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

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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. 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:

\[
ICER = \frac{\text{cost transplantation} - \text{cost chemotherapy-only}}{\text{effect transplantation} - \text{effect chemotherapy-only}} = \frac{\Delta \text{costs}}{\Delta \text{effects}}
\]  

(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, be implemented.

\[
ICER < WTP
\]

(2)

The model

We used a Markov model to estimate health effects and costs. 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. 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 80\(\mu\)g/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. 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. 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).

Despite a 0% postoperative mortality rate in the SECA-I trial, we assumed a 2% probability of postoperative mortality of LTx based on literature. From Disease free and Recurrence, we assumed a similar probability of death as the background mortality in the Norwegian general population. 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 and best supportive care.

We quantified resource use through patient records (SECA-I trial), liver transplantation guidelines 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. 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.

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.
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. We used data from the PSA to estimate the probability that liver transplantation and chemotherapy alone was cost-effective for increasing WTP-thresholds. 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.

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\textsuperscript{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\textsuperscript{41,42}. Van der Hilst and colleagues\textsuperscript{42} evaluated which factors that influenced the cost differences for the initial hospital stay between the USA ($158,028\textsuperscript{2}$) and other OECD countries ($100,121\textsuperscript{2}$). 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\textsuperscript{41,42}. However, other factors such as the unit cost of chemotherapy or different treatment patterns might also influence the ICER\textsuperscript{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\textsuperscript{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\textsuperscript{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 $61,903\textsuperscript{2}$, $102,460\textsuperscript{2}$ and $44,826\textsuperscript{2}$, respectively\textsuperscript{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\textsuperscript{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 $51,495\textsuperscript{2}$ and $77,493\textsuperscript{2}$.

\textsuperscript{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. 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 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.

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. 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. The waiting time and wait list mortality in the Nordic countries are relatively low. 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). 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. 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. 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.
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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).

<table>
<thead>
<tr>
<th>Quantification</th>
<th>Cost</th>
<th>Value</th>
<th>Source of valuation</th>
</tr>
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<td></td>
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<td>[distribution (parameters)]</td>
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<tr>
<td><strong>Costs &quot;Disease free&quot; (first cycle)</strong></td>
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<tr>
<td><strong>Primary procedure</strong></td>
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<tr>
<td>Organ harvesting</td>
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<td>23.00 (100 %)</td>
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<tr>
<td>Transplantation</td>
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<td>23.00 (100 %)</td>
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<tr>
<td>Organ harvesting (re-transplantation)</td>
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<td>2.00 (9 %)</td>
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<tr>
<td>Re-transplantation*</td>
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<tr>
<td>Rejection</td>
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<tr>
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<tr>
<td><strong>SUM &quot;Disease free&quot; (first cycle)</strong></td>
<td></td>
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<td>147 420 [gamma (96.04,12892)]</td>
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<td><strong>Cost &quot;Disease free&quot;</strong></td>
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<tr>
<td>Oophorectomy</td>
<td>(1)</td>
<td>1.00</td>
<td>0.65 (3 %)</td>
</tr>
<tr>
<td>Resection of lymph nodes**</td>
<td>(1)</td>
<td>1.00</td>
<td>0.32 (1 %)</td>
</tr>
<tr>
<td>Resection lung</td>
<td>(1)</td>
<td>1.00</td>
<td>4.24 (18 %)</td>
</tr>
<tr>
<td>Ablation lung</td>
<td>(1)</td>
<td>1.00</td>
<td>0.32 (1 %)</td>
</tr>
<tr>
<td>Brain tumor resection</td>
<td>(1)</td>
<td>1.00</td>
<td>0.32 (1 %)</td>
</tr>
<tr>
<td><strong>Treatment for metastases (first year)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>(1)</td>
<td>1.00</td>
<td>0.25 (1 %)</td>
</tr>
<tr>
<td>Resection lung</td>
<td>(1)</td>
<td>1.00</td>
<td>0.99 (4 %)</td>
</tr>
<tr>
<td>Resection of colon</td>
<td>(1)</td>
<td>1.00</td>
<td>0.12 (1 %)</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>(2)</td>
<td>0.25</td>
<td>23.00 (100 %)</td>
</tr>
<tr>
<td>Follow up hospital</td>
<td>(3)</td>
<td>0.25</td>
<td>23.00 (100 %)</td>
</tr>
<tr>
<td>General practitioner</td>
<td>(2)</td>
<td>6.43</td>
<td>23.00 (100 %)</td>
</tr>
<tr>
<td><strong>Immunosuppressant drugs</strong></td>
<td>(3)</td>
<td>90.00</td>
<td>23.00 (100 %)</td>
</tr>
<tr>
<td><strong>SUM &quot;Recurrence&quot; first year</strong></td>
<td></td>
<td></td>
<td>8 258 [gamma (96.04,722)]</td>
</tr>
<tr>
<td>SUM &quot;Recurrence&quot; year 2 - 25</td>
<td>4,331 [gamma (96.04,379)]†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Cost "Palliative"**

