**Supplementary Material to:**

**Model-based assess­ment of the­ cost-effectiveness of conventional and innovative chemo-radiation schemes in non-small cell lung cancer**

Page

Supplementary Figure 1 2

Supplementary Figure 2 3

Supplementary Figure 3 4

Supplementary Figure 4 5

Supplementary Figure 5 6

Supplementary Table 1 7

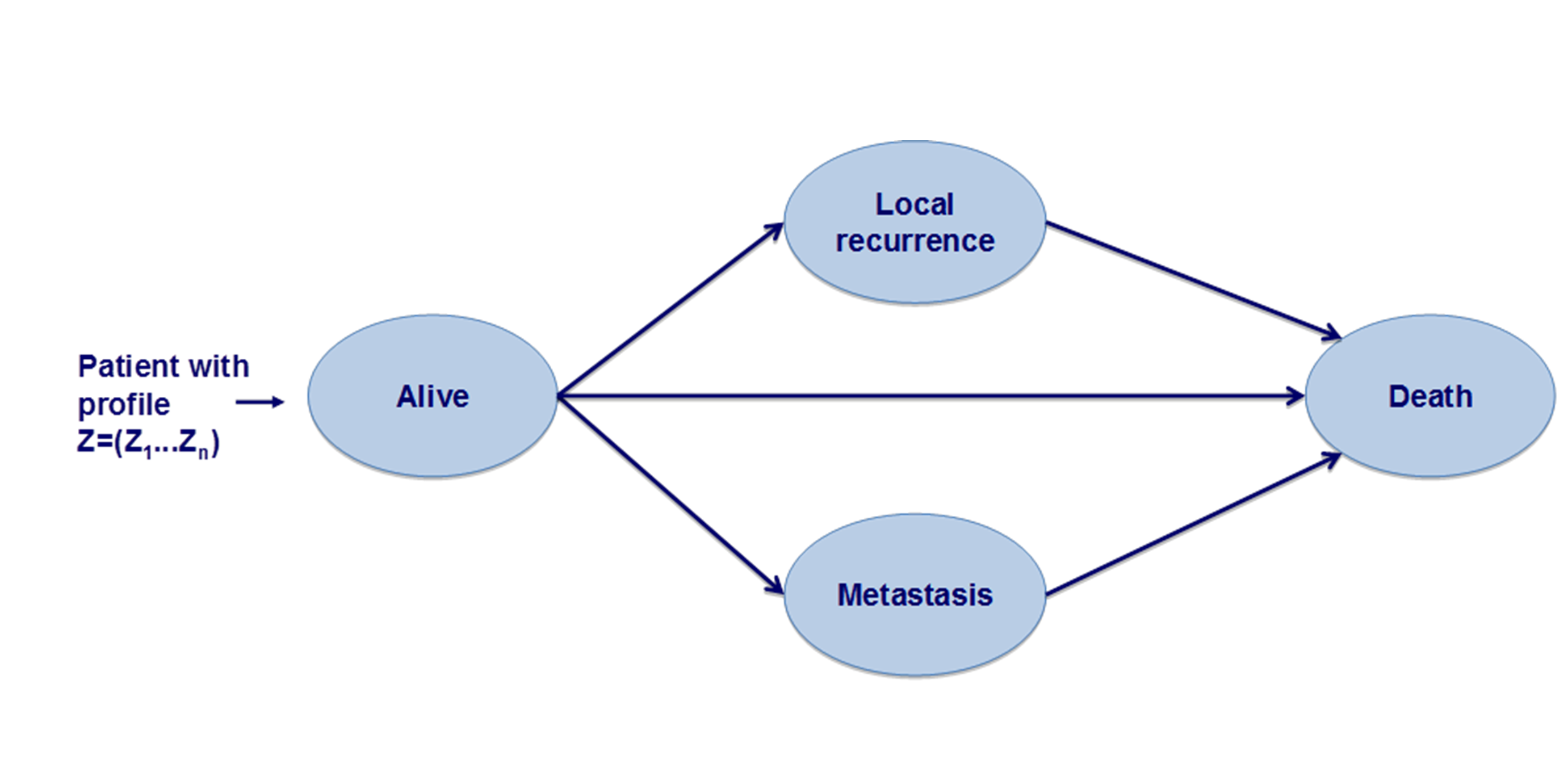
Supplementary Table 2 9

Supplementary Table 3 10

Supplementary Table 4 11

Supplementary Table 5 12

Supplementary Table 6 13



**Supplementary Figure 1.** Flowchart of the lung cancer chemo-radiotherapy model. Z refers to the vector of covariates that influences the transitions in the model and (z1,…,zn) refers to the specific values for these covariates for a specific patient.



