could also develop cardiotoxicity, dyspnea or
cardiotoxicity concurrently with dyspnea, all with or without disease progression (figure 1.) Disease
progression was defined as loco-regional or distant dissemination of cancer cells. “Death” was the
absorbing health state in the model, either due to cancer or due to other causes.
Toxicity was graded according to the Common Terminology Criteria of Adverse Events (CTCAE) 3.0. Grade 2 was set as cut-off point. Costs and resource use for toxicities were incorporated for grade 2 and grade ≥3 separately to provide more granularity to reflect toxicity costs and resource use. The occurrence ratio of grade 2 and grade ≥3 toxicities, based transition probabilities, was used to calculate a weighted cost average. Microsoft Office Excel 2016 was used to implement the state-transition model.

Model assumptions

Regarding the model, several assumptions were made:

1. Within the first six months after treatment, patients could only experience one toxicity at a time.
2. The probability of late onset dyspnea and dysphagia after six months was not taken into account. NTCP models only accurately predict dyspnea onset until six months. Acute dysphagia is most common in the first 2-3 weeks after treatment initiation. Based on expert opinion, occurrence of dysphagia after six months is rare.
3. For patients with dyspnea and/or cardiotoxicity at six months, it was assumed that these toxicities were irreversible.
4. After experiencing disease progression, either in acute or late time frame, patients entered a progressed disease state reflecting the same toxicities as before disease progression.

Transition probabilities
NTCP models for dyspnea, dysphagia and two-year mortality related to heart dose (used to adjust OS until two years) were used to derive treatment dependent transition probabilities (table 1) of grade 2 and grade ≥3 toxicities using dosimetric parameters and patient characteristics (appendix A). Dosimetric parameters were extracted from results of a multicentric in silico clinical trial (ROCOCO), which compared XRT and PT for patients with stage I-III NSCLC (72% stage III patients). Patient characteristics (age, gender, smoking, WHO performance status, chemotherapy, GTV and baseline dyspnea) were extracted from literature. However, these studies only reported mean values. Therefore, patient values were randomly sampled from a Gaussian distribution (patient characteristics) or Gamma distribution (dosimetric parameters and Gross Tumor Volume (GTV)).

Treatment independent transition probabilities were estimated for cardiac events (cardiotoxicity) as this is expected to have a substantial impact on costs and consequences. These probabilities were derived from time to event data from a study by Degens et al. This study investigated the incidence of cardiac events in patients with stage III NSCLC within five years after conformal radiotherapy treatment completion. The probability of cardiotoxicity was based on three most common categories: arrhythmia (43.9%), heart failure (HF) (including valve defects) (33.9%) and ischemic heart disease (IHD) (22.2%). From the time to event dataset, a Kaplan-Meier curve of these merged categories was generated in R Statistical Software (version 3.5.1) to calculate time dependent transition probabilities (appendix C). The randomized Phase III NVALT-11/DLCRG-02 study was used to extract overall survival (OS) and progression free survival (PFS) rates with a median follow-up time of 51.3 months (95% CI: 47.5 - 60.2 months). Additionally, Table 1 presents transition probabilities derived from NTCP models. Detailed information about NTCP models and cardiotoxicity can be found in appendix B and C, respectively.
Table 1. Treatment dependent probabilities estimated based on NTCP models

| Parameter                                                      | Estimated Value | SE  | Distribution | Source |
|---------------------------------------------------------------|-----------------|-----|--------------|--------|
| **Photon-based radiotherapy for all patients (once only probability implemented in the first cycle)** |                 |     |              |        |
| Probability of dyspnea grade 2                               | 14.0 %          | 12.1| Normal*      | 16     |
| Probability of dyspnea grade ≥3                              | 17.3 %          | 18.0| Normal*      | 16     |
| Probability of dysphagia grade 2                             | 30.3 %          | 25.8| Normal*      | 18     |
| Probability of dysphagia grade ≥3                            | 10.8 %          | 13.9| Normal*      | 18     |
| Probability of mortality related to heart dose (two-year)     | 16.6 %          | 0.04| Normal*      | 19     |
| **Proton radiotherapy for all patients (once only probability implemented in the first cycle)** |                 |     |              |        |
| Probability of dyspnea grade 2                               | 12.9 %          | 10.4| Normal*      | 16     |
| Probability of dyspnea grade ≥3                              | 13.5 %          | 14.8| Normal*      | 16     |
| Probability of dysphagia grade 2                             | 28.4 %          | 24.8| Normal*      | 18     |
| Probability of dysphagia grade ≥3                            | 10.3 %          | 13.1| Normal*      | 18     |
| Probability of mortality related to heart dose (two-year)     | 13.7 %          | 0.03| Normal*      | 19     |
| **Proton radiotherapy for selected patients (once only probability implemented in the first cycle)** |                 |     |              |        |
| Probability of dyspnea grade 2                               | 13.2 %          | 12.6| Normal*      | 16     |
| Probability of dyspnea grade ≥3                              | 14.3 %          | 14.2| Normal*      | 16     |
| Probability of dysphagia grade 2                             | 28.9 %          | 26.4| Normal*      | 18     |
| Probability of dysphagia grade ≥3                            | 10.5 %          | 12.7| Normal*      | 18     |
| Probability of mortality related to heart dose (two-year)     | 14.6 %          | 0.03| Normal*      | 19     |
| **Survival rates (per three-month cycle)**                    |                 |     |              |        |
| Progression free survival for all strategies                  | 83.5 %          | 0.03| Gamma**      | 27     |
| Overall survival XRT                                          | 90.9 %          | 0.02| Gamma**      | 27     |
| Overall survival PT for all patients (adjusted mortality related to heart dose) | 92.5 %          | 0.02| Gamma**      | -      |
| Overall survival PT for selected patients (adjusted mortality related to heart dose) | 92.3 %          | 0.01| Gamma**      | -      |

SE = Standard error
* Distribution based on used NTCP models
** Distribution based on OS and PFS months

Detailed information about NTCP models and cardiotoxicity can be found in appendix B and C.

Health related quality of life

Utility scores were used to reflect the impact of toxicity, disease progression and mortality on quality of life. “No toxicity” utilities for both progression free and progressed disease were derived from a study of Ramaekers et al\textsuperscript{28}, in which utilities were based on the Dutch EuroQoL-SD-3L\textsuperscript{28}. Disutilities were assigned to patients with toxicity. Since cardiotoxicity was based on three major categories, a weighted disutility, consisting of a disutility for arrhythmia (43.9%), HF (33.9%) and myocardial infarction (22.2%), was used to calculate a utility for patients with cardiotoxicity. An accurate disutility for dysphagia could not be found, therefore the disutility for dyspnea was also assigned to patients with dysphagia. No distinction could be made between grade 2 and grade ≥3 (dis)utilities due to lack of data. Therefore, the same disutility was used for both grade 2 and ≥3. Additionally, an age related disutility, based on gender, was assigned to patients aged 75 or over. (Dis)utilities are reported in table 2.
Table 2. Input parameters: Health state utilities (reference value) and disutilities

| Parameter                          | Estimated Value | SE   | Distribution | Source |
|------------------------------------|-----------------|------|--------------|--------|
| Health state utility               |                 |      |              |        |
| Progression Free - No Toxicity     | 0.800           | 0.029| Beta         | 28     |
| Progressed Disease - No Toxicity   | 0.794           | 0.038| Beta         | 28     |
| Disutility                         |                 |      |              |        |
| Dyspnea                            | -0.05           | 0.012| Normal       | 29     |
| Dysphagia                          | Assumed the same as dyspnea | | | |
| Cardiotoxicity                     |                 |      |              |        |
| Myocardial infarction              | -0.06           | 0.011| Normal       | 30     |
| Heart Failure                      | -0.14           | 0.022| Normal       | 30     |
| Arrhythmia                         | -0.02           | 0.004| Normal       | 31     |
| Age 75+                            | (Age at baseline: 66) | -0.01| 0.002       | Normal | 32     |

Treatment costs for proton radiotherapy and photon-based radiotherapy

For treatment costs of PT and XRT a separate cost-analysis was performed (table 3 and appendix D). The study of Peeters et al\textsuperscript{33} was used as starting point to extract purchase prices and operational information. Depreciation values, annuity factors, personnel costs, overhead percentages and maintenance costs were based on the Dutch costing manual\textsuperscript{34}, expert opinion and news articles\textsuperscript{35}.

Costs were divided in three main categories: Building (incl. structure costs, depreciation and interest charges), medical equipment (incl. depreciation and interest charges) and personnel costs of radiation technologists, physicians and physicists (incl. allowances). Based on these categories, total annual costs were defined. Total annual costs included maintenance, overhead and housing costs which were based on annual depreciation costs and interest charges of both building and medical equipment. Next, total costs per fraction for PT and XRT was calculated based on information of the operation of a facility.

