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Short Report

Cost-effectiveness of liver transplantation *versus* last-resort systemic therapy for colorectal liver metastases

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Introduction

Approximately 50 per cent of patients with colorectal cancer have metastases at the time of diagnosis or subsequently develop metastases. The most frequent metastatic site is the liver[1–3]. Palliative chemotherapy is the treatment option for most patients with colorectal liver metastases (CRLMs). Regorafenib and TAS-102 have recently been approved by the European Medicines Agency and US Food and Drug Administration for patients with CRLMs who have progressed from second- or third-line treatments[4–6]. In randomized studies, regorafenib and TAS-102 prolonged median overall survival by 1.4–1.8 months compared with best supportive care (BSC)[7,8]. The authors have previously shown that deceased-donor liver transplantation (LT) is a cost-effective treatment alternative for patients with CRLMs compared with chemotherapy alone, particularly for selected low-risk patients (those with a low Oslo Score)[9,10]. LT may also be an option for patients with advanced liver-only CRLMs[11]. In the present study, a previously validated model was used to evaluate the cost-effectiveness of LT in patients with progressive disease, for whom the only available treatment options were TAS-102, regorafenib or BSC[9].

Methods

Cost-effectiveness analysis

An economic evaluation framework was used, with the aim of informing decision-makers on the cost per additional health effect (cost-effectiveness) of introducing a new treatment compared with relevant treatment options (*Appendix S1*). A previously published mathematical simulation model (Markov model)[9] was used to estimate health effects and healthcare costs for patients with CRLMs who had previously failed second- or third-line chemotherapy. In the model, treatment with BSC in combination with LT, TAS-102 or regorafenib, or with BSC alone was simulated (*Appendix S2*).

Effects were estimated as life-years (LYs) and quality-adjusted life years (QALYs) gained (*Appendix S3*). Costs were estimated from a healthcare perspective, and included cost of organ retrieval, transplantation, retransplantation, postoperative complications, routine follow-up, immunosuppressive drugs, tumour-targeting treatments for recurrent cancer, chemotherapy, and BSC. Costs were estimated on a present-value basis, using 2019 euros (€1 = 9.8527 Norwegian kroner, average exchange rate in 2019)[12] (*Appendix S4*).

Results from cost-effectiveness analyses are presented as incremental cost-effectiveness ratios (ICERs), defined as the cost difference divided by the effect difference between an intervention (LT) and comparators (BSC, TAS-102, and regorafenib). An ICER below the Norwegian willingness-to-pay (WTP) threshold of €72 500 was considered cost-effective[13,14].

Data

For LTs, data from records of the six patients who had progressive disease after the last available line of chemotherapy in the SECA-I trial were used. For regorafenib, TAS-102, and BSC, overall survival data published in reports from the CORRECT[7] and RECOURSE[8] trials were extracted using WebPlotDigitizer[15]. All patients included from the SECA-I, CORRECT, and RECOURSE trials had received at least second- or third-line chemotherapy (the latter in patients with *KRAS* wild-type tumours), and had good performance status (Eastern Cooperative Oncology Group score 0–1). Patients included from the different studies had relatively similar baseline characteristics and treatment histories, except that those in SECA-I were, on average mean, 10 years younger and had less frequently received bevacizumab (*Appendix S5* and *S6*). Guidelines, existing literature, and expert opinions were also used to populate the model.

Statistical analysis

A cohort of 1000 patients aged 55 years was simulated through the model. The time horizon of the model was 25 years, which was

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assumed equivalent to a lifetime perspective. The cohorts' expected LYs and QALYs gained and healthcare costs were estimated, and costs and effects were discounted by 4 per cent. To assess uncertainty in the input parameters, probabilistic sensitivity analyses (PSAs) with 1000 iterations were performed. In these analyses, all input parameters were drawn randomly from predefined distributions (*Table S1*, *Table S2* and *Table S4*).

The uncertainty in the model output is reported as confidence bounds (CB). For LTs, 50 per cent CB are presented because of the small number of participants from SECA-I. For TAS-102, regorafenib, and BSC, 95 per cent CB are reported. Using results from the PSAs, the probability that the treatment alternatives would be cost-effective under different WTP thresholds was further estimated. Findings are presented as cost-effectiveness acceptability curves.

Three scenario analyses were also undertaken in which the authors estimated: the minimum expected increase in survival needed for LT to be considered cost-effective; the maximum cost of the LT procedure for transplant to be cost-effective; and the effect of reducing the price of the drugs (TAS-102 and regorafenib) to zero. In the latter analyses, costs still accumulated owing to the cost of managing drugs and adverse events. For details, see *Appendix S7*.

Analyses were carried out using Stata® version 14 (StataCorp, College Station, Texas, USA) and Excel® (Microsoft, Redmond, Washington, USA). More detailed methods are described in Supplementary material.