**Supplementary Figure 2.** Stacked cumulative baseline hazards over time for transition 1-3.



**Supplementary Figure 3.** Cumulative baseline hazards over time for transition 4 and 5.

****

**Supplementary Figure 4.** Model validation for SRT1 and SRT2. Model output is the result of a simulation round with a case-mix of patients in the patient cohort similar to the data. SRT1 = conventional sequential chemo-radiation, SRT2 = sequential PET-CT-based isotoxic accelerated chemo-radiation.



**Supplementary Figure 5.** Results of the two scenario and four sensitivity analysis. SRT1: conventional sequential chemo-radiation, CRT1: conventional concurrent chemo-radiation, SRT2: sequential PET-CT-based isotoxic accelerated chemo-radiation, CRT2: concurrent chemo-radiation with daily low-dose cisplatin administration and daily radiation.

**Supplementary Table 1:** Estimation of health parameters by statistical modelling

|  |
| --- |
| A flowchart of the model is depicted in Supplementary Figure 1. To estimate individualized time-dependent hazard rates for each transition in the model we used multi-state modelling. This is a statistical technique for time-to-event data in which all patients start in one or more starting states and end up in one or more absorbing states (often death)\*. The method is an extension of the Cox proportional hazards model. It allows for simultaneously estimating the hazard rate ratios for each included clinical or tumor feature for all transitions as well as their covariance.  For each transition k in the model (k=1,…,5) and individual patient profile z=(z1,…,zm), the hazard rate equals:  (1)  Where λk,0 (t) is the baseline time-dependent hazard for each transition k, and βk for each transition k (k=1,…,5) is a vector of coefficients specifying the personal hazard rate, ie the natural logarithm of the hazard rate ratio for each of the patient and tumor features included in the model.  In the statistical model, we included factors that were available in the database; ‘WHO performance status’, ‘N- stage’, ‘gross tumor volume (GTV)’, ‘history of chemotherapy’, ‘age’ and ‘gender’. We first tested whether these covariates and the type of RT treatment ‘RT2’ (isotoxic compared to fixed dose radiotherapy) were prognostic for any of the 5 transitions in our simulation model. We used backward selection to identify the variables that were most significantly associated with timing of LR, M and Death. We found the factors ‘WHO performance status’, ‘N- stage’, ‘GTV’, ‘history of chemotherapy’ and ‘RT2’ to be prognostic for transitions 1-3 in our statistical model. For transition 4 and 5, only ‘RT2’ was included in the model, by forced entry. Gender and age were removed from the model.  We used the *mstate* package in R version 2.15.  To allow prediction of individual life histories in the micro-simulation model, also an estimate of the baseline hazard is required. In formula (1), when the personal time-independent hazard ratios are equal to 1, the obtained personal hazard rate narrows down to the baseline hazard λ0,k (t) for each transition k. Thus, the baseline hazards were obtained by applying the estimated multi-state statistical model to a hypothetical patient with scores 0 on all covariates, by using the *msfit* function in the *mstate* package in R. The baseline hazards for each transition over time are presented in Supplementary Figures 2 and 3.  Note that, using mstate, we have estimated cause-specific hazard rates, which means that individuals experiencing a competing event are treated as censored for the event of interest. As LR, DM, and Death are mutually exclusive events in the micro-simulation model, a competing risk correction is required. This is done by calculating the cumulative incidence from the separate cause-specific hazards. Application of the competing risk correction for transition 1 to 3 results in three cumulative risk curves, as is shown in Supplementary Figure 2 for a specific patient profile (scores of 0 on all covariates). The curves are depicted in a stacked manner.  The probabilities to obtain dysphagia for SRT1 and SRT2 were estimated by using a ordered logit model, with three categories ( 0 = no dysphagia, 1= grade 1 and 2 dysphagia and 2= grade 3+ dysphagia, based on CTC scores).  Based on patient profiles, we calculated for each patient two numbers between 0 and 1 that are the cut-off values between the three categories, according to the formula for ordered logistic regression:    where **α**j (j{1,2}) is the intercept for the cut-off probability Pj between category 0 and 1 and between category 1 and 2. The linear predictors for j=1 and j=2 are :  Linear predictor for j=1 : (βPET-CT-based \* XPET-CT-based+ βNstage\* XNstatus)-α1  Linear predictor for j=2 : (βPET-CT-based \* XPET-CT-based βNstage\* XNstatus)-α2 |

\*Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007;26(11):2389–430.