Table 3. Treatment costs for proton radiotherapy and radiotherapy

| Parameter                          | PT                      | XRT                     | Source |
|------------------------------------|-------------------------|-------------------------|--------|
| Building                           |                         |                         |        |
| Depreciation period (Years)        | 50                      | 50                      | 34     |
| Interest rate                      | 4.2%                    | 4.2%                    | 34     |
| Building                           | €15,500,000             | €10,798,444             | PT: 35 XRT: 33 |
| Medical equipment                  |                         |                         |        |
| Depreciation period (Years)        | 10                      | 10                      | 34     |
| Interest rate                      | 4.2%                    | 4.2%                    | 34     |
| Medical equipment                  | €25,000,000             | €5,881,506              | PT: 35 XRT: 33 |
| Personnel                          |                         |                         |        |
| Total annual personnel costs       | €392,091                | €392,091                | MC, 34, 36 |
| Other charges                      |                         |                         |        |
| Maintenance                        | 5%                      | 5%                      | 34     |
| Housing and depreciation           | 6%                      | 6%                      | 34     |
| Overhead                           | 38%                     | 38%                     | 34     |
| Operation                          |                         |                         |        |
| Working days per week              | 5                       | 5                       | 33     |
| Working hours per day              | 14                      | 14                      | 33     |
| Days of operation per year         | 251                     | 251                     | 33     |
| Treatment room utilization         | 98%                     | 100%                    | 33     |
Treatment room availability 98% 98% 33
Time per fraction in minutes (Range) 35 (30-40) 15 (10-20) EO, 33
Fractions per year 5,783 13,769 -
Costs per fraction €1,062 €256 -

EO = Expert Opinion, MC = MAASTRO Clinic (G. Bosman, personal communication, May 29, 2019)

Health state and event resource use and costs

We included related and unrelated healthcare costs, patient and family costs and inter-sectoral costs. Costs of toxicities were calculated for grade 2 and grade ≥3 separately, except for cardiotoxicity. Since it is difficult to distinguish the origin of dyspnea, which could be either from cardiac or lung diseases, guidelines for treating (radiation-induced) dyspnea are lacking. Therefore, costs of Chronic Obstructive Pulmonary Disease (COPD) were assumed to reflect healthcare utilization for dyspnea. The healthcare costs were derived from a study which included costs of primary, hospital and paramedical care (homecare and rehabilitation), as well as medication. Costs of moderate and severe COPD were assumed to reflect costs of grade 2 and grade ≥3 dyspnea, respectively. For dysphagia, hospitalization, medication use and portion of liquid nutrition were derived from literature. Other resource use was based on expert opinion. According to CTCAE 3.0, hospitalization regarding dysphagia is indicated for grade ≥3. Hence, it was assumed that hospitalization was not applicable to grade 2 dysphagia and therefore not included in the cost calculation. For implementation in the model, costs for grade 2 and grade ≥3 were merged for dyspnea and dysphagia according to the proportion of probabilities. Dysphagia was only included once, as it only occurs during the first cycle.

For healthcare costs of cardiotoxicity, the Practical Application tool to Include Disease Costs (PAID), version 1.1 was used. Based on ICD-9 codes, coronary heart diseases reflected the costs of IHD and other heart diseases and HF reflected the costs of arrhythmia and HF (including valve defects). A weighted average of cardiotoxicity costs was based on the categories as previously described. Costs of cardiotoxicity were age- and gender specific, which implies different costs per patient in each cycle. Follow-up costs were distributed among different cycles in the first five years. The PAID tool was also used to estimate unrelated healthcare costs.

Travel distance for PT was defined using the geographical midpoint of the Netherlands. A weighted average for distance was calculated based on the annual capacity of three PT centers (appendix E). Distance for XRT was extracted from a report in which frequencies in distance categories were reported. In case of private vehicle traveling, it was assumed that the patient would be accompanied by an informal caregiver. Unit costs were based on the Dutch costing manual.

Productivity losses were included and were calculated using the Friction cost approach (consistent with the Dutch pharmacoeconomic guideline). Information of age-specific full-time and part-time labor
participation was based on data from CBS Statline.\textsuperscript{41} The distribution was used to calculate a weighted average of costs for productivity losses (appendix F). These costs were implemented once for each patient at baseline, assuming that all patients will pose costs of productivity losses after diagnosis.

All costs were converted to 2019 price levels and reported in Euros (Table 4).

### Table 4. Costs and resource use (Price level: 2019)

| Parameter | Estimated Value | SE | Distribution | Source |
|-----------|-----------------|----|--------------|--------|
| **Costs** |                 |    |              |        |
| **Treatment Costs** |             |    |              |        |
| *Photon* |                 |    |              |        |
| Number of fractions | 30 | 0.2 | Gamma | 28 |
| Minutes per fraction | 15 | 5 | Gamma | EO |
| Costs per fraction | €256 | - | Beta (PERT) | CA |
| *Proton* |                 |    |              |        |
| Number of fractions | 30 | 0.2 | Gamma | 28 |
| Minutes per fraction | 35 | 5 | Gamma | EO |
| **Related Health Care Costs** |             |    |              |        |
| *Dyspnea grade 2* | Total costs incl. home care and rehab. | €974 | - | Fixed | 37 |
| *Dyspnea grade ≥3* | Total costs incl. home care and rehab. | €2,859 | - | Fixed | 37 |
| *Dysphagia grade 2* | Months of medication for dysphagia | 1 | 0.2 | Gamma | EO |
| Costs of medication per month | €46 | - | Fixed | MP, 42 |
| Days of liquid nutrition | 28 | 5.6 | Gamma | EO |
| Portion of liquid nutrition per day | 3.7 | 0.74 | Gamma | 38 |
| Costs of liquid nutrition per portion | €3.60 | - | Fixed | MP |
| *Dysphagia grade ≥3* | Months of medication for dysphagia | 1 | 0.2 | Gamma | EO |
| Costs of medication per month | €46 | - | Fixed | 42 |
| Hospitalization days | 6 | 0.9 | Gamma | 28 |
| Costs of hospital stay per day | €505 | - | Fixed | 34 |
| Tube feeding days | 14 | 2.8 | Gamma | EO |
| Costs of tube feeding per day | €12 | - | Fixed | MP |
| Costs of placing and removing tube | €335 | - | Fixed | 28 |
| Hours of Home care per day | 0.5 | 0.1 | Gamma | EO |
| Home care days | 14 | 2.8 | Gamma | EO |
| Costs of Home care per hour (nurse) | €77 | - | Fixed | 34 |
| **Cardiotoxicity** | Ischemic Heart disease (Age range: 66-99) | Range: €62 - €293 | - | - | 39 |
| Heart failure and arrhythmia (Age range: 66 - 99) | Range: €53 - €710 | - | - | 39 |
| **Follow-up visits** | Follow-up visits first year | 4 | 0.8 | Gamma | 43 |
| CT-scan first year | 1 | 0.2 | Gamma | 43 |
| Follow-up visits second year | 2 | 0.4 | Gamma | 43 |
| CT-scan second year | 1 | 0.2 | Gamma | 43 |
| Follow-up visits per year after the second year until 5 years | 1 | 0.2 | Gamma | 43 |
| CT-scan per year after the second year until 5 years | 1 | 0.2 | Gamma | 43 |
| Costs per follow-up visit | €97 | - | Fixed | 34 |
| Costs per CT-scan | €154 | - | Fixed | 34 |
| **Patient and Family Costs** | Traveling costs | Parking costs per day | €3.18 | - | Fixed | 34 |
| Number of km (return) PT | 148 | 45.5 | Gamma | - |
| Number of km (return) XRT | 46 | 9.2 | Gamma | 34 |
| Taxi use (%) | 58.7% | 0.25 | Beta | - |
| Private vehicle use (%) | 41.3% | 0.25 | Beta | - |
**Informal care**

- Costs Taxi (constant + costs per km)
  - €3.13 + €2.82
- Hours of informal care PT
  - 5 hours
- Hours of informal care XRT
  - 2 hours
- Costs per hour of informal care
  - €15

**Unrelated healthcare costs**

- **Unrelated disease costs**
  - Costs of diseases in life-years gained (Age range: 66 - 99)
    - Range: €1,235 - €17,778
  - Costs of last year of living (Age range: 66 - 99)
    - Range: €3,517 - €8,815

**Inter-sectoral cost**

- Friction period (weeks)
  - 12.1 weeks
- Working population (%)
  - 17.5%
- Full-time (%)
  - 28%
- Part-time (%)
  - 72%

**Base case analysis**

Expected life years (LYs), progression free life years (PFLYs), quality adjusted life-years (QALY), costs and net monetary benefit (NMB) were calculated for all strategies. Additionally, incremental cost-effectiveness ratios (ICERs) were calculated. A threshold value of €80,000 per QALY, established by the Dutch Healthcare Institute was used. The analysis was performed in Microsoft Office Excel 2016.

