The Cost-Effectiveness of Liver Transplantation Compared to Chemotherapy Alone for Patients with Non-Resectable Liver-Only Colorectal Metastases: a Model Based Analysis.

Gudrun Bjørnelv M. Phil[1,2]

Svein Dueland M.D., PhD[3]

Pål-Dag Line M.D., PhD[4,7]

Pål Joranger M.Phil., PhD[5]

Åsmund Avdem Fretland M.D.[1,6,7]

Bjørn Edwin M.D. PhD[1,6,7]

Halfdan Sorbye M.D. PhD[8]

Eline Aas M.Phil., PhD[2]

1. The Intervention Center, Oslo University Hospital, Oslo, Norway
2. Institute of Health and Society, University of Oslo, Oslo, Norway
3. Department of Oncology, Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway
4. Section for Transplantation Surgery, Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway
5. Faculty of Health Sciences, Oslo Metropolitan University, Oslo, Norway
6. Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital, Oslo, Norway
7. Institute of Clinical Medicine, University of Oslo, Oslo, Norway
8. Department of Oncology and Clinical Science, Haukeland University Hospital, Bergen, Norway

Corresponding Author/ Reprints: Gudrun Maria Waaler Bjørnelv, The Intervention Center, Oslo University Hospital, Postboks 4950 Nydalen, 0424 Oslo, Norway. Telephone number: +47 93018882. E-mail: gudrunmw@medisin.uio.no

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ABSTRACT

Background: Patients with non-resectable liver-only colorectal metastases (mCRC) are currently treated with chemotherapy alone. Liver transplantation can increase their 5-year survival from 9% to 56%. Our aim was to estimate the cost-effectiveness of liver transplantation for these patients.

Material and methods: We developed a Markov model with a lifetime-perspective, and predicted the Life-Years (LY), Quality-Adjusted Life-Years (QALYs), direct healthcare costs and cost-effectiveness of patients aged 55 years with non-resectable liver-only mCRC who received liver transplantation or chemotherapy alone.

Results: Liver transplantation increased life expectancy with 3.12 LY (2.47 QALYs), to a cost of $231 336, giving an incremental cost-effectiveness ratio (ICER) of $74 264 per LY gained ($93 651 per QALY gained). When selecting patients based on tumor diameter, time from primary cancer, carcinoembryonic antigen (CEA) levels and response to chemotherapy, the effect of liver transplantation increased to 4.23 LY (3.41 QALYs), at higher costs, $254 718, and the ICER decreased to $60 246 per LY gained ($74 673 per QALY gained). Given a willingness to pay of $78 000, the likelihood for transplantation to be cost-effective was 0.66 and 0.97 (0.23 and 0.67 QALYs) for non-selected and selected cohorts, respectively.

Conclusion: Liver transplantation was cost-effective when estimating the cost per LY gained, but only for highly selected patients when estimating the cost per QALY gained. Based on our findings, decision makers should consider selected mCRC patients for liver transplantation, however, this might only be possible in countries with low wait list mortality and adequate access to liver grafts.

INTRODUCTION

Globally, colorectal cancer (CRC) is the third most common cancer[1]. Approximately 27% of patients with CRC are either diagnosed with liver metastases or develop liver metastases within the first three years after diagnosis[2]. If the liver metastases are non-resectable, no curative treatment is available, and patients receive chemotherapy or best supportive care [2, 3]. The expected 5-year survival for patients with non-resectable colorectal liver metastases receiving chemotherapy is about 10% [4, 5].

Metastatic colorectal cancer (mCRC) has been considered a contraindication for liver transplantation (LTx) due to poor results in the early days of LTx; prior to 1995, the 1- and 5-year survival rate was 76% and 12%, respectively [6-10]. In recent years, the overall survival after LTx has improved in general, immunosuppressant drugs with anti-proliferative properties have been developed, better diagnostic imaging is available and patients with other malignant diseases, such as selected patients with hepatocellular carcinoma (HCC), are treated with LTx, with good results [6, 7]. The SECA-I trial re-examined LTx as a treatment option for patients with mCRC [6, 11]. In SECA I, the 5-year survival after LTx was 56% compared to 9% for a cohort of similar patients receiving chemotherapy alone [12]. The survival was comparable with the survival in patients with other disease indications who are currently being liver transplanted [13].

In western countries, health care budgets are increasingly being used on new oncological treatments targeting cancer patients at their end-of-life, where the effects are marginal, and costs are high both for the society and for patients (in terms of toxicity) [14-16]. In countries where the time on waiting list is short and wait list mortality is low, decision makers now have to consider whether LTx is an alternative treatment for patients with non-resectable mCRC. As a part of their decision, they demand information on the cost-effectiveness of LTx; analyses that inform decision makers on how to maximize health outcomes within constrained

health care budgets [17]. To our knowledge, no studies have estimated the cost-effectiveness of implementing LTx to mCRC patients. Hence, the objective of this paper was to estimate the long term expected Life-Years (LY) and Quality-Adjusted Life-Years (QALYs), cost consequences and cost-effectiveness of introducing liver transplantation to mCRC patients compared to the standard care; chemotherapy alone.

METHODS

Cost-effectiveness analyses

The goal of a cost-effectiveness analysis is to inform decision makers on the cost per additional effect of introducing a new treatment, compared to relevant treatment options. We do this by estimating the Incremental Cost-Effectiveness Ratio (ICER), defined as:

$$ICER = \frac{cost\ transplantation - cost\ chemotherapy - only}{effect\ transplantation - effect\ chemotherapy - only} = \frac{\Delta\ costs}{\Delta\ effects} \tag{1}$$

If the ICER falls below the willingness to pay-threshold (WTP), the intervention is considered cost-effective and should, if other prioritization criteria are met[1], be implemented [18-20].

$$ICER < WTP \tag{2}$$

The model

We used a Markov model to estimate health effects and costs [18, 19]. The model consisted of health states (circles) and transition probabilities (arrows), Figure 1. We included the health