**Supplementary Table 2:** Overview of the baseline characteristics per strategy in original data sources

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | SRT1 | CRT1 | SRT2 | CRT2 |
|  |  |  |  |  |  |
| WHO performance status | 0-1 | 0.89 | 0.98 | 0.84 | 0.8 |
|  | >=2 | 0.11 | 0.02 | 0.16 | 0.2 |
|  |  |  |  |  |  |
| Nstatus | 0-1 | 0.26 | 0.75 | 0.25 | 0.82 |
|  | >=2 | 0.74 | 0.25 | 0.75 | 0.18 |
|  |  |  |  |  |  |
| GTV | mean | 78 | 115 | 54 | 137 |

SRT1: conventional sequential chemo-radiation, CRT1: conventional concurrent chemo-radiation, SRT2: sequential PET-CT-based isotoxic accelerated chemo-radiation, CRT2: concurrent chemo-radiation with daily low-dose cisplatin administration and daily radiation, WHO: World Health Organization, GTV: gross tumor volume.

**Supplementary Table 3:** Calibration procedure and model validation

|  |
| --- |
| *Calibration procedure CRT1 and CRT2*  The calibration procedure itself was carried out as follows. First, we randomly drew a cohort of patients with clinical and tumor characteristics similar to the distribution of those features in the original data sources for CRT1 and CRT2, respectively. Simulating the disease course for this cohort with the micro-simulation model while setting the five HRs for treatment effect to 1 results in predicted survival as if the cohort were treated with SRT1*.*  Subsequently, 1000 sets of five HRs specifying the treatment effect of CRT1 (CRT2) versus SRT1 for each transition were drawn at random from lognormal distributions with mean zero and standard error 1. For each random set of 5 HRs, the micro simulation model was run for a cohort of 50000 patients, again with baseline features similar to the data source for calibration. The results of each run were used to calculate the goodness of fit (GOF) measure for each random set of 5 HRs. The GOF measure used was the weighed Sum of Squared Errors (SSE). That is, we summed the squared differences between the model predictions for the proportion survivors at 1, 2 and 3 year and the corresponding calibrations targets. |
| *Model validation SRT1 and SRT2*  The micro-simulation model was initially quantified with data on patients that either received sequential chemoradiotherapy or received radiotherapy alone. To validate the model for patients that received sequential chemoradiotherapy only, we performed a subgroup analysis simulating patients that received sequential chemoradiation and comparing those predictions to the corresponding subset in the data. The results of this model validation are presented in Supplementary Figure 4. |

SRT1: conventional sequential chemo-radiation, CRT1: conventional concurrent chemo-radiation, SRT2: sequential PET-CT-based isotoxic accelerated chemo-radiation, CRT2: concurrent chemo-radiation with daily low-dose cisplatin administration and daily radiation.