**Sensitivity analysis**

Distributions were assigned to each individual input parameter in order to perform a probabilistic sensitivity analysis (PSA) with Monte Carlo simulation (2,000 simulations). The ICER was calculated based on the outputs of the PSA. To illustrate uncertainty surrounding the ICER, a cost-effectiveness plane was created. A cost-effectiveness acceptability curve (CEAC) was created to present the probability of strategies being cost-effective at different ceiling ratios. Additionally, deterministic one-way sensitivity analyses were performed.
Scenario analysis

Scenario analyses were performed to examine the cost-effectiveness from a healthcare perspective and possible future or alternative scenarios. Since PT is still in start-up phase in the Netherlands and fraction duration is expected to decrease over time, an analysis assuming that minutes per fraction of PT and XRT are equal was performed (15 minutes). Additionally, a threshold analysis was conducted in order to identify the maximum fraction duration for $PT_{\text{individualized}}$ still being cost-effective at the threshold value. In a second scenario analysis, productivity losses were excluded for PT since toxicity probabilities were lower compared to XRT and less toxicity might reduce productivity losses.

Value of information analysis

The expected value of perfect information (EVPI) represents the risk associated with the decision, i.e. the probability of making a wrong adoption decision (from the CEAC described above) multiplied by the consequences of a wrong adoption decision. In other words, the EVPI provides a maximum value to the amount of resources that should be spend on research to decrease the decision uncertainty. By multiplying the per patient EVPI by the effective population, which reflects the number of patients that are affected by the decision, the population EVPI was calculated. The effective population for the next 10 years of 83,029 patients was based on the incidence of patients with NSCLC in 2019 in the Netherlands. Additionally, the value of partial perfect information (EVPPI) was calculated to determine which parameter(s) contributed the most to decision uncertainty (i.e. the EVPI for specific (groups) of parameters). Sheffield Accelerated Value of Information (SAVI) version 2.1.2 was used to retrieve the EVPPI.

Results

Total expected life-time cost per patient from a societal perspective were estimated to be €79,695 for $PT_{\text{All}}$, €68,904 for $PT_{\text{individualized}}$, and €41,231 for $XRT_{\text{All}}$. $PT_{\text{All}}$ yielded most QALYs (1.951) and LYS (2.558). $XRT_{\text{All}}$ was the least effective (1.769 QALYs), the least expensive strategy, and the most cost-effective strategy. For thresholds higher than €163,467 per QALY gained, $PT_{\text{individualized}}$ was cost-effective. $PT_{\text{All}}$ will be cost-effective above a willingness to pay of €301,396 per QALY gained. $XRT_{\text{All}}$ had the highest probability of being cost-effective (97%) at a threshold of €80,000 per QALY gained. CEACs and CE planes are presented in appendix G.

The scenario analysis using a healthcare perspective resulted in similar outcomes with $XRT_{\text{All}}$ as the most cost-effective treatment strategy until a value of €134,256 per QALY gained followed by $PT_{\text{individualized}}$ as next best up to €245,053 per QALY gained. Excluding productivity losses had a minor impact on cost and cost-effectiveness results. However, when considering equal minutes per fraction as future perspective,
XRT\textsubscript{All} was cost-effective until a value of €76,299 per QALY gained followed by PT\textsubscript{Individualized} until a value of €124,719 per QALY gained. Above the latter value, PT\textsubscript{All} became cost-effective. The probabilities of PT\textsubscript{All}, XRT\textsubscript{All} and PT\textsubscript{Individualized} being cost-effective at the threshold value were 16%, 47%, and 38% respectively. When increasing the PT fraction duration by one minute, the ICER exceeded the threshold value (€81,665).

Result are reported in table 5. The deterministic one-way sensitivity analyses showed that the cardiac event categories and “no toxicity” utilities were the most influential parameters. The tornado diagram can be found in appendix G.

Table 5. Results of probabilistic sensitivity analyses (Sorted by costs)

| Analysis          | Strategy       | Costs  | QALY | NMB    | ∆Costs | ∆QALY | ICER  |
|-------------------|----------------|--------|------|--------|--------|-------|-------|
|                   |                | €45,91 | 1.76 | €95,627|        |       |       |
|                   |                | 2      | 9    |        |        |       |       |
| Base Case         | XRT\textsubscript{All} |    |      |        |        |       |       |
|                   | PT\textsubscript{Individualized} | €70,86 | 1.92 | €82,885| €24.95 | 7     | €163,467 |
|                   |                | 6      | 2    |        |        |       |       |
|                   | PT\textsubscript{All} | €79,69 | 1.95 | €76,400| €33.78 | 3     | €185,677 |
|                   |                | 5      | 1    |        |        |       |       |
| Healthcare        | XRT\textsubscript{All} | €41,23 | 1.76 | €100.28|        |       |       |
| perspective       |                | 1      | 9    |        |        |       |       |
|                   | PT\textsubscript{Individualized} | €61,72 | 1.92 | €92,034| €20.49 | 5     | €134,256 |
|                   |                | 6      | 2    |        |        |       |       |
|                   | PT\textsubscript{All} | €68,90 | 1.95 | €87,176| €27.67 | 3     | €152,096 |
|                   |                | 4      | 1    |        |        |       |       |
| Excluding         | XRT\textsubscript{All} | €45,91 | 1.76 | €95,608|        |       |       |
| productivity      |                | 2      | 9    |        |        |       |       |
| losses PT         | PT\textsubscript{Individualized} | €69,66 | 1.92 | €84,098| €23.75 | 0     | €155,582 |
|                   |                | 2      | 2    |        |        |       |       |
|                   | PT\textsubscript{All} | €78,02 | 1.95 | €78,057| €32.11 | 1     | €176,487 |
|                   |                | 3      | 1    |        |        |       |       |
| Equal minutes     | XRT\textsubscript{All} | €45,41 | 1.75 | €97,794|        |       |       |
| per fraction      |                | 0      | 3    |        |        |       |       |
|                   | PT\textsubscript{Individualized} | €57,41 | 1.91 | €95,376| €12.00 | 7     | €76,299 |
|                   |                | 6      | 0    |        |        |       |       |
|                   | PT\textsubscript{All} | €61,18 | 1.94 | €94,023| €15.78 | 0     | €84,106 |
|                   |                | 9      | 0    |        |        |       |       |

QALY = Quality Adjusted Life Years  
NBM = Net Monetary Benefit  
ICER = Incremental Cost Effectiveness Ratio

Regarding base case scenario, the estimated EVPI per patient was €84 at a threshold value of €80,000, the population EVPI for the effective population was €7 million. Further research focusing on NTCP models for mortality based on heart dose and OS (NTCP+OS: €388,629; OS: €244,312) would be most worthwhile. The population EVPI for different threshold values is shown in appendix G figure G.5.
Assuming equal minutes for PT and XRT, the estimated EVPI per patient was €2,347, the population EVPI for the effective population was €195 million. The maximum expected value of further research that will jointly inform the set of parameters of NTCP models, patient and family cost (related to PT), utilities and related healthcare cost was €20 million, €3.7 million, €996,325 and €342,253, respectively.

**Discussion**

This study aimed to examine the cost-effectiveness of three treatment strategies for patients with stage III NSCLC: 1. XRT<sub>All</sub>; 2. PT<sub>All</sub>; 3. PT<sub>Individualized</sub>. In the base-case analysis, PT<sub>All</sub> was not cost-effective neither from a societal perspective, nor from a healthcare perspective when assuming a threshold value of €80,000. There was a substantial cost difference between PT and XRT which can be explained by primary treatment cost that are 4.1 times higher for PT compared to XRT. These results are uncertain and conditional on different assumptions. PT<sub>Individualized</sub> will potentially be cost-effective compared to XRT<sub>All</sub> when the fraction duration or the number fractions of PT decreases and would become more cost-effective if patient selection is further optimized. Therefore, selection of patients for whom PT is expected to be beneficial is crucial at this point to improve the cost-effectiveness of PT.

To the authors knowledge, the present study is the first study in the Netherlands evaluating the cost-effectiveness of PT versus XRT for patients with stage III NSCLC from a societal perspective based on NTCP models. The previous model, developed in 2010 by Grutters et al.,<sup>14</sup> only included patients with early stage NSCLC and the model was restricted to two grade ≥3 toxicities (pneumonitis and esophagitis). The study showed that PT was cost-effective relative to conventional radiotherapy from a healthcare perspective. Differences between the previous and the current model can be explained by the newly performed cost-analysis which updated and expanded the previous analysis of Peeters et al.<sup>33</sup> with additional information. With the current clinical experience, PT proved to be more expensive as essentially calculated in 2010. Additionally, the use of NTCP models allows individual toxicity probability calculation based on planning data and enables to distinguish between grade 2 and grade ≥3 toxicity which improves the accuracy of predicting potential benefit and moreover cost difference.