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[1] In Norway, the three prioritizing criteria are: 1) effect of the intervention, 2) resource use and 3) severity of the disease. (20)

states: *Disease free*, *Recurrence*, *Palliative* and *Death*. Transition probabilities indicated possible movement between the health states. We ran the model using 3-month cycles; for every cycle, patients could either stay in the current health state or move to another health state. In our analyses, one cohort of patients was allocated to receive standard treatment, chemotherapy alone, while another cohort was allocated to receive LTx. Patients entered the model in *Palliative* (if allocated to chemotherapy alone) or in *Disease free* (if allocated to LTx). From *Disease free*, patients could either stay in *Disease free*, or move to *Recurrence* or *Death*. From *Recurrence*, patients could either stay in *Recurrence*, or move to *Palliative* or *Death*. From *Palliative*, patients could either stay in *Palliative* or move to *Death*. *Death* was an absorbing state. We assigned QALYs and costs to all health states, so when running the model, LY, QALYs and costs accumulated depending on the number of patients that stayed in the different health states per cycle. We applied *tunnel states* to account for time dependency in the model to capture differences in costs and transition probabilities depending on how long a patient has stayed in a health state [19]. When a patient entered a health state with time dependency, the patient could only stay in the tunnel state for one cycle before either moving to the next tunnel state, or moving to another health state. *Disease free* included one tunnel state, to reflect the initial high costs of liver transplantation. *Recurrence* included 40 tunnel states, to reflect the difference in the number and types of resection surgeries that patients receive in the first year after recurrence compared to the preceding years after recurrence. *Palliative* included 40 tunnel states, to reflect the difference in the type of chemotherapy regiments that patients received. The 40 tunnel states in *Recurrence* and *Palliative* also allowed for time dependent transition probabilities. We ran the model in 100 cycles (25 years), assumed equivalent to a lifetime perspective.

Model input

Data sources

We populated the model using the SECA-I trial and the NORDIC-VII trial [11, 12, 21].

In SECA-I, 23 patients with non-resectable liver-only mCRC were liver transplanted between 2006 and 2012. A multidisciplinary team evaluated the patients' non-resectability [11]. We simulated two LTx cohorts through the model: 1) 'LTx (all)', based on the original SECA-I population (n = 23), and 2) 'LTx (selected)', based on a sub-group of the SECA-I population (n = 16). Selection for LTx (selected) was based on risk factors associated with poor survival: tumor diameter above 5.5 cm, time from primary cancer surgery less than 2 years, carcinoembryonic antigen (CEA) levels above 80µg/L, and progressive disease after chemotherapy at the time of liver transplantation (11). In LTx (selected), patients with three or less of the risk factors were included.

In the NORDIC-VII trial, 566 patients were randomized to Nordic FLOX, FLOX + Cetuximab, or FLOX intermittently + Cetuximab continuously [21]. There were no significant differences in the progression free or overall survival between groups [21]. For comparison, we used the same cohort of patients from the NORDIC-VII trial, as Dueland and colleagues used in their comparison [12]. Here, all patients from the NORDIC-VII trial were combined and patients were thereafter selected using similar selection criteria as the ones used in the SECA-I trial: non-resectable liver-only metastases, BRAF non-mutated and age < 66 years. Patients who received liver resection after inclusion were excluded [12]. We simulated two chemotherapy cohorts through the model: 1) 'Chemotherapy (all)', the selected cohort from the NORDIC-VII (n = 47), and 2) 'Chemotherapy (selected)', the *longest survivors* among the selected cohort, (n = 21) [12]. Since 57% of patients in the SECA-I trial had progressed on first

line chemotherapy at inclusion, we simulated that 57% of patients in the chemotherapy

cohorts started with second line chemotherapy in the model.

Transition probabilities

For all liver transplanted patients, we identified the time of transplantation, time of

recurrence, time of start of chemotherapy and time of death from the patient records (SECA-I

trial), with a 5-year cut off. For all chemotherapy patients, we identified the start of

chemotherapy and death from published Kaplan Meier curves on the overall survival, and

extracted data using WebPlotDigitizer [12, 22]. We ran separate parametric survival analyses for

the four cohorts to estimate the transition probability between the health states *Disease free*,

Recurrence, Palliative and *Death* [19]. For all specification of the survival function, we assessed

the goodness of fit from six distributions between the predicted probabilities and the observed

data using Akaike information criterion (AIC) and Bayesian information criterion (BIC) [23].

Despite a 0% postoperative mortality rate in the SECA-I trial, we assumed a 2% probability

of postoperative mortality of LTx based on literature [24, 25]. From *Disease free* and *Recurrence,*

we assumed a similar probability of death as the background mortality in the Norwegian

general population [26]. See the supplementary appendix for a table of the transition

probabilities used in the model.

Costs

We estimated the direct healthcare costs, including the cost of transplantation, organ

harvesting, re-transplantation, postoperative complications (re-hospitalizations within 3

months after transplantation), routine follow-up at hospital and general practitioners,

immunosuppressive drugs, all tumor-targeting treatments patients received in hospital for

recurring cancer, chemotherapy (chemotherapy drugs, administration of the cures and

hospitalization due to side effects from chemotherapy) and best supportive care. We quantified resource use through patient records (SECA-I trial), liver transplantation guidelines [27], using a Markov model on the treatment path of CRC patients by Joranger and colleagues [28] and through experts opinions. We assumed that costs were equal for all patients once they entered the health state *Palliative*, except for immunosuppressive drugs that the LTx -patients continue to use while receiving chemotherapy. The cost of best supportive care was assigned to all patients in the 3-month cycle before they died, except for patients who died directly after LTx. All hospital treatments, GP-consultations and medication were valued using the Norwegian Diagnosis Related Groups (DRG), the Norwegian GP-Tariffs and The Norwegian Medical Agency [29-31]. We estimated the costs on a present value basis, using USD 2016 ($1 = NOK 8.3987), Table 1. For further details about the cost estimates, see the supplementary appendix.

Effects

Effects were estimated as LY and QALYs. QALYs combine time with health-related quality of life (HRQoL). HRQoL is a measure anchored in dead [0] and perfect health [1]. We performed a literature search to identify papers reporting the HRQoL for patients after LTx and for patients with mCRC, and based on our findings, assigned HRQoL values to the different health states, Table 1 [32,33].

Analyses

A cohort of 1,000 patients aged 55 years were simulated through the model. Costs and effects were discounted with a 4 % discount rate, and we used a WTP-threshold of $78,000 according to Norwegian guidelines [34].

Outcomes of the model include LY, QALYs, direct health care costs and incremental cost-effectiveness ratios (ICER). We performed one-way sensitivity analyses and probabilistic sensitivity analyses (PSA). In the PSA we used 1 000 iterations, and varied all input parameters per iteration based on predefined distributions, Table 1 [35]. We used data from the PSA to estimate the probability that liver transplantation and chemotherapy alone was cost-effective for increasing WTP-thresholds [36]. From the PSA, we also estimated the individual expected value of perfect information (EVPI) which quantifies the monetary loss of adopting the wrong treatment strategy [37,38].