**Supplementary Table 4:** Detailed overview of cost calculations for chemotherapy per strategy.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Drug | Vial | Unit cost (EUR)\* |  | SRT1\*\* | | | CRT1\*\* | | | SRT2\*\* | | | CRT2\*\* | | |
|  |  |  |  | N | Total |  | N | Total |  | N | Total |  | N | Total |  |
| Gemcitabine | 2000 mg | 245 |  | 2 | 490 |  |  |  |  | 2 | 490 |  |  |  |  |
|  | 1000 mg | 130 |  | 0 | 0 |  |  |  |  | 0 | 0 |  |  |  |  |
|  | 200 mg | 25 |  | 2 | 50 |  |  |  |  | 2 | 50 |  |  |  |  |
| Subtotal (EUR) |  |  |  |  |  | 540 |  |  |  |  |  | 540 |  |  |  |
| Vinblastine | 10 ml | 25.3 |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Cisplatine | 100 mg | 46 |  | 2 | 92 |  | 2 | 92 |  | 2 | 92 |  | 0 | 0 |  |
|  | 50 mg | 23 |  | 0 | 0 |  | 0 | 0 |  | 0 | 0 |  | 0 | 0 |  |
|  | 20 mg | 11.6 |  | 2 | 23 |  | 4 | 46 |  | 2 | 23 |  | 24 | 278 |  |
|  | 10 mg | 4.6 |  | 2 | 9 |  | 0 | 0 |  | 2 | 9 |  | 0 | 0 |  |
| Subtotal (EUR) |  |  |  |  |  | 124 |  |  | 138 |  |  | 124 |  |  | 278 |
| Etoposide | 50 mg | 147.23 |  |  |  |  | 9 | 1325 |  |  |  |  |  |  |  |
|  | 25 mg | 71.95 |  |  |  |  | 0 | 0 |  |  |  |  |  |  |  |
|  | 20 mg | 57.57 |  |  |  |  | 3 | 173 |  |  |  |  |  |  |  |
|  | 12,5 mg | 36.07 |  |  |  |  | 0 | 0 |  |  |  |  |  |  |  |
|  | 10 mg | 28.8 |  |  |  |  | 0 | 0 |  |  |  |  |  |  |  |
|  | 5 mg | 14.4 |  |  |  |  | 0 | 0 |  |  |  |  |  |  |  |
| Subtotal (EUR) |  |  |  |  |  |  |  |  | 1494 |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Subtotal Chemo (EUR) |  |  |  |  |  | 664 |  |  |  |  |  | 664 |  |  |  |
| Hospital admission per night |  | 462 |  | 0 |  |  |  | 2 |  | 0 |  |  | 24 |  |  |
| Outpatient day |  | 236 |  | 2 |  |  |  | 1 |  | 2 |  |  | 0 |  |  |
| Cycli |  |  |  | 4 |  |  |  | 4 |  | 4 |  |  | 0 |  |  |
| Subtotal hospital (EUR) |  |  |  |  |  | 2104 |  |  | 2378 |  |  | 2104 |  |  | 6312 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Total (EUR) |  |  |  |  |  | **2768** |  |  | **4014** |  |  | **2768** |  |  | **6590** |

N: number of units, SRT1: conventional sequential chemo-radiation, CRT1: conventional concurrent chemo-radiation, SRT2: sequential PET-CT-based isotoxic accelerated chemo-radiation, CRT2: concurrent chemo-radiation with daily low-dose cisplatin administration and daily radiation.

\*prices are obtained from zorgkosten.nl, accessed at 16-11-2014  
\*\* numbers are rounded

**Supplementary Table 5:** Break-down of total costs per strategy (EUR)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Cost item** | **SRT1** | **CRT1** | **SRT2** | **CRT2** |
| Radiotherapy treatment | 7560 | 7560 | 8716 | 5864 |
| PET-imaging | 0 | 0 | 1406 | 0 |
| Chemotherapy treatment | 2768 | 4014 | 2768 | 6590 |
| Follow-up visits | 238 | 268 | 282 | 295 |
| Toxicity | 1077 | 1684 | 1253 | 421 |
| End-of-life care | 5645 | 5230 | 4647 | 4191 |
|  |  |  |  |  |
| Total costs (EUR) | 17288 | 18756 | 19072 | 17361 |
| Discounted costs (EUR) | 17156 | 18627 | 18958 | 17257 |

SRT1: conventional sequential chemo-radiation, CRT1: conventional concurrent chemo-radiation, SRT2: sequential PET-CT-based isotoxic accelerated chemo-radiation, CRT2: concurrent chemo-radiation with daily low-dose cisplatin administration and daily radiation.