Due to limited clinical experience treating patients with NSCLC in the Netherlands, there are some limitations. First, data necessary for treatment cost calculation is mainly not publicly available and hence difficult to get access to. Though, based on expert opinion and the best available evidence we attempted to estimate the treatment costs. However, the estimation of treatment costs might vary dramatically between PT centers and hence might limit the generalizability of our findings. Also, assumptions related to the depreciation period of radiotherapy equipment (based on the physical life of a piece of equipment
and its useful clinical life), affects costs. Nevertheless, the main conclusions that PT is not cost-effective for all patients and with improving clinical experience, fraction duration or the number of fractions can decrease over time, potentially improving the cost-effectiveness of PT, is likely widely applicable. Similarly, the current analyses could be considered conservative for PT from multiple perspectives. The cost effectiveness might be improved through developments that would, among others, decrease the time per fraction, decrease the number of fractions, advancement of PT techniques and interaction of PT with immunotherapy. Second, we assumed no excess mortality due to heart dose after a time point of two years. This assumption can be influential when assessing the long-term effect of PT on mortality and the impact on cost-effectiveness. If there would be a benefit after two year receiving PT, PT would most likely become more cost-effective. Time restriction for dyspnea and dysphagia models is less important since late-onset of both toxicities is rare. For cardiotoxicity, a time-dependent probability could be calculated for a life-time time horizon. However, no distinction could be made between PT and XRT, since no NTCP model is available yet to calculate dose-related probabilities, which is a third limitation of the study. Using PT significantly lowers the MHD relative to XRT which would presumably result in a lower cardiotoxicity probability. Fourth, cardiotoxicity is the only toxicity for which no distinction could be made between grade 2 and ≥3 costs, since it has a broad spectrum of diseases which are often interrelated. Hence, it is difficult to separate costs per grade. Fifth, not having access to individual dose distributions and thus relying on the published aggregate data from the ROCOCO study has limitations. This includes sampling different dose parameters independently. Moreover, it was unclear whether organ motion was incorporated (i.e. whether static dose was used or not). Finally, utilities could not be defined per grade as (dis)utilities are often not reported per grade.

The current model based approach adopted in the Netherlands\textsuperscript{10} has resulted in indication protocols that recommend PT in case a certain difference in NTCP between PT and XRT (ΔNTCP) is expected to be achieved. This ΔNTCP threshold differs according to grade of toxicity but not for type of toxicity. The current analyses showed that selecting patients based on anticipated benefit is expected to improve cost-effectiveness (compared to providing PT, unselected, to all patients). However, patient selection might be optimized further to increase cost-effectiveness. Optimal patient selection could potentially be achieved through applying different ΔNTCP thresholds according to toxicity type based on the impact on (cost-)effectives and could be explored using the model described in this paper. Without optimal patient selection, costs will be unnecessarily high and might impede healthcare provision to people who can potentially benefit of PT. Patient selection might change at a threshold of €80,000 per QALY when fraction duration of PT decreases towards XRT fraction duration (decreasing treatment costs of PT). Moreover, costs for PT are based on both the number of fractions and fractions duration. Hence, the cost effectiveness of PT can be improved by a reduced number of fractions (potentially in combination with a
reduced duration per fraction). For example, PT can be considered cost effective when administered in 18 fractions with a 25 minute duration (assuming reducing the number of fractions will only affect costs), similarly for 15 fractions of 30 minutes and 25 fractions of 18 minutes.

Based on the value of information analysis, it would be most valuable to perform further research on unrelated healthcare costs and NTCP models for mortality related to heart dose. Both are related, since unrelated healthcare costs are based on mortality. When fraction duration of PT decreases, the ICER will possibly become closer to the threshold value of €80,000. More or different parameters will then become more valuable to focus further research on. Additionally, in further research it would be worthwhile to include costs of multiple PT centers to get a comprehensive overview of PT cost in general. Furthermore, it would be of great value to incorporate NTCP models for cardiotoxicity when becoming available to obtain dose-related probabilities.

This study illustrates a methodological approach to assess the cost-effectiveness of PT vs XRT and supporting optimization of patients selection for PT. In conclusion, based on this explorative analysis of the model-based approach, $PT_{All}$ is not cost-effective in the current situation compared to $XRT_{All}$ and $PT_{individualized}$. With optimal patient selection, $PT_{individualized}$ can potentially become a cost-effective treatment when minutes per fraction decrease, the number of fractions decrease or an optimization by the interaction of both.
Appendices

Appendix A: Patient characteristics

Table A.1. Patient characteristics

|                          | XRT       | PT       | P      | Source |
|--------------------------|-----------|----------|--------|--------|
| Mean age (years)         | 66 (SD 10)| 24       |        |        |
| Gender                   |           | 24       |        |        |
| Male                     | 69.2%     |          |        |        |
| Female                   | 30.8%     |          |        |        |
| Smoking (yes)            | 36.9%     |          |        |        |
| Chemotherapy             | 88.0%     |          |        |        |
| Concurrent               | 36.9%     |          |        |        |
| WHO-PS (≥2)              | 11.6%     |          |        |        |
| Baseline dyspnea grade 1 | 28.7%     |          |        |        |
| Baseline dyspnea grade ≥2| 11.0%     |          |        |        |
| Mean GTV (cm³)           | 112.6 (SD 64.3) |        |        |
| OTT (days)               | 40 (SD 8.0) |        |        |        |
| MHD_mean (Gy)            | 14.3 (SD 10.3) | 7.6 (SD 7.2) | <0.001 | 23      |
| MLD_mean (Gy)            | 16.4 (SD 5.5) | 13.5 (SD 6.2) | <0.001 | 23      |
| MED_mean (Gy)            | 26.0 (SD 12.1) | 24.4 (SD 13.7) | <0.001 | 23      |
| MAXED_mean (Gy)          | 64.7 (SD 15.8) | 63.6 (SD 17.8) | <0.001 | 23      |

Abbreviations: WHO-PS = World Health Organizations Performance Status; GTV = Gross Tumor Volume; OTT = Overall Treatment Time; MHD = Mean Heart Dose; MLD = Mean Lung Dose; MED = Mean Esophagus Dose; MAXED = Maximum Esophagus Dose; Gy = Gray.

Appendix B: NTCP Models used for transition probabilities

Table B.1. 24 months’ mortality NTCP models → GTV-smoker-MHD model

| Coefficient | SE     | OR    | 95% CI    |
|-------------|--------|-------|-----------|
| Intercept B0| -0.090 | 0.018 | 0.914     |
| Gross Tumor Volume (GTV) (+1 cc) | 0.005 | 0.003 | 1.005     | Normal |
| Current smoker (yes/no)         | 0.456 | 0.432 | 2.490     | 1.067 - 5.809 | Normal |
| Mean Heart Dose (MHD) (+1 Gy)   | 0.033 | 0.025 | 1.033     | 0.985 - 1.084 | Normal |

Table B.2. NTCP model Dyspnea = 2

| Coefficient | SE     | OR    | 95% CI    |
|-------------|--------|-------|-----------|
| Intercept B0| -3.186 | 0.948 | 0.041     | 0.006 - 0.266 | Normal |
| Mean Lung Dose (MLD) (+1Gy)   | 0.043 | 0.048 | 1.044     | 0.950 - 1.147 | Normal |
| Chemotherapy (vs none)         | -0.807 | 0.483 | 0.446     | 0.173 - 1.150 | Normal |
| Baseline dyspnea grade 1 vs 0  | 1.635 | 0.791 | 5.129     | 1.087 - 24.191 | Normal |
| Baseline dyspnea grade ≥2 vs 0 | 3.382 | 0.802 | 29.430    | 6.110 - 141.741 | Normal |
### Table B.3. NTCP model Dyspnea ≥ 3 Endpoint 16

| Coefficient | SE   | OR   | 95% CI         | Distribution |
|-------------|------|------|----------------|--------------|
| Intercept 80| -4.081 | 1.020 | 0.017 | 0.002 - 0.125 | Normal       |
| Mean Lung Dose (MLD) (+1Gy) | 0.150 | 0.061 | 1.162 | 1.031 - 1.309 | Normal       |
| Chemotherapy (vs none) | -0.937 | 0.572 | 0.392 | 0.128 - 1.202 | Normal       |
| Baseline dyspnea grade 1 vs 0 | 0.299 | 0.692 | 1.349 | 0.348 - 5.233 | Normal       |
| Baseline dyspnea grade ≥2 vs 0 | 2.516 | 0.666 | 12.380 | 3.350 - 45.696 | Normal       |