Since we extrapolated results beyond 5 years using parametric survival analyses, we ran a range of scenario analyses to see how optimistic extrapolation (predicting slow progression through the model) and pessimistic extrapolation (predicting fast progression through the model) in the LTx cohorts would alter the results, see supplementary appendix for details. We assessed the models face validity, internal validity and external validity, see supplementary appendix for details.

We used the statistical software STATA (version 14) and Excel (2016).

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics in Norway and by the Institutional Review Board at Oslo University Hospital.

RESULTS

Effect

Patients in LTx (all) had an incremental effect of 3.12 LY (2.47 QALYs), compared to Chemotherapy (all). Patients in LTx (selected) had an incremental effect of 4.23 LY (3.41 QALYs), compared to Chemotherapy (selected), Table 2.

Costs

The lifetime costs were $266 438 for LTx (all), $35 103 for Chemotherapy (all), $302 341 for LTx (selected) and $47 623 for Chemotherapy (selected). The LTx procedure costs, including re-transplantation and treatment for complications, accounted for 52% and 44% of the total costs for LTx (all) and LTx (selected), respectively. In the LTx cohorts, the majority of costs occurred during the first years, and decreased with time, Figure 2 and 3.

Cost-effectiveness

The ICER was $74 264 per LY gained ($93 651 per QALY gained) in the non-selected cohorts and $60 246 per LY gained ($74 673 per QALY gained) in the selected cohorts. Given a WTP of $78 000, the likelihood for transplantation to be cost-effective was 0.66 and 0.97 when estimating the cost per LY gained and 0.23 and 0.67 when estimating cost per QALY gained for the non-selected and selected cohorts, respectively, Table 2. The individual EVPI at the WTP-threshold was ~$7 000 when evaluating the non-selected cohorts and ~$1 000 when evaluating the selected cohorts, using LY as an effect measure, Figure 4.

Scenario analyses

The estimated 5-year survival was similar across all scenario analyses, while the long-term effect and costs differed between scenarios, Figures 2 and 3. When LY were used as effect measure, LTx was cost-effective in all scenario analyses, both for the selected and non-

selected cohorts. When QALYs were used as effect measure, LTx was cost-effective in 2 out of 7 scenarios for Ltx (all), and in 5 out of 7 scenarios for Ltx (selected), Table 2. Overall, the one-way sensitivity analyses did not alter the results substantially, see supplementary appendix for details.

DISCUSSION

With increasing pressure on the health care sector's scarce resources, costs are inevitably a point of discussion when considering the implementation of new interventions [14,17]. Analysis such as ours bring valuable information to the surgeon advising a patient in a progressed stage of the disease, and shows that the high effect (long overall survival) may justify a resource demanding procedure such as LTx. We showed that given a WTP of $78 000, LTx was cost-effective with a likelihood of 0.66 and 0.97 in the selected and non-selected cohorts, respectively, when estimating the cost per LY gained. When estimating the cost per QALY gained, LTx was only cost-effective in highly selected patients (likelihood of 0.67), but not cost-effective in the non-selected patients (likelihood of 0.23).

Comparison to other studies

No previous study has published results on the cost-effectiveness of LTx for mCRC patients. Clinical outcomes have been reported in 11 studies (9, 10). In the only study which included more than 10 patients, they reported a 1-, 3- and 5- year survival of 76%, 31% and 12%, in a series of 25 patients [9, 10]. In the study, published in 1991, perioperative mortality was 30%, however, they also demonstrated that long-term survival after LTx for mCRC was possible [10]. The longest post-transplant survival observed so far is 30 years [9, 10]. Long-term survival for patients who receive chemotherapy alone has only been observed in 1% of large patient

populations [39, 40]. Currently, two patients in the SECA-I trial have lived for 10 years or more, while all patients in the NORDIC-VII who were used as comparators in these analyses, were dead within 6 years (data not shown).

The mean cost for LTx varies between countries [41,42]. Van der Hilst and colleagues [42] evaluated which factors that influenced the cost differences for the initial hospital stay between the USA ($158 028[2]) and other OECD countries ($100 121[2]). They found that the differences were largely explained by health system characteristics (38). Our estimated cost for the initial hospital stay was $139 947. Given similar health effects when evaluating LTx to patients with mCRC, the ICER might be higher in the USA and lower in other OECD countries [41,42]. However, other factors such as the unit cost of chemotherapy or different treatment patterns might also influence the ICER [43, 44]. High drug costs in the USA might therefore lead to lower ICERs for LTx in the USA compared to the findings in our study [45].

Because of the limited number of liver allografts, the ICER of LTx for patients with mCRC could also be compared to the ICER of LTx for patients with other disease indications, since the ICER incorporates both the incremental costs and effects between LTx and the next best alternative (comparator). ICERs have rarely been estimated for LTx previously. Longworth and colleagues [46] estimated the ICER of LTx compared to no LTx in a 27-month perspective for patients with primary biliary cirrhosis (PBC), alcoholic liver disease (ALD) and primary sclerosing cholangitis (PSC) to be $61 903[2], $102 460[2] and $44 826[2], respectively [46]. If we used a 2-year perspective in our model, the ICER was ~ $400 000 for both cohorts, due to the fact that the initial costs were high while the effects accumulated over several years (Figure 2 and 3). Åberg and colleagues [47] estimated the 5-year cost per QALY for LTx compared to no LTx in patients with chronic liver disease (CLD) and ALD to be $51 495[2] and $77 493[2],

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[2] The number is adjusted for currency and time differences by the author

respectively [47]. If estimating the cost per QALY similarly to how Åberg and colleagues did [47], LTx for mCRC-patients would yield \$78 782 per QALY for the non-selected cohorts and \$70 439 per QALY for the selected cohorts. A comparison to Longworth [46] and Åberg [47] is difficult, due to methodological differences. However, the ICER of LTx for mCRC patients seems to be above that for patients with PBC, ALD and PSC as estimated by Longworth [46], while LTx for the selected cohorts of mCRC patients seems to be within the range of that for patients with CLD and ALD as estimated by Åberg [47].