**Supplementary Table 6:** Results of the scenario and sensitivity analyses. Discounted costs, LYs, QALYs, ICERs and ICURs are presented. A strategy is termed ‘dominated’ if there is an alternative strategy that is more effective at equal or lower costs. We use the term ‘dominant’ if a strategy is more effective at equal or lower costs than the other strategies.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Base-case scenario | |  |  | Comparator is SRT1 | |  |  | Comparator is next best non-dominated strategy | | |
|  | **Costs** | **LY** | **QALYs** | **ICER** | **ICUR** |  |  | **ICER** | **ICUR** | **Comparator** |
| SRT1 | 17156 | 1,37 | 1,09 |  |  |  | SRT1 | Reference | | |
| CRT1 | 18627 | 1,42 | 1,13 | 29814 | 38024 |  | CRT1 | Dominated by CRT2 | | |
| SRT2 | 18958 | 1,75 | 1,38 | 4708 | 6249 |  | SRT2 | Dominated by CRT2 | | |
| CRT2 | 17257 | 1,75 | 1,38 | 263 | 346 |  | CRT2 | 263 | 346 | SRT1 |
|  | | | | | | | | | | |
| Scenario 1: patients in the simulation have a good WHO ps status, good Nstatus (75% N-status 0 or 1) and a gross tumour volume of 100cc | | | | Comparator is SRT1 | |  |  | Comparator is next best non-dominated strategy | | |
|  | **Costs** | **LY** | **QALYs** | **ICER** | **ICUR** |  |  | **ICER** | **ICUR** | **Comparator** |
| SRT1 | 16846 | 1,53 | 1,23 |  |  |  | SRT1 | Dominated by CRT2 | | |
| CRT1 | 18355 | 1,55 | 1,24 | 74937 | 140866 |  | CRT1 | Dominated by SRT2 and CRT2 | | |
| SRT2 | 18321 | 1,97 | 1,55 | 3352 | 4609 |  | SRT2 | 31020 | 55746 | CRT2 |
| CRT2 | 16838 | 1,92 | 1,52 | Dominant | Dominant |  | CRT2 | Reference | | |
|  | | | | | | | | | | |
| Scenario 2: costs and disutilities of toxicities are assumed to be 0 | | | | Comparator is SRT1 | |  |  | Comparator is next best non-dominated strategy | | |
|  | **Costs** | **LY** | **QALYs** | **ICER** | **ICUR** |  |  | **ICER** | **ICUR** | **Comparator** |
| SRT1 | 16080 | 1,37 | 1,12 |  |  |  | SRT1 | Reference | | |
| CRT1 | 16944 | 1,42 | 1,16 | 17516 | 21361 |  | CRT1 | Dominated by CRT2 | | |
| SRT2 | 17708 | 1,75 | 1,44 | 4254 | 5188 |  | SRT2 | Dominated | 87000 | CRT2 |
| CRT2 | 16838 | 1,75 | 1,43 | 1983 | 2419 |  | CRT2 | 1983 | 2419 | SRT1 |
|  | | | | | | | | | | |
| Sensitivity analysis 1a: Treatment effects are according to the lower band of the 95% CI of survival | | | | Comparator is SRT1 | |  |  | Comparator is next best non-dominated strategy | | |
|  | **Costs** | **LY** | **QALYs** | **ICER** | **ICUR** |  |  | **ICER** | **ICUR** | **Comparator** |
| SRT1 | 17156 | 1,37 | 1,09 |  |  |  | SRT1 | Reference | | |
| CRT1 | 18910 | 1,19 | 0,94 | Dominated | |  | CRT1 | Dominated by CRT2 | | |
| SRT2 | 19876 | 1,35 | 1,06 | Dominated | |  | SRT2 | Dominated by CRT2 | | |
| CRT2 | 17755 | 1,61 | 1,27 | 2435 | 3325 |  | CRT2 | 2435 | 3325 | SRT1 |
|  | | | | | | | | | | |
| Sensitivity analysis 1b: treatment effects are according to the upper band of the 95% CI of survival | | | | Comparator is SRT1 | |  |  | Comparator is next best non-dominated strategy | | |
|  | **Costs** | **LY** | **QALYs** | **ICER** | **ICUR** |  |  | **ICER** | **ICUR** | **Comparator** |
| SRT1 | 17156 | 1,37 | 1,09 |  |  |  | SRT1 | Dominated by CRT2 | | |
| CRT1 | 18134 | 1,60 | 1,27 | 4186 | 5385 |  | CRT1 | Dominated by CRT2 | | |
| SRT2 | 18775 | 1,91 | 1,51 | 2963 | 3874 |  | SRT2 | Dominated by CRT2 | | |