### Table B.4. NTCP model Dysphagia grade ≥2 18

| Coefficient | SE   | OR   | 95% CI         | Distribution |
|-------------|------|------|----------------|--------------|
| Intercept 80| -0.195 | 0.936 | 0.823 | 0.128 - 5.156 | Normal       |
| Age         | -0.030 | 0.010 | 0.970 | 0.950 - 0.990 | Normal       |
| Female (vs male) | 0.501 | 0.198 | 1.650 | 1.120 - 2.430 | Normal       |
| WHO-PS ≥2 (vs 0-1) | 0.568 | 0.228 | 1.760 | 1.130 - 2.750 | Normal       |
| Concurrent chemotherapy (vs no/sequential) | 0.928 | 0.222 | 2.530 | 1.640 - 3.910 | Normal       |
| Mean esophagus dose (MED) | 0.061 | 0.014 | 1.060 | 1.040 - 1.090 | Normal       |
| Maximum esophagus dose (MAXED) | 0.030 | 0.010 | 1.030 | 1.010 - 1.050 | Normal       |
| Overall treatment time (OTT) | -0.059 | 0.011 | 0.940 | 0.920 - 0.960 | Normal       |

### Table B.5. NTCP model Dysphagia grade ≥3 18

| Coefficient | SE   | OR   | 95% CI         | Distribution |
|-------------|------|------|----------------|--------------|
| Intercept 80| -2.351 | 0.919 | 0.095 | 0.015 - 0.577 | Normal       |
| Age         | -0.030 | 0.010 | 0.970 | 0.950 - 0.990 | Normal       |
| Female (vs male) | 0.501 | 0.198 | 1.650 | 1.120 - 2.430 | Normal       |
| WHO-PS ≥2 (vs 0-1) | 0.568 | 0.228 | 1.760 | 1.130 - 2.750 | Normal       |
| Concurrent chemotherapy (vs no/sequential) | 0.928 | 0.222 | 2.530 | 1.640 - 3.910 | Normal       |
| Mean esophagus dose (MED) | 0.061 | 0.014 | 1.060 | 1.040 - 1.090 | Normal       |
| Maximum esophagus dose (MAXED) | 0.030 | 0.010 | 1.030 | 1.010 - 1.050 | Normal       |
| Overall treatment time (OTT) | -0.059 | 0.011 | 0.940 | 0.920 - 0.960 | Normal       |

Abbreviations: Se = standard error, OR = Odds ratio, CI = confidence interval, NTCP = normal tissue complication probability
Appendix C: Cardiotoxicity

Table C.1. Distribution of Cardiac events

| Condition                               | Percentage | SE  | Distribution |
|-----------------------------------------|------------|-----|--------------|
| Arrhythmia                              | 43.9%      | 11.5| Beta         |
| Atrial + Ventricular                     |            |     |              |
| Ischemic heart disease                   | 22.2%      | 3.3 | Beta         |
| Myocardial infarction + Coronary artery disease + Angina pectoris (cardiac cause) |      |     |              |
| Heart Failure                           | 33.9%      | 5.1 | Beta         |
| Acute + Chronic heart failure + Valve defects |      |     |              |

Cumulative incidence Cardiac Events

![Cumulative incidence curve Cardiac Events](image)

Fig. C.1. Cumulative incidence curve Cardiac Events
Table C.2. Lognormal parametric time to event model for cardiotoxicity

|                | Estimated value | SE   | 95% CI      | Distribution |
|----------------|-----------------|------|-------------|--------------|
| MeanLog        | 2.03            | 0.173| 1.69 – 2.37 | Normal       |
| SDLog          | 0.785           | 0.067| 0.65 – 0.91 | Normal       |

**Fig. C.2. Parametric model curve Cardiac Events**

**Transition probabilities cardiotoxicity**
## Appendix D: Cost-analysis Treatment costs

### Table D.1. Cost-analysis PT vs XRT

| Description                                                                 | XRT     | PT     | Source |
|----------------------------------------------------------------------------|---------|--------|--------|
| **Equipment**                                                              |         |        |        |
| Depreciation period (years)                                                | 10      | 34     | 34     |
| Interest rate                                                              | 4.2%    | 34     | 34     |
| Annuity factor                                                             | 8.0     |        |        |
| Purchase price                                                             | €5,881,506 | €25,000,000 | XRT: 33 | PT: 35 |
| Annual depreciation and interest costs                                     | €732,374 | €3,113,038 |        |
| **Building**                                                               |         |        |        |
| Depreciation period (years)                                                | 50      | 34     | 34     |
| Interest rate                                                              | 4.2%    | 34     | 34     |
| Annuity factor                                                             | 20.8    |        |        |
| Purchase price                                                             | €10,798,444 | €15,500,000 | XRT: 33 | PT: 35 |
| Annual depreciation and interest costs                                     | €520,004 | €746,409 |        |
| **Personnel**                                                              |         |        |        |
| Irregularity rate radiation technologists and physicist per month (between 20.00-22.00h) | 7%   | 34     | 34     |
| Irregularity rate physician per month                                       | 10%     | 34     | 34     |
| Allowances rate radiation technologist/physicist per month                 | 37%     | 34     | 34     |
| Allowances radiation physician per month                                   | €523    | 36     | 36     |
| Monthly salary radiation technologist (excl.)                              | €3,242  | 36     | 36     |
| Monthly salary physicist (excl.)                                           | €6,361  | 36     | 36     |
| Monthly salary physician (excl.)                                           | €9,941  | 36     | 36     |
| FTE radiation technologist                                                 | 4       | MC     |        |
| FTE physicist                                                              | 0.5     | MC     |        |
| FTE physician                                                              | 0.6     | MC     |        |
| **Annual costs**                                                           |         |        |        |
| Overhead                                                                   | 38%     | 34     | 34     |
| Depreciation rate                                                          | 6%      | 34     | 34     |
| Maintenance rate                                                           | 5%      | 34     | 34     |
| Total annual costs                                                         | €3,535,98 | €6,142,667 |        |
| **Operational information**                                                |         |        |        |
| Working days per week                                                      | 5       | 33     | 33     |
| Hours per day                                                              | 14      | 33     | 33     |
| Downtime days per year                                                     | 10      | 33     | 33     |
| Utilizations                                                               | 100%    | 98%    | 33     |
| Availability                                                               | 98%     | 98%    | 33     |
| Time per fraction (minutes)                                                | 15 ± 5  | 35 ± 5 | MC     |
| Fractions per years                                                        | 13,769  | 5,783  |        |
| Total costs per fraction                                                  | €256    | €1,062 |        |
Appendix E: Calculation of average travel distance to PT center

Table E.1. Average travel distance PT centers

| Distance from Amersfoort to: | Km | Annual capacity per PT center | %   |
|------------------------------|----|-------------------------------|-----|
| Holland-PTC (Delft)          | 90 | 600                           | 37,5% |
| ZON-PTC (Maastricht)         | 196| 400                           | 25,0% |
| Groningen-PTC                | 173| 600                           | 37,5% |
| **Total annual capacity**    | 1600|                               | 100% |
| **Weighted average distance**| 147.6 ± 45.5 Km | Return |

Appendix F: Calculation of productivity losses per working category

Table F.1. Productivity losses

| Hours per week | SE | Nr. of people | %   | Costs friction period |
|----------------|----|---------------|-----|-----------------------|
| Working population | 32,000 | 17.5 |            |                      |
| Fulltime         | 37.5 | 2.5 | 9,000     | 28.1 | €16,309               |
| Less than 12 hours per week | 8 | 4 | 11,000 | 34.4 | €3,479               |
| 12 – 20 hours per week | 16 | 4 | 4,000     | 12.5 | €6,959               |
| 20 – 35 hours per week | 27.5 | 7.5 | 8,000     | 25.0 | €11,960              |
| Friction period  | 12.1 | 2.4 |            |      |                      |
| Costs per hour   | €36.88 |            |      |                      |
| **Weighted average** | €1,731 | Per treatment |     |                      |

Appendix G: Cost-effectiveness (CE) plane, cost-effectiveness acceptability curves (CEAC), expected value of perfect information (EVPI) and deterministic one-way sensitivity analysis

Cost-effectiveness plane - Base Case
Fig. G.1. CE plane: Base case analysis

Fig. G.2. CEAC: Base case analysis

Cost-effectiveness acceptability curves - Base Case

Cost-effectiveness plane - Equal minutes assumed

Threshold
- PT all patients vs. RT all patients
- PT individualized vs. RT all patients
- PT all patients vs. PT individualized
Fig. G.3. CE plane: Scenario analysis - Equal minutes per fraction assumed (15 minutes)