Limitations and strengths

A limitation of our study was that the SECA-I trial was small, had no control group and that it currently has a relatively short follow-up [11]. It is important to point out that baseline characteristics of the cohorts from the SECA-I trial and the NORDIC-VII trial were similar, but that we cannot rule out unobserved selection bias [12]. Ideally, model based cost-effectiveness analyses should utilize high quality effect data, preferably based on meta-analyses from several appropriate RCTs [48]. However, under some circumstances, for example when the effect of a treatment is as large as the effect found for LTx compared to chemotherapy for patients with non-resectable mCRC, a decision of whether to implement the new treatment should be made before evidence from an RCT is available. It can also be argued that randomizing patients between LTx and chemotherapy is unethical, considering that the findings from the SECA-I trial showed that LTx has the potential to increase patient's five-year survival from 9% to 56% [12, 49]. Model-based analyses can be used as tools to explicitly model the uncertainty of the decision of whether to introduce a new treatment. We did this in our analysis by running several one-way and probabilistic sensitivity analyses. In addition, we ran several scenario analyses to test how different methods for extrapolation would alter our results. Therefore, despite the fact that model-based cost-effectiveness

analyses should ideally be made with evidence from (several) RCTs, we demonstrated that models can also be used to give timely information to decision makers on the expected costs and effects before evidence from an RCT is available, while explicitly showing the uncertainty surrounding the decision. In the future, more analyses performed within the safe framework of decision analytic models should be performed to estimate the post-transplant survival needed to justify LTx to patients with mCRC [50]. Availability of liver allografts, waiting list length and wait list mortality should be included in the models.

We find that the level of patients' HRQoL play an important role for whether LTx is cost-effective or not, but there is sparse knowledge regarding the patients' HRQoL. Andersen and colleagues [51] estimated the HRQoL of *ten* patients in the SECA-I trial, and found that patients had good global health status, and function with minor symptoms, at 3, 6 and 12 months when using the EORTC QLQ-C30. In the future, HRQoL after LTx for mCRC should be measured using a multi attribute utility instrument in more mCRC patients undergoing LTx, allowing for more accurate QALY calculations [32, 33].

Policy implications

There is a discrepancy between the demand for LTx and the number of liver allografts that are available for transplantation. Decision makers should be reluctant to increase the list of transplantable diseases [52]. The limitation of available liver allografts plays a greater role than the costs of LTx as to why LTx for mCRC has been slow to implement across the world, despite prior reports on good overall survival [11, 12]. The waiting time and wait list mortality in the Nordic countries are relatively low [25]. Through the SECA-I trial and the current study, we found that the estimated 5-year survival after LTx was 52% for LTx (all) and 72% for LTx (selected) [12]. This is comparable with the survival in patients who are currently being liver

transplanted in the Nordic countries, which ranges from 87% in patients with primary sclerosing cholangitis to 42% in patients with cholangiocarcinoma [25]. LTx to patients with non-resectable mCRC should therefore be considered as an option in Norway, and may be considered in countries with similar settings as Norway. In countries with longer waiting times and higher wait list mortality, LTx for non-resectable mCRC patients might not be a real option for the time being. However, there is a focus on how to increase the access to liver allografts through procedures such as extended donor criteria, split liver transplantation and living donor transplantation [52, 53]. If this leads to decreasing waiting times and wait list mortality, LTx for non-resectable mCRC patients might be possible in more countries in the future.

In conclusion, we found that liver transplantation was cost-effective compared to chemotherapy alone when evaluating the cost per life-year gained for patients with non-resectable mCRC. When evaluating the cost per QALY gained, liver transplantation was cost-effective only in highly selected patients. Based on our findings, the costs of liver transplantation should not prohibit decision makers to consider highly selected mCRC patients for liver transplantation. However, the lack of liver allografts is the major obstacle to LTx for mCRC in most countries, and a continuous effort to increase the access to liver allografts is necessary.

References

1. Rabeneck L, Horton S, Zauber AG et al: Chapter 6. Colorectal Cancer, in Gelband H, Jha P, Sankaranarayanan R et al. (ed). Cancer: Disease Control Priorities, 3rd edn. Volume 3: cancer. USA: The World Bank; 2015. Available at: http://dcp-3.org/node/2163

2. Leporrier J, Maurel J, Chiche L et al: A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. Br J Surg 93(4):465-74, 2006

3. Costi R, Leonardi F, Zanoni D et al: Palliative care and end-stage colorectal cancer management: the surgeon meets the oncologist. World J Gastroenterol 20(24):7602-21, 2014

4. Masi G, Vasile E, Loupakis F et al: Randomized trial of two induction chemotherapy regimens in metastatic colorectal cancer: an updated analysis. J Natl Cancer Inst 103(1):21-30, 2011

5. Van Cutsem E, Kohne CH, Hitre E, Zaluski J et al: Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 360(14):1408-17, 2009

6. Foss A, Adam R, Dueland S. Liver transplantation for colorectal liver metastases: revisiting the concept. Transpl Int 23(7):679-85, 2010

7. Hoti E, Adam R: Liver transplantation for primary and metastatic liver cancers. Transpl Int 21(12):1107-17, 2008

8. Adam R, Karam V, Delvart V et al: Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). J Hepatol 57(3):675-88. 2012

9. Moris D, Tsilimigras DI, Chakedis J, Beal EW, Felekouras E, Vernadakis S, et al. Liver transplantation for unresectable colorectal liver metastases: A systematic review. J Surg Oncol, 2017.

10. Muhlbacher F, Huk I, Steininger R et al: Is orthotopic liver transplantation a feasible treatment for secondary cancer of the liver? Transplant Proc 23(1 Pt 2):1567-8, 1991

11. Hagness M, Foss A, Line PD et al: Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg 257(5):800-6, 2013

12. Dueland S, Guren TK, Hagness M et al: Chemotherapy or liver transplantation for nonresectable liver metastases from colorectal cancer? Ann Surg 261(5):956-60, 2015

13. Fosby B, Melum E, Bjoro K et al: Liver transplantation in the Nordic countries - An intention to treat and post-transplant analysis from The Nordic Liver Transplant Registry 1982-2013. Scand J Gastroenterol 50(6):797-808, 2015

14. Garattini L, van de Vooren K, Zaniboni A: Ethics for end-of-life treatments: metastatic colorectal cancer is one example. Health Policy 109(1):97-103, 2013

15. Bullement A, Underhill S, Fougeray R et al: Cost-effectiveness of Trifluridine/tipiracil for Previously Treated Metastatic Colorectal Cancer in England and Wales. Clin Colorectal Cancer. 2017.

16. Goldstein DA, Ahmad BB, Chen Q, Ayer T, Howard DH, Lipscomb J, et al. Cost-Effectiveness Analysis of Regorafenib for Metastatic Colorectal Cancer. J Clin Oncol 33(32):3727-32, 2015

17. Sullivan R, Peppercorn J, Sikora K et al: Delivering affordable cancer care in high-income countries. Lancet Oncol 12(10):933-80, 2011

18. Hogendoorn W, Moll FL, Sumpio BE et al: Clinical Decision Analysis and Markov Modeling for Surgeons: An Introductory Overview. Ann Surg 264(2):268-74, 2016

19. Briggs A, Claxton C, Sculpher M: Decision Modelling for Health Economic Evaluation. UK: Oxford University Press; 2008.