| CRT2 | 16294 | 2,09 | 1,65 | Dominant | Dominant |  | CRT2 | Dominant | | |
|  | | | | | | | | | | |
| Sensitivity analysis 2: disutilties of toxicities are assumed -50% | | | | Comparator is SRT1 | |  |  | Comparator is next best non-dominated strategy | | |
|  | **Costs** | **LY** | **QALYs** | **ICER** | **ICUR** |  |  | **ICER** | **ICUR** | **Comparator** |
| SRT1 | 17156 | 1,37 | 1,11 |  |  |  | SRT1 | Reference | | |
| CRT1 | 18627 | 1,42 | 1,16 | 29814 | 26437 |  | CRT1 | Dominated by CRT2 | | |
| SRT2 | 18958 | 1,75 | 1,41 | 4708 | 5985 |  | SRT2 | Dominated by CRT2 | | |
| CRT2 | 17257 | 1,75 | 1,41 | 263 | 333 |  | CRT2 | 263 | 333 | SRT1 |
|  | | | | | | | | | | |
| Sensitivity analysis 3a: costs of toxicities are assumed -50% | | | | Comparator is SRT1 | |  |  | Comparator is next best non-dominated strategy | | |
| **Costs** | **Costs** | **LY** | **QALYs** | **ICER** | **ICUR** |  |  | **ICER** | **ICUR** | **Comparator** |
| SRT1 | 16618 | 1,37 | 1,09 |  |  |  | SRT1 | Reference | | |
| CRT1 | 17785 | 1,42 | 1,13 | 23665 | 30182 |  | CRT1 | Dominated by CRT2 | | |
| SRT2 | 18333 | 1,75 | 1,38 | 4481 | 5947 |  | SRT2 | Dominated by CRT2 | | |
| CRT2 | 17047 | 1,75 | 1,38 | 1123 | 1509 |  | CRT2 | 1123 | 1509 | SRT1 |
|  | | | | | | | | | | |
| Sensitivity analysis 3b: costs of toxicities are assumed +50% | | | | Comparator is SRT1 | |  |  | Comparator is next best non-dominated strategy | | |
|  | **Costs** | **LY** | **QALYs** | **ICER** | **ICUR** |  |  | **ICER** | **ICUR** | **Comparator** |
| SRT1 | 17695 | 1,37 | 1,09 |  |  |  | SRT1 | Dominated by CRT2 | | |
| CRT1 | 19469 | 1,42 | 1,13 | 35964 | 45867 |  | CRT1 | Dominated by CRT2 | | |
| SRT2 | 19584 | 1,75 | 1,38 | 4936 | 6551 |  | SRT2 | Dominated by CRT2 | | |
| CRT2 | 17466 | 1,75 | 1,38 | Dominant | Dominant |  | CRT2 | Dominant | | |
|  | | | | | | | | | | |
| Sensitivity analysis 4a: costs of end-of-life care are assumed -50% | | | | Comparator is SRT1 | |  |  | Comparator is next best non-dominated strategy | | |
|  | **Costs** | **LY** | **QALYs** | **ICER** | **ICUR** |  |  | **ICER** | **ICUR** | **Comparator** |
| SRT1 | 14400 | 1,37 | 1,09 |  |  |  | SRT1 | Reference | | |
| CRT1 | 16077 | 1,42 | 1,13 | 33984 | 43342 |  | CRT1 | Dominated by CRT2 | | |
| SRT2 | 16692 | 1,75 | 1,38 | 5986 | 7945 |  | SRT2 | Dominated by CRT2 | | |
| CRT2 | 15213 | 1,75 | 1,38 | 2127 | 2802 |  | CRT2 | 2127 | 2802 | SRT1 |
|  | | | | | | | | | | |
| Sensitivity analysis 4b: costs of end-of-life care are assumed +50% | | | | Comparator is SRT1 | |  |  | Comparator is next best non-dominated strategy | | |
|  | **Costs** | **LY** | **QALYs** | **ICER** | **ICUR** |  |  | **ICER** | **ICUR** | **Comparator** |
| SRT1 | 19912 | 1,37 | 1,09 |  |  |  | SRT1 | Dominated by CRT2 | | |
| CRT1 | 21177 | 1,42 | 1,13 | 25645 | 32707 |  | CRT1 | Dominated by CRT2 | | |
| SRT2 | 21225 | 1,75 | 1,38 | 3430 | 4553 |  | SRT2 | Dominated by CRT2 | | |
| CRT2 | 19300 | 1,75 | 1,38 | Dominant | Dominant |  | CRT2 | Dominant | | |

SRT1: conventional sequential chemo-radiation, CRT1: conventional concurrent chemo-radiation, SRT2: sequential PET-CT-based isotoxic accelerated chemo-radiation, CRT2: concurrent chemo-radiation with daily low-dose cisplatin administration and daily radiation, LYs: life years, QALYs: Quality adjusted life years , ICER: incremental cost-effectiveness ratio, ICUR: incremental cost-utility ratio.