Cost-effectiveness acceptability curves - Equal minutes assumed

Fig. G.4. CEAC: Scenario analysis – Equal minutes per fraction assumed

Expected Value of Perfect Information

Fig. G.5. Population EVPI for different threshold values
Fig. G.6. Deterministic one-way sensitivity analysis (DOWSA) - Tornado diagram
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Highlights

- Patient selection for whom PT is expected to be beneficial is crucial
- Normal tissue complication probability models are important for patient selection
- Clinical experience can increase throughput, improving cost-effectiveness of PT

Table 1. Treatment dependent probabilities estimated based on NTCP models

| Parameter | Estimated Value | SE   | Distribution | Source |
|-----------|-----------------|------|--------------|--------|
| **Photon-based radiotherapy for all patients (once only probability implemented in the first cycle)** | | | |
| Probability of dyspnea grade 2 | 14.0 % | 12.1 | Normal* | 16 |
| Probability of dyspnea grade ≥3 | 17.3 % | 18.0 | Normal* | 16 |
| Probability of dysphagia grade 2 | 30.3 % | 25.8 | Normal* | 18 |
| Probability of dysphagia grade ≥3 | 10.8 % | 13.9 | Normal* | 18 |
| Probability of mortality related to heart dose (two-year) | 16.6 % | 0.04 | Normal* | 19 |
| **Proton radiotherapy for all patients (once only probability implemented in the first cycle)** | | | |
| Probability of dyspnea grade 2 | 12.9 % | 10.4 | Normal* | 16 |
| Probability of dyspnea grade ≥3 | 13.5 % | 14.8 | Normal* | 16 |
| Probability of dysphagia grade 2 | 28.4 % | 24.8 | Normal* | 18 |
| Probability of dysphagia grade ≥3 | 10.3 % | 13.1 | Normal* | 18 |
| Probability of mortality related to heart dose (two-year) | 13.7 % | 0.03 | Normal* | 19 |
| **Proton radiotherapy for selected patients (once only probability implemented in the first cycle)** | | | |
| Probability of dyspnea grade 2 | 13.2 % | 12.6 | Normal* | 16 |
| Probability of dyspnea grade ≥3 | 14.3 % | 14.2 | Normal* | 16 |
| Probability of dysphagia grade 2 | 28.9 % | 26.4 | Normal* | 18 |
| Probability of dysphagia grade ≥3 | 10.5 % | 12.7 | Normal* | 18 |
Probability of mortality related to heart dose (two-year) 14.6% 0.03 Normal* 19
Survival rates (per three-month cycle)
Progression free survival for all strategies 83.5% 0.03 Gamma** 27
Overall survival XRT 90.9% 0.02 Gamma** 27
Overall survival PT for all patients (adjusted mortality related to heart dose) 92.5% 0.02 Gamma** -
Overall survival PT for selected patients (adjusted mortality related to heart dose) 92.3% 0.01 Gamma** -

SE = Standard error
* Distribution based on used NTCP models
** Distribution based on OS and PFS months
Detailed information about NTCP models and cardiotoxicity can be found in appendix B and C.

Table 2. Input parameters: Health state utilities (reference value) and disutilities

| Parameter                      | Estimated Value | SE   | Distribution | Source |
|--------------------------------|-----------------|------|--------------|--------|
| Health state utility           |                 |      |              |        |
| Progression Free - No Toxicity | 0.800           | 0.029| Beta         | 28     |
| Progressed Disease - No Toxicity| 0.794           | 0.038| Beta         | 28     |
| Disutility                    |                 |      |              |        |
| Dyspnea                       | -0.05           | 0.012| Normal       | 29     |
| Dysphagia                     |                 |      |              |        |
| Cardiotoxicity                |                 |      |              |        |
| Myocardial infarction         | -0.06           | 0.011| Normal       | 30     |
| Heart Failure                 | -0.14           | 0.022| Normal       | 30     |
| Arrhythmia                    | -0.02           | 0.004| Normal       | 31     |
| Age 75+ (Age at baseline: 66) | -0.01           | 0.002| Normal       | 32     |

Table 3. Treatment costs for proton radiotherapy and radiotherapy

| Parameter                      | PT               | XRT             | Source |
|--------------------------------|------------------|-----------------|--------|
| Building                       |                  |                 |        |
| Depreciation period (Years)    | 50               | 50              | 34     |
| Interest rate                  | 4.2%             | 4.2%            | 34     |
| Building                       | €15,500,000      | €10,798,444     | PT: 35 XRT: 31 |
| Medical equipment              |                  |                 |        |
| Depreciation period (Years)    | 10               | 10              | 34     |
| Interest rate                  | 4.2%             | 4.2%            | 34     |
| Medical equipment              | €25,000,000      | €5,881,506      | PT: 35 XRT: 33 |
| Personnel                      |                  |                 |        |
| Total annual personnel costs   | €392,091         | €392,091        | MC, 34, 36 |
| Other charges                  |                  |                 |        |
| Maintenance                    | 5%               | 5%              | 34     |
| Housing and depreciation       | 6%               | 6%              | 34     |
| Overhead                       | 38%              | 38%             | 34     |
| Operation                      |                  |                 |        |
| Working days per week          | 5                | 5               | 33     |
| Working hours per day          | 14               | 14              | 33     |
| Days of operation per year     | 251              | 251             | 33     |
| Treatment room utilization     | 98%              | 100%            | 33     |
| Treatment room availability    | 98%              | 98%             | 33     |
| Time per fraction in minutes (Range) | 35 (30-40) | 15 (10-20) | EO, 33 |
| Fractions per year             | 5,783            | 13,769          | -      |
| Costs per fraction             | €1,062           | €256            | -      |
Table 4. Costs and resource use (Price level: 2019)

| Parameter                                      | Estimated Value | SE  | Distribution | Source |
|------------------------------------------------|-----------------|-----|--------------|--------|
| **Treatment Costs**                            |                 |     |              |        |
| **Photon**                                      |                 |     |              |        |
| Number of fractions                            | 30              | 0.2 | Gamma        | 28     |
| Minutes per fraction                           | 15              | 5   | Gamma        | EO     |
| Costs per fraction b                           | €256            |     | Beta (PERT)  | CA     |
| **Radiotherapy**                                |                 |     |              |        |
| Number of fractions                            | 30              | 0.2 | Gamma        | 28     |
| Costs per fraction b                           | €1,062          |     | Beta (PERT)  | CA     |
| **Proton**                                      |                 |     |              |        |
| Minutes per fraction                           | 35              |     | Gamma        | EO     |
| **Related Health Care Costs**                  |                 |     |              |        |
| Dyspnea grade 2                                 |                 |     |              |        |
| Total costs incl. home care and rehab.          | €974            |     | Fixed        | 37     |
| Dyspnea grade ≥3                               | €2,859          |     | Fixed        | 37     |
| Dysphagia grade 2                              |                 |     |              |        |
| Months of medication for dysphagia              | 1               | 0.2 | Gamma        | EO     |
| Costs of medication per month                  | €46             |     | Fixed        | MP, 42 |
| Days of liquid nutrition                       | 28              | 5.6 | Gamma        | EO     |
| Portion of liquid nutrition per day            | 3.7             | 0.74| Gamma        | 38     |
| Costs of liquid nutrition per portion          | €3.60           |     | Fixed        | MP     |
| Dysphagia grade ≥3                             |                 |     |              |        |
| Months of medication for dysphagia              | 1               | 0.2 | Gamma        | EO, 14 |
| Costs of medication per month                  | €46             |     | Fixed        | 42     |
| Hospitalization days                           | 6               | 0.9 | Gamma        | 28     |
| Costs of hospital stay per day                 | €505            |     | Fixed        | 34     |
| Tube feeding days                              | 14              | 2.8 | Gamma        | EO     |
| Costs of tube feeding per day                  | €12             |     | Fixed        | MP     |
| Costs of placing and removing tube             | €335            |     | Fixed        | 28     |
| Hours of Home care per day                     | 0.5             | 0.1 | Gamma        | EO     |
| Home care days                                 | 14              | 2.8 | Gamma        | EO     |
| Costs of Home care per hour (nurse)            | €77             |     | Fixed        | 34     |
| **Cardiotoxicity**                             |                 |     |              |        |
| Ischemic Heart disease (Age range: 66-99)      | Range:          |     | -            | 39     |
| Heart failure and arrhythmia (Age range: 66-99)| Range:          |     | -            | 39     |
| **Follow-up visits**                           |                 |     |              |        |
| Follow-up visits first year                    | 4               | 0.8 | Gamma        | 43     |
| CT-scan first year                             | 1               | 0.2 | Gamma        | 43     |
| Follow-up visits second year                   | 2               | 0.4 | Gamma        | 43     |
| CT-scan second year                            | 1               | 0.2 | Gamma        | 43     |
| Follow-up visits per year after the second year| 1               | 0.2 | Gamma        | 43     |
| Until 5 years                                  |                 |     |              |        |
| CT-scan per year after the second year until 5 years | 1               | 0.2 | Gamma        | 43     |
| Costs per follow-up visit                     | €97             |     | Fixed        | 34     |
| Costs per CT-scan                             | €154            |     | Fixed        | 34     |
| **Patient and Family Costs**                   |                 |     |              |        |
| **Traveling costs**                            |                 |     |              |        |
| Parking costs per day                          | €3.18           |     | Fixed        | 34     |
| Number of km (return) PT                      | 148             | 45.5| Gamma        | -      |
| Number of km (return) XRT                     | 46              | 9.2 | Gamma        | 34     |
| Taxi use (%)                                   | 58.7%           | 0.25| Beta         |        |
| Private vehicle use (%)                       | 41.3%           | 0.25| Beta         |        |
| Costs Taxi (constant + costs per km)          | €3.13 + €2.82   |     | Fixed        | 34     |
| **Informal care**                              |                 |     |              |        |
| Hours of informal care PT                     | 5               | 1   | Gamma        | -      |
| Hours of informal care XRT                    | 2               | 0.4 | Gamma        | -      |
| Costs per hour of informal care               | €15             |     | Fixed        | 34     |
| **Unrelated healthcare costs**                 |                 |     |              |        |
Unrelated disease costs  
Costs of diseases in life-years gained (Age range: 66 - 99)  
Range: €1,235 - €17,778