20. Lovdata. Prioriteringsforskriften [Prioritizing Regulations]. 2001. Available at: https://lovdata.no/dokument/SF/forskrift/2000-12-01-1208/KAPITTEL_1#KAPITTEL_1

21. Tveit KM, Guren T, Glimelius B et al: Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. J Clin Oncol 30(15):1755-62, 2012

22. Rohatgi A. [WebPlotDigitizer]. Version 3.12. Austin, USA; 2017. Available from: http://arohatgi.info/WebPlotDigitizer

23. Latimer NR: Survival analysis for economic evaluations alongside clinical trials-- extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. Med Decis Making 33(6):743-54, 2013

24. Bruns H, Lozanovski VJ, Schultze D et al: Prediction of postoperative mortality in liver transplantation in the era of MELD-based liver allocation: a multivariate analysis. PLoS One 9(6):e98782, 2014

25. Fosby B, Melum E, Bjoro K et al: Liver transplantation in the Nordic countries - An intention to treat and post-transplant analysis from The Nordic Liver Transplant Registry 1982-2013. Scand J Gastroenterol 50(6):797-808, 2015

26. Statistics Norway. Dødelighetstabeller [Background Mortality]. 2014. Available at: https://www.ssb.no/220943/d%C3%B8delighetstabeller

27. Oslo University Hospital. Protocol for Liver Transplantation. Version 1. 2015. Available at: https://oslo-universitetssykehus.no/Documents/Lever%20Protokoll%201st%20Q%202015.pdf

28. Joranger P, Nesbakken A, Hoff G et al: Modeling and validating the cost and clinical pathway of colorectal cancer. Med Decis Making 35(2):255-65, 2015

29. The Norwegian Directorate of Health. Innsatsstyrt finansiering 2016 [Activity Based Finansing 2016]. 2016. Available at: https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/1265/Innsatsstyrt%20finansiering%202017%20IS-2568.pdf

30. The Norwegian Medical Association. Normaltariff for fastleger og legevakt [The Normal Tariff for general practitioners and emergency care units]. 2015. Available at: http://normaltariffen.legeforeningen.no/pdf/Fastlegetariff_2015.pdf

31. The Norwegian Medicines Agency. Legemiddelsøk. [Search for medicine]. 2017. Available at: https://www.legemiddelsok.no/

32. Farkkila N, Sintonen H, Saarto T et al: Health-related quality of life in colorectal cancer. Colorectal Dis 15(5):e215-22, 2013

33. Ratcliffe J, Longworth L, Young T et al: Assessing health-related quality of life pre- and post-liver transplantation: a prospective multicenter study. Liver Transpl 8(3):263-70, 2002

34. The Norwegian Directorate of Health. Økonomisk evaluering av helsetiltak – en veileder [Recommendations for the economic evaluation of new interventions in the Norwegian health sector]. 2012. Available at: https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/624/Okonomisk-evaluering-av-helsetiltak-IS-1985.pdf. Accessed April 8, 2017.

35. Briggs A: Chapter 8. Handling uncertainty in economic evaluation and presenting the results, in: Drummon M, McGuire, A (ed). Economic evaluation in health care. Merging theory with practice. USA: Oxford University Press; 2001.

36. Barton GR, Briggs AH, Fenwick EA: Optimal cost-effectiveness decisions: the role of the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness acceptability frontier (CEAF), and the expected value of perfection information (EVPI). Value Health 11(5):886-97, 2008

37. Briggs AH, Weinstein MC, Fenwick EA et al: Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6. Med Decis Making 32(5):722-32, 2012

38. Oostenbrink JB, Al MJ, Oppe M et al: Expected value of perfect information: an empirical example of reducing decision uncertainty by conducting additional research. Value Health 11(7):1070-80, 2008

39. Giacchetti S, Itzhaki M, Gruia G al: Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. Ann Oncol 10(6):663-9, 1999

40. Ferrarotto R, Pathak P, Maru D et al: Durable complete responses in metastatic colorectal cancer treated with chemotherapy alone. Clin Colorectal Cancer 10(3):178-82, 2011

41. Harries L, Schrem H, Stahmeyer JT et al: High resource utilization in liver transplantation-how strongly differ costs between the care sectors and what are the main cost drivers?: a retrospective study. Transpl Int 30(6):621-37, 2017

42. van der Hilst CS, Ijtsma AJ, Slooff MJ et al: Cost of liver transplantation: a systematic review and meta-analysis comparing the United States with other OECD countries. Med Care Res Rev 66(1):3-22, 2009

43. Goeree R, Burke N, O'Reilly D et al: Transferability of economic evaluations: approaches and factors to consider when using results from one geographic area for another. Curr Med Res Opin 23(4):671-82, 2007

44. Drummond M, Barbieri M, Cook J et al. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. Value Health 12(4):409-18, 2009

45. Kesselheim AS, Avorn J, Sarpatwari A: The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform. JAMA 316(8):858-71, 2016

46. Longworth L, Young T, Buxton MJ et al: Midterm cost-effectiveness of the liver transplantation program of England and Wales for three disease groups. Liver Transpl 9(12):1295-307, 2003

47. Aberg F, Maklin S, Rasanen P et al: Cost of a quality-adjusted life year in liver transplantation: the influence of the indication and the model for end-stage liver disease score. Liver Transpl 17(11):1333-43, 2011

48. Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3. Value Health. 2012;15(6):812-20.

49. Adam R. Assistance Publique−Hôpitaux de Paris. Liver Transplantation in Patients With Unresectable Colorectal Liver Metastases Treated by Chemotherapy (TRANSMET). In: ClinicalTrialsgov [Internet] Bethesda (MD): National Library of Medicine (US) 2000- [cited 2017 september 29] Available from: https://clinicaltrialsgov/show/ NCT02597348 NLM Identifier: NCT02597348

50. Volk ML, Vijan S, Marrero JA. A novel model measuring the harm of transplanting hepatocellular carcinoma exceeding Milan criteria. Am J Transplant 8(4):839-46, 2008

51. Andersen MH, Dueland S, Hagness M et al. Quality of life following liver transplantation in patients with liver metastases from colorectal carcinoma. Scand J Caring Sci 26(4):713-9, 2012

52. Zamora-Valdes D, Leal-Leyte P, Kim PT, Testa G. Fighting Mortality in the Waiting List: Liver Transplantation in North America, Europe, and Asia. Ann Hepatol. 2017;16(4):480-6.