Results

Patients who underwent liver transplantation survived for a mean of 4.28 (50 per cent CB 3.94 to 5.74) years, which was more than 3 years longer than patients treated with TAS-102 (0.86 (95 per cent CB 0.82 to 0.91) LYs), regorafenib (0.83 (0.78 to 0.87) LYs) or BSC (0.76 (0.72 to 0.81) LYs). The cost of LT (€217 517, 50 per cent CB 209 179 to 241 806) was substantially higher than the cost of regorafenib (€35 737, 95 per cent CB 31 366 to 40 179), TAS-102 (€20 352, 16 941 to 24 108), and BSC (€14 366, 11 423 to 18 077) (*Table 1*).

For WTP thresholds below €52 000, BSC had the highest probability of being cost-effective, and for higher thresholds LT was the treatment most likely to be cost-effective (*Fig. 1*). Given the current Norwegian WTP threshold (€72 500), there was a 91 per cent probability that LT was cost-effective, an 8 per cent probability that TAS-102 was cost-effective, a 0.1 per cent probability that BSC was cost-effective, and zero probability that regorafenib was cost-effective (*Fig. 1*).

Scenario analyses showed that, if survival in the LT group decreased by 1.28 years, to 3 (50 per cent CB 2.73 to 4.10) LYs, LT and TAS-102 were equally (45 per cent) likely to be cost-effective; when costs of LT increased by 60 per cent (from €134 336 to €214 937 see *Table S2*), there was an equal probability (45 per cent) that TAS-102 and LT were cost-effective; and LT was still 89 per cent likely to be cost-effective when the drug costs of TAS-102 and regorafenib were reduced to zero. More detailed results are available in *Appendix S8 and S9*.

Discussion

If prioritizing purely based on cost-effectiveness, these findings support implementation of LT as a treatment option for patients with CRLMs in countries where the WTP-threshold is over €52 000. The scarcity of liver grafts, however, inevitably influences this decision. Five-year survival rates for patients currently listed for LT in

Table 1 Summary of mean life-years, quality-adjusted life-years, and costs for the base-case probabilistic sensitivity analysis

	Mean LYs	Mean QALYs	Mean costs (€)	Δ LYs	Δ QALYs	Δ Cost (€)	ICER LYs	ICER QALYs
Best supportive care	0.76 (0.72, 0.81)	0.62 (0.59, 0.66)	14 366 (11 423, 18 077)	–	–	–		
TAS-102	0.86 (0.82, 0.91)	0.71 (0.67, 0.74)	20 352 (16 941, 24 108)	0.09	0.1	5986	66 511	59 860
Regorafenib	0.83 (0.78, 0.87)	0.68 (0.64, 0.72)	35 737 (31 366, 40 179)	−0.03	−0.03	15 385	Dominated*	Dominated*
Liver transplantation	4.28 (3.94, 5.74)	3.51 (3.22, 4.73)	217 517 (209 179, 241 806)	3.42	2.80	197 163	57 650	70 415

Values in parentheses are 50 per cent confidence bounds for liver transplantation, and 95 per cent confidence bounds for best supportive care, TAS-102, and regorafenib. LY, life-year; QALY, quality adjusted life-year; Δ, difference compared with the treatment listed above (second most costly treatment), except LT, which is compared to TAS-102 since regorafenib was dominated i.e., TAS-102 compared to BSC, regorafenib compared to TAS-102 and LT compared to TAS-102; ICER, incremental cost-effectiveness ratio. *When incremental effects are negative, but costs are positive, the treatment is dominated, that is, clearly not cost-effective.

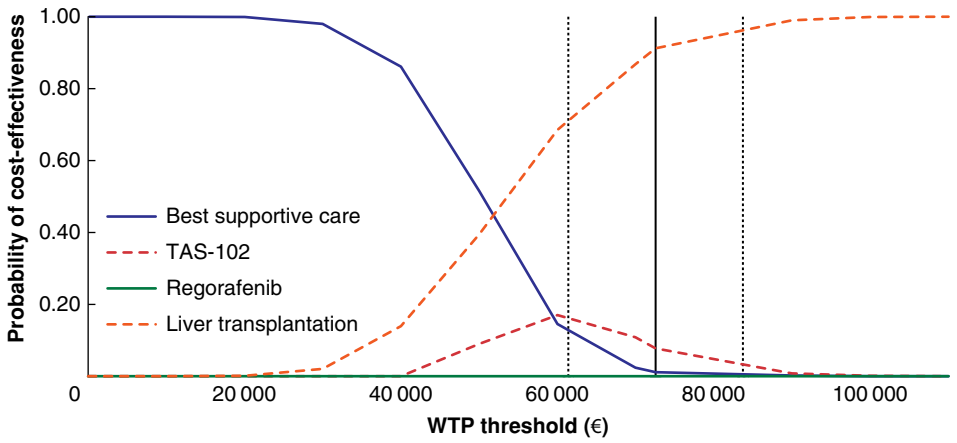

Fig. 1 Cost-effectiveness acceptability curve comparing liver transplantation, TAS-102, regorafenib, and best supportive care

The black vertical line indicates a willingness-to-pay threshold (WTP) of €72 500, and the dotted lines indicate a low (€61 404) and a high (€83 733) WTP threshold. The plot for regorafenib is not visible in the figure because it always lies on the horizontal line (0 per cent probability of being cost-effective).