**Chemotherapy (cycle 1 and 2)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>(4)</th>
<th>Price</th>
<th>Coverage</th>
<th>Records</th>
<th>Joranger et al (28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLOX</td>
<td>7.50</td>
<td>4.14</td>
<td>(18 %)</td>
<td>939</td>
<td>1,267</td>
</tr>
<tr>
<td>FLIRI</td>
<td>7.50</td>
<td>9.66</td>
<td>(42 %)</td>
<td>913</td>
<td>2,875</td>
</tr>
<tr>
<td>FLOX + Bevacizumab</td>
<td>5.50</td>
<td>0.92</td>
<td>(4 %)</td>
<td>2,764</td>
<td>608</td>
</tr>
<tr>
<td>FLIRI + Bevacizumab</td>
<td>5.50</td>
<td>8.28</td>
<td>(36 %)</td>
<td>2,695</td>
<td>5,336</td>
</tr>
</tbody>
</table>

**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)]† |

**Chemotherapy (cycle 3 and 4)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>(4)</th>
<th>Price</th>
<th>Coverage</th>
<th>Records</th>
<th>Joranger et al (28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLOX</td>
<td>4.00</td>
<td>7.45</td>
<td>(32 %)</td>
<td>938</td>
<td>1,215</td>
</tr>
<tr>
<td>FLIRI</td>
<td>4.00</td>
<td>6.35</td>
<td>(28 %)</td>
<td>964</td>
<td>1,064</td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>0.00</td>
<td>9.20</td>
<td>(40 %)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**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)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>(4)</th>
<th>Price</th>
<th>Coverage</th>
<th>Records</th>
<th>Joranger et al (28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab + Irinotecan</td>
<td>4.00</td>
<td>8.28</td>
<td>(36 %)</td>
<td>2,359</td>
<td>3,397</td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>0.00</td>
<td>14.72</td>
<td>(64 %)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**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**

<table>
<thead>
<tr>
<th>Value</th>
<th>[Distribution (parameters)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Disease free&quot; - cycle 1</td>
<td>0.64 [beta (2137, 1202)] (29)</td>
</tr>
<tr>
<td>&quot;Disease free&quot; - cycle 2 and onward</td>
<td>0.71 [beta (2119, 866)] (29)</td>
</tr>
<tr>
<td>&quot;Recurrence&quot; first year</td>
<td>0.82 [beta (1790, 393)] (28)</td>
</tr>
<tr>
<td>&quot;Recurrence&quot; year 2 and onward</td>
<td>0.85 [beta (1466, 259)] (28)</td>
</tr>
<tr>
<td>&quot;Palliative&quot;</td>
<td>0.82 [beta (1790, 393)] (28)</td>
</tr>
</tbody>
</table>

(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

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Selected patients</th>
<th>Range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LY</td>
<td>LTx</td>
<td>CT</td>
<td>Δ</td>
</tr>
<tr>
<td>LYs</td>
<td>5.18</td>
<td>2.07</td>
<td>3.12</td>
</tr>
<tr>
<td>QALYs</td>
<td>4.17</td>
<td>1.70</td>
<td>2.47</td>
</tr>
<tr>
<td>Costs, $</td>
<td>266 438</td>
<td>35 103</td>
<td>231 336</td>
</tr>
<tr>
<td>ILR, $</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LY</td>
<td>74 264</td>
<td>60 895 – 74 264</td>
<td>60 246</td>
</tr>
<tr>
<td>CE (prob)</td>
<td>0.66</td>
<td>0.066 – 0.91</td>
<td>0.97</td>
</tr>
<tr>
<td>QALY</td>
<td>93 651</td>
<td>75 401 – 93 651</td>
<td>74 673</td>
</tr>
<tr>
<td>CE (prob)</td>
<td>0.23</td>
<td>0.23 – 0.60</td>
<td>0.67</td>
</tr>
</tbody>
</table>

* 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.