53. Line PD, Hagness M, Berstad AE, Foss A, Dueland S. A Novel Concept for Partial Liver Transplantation in Nonresectable Colorectal Liver Metastases: The RAPID Concept. Ann Surg 262(1):e5-9, 2015
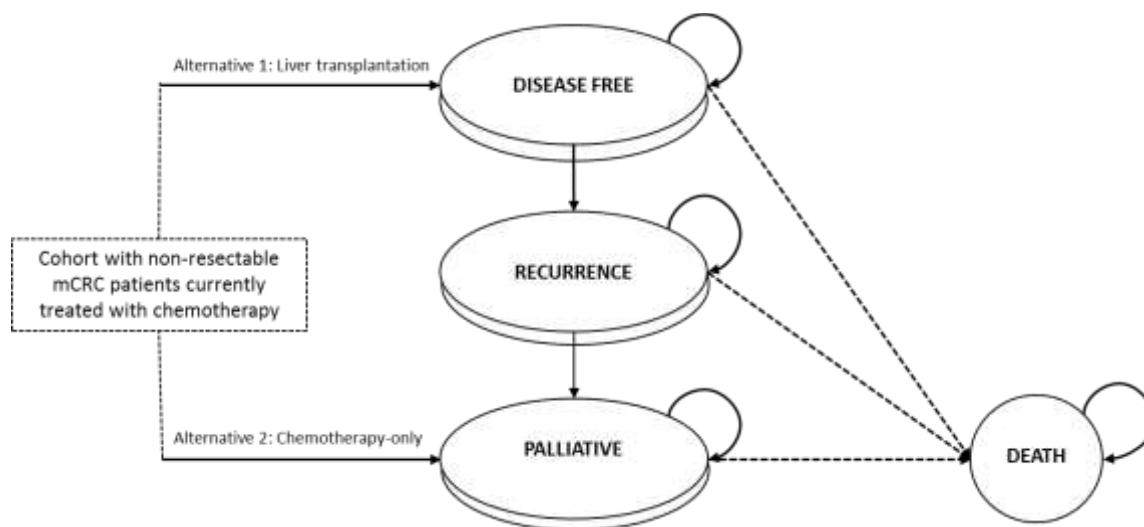
Figures and Tables

Figure 1: Structure of the Markov Model

Table 1: Cost estimates according to health states. Numbers are reported as occurring in one cycle (3-months).

		Quantification			Cost	Value	Source of valuation
	Source	#	n	(%)	$	Sum	[distribution (parameters)]
Costs "Disease free" (firs cycle)							
Primary procedure							
Organ harvesting	(1)	1.00	23.00	(100 %)	29 762	29 762	DRG YJA10 (29)
Transplantation	(1)	1.00	23.00	(100 %)	107 597	107 597	DRG 480 (29)
Re-transplantation							
Organ harvesting (re-transplantation)	(1)	1.00	2.00	(9 %)	29 762	2 588	DRG YJA10 (29)
Re-transplantation^	(1)	1.00	2.00	(9 %)	0	0	DRG 480 (29)
Complications leading to hospital treatment							
Rejection	(1)	1.00	5.00	(22 %)	10 487	2 280	DRG 493 (29)
Suspected rejection	(1)	1.00	5.00	(22 %)	9 314	2 025	DRG 205 (29)
Pneumonia	(1)	1.00	2.00	(9 %)	6 413	558	DRG 89 (29)
Fatigue	(1)	1.00	1.00	(4 %)	371	16	DRG 816R (29)
Wound rupture	(1)	1.00	1.00	(4 %)	1 453	63	DRG 266O (29)
General practitioner	(2)	17.14	23.00	(100 %)	81	1 396	NT (30)
*Immunosuppressant drugs**	(3)	60.00	23.00	(100 %)	19	1 136	NMA (31)
SUM "Disease free" (firs cycle)						147 420	[gamma (96.04,12892)]Ŧ
Cost "Disease free"							
Follow up hospital	(3)	1.00	23.00	(100 %)	4 184	4 184	DRG 206 (29)
Colonoscopy	(2)	0.25	23.00	(100 %)	321	80	DRG 710O (29)
General practitioner	(2)	6.43	23.00	(100 %)	81	524	NT (30)
*Immunosuppressant drugs**	(3)	90.00	23.00	(100 %)	19	1 703	NMA (31)
SUM "Disease free"						6 491	[gamma (96.04,568)]Ŧ
Cost "Recurrence"							
*Treatment for metastases (**first year**)*							
Rectum resection**	(1)	1.00	0.32	(1 %)	27 602	382	DRG 146 (29)
Pancreatic resection	(1)	1.00	0.32	(1 %)	29 171	404	DRG 191B (29)
Adrenalectomy	(1)	1.00	0.32	(1 %)	12 406	172	DRG 286 (29)
Oophorectomy	(1)	1.00	0.65	(3 %)	18 839	530	DRG 353 (29)
Resection of lymph nodes**	(1)	1.00	0.32	(1 %)	24 195	335	DRG 406 (29)
Resection lung	(1)	1.00	4.24	(18 %)	15 222	2 808	DRG 76 (29)
Ablation lunge	(1)	1.00	0.32	(1 %)	6 323	88	DRG 82 (29)
Brain tumor resection	(1)	1.00	0.32	(1 %)	13 498	187	DRG 1A (29)
*Treatment for metastases (**year 2 - 25**)*							
Oophorectomy	(1)	1.00	0.25	(1 %)	18 839	207	DRG 353 (29)
Resection lung	(1)	1.00	0.99	(4 %)	15 222	655	DRG 76 (29)
Resection of colon	(1)	1.00	0.12	(1 %)	21 590	116	DRG 148 (29)
Colonoscopy	(2)	0.25	23.00	(100 %)	321	80	DRG 710O (29)
Follow up hospital	(3)	0.25	23.00	(100 %)	4 184	1 046	DRG 206 (29)
General practitioner	(2)	6.43	23.00	(100 %)	81	524	NT (30)
*Immunosuppressant drugs**	(3)	90.00	23.00	(100 %)	19	1 703	NT (30)
SUM "Recurrence" first year						8 258	[gamma (96.04,722)]Ŧ