Scandinavia range from 87 per cent (primary sclerosing cholangitis) to 42 per cent (cholangiocarcinoma)[16]. By comparison, the present model predicted a 5-year survival rate of 42 per cent, with a high level of uncertainty: 50 per cent CB of 36–64 per cent and 95 per cent CB of 22–90 per cent. Given the scarcity of liver grafts, it is therefore unlikely that these patients will be listed for LT with standard donor grafts. These estimates, however, support the continued exploration of how LTs can be made possible in such patients through expansion of the donor pool, using techniques such as extended-criteria donation[17], resection and partial liver segment II–III transplantation with delayed total hepatectomy (RAPID)[18], or allowing living donation combined with the RAPID procedure[19]. Ongoing studies are evaluating both the expected clinical outcomes and ethical issues related to using these techniques (ClinicalTrials.gov, NCT02864485). In addition, mathematical simulation models should continue to be used to simulate expected costs and benefits for both patients undergoing LT, and others affected; for example, those currently listed for LT or those donating livers under the condition of living-donor LT. For details, see *Appendix* S10.

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Disclosure. The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

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European Colorectal Congress

28 November – 1 December 2022, St.Gallen, Switzerland

Monday, 28 November 2022

09.50
Opening and welcome
Jochen Lange, St.Gallen, CH

10.00
It is leaking! Approaches to salvaging an anastomosis
Willem Bemelman, Amsterdam, NL

10.30
Predictive and diagnostic markers of anastomotic leak
Andre D'Hoore, Leuven, BE

11.00
SATELLITE SYMPOSIUM
ETHICON

11.45
Of microbes and men – the unspoken story of anastomotic leakage
James Kinross, London, UK

12.15
LUNCH

13.45
Operative techniques to reduce anastomotic recurrence in Crohn's disease
Laura Hancock, Manchester, UK

14.15
Innovative approaches in the treatment of complex Crohn Diseases perianal fistula
Christianne Buskens, Amsterdam, NL

14.45
To divert or not to divert in Crohn surgery – technical aspects and patient factors
Pär Myrelid, Linköping, SE

15.15
COFFEE BREAK

15.45
Appendiceal neoplasia – when to opt for a minimal approach, when and how to go for a maximal treatment
Tom Cecil, Basingstoke, Hampshire, UK

16.15
SATELLITE SYMPOSIUM
Medtronic
Further,Together

17.00
Outcomes of modern induction therapies and Wait and Watch strategies, Hope or Hype
Antonino Spinelli, Milano, IT

17.30
EAES Presidential Lecture - Use of ICG in colorectal surgery: beyond bowel perfusion
Salvador Morales-Conde, Sevilla, ES

18.00
Get-Together with your colleagues
Industrial Exhibition

Tuesday, 29 November 2022

9.00
CONSULTANT'S CORNER
Michel Adamina, Winterthur, CH

10.30
COFFEE BREAK

11.00
SATELLITE SYMPOSIUM
INTUITIVE

11.45
Trends in colorectal oncology and clinical insights for the near future
Rob Glynne-Jones, London, UK

12.15
LUNCH

13.45
VIDEO SESSION

14.15
SATELLITE SYMPOSIUM
BD

15.00
COFFEE BREAK

15.30
The unsolved issue of TME: open, robotic, transanal, or laparoscopic – shining light on evidence and practice
Des Winter, Dublin, IE
Jim Khan, London, UK
Brendan Moran, Basingstoke, UK

16.30
SATELLITE SYMPOSIUM
Takeda

17.15
Lars Pahlman lecture
Søren Laurberg, Aarhus, DK

Thursday, 1 December 2022
Masterclass in Colorectal Surgery
Proctology Day

Wednesday, 30 November 2022

9.00
Advanced risk stratification in colorectal cancer – choosing wisely surgery and adjuvant therapy
Philip Quirke, Leeds, UK

09.30
Predictors for Postoperative Complications and Mortality
Ronan O'Connell, Dublin, IE

10.00
Segmental colectomy versus extended colectomy for complex cancer
Quentin Denost, Bordeaux, FR

10.30
COFFEE BREAK

11.00
Incidental cancer in polyp - completion surgery or endoscopy treatment alone?
Laura Beyer-Berjot, Marseille, FR

11.30
SATELLITE SYMPOSIUM
EVOLUZIONE DISPOSITIVI MEDICI

12.00
Less is more – pushing the boundaries of full-thickness rectal resection
Xavier Serra-Aracil, Barcelona, ES

12.30
LUNCH

14.00
Management of intestinal neuroendocrine neoplasia
Frédéric Ris, Geneva, CH

14.30
Poster Presentation & Best Poster Award
Michel Adamina, Winterthur