Costs of progression  
Costs of last year of living (Age range 66 - 99)  
Range: €3,517 - €8,815

Inter-sectoral cost  
Friction period (weeks)  
12.1  2.4

Productivity losses  
Working population (%)  
17.5%  3.5

Full-time (%)  
28%  5.6

Part-time (%)  
72%  14.4

Table 5. Results of probabilistic sensitivity analyses (Sorted by costs)

| Analysis                      | Strategy            | Costs    | QALY | NMB     | ΔCosts | ΔQALY | ICER     | Compared with XRT For all patients | Compared with next best ICER |
|-------------------------------|---------------------|----------|------|---------|--------|--------|----------|-------------------------------------|-----------------------------|
|                               |                     |          |      |         |        |        |          |                                     |                             |
|                               |                     | €45,91   | 1.76 | €95,627 |        |        |          |                                     |                             |
|                               |                     | 2        |      |         |        |        |          |                                     |                             |
| Base Case                     | XRTAll              | €41,23   | 1.76 | €100,28 |        |        |          |                                     |                             |
|                               |                     | 1        |      |         |        |        |          |                                     |                             |
|                               | PT Individualize d   | €61,72   | 1.92 | €92,034 | €20,49 | 0.153  | €134,25  | €134,256                            |                             |
|                               |                     | 6        |      |         |        |        |          |                                     |                             |
|                               |                     | €68,90   | 1.95 | €87,176 | €27,67 | 0.182  | €152,09  | €245,053                            |                             |
|                               |                     | 4        |      |         |        |        |          |                                     |                             |
|                               | PTAll               | €41,91   | 1.76 | €95,608 |        |        |          |                                     |                             |
|                               |                     | 2        |      |         |        |        |          |                                     |                             |
|                               |                     | €69,66   | 1.92 | €84,098 | €23,75 | 0.153  | €155,58  | €155,582                            |                             |
|                               |                     | 6        |      |         |        |        |          |                                     |                             |
|                               |                     | €78,02   | 1.95 | €78,057 | €32,11 | 0.181  | €176,48  | €285,415                            |                             |
|                               |                     | 3        |      |         |        |        |          |                                     |                             |
|                               | XRTAll              | €57,41   | 1.91 | €95,376 | €12,00 | 0.157  | €76,299  | €76,299                             |                             |
|                               |                     | 6        |      |         |        |        |          |                                     |                             |
|                               | PT Individualize d   | €61,18   | 1.94 | €94,023 | €15,78 | 0.188  | €84,106  | €124,719                            |                             |
|                               |                     | 9        |      |         |        |        |          |                                     |                             |

QALY = Quality Adjusted Life Years  
NBM = Net Monetary Benefit  
ICER = Incremental Cost Effectiveness Ratio

Table A.1. Patient characteristics

| Mean age (years) | XRT     | PT     | P | Source |
|------------------|---------|--------|---|--------|
|                  | 66 (SD 10) |        |   | 24     |
**Gender**
- Male: 69.2%
- Female: 30.8%

**Smoking (yes)**: 36.9%

**Chemotherapy**: 88.0%

**Concurrent WHO-PS (≥2)**: 11.6%

**Baseline dyspnea grade 1**: 28.7%

**Baseline dyspnea grade ≥2**: 11.0%

**Mean GTV (cm$^3$)**: 112.6 (SD 64.3)

**OTT (days)**: 40 (SD 8.0)

**MHD (Mean (Gy))**:
- Normal: 14.3 (SD 10.3) 7.6 (SD 7.2) <0.001
- Current smoker (yes/no): 16.4 (SD 5.5) 13.5 (SD 6.2) <0.001
- Baseline dyspnea grade 1 vs 0: 26.0 (SD 12.1) 24.4 (SD 13.7) <0.001
- Baseline dyspnea grade ≥2 vs 0: 64.7 (SD 15.8) 63.6 (SD 17.8) <0.001

**MLD (Mean (Gy))**:
- Normal: 16.4 (SD 5.5) 13.5 (SD 6.2) <0.001
- Current smoker (yes/no): 26.0 (SD 12.1) 24.4 (SD 13.7) <0.001
- Baseline dyspnea grade 1 vs 0: 64.7 (SD 15.8) 63.6 (SD 17.8) <0.001
- Baseline dyspnea grade ≥2 vs 0: 64.7 (SD 15.8) 63.6 (SD 17.8) <0.001

**MED (Mean (Gy))**:
- Normal: 16.4 (SD 5.5) 13.5 (SD 6.2) <0.001
- Current smoker (yes/no): 26.0 (SD 12.1) 24.4 (SD 13.7) <0.001
- Baseline dyspnea grade 1 vs 0: 64.7 (SD 15.8) 63.6 (SD 17.8) <0.001
- Baseline dyspnea grade ≥2 vs 0: 64.7 (SD 15.8) 63.6 (SD 17.8) <0.001

**MAXED (Mean (Gy))**:
- Normal: 16.4 (SD 5.5) 13.5 (SD 6.2) <0.001
- Current smoker (yes/no): 26.0 (SD 12.1) 24.4 (SD 13.7) <0.001
- Baseline dyspnea grade 1 vs 0: 64.7 (SD 15.8) 63.6 (SD 17.8) <0.001
- Baseline dyspnea grade ≥2 vs 0: 64.7 (SD 15.8) 63.6 (SD 17.8) <0.001

**Abbreviations**: WHO-PS = World Health Organizations Performance Status; GTV = Gross Tumor Volume; OTT = Overall Treatment Time; MHD = Mean Heart Dose; MLD = Mean Lung Dose; MED = Mean Esophagus Dose; MAXED = Maximum Esophagus Dose; Gy = Gray.

### Table B.1. 24 months’ mortality NTCP models → GTV-smoker-MHD model

| Coefficient | SE   | OR   | 95% CI          |
|------------|------|------|-----------------|
| Intercept 80 | -0.090 | 0.018 | 0.914 Normal    |
| Gross Tumor Volume (GTV) (+1 cc) | 0.005 | 0.003 | 1.005 0.999 - 1.011 Normal |
| Current smoker (yes/no) | 0.456 | 0.432 | 2.490 1.067 - 5.809 Normal |
| Mean Heart Dose (MHD) (+1 Gy) | 0.033 | 0.025 | 1.033 0.985 - 1.084 Normal |

### Table B.2. NTCP model Dyspnea = 2

| Coefficient | SE   | OR   | 95% CI          |
|------------|------|------|-----------------|
| Intercept 80 | -3.186 | 0.948 | 0.041 0.006 - 0.266 Normal |
| Mean Lung Dose (MLD) (+1 Gy) | 0.043 | 0.048 | 1.044 0.950 - 1.147 Normal |
| Chemotherapy (vs none) | -0.807 | 0.483 | 0.446 0.173 - 1.150 Normal |
| Baseline dyspnea grade 1 vs 0 | 1.635 | 0.791 | 5.129 1.087 - 24.191 Normal |
| Baseline dyspnea grade ≥2 vs 0 | 3.382 | 0.802 | 29.430 6.110 - 141.741 Normal |