						Value	[Distribution (parameters)]
SUM "Recurrence" year 2 - 25						4,331	[gamma (96.04,379)]〒
Cost "Palliative"							
Chemotherapy (cycle 1 and 2)							
FLOX	(4)	7.50	4.14	(18 %)	939	1 267	Joranger et al (28)
FLIRI	(4)	7.50	9.66	(42 %)	913	2 875	Joranger et al (28)
FLOX + Bevacizumab	(4)	5.50	0.92	(4 %)	2 764	608	Joranger et al (28)
FLIRI + Bevacizumab	(4)	5.50	8.28	(36 %)	2 695	5 336	Joranger et al (28)
*Immunosuppressant drugs**	(3)	90.00	23.00	(100 %)	15	1 350	NMA (31)
SUM "palliative" cycle 1 and 2 *ct*						10 087	[gamma (96.04,1000)]〒
SUM "palliative" cycle 1 and 2 LTx *						11 437	[gamma (96.04,882)]〒
Cost Chemotherapy (cycle 3 and 4)							
FLOX	(4)	4.00	7.45	(32 %)	938	1 215	Joranger et al (28)
FLIRI	(4)	4.00	6.35	(28 %)	964	1 064	Joranger et al (28)
No chemotherapy	(4)	0.00	9.20	(40 %)	0	0	Joranger et al (28)
*Immunosuppressant drugs**	(3)	90.00	23.00	(100 %)	15	1 350	NMA (31)
SUM "palliative" cycle 3 and 4 *ct*						2 279	[gamma (96.04,317)]〒
SUM "palliative" cycle 3 and 4 *LTx* *						3 630	[gamma (96.04,199)]〒
Chemotherapy (cycle 5 and onward)							
Cetuximab + Irinotecan	(4)	4.00	8.28	(36 %)	2 359	3 397	Joranger et al (28)
No chemotherapy	(4)	0.00	14.72	(64 %)	0	0	Joranger et al (28)
*Immunosuppressant drugs**	(3)	90.00	23.00	(100 %)	15	1 350	NMA (31)
SUM "palliative" cycle 5 and onward *ct*						3 397	[gamma (96.04,415)]〒
SUM "palliative" cycle 5 and onward *LTx* *						4 747	[gamma (96.04,297)]〒
Best supportive care						6 624	DRG 172 (28)
SUM Best supportive care						6 624	[gamma (96.04,579)]〒
HRQoL						**Value**	**[Distribution (parameters)]**
"Disease free" - cycle 1						0.64	[beta (2137, 1202)] (29)
"Disease free" - cycle 2 and onward						0.71	[beta (2119, 866)] (29)
"Recurrence" first year						0.82	[beta (1790, 393)] (28)
"Recurrence" year 2 and onward						0.85	[beta (1466, 259)] (28)
"Palliative"						0.82	[beta (1790, 393)] (28)

(1) = patient records SECA-I, (2) = Guidelines, (3) = Experts' opinions, (4) = Joranger et al. (12)

ct = chemotherapy, LTx = liver transplantation, NT = Normal tariff GP, NMA = The Norwegian Medical Agency

* Immunosuppressant drugs only provided to the transplantation cohorts

^ The two re-transplantations were performed while the patients were in the hospital for their first LTx. The costs were therefore included in the initial hospital stay, where complications are included by definition.

** Including radiation therapy (25 * 2 GY)

〒 Alfa and beta were estimated based on the assumption that the cost estimate can vary +/- 20% from the mean estimate

Table 2: Expected LY, QALYs, costs and cost-effectiveness of liver transplantation (LTx) compared to chemotherapy

	All patients				Selected patients			
	LTx	CT	Δ	Range*	LTx	CT	Δ	Range*
LYs	5.18	2.07	3.12	3.12 – 4.03	7.09	2.87	4.23	3.73 – 5.42
QALYs	4.17	1.70	2.47	2.47 – 3.25	5.76	2.35	3.41	2.99 – 4.44
Costs, $	266 438	35 103	231 336	231 208 – 245 277	302 341	47 623	254 718	246 465 – 273 465
ICER, $								
LY			74 264	60 895 – 74 264			60 246	50 273 – 66 054
CE (prob)			0.66	0.0,66- 0.91			0.97	0.74 – 0.97
QALY			93 651	75 401 – 93 651			74 673	61 383 – 82 432
CE (prob)			0.23	0.23 – 0.60			0.67	0.49 – 0.90

* Ranges represent the minimum and maximum value achieved for the 7 scenario analyses.

LY = life-years, QALYs = quality-adjusted life-years, LTx = liver transplantation, CT = chemotherapy, CE (prop) = probability that liver transplantation is cost-effective

Below is a description of the different scenarios:

Optimistic 1 (O1): in the scenario, we use the most optimistic survival function from Recurrence to Chemotherapy (slow progression from Recurrence to Chemotherapy)

Optimistic 2 (O2): in the scenario, we use the most optimistic survival function from Recurrence to Chemotherapy and the most optimistic survival function from Chemotherapy to Death (slow progression from Recurrence to Chemotherapy and from Chemotherapy to Death)

Pessimistic 1 (P1): in the scenario, we use the most pessimistic survival function from Recurrence to Chemotherapy (fast progression from Recurrence to Chemotherapy)

Pessimistic 2 (P2): in the scenario, we use the most pessimistic survival function from Recurrence to Chemotherapy and the most pessimistic survival function from Chemotherapy to Death (fast progression from Recurrence to Chemotherapy and from Chemotherapy to Death)

Survivors (S): in the scenario, we assume that patients' who are still in Recurrence after 10 years, have similar background mortality as the general population

Optimistic survivors (OS): in the scenario, we assume the most optimistic survival function from Recurrence to Chemotherapy (slow progression from Recurrence to Chemotherapy) and that patients who are still in Recurrence after 10 years, have similar background mortality as the general population
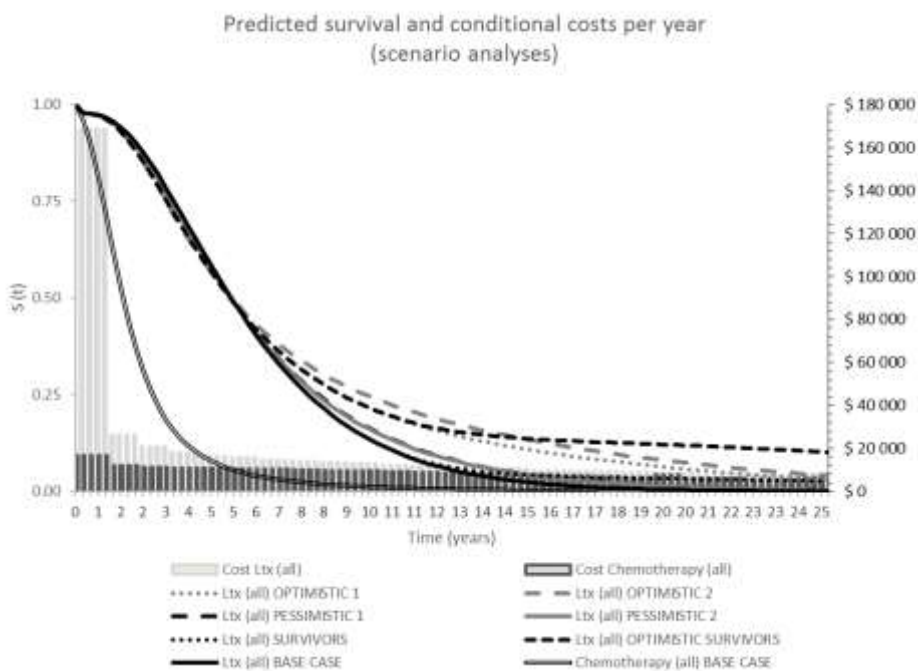
Figure 2: Predicted survival and costs (costs for the base case analyses) for patients receiving transplantation and chemotherapy, for the non-selected cohorts. Costs are accumulated to total costs ($) during 1 year periods and conditioned on that patients were alive in the beginning of the year.
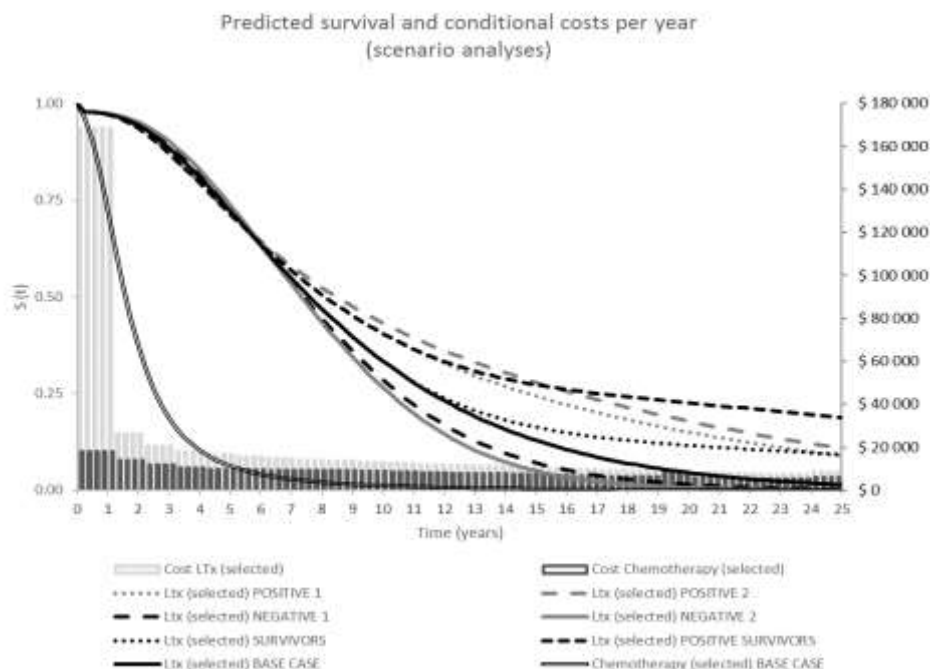

Figure 3: Predicted survival and costs (costs for the base case analyses) for patients receiving transplantation and chemotherapy, for the selected cohorts. Costs are accumulated to total costs ($) during 1 year periods and conditioned on that patients were alive in the beginning of the year.
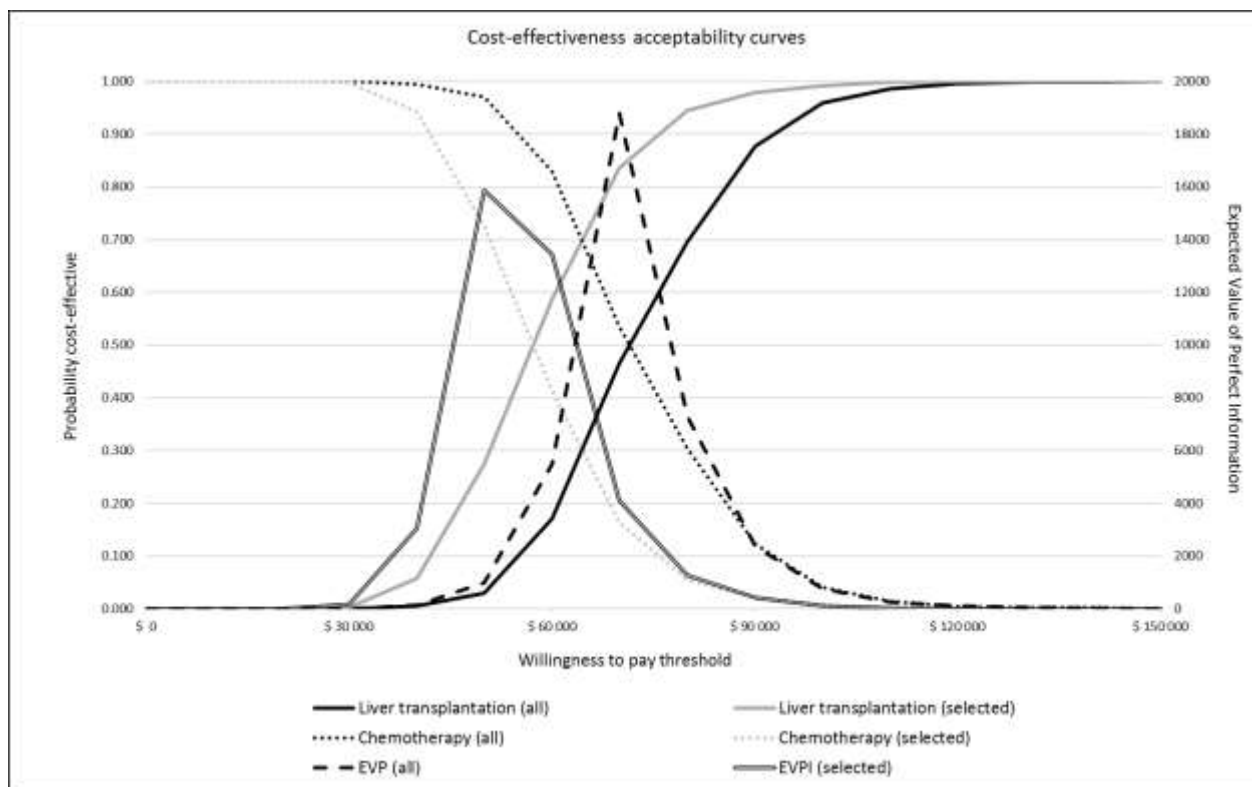
Figure 4: Cost-effectiveness acceptability curves (primary axis) and the Individual Value of Perfect Information (secondary axis) for the non-selected and selected cohorts.