### Table B.3. NTCP model Dyspnea ≥ 3 Endpoint

| Coefficient | SE   | OR   | 95% CI          |
|------------|------|------|-----------------|
| Intercept 80 | -4.081 | 1.020 | 0.017 0.002 - 0.125 Normal |
| Mean Lung Dose (MLD) (+1 Gy) | 0.150 | 0.061 | 1.162 1.031 - 1.309 Normal |
| Chemotherapy (vs none) | -0.937 | 0.572 | 0.392 0.128 - 1.202 Normal |
Baseline dyspnea grade 1 vs 0  
0.299 0.692 1.349 0.348 - 5.233 Normal

Baseline dyspnea grade ≥2 vs 0  
2.516 0.666 12.380 3.350 - 45.696 Normal

Table B.4. NTCP model Dysphagia grade ≥2

| Coefficient | SE  | OR   | 95% CI          | Distribution |
|--------------|-----|------|-----------------|--------------|
| Intercept β0 | -0.195 | 0.936 | 0.823 0.128 - 5.156 | Normal       |
| Age          | -0.030 | 0.010 | 0.970 0.950 - 0.990 | Normal       |
| Female (vs male) | 0.501 | 0.198 | 1.650 1.120 - 2.430 | Normal       |
| WHO-PS ≥2 (vs 0-1) | 0.568 | 0.228 | 1.760 1.130 - 2.750 | Normal       |
| Concurrent chemotherapy (vs no/sequential) | 0.928 | 0.222 | 2.530 1.640 - 3.910 | Normal       |
| Mean esophagus dose (MED) | 0.061 | 0.014 | 1.060 1.040 - 1.090 | Normal       |
| Maximum esophagus dose (MAXED) | 0.030 | 0.010 | 1.030 1.010 - 1.050 | Normal       |
| Overall treatment time (OTT) | -0.059 | 0.011 | 0.940 0.920 - 0.960 | Normal       |

Table B.5. NTCP model Dysphagia grade ≥3

| Coefficient | SE  | OR   | 95% CI          | Distribution |
|--------------|-----|------|-----------------|--------------|
| Intercept β0 | -2.351 | 0.919 | 0.095 0.015 - 0.577 | Normal       |
| Age          | -0.030 | 0.010 | 0.970 0.950 - 0.990 | Normal       |
| Female (vs male) | 0.501 | 0.198 | 1.650 1.120 - 2.430 | Normal       |
| WHO-PS ≥2 (vs 0-1) | 0.568 | 0.228 | 1.760 1.130 - 2.750 | Normal       |
| Concurrent chemotherapy (vs no/sequential) | 0.928 | 0.222 | 2.530 1.640 - 3.910 | Normal       |
| Mean esophagus dose (MED) | 0.061 | 0.014 | 1.060 1.040 - 1.090 | Normal       |
| Maximum esophagus dose (MAXED) | 0.030 | 0.010 | 1.030 1.010 - 1.050 | Normal       |
| Overall treatment time (OTT) | -0.059 | 0.011 | 0.940 0.920 - 0.960 | Normal       |

Abbreviations: Se = standard error, OR = Odds ratio, CI = confidence interval, NTCP = normal tissue complication probability

Table C.1. Distribution of Cardiac events

| Percentage | SE  | Distribution |
|------------|-----|--------------|
| Arrhythmia | 43.9% | 11.5 | Beta |
| Atrial + Ventricular |

Ischemic heart disease | 22.2% | 3.3 | Beta |
| Myocardial infarction + Coronary artery disease + Angina pectoris (cardiac cause) |

Heart Failure | 33.9% | 5.1 | Beta |
| Acute + Chronic heart failure + Valve defects |

Table C.2. Lognormal Time to event model for cardiotoxicity
### Table D.1. Cost-analysis PT vs XRT

| Description                                                                 | XRT       | PT        | Source |
|----------------------------------------------------------------------------|-----------|-----------|--------|
| **Equipment**                                                              |           |           |        |
| Depreciation period (years)                                                | 10        | 34        |        |
| Interest rate                                                              | 4.2%      | 34        |        |
| Annuity factor                                                             | 8.0       | 34        |        |
| Purchase price                                                             | €5,881,506| €25,000,00|        |
| Annual depreciation and interest costs                                      | €732,374  | €3,113,038|        |
| **Building**                                                               |           |           |        |
| Depreciation period (years)                                                | 50        | 34        |        |
| Interest rate                                                              | 4.2%      | 34        |        |
| Annuity factor                                                             | 20.8      | 34        |        |
| Purchase price                                                             | €10,798,44| €15,500,00|        |
| Annual depreciation and interest costs                                      | €520,004  | €746,409  |        |
| **Personnel**                                                              |           |           |        |
| Irregularity rate radiation technologists and physicist per month (between 20.00-22.00h) | 7%        | 34        |        |
| Irregularity rate physician per month                                       | 10%       | 34        |        |
| Allowances rate radiation technologist/physicist per month                 | 37%       | 34        |        |
| Allowances radiation physician per month                                   | €523      | 36        |        |
| Monthly salary radiation technologist (excl.)                              | €3,242    | 36        |        |
| Monthly salary physicist (excl.)                                           | €6,361    | 36        |        |
| Monthly salary physician (excl.)                                           | €9,941    | 36        |        |
| FTE radiation technologist                                                 | 4         | MC        |        |
| FTE physicist                                                              | 0.5       | MC        |        |
| FTE physician                                                              | 0.6       | MC        |        |
| **Annual costs**                                                           |           |           |        |
| Overhead                                                                   | 38%       | 34        |        |
| Depreciation rate                                                          | 6%        | 34        |        |
| Maintenance rate                                                           | 5%        | 34        |        |
| Total annual costs                                                         | €3,535,598| €6,142,667|        |
| **Operational information**                                                |           |           |        |
| Working days per week                                                      | 5         | 33        |        |
| Hours per day                                                              | 14        | 33        |        |
| Downtime days per year                                                     | 10        | 33        |        |
| Utilizations                                                               | 100%      | 98%       | 33     |
Availability  
98%  
98%  

Time per fraction (minutes)  
15 ± 5  
35 ± 5  
MC

Fractions per years  
13,769  
5,783

Total costs per fraction  
€256  
€1,062

MC = MAASTRO Clinic (G. Bosman, personal communication, May 29, 2019)

Table E.1. Average travel distance PT centers

| Distance from Amersfoort to: | Km | Annual capacity per PT center | % |
|-------------------------------|----|-------------------------------|---|
| Holland-PTC (Delft)           | 90 | 600                           | 37.5% |
| ZON-PTC (Maastricht)          | 196| 400                           | 25.0% |
| Groningen-PTC                 | 173| 600                           | 37.5% |
| Total annual capacity         | 1600| 100%                        |

Weighted average distance 147.6 ± 45.5 Km

Table F.1. Productivity losses

| Hours per week | SE | Nr. of people | % | Costs friction period |
|----------------|----|---------------|---|-----------------------|
| Working population | 32,000| 17.5         |    |                       |
| Fulltime        | 37.5| 2.5           | 9,000| 28.1 | €16,309                   |
| Less than 12 hours per week | 8| 4            | 11,000| 34.4 | €3,479                   |
| 12 – 20 hours per week      | 16| 4            | 4,000| 12.5 | €6,959                    |
| 20 – 35 hours per week      | 27.5| 7.5          | 8,000| 25.0 | €11,960                   |
| Friction period | 12.1| 2.4           |    |                       |
| Costs per hour | €36.88|               |    |                       |

Weighted average €1,731 Per treatment

Figure 1. Schematic representation of the Markov Model structure. The model is divided into acute (<6 months) and late (≥ 6 months) time
frame. Additionally, the model consists a progression free and progressed disease part.
Grading of toxicities was not used in the schematic model structure in order to prevent unnecessary complexity.
PF = Progression free; PD = Progressed disease.

**Cumulative incidence Cardiac Events**

*Fig. C.1. Cumulative incidence curve Cardiac Events*

*Fig. C.2. Parametric model curve Cardiac Events*
**Expected Value of Perfect Information**

![Graph showing the expected value of perfect information (EVPI) as a function of the ceiling ratio/willingness-to-pay. The graph illustrates the relationship between EVPI and the ceiling ratio/willingness-to-pay, with a peak at €544 million at a ceiling ratio of €19,000.]

**INMB DOWSA**

| Condition                        | INMB Minimum Value | INMB Maximum Value |
|----------------------------------|--------------------|--------------------|
| Percentage Arrhythmia            |                    |                    |
| Percentage Heart Failure         |                    |                    |
| Percentage Myocardial Infarction |                    |                    |
| PD - No toxicity (<6 mo)         |                    |                    |
| Disutility Age ≥ 75              |                    |                    |

Legend:
- iNMB minimum value
- iNMB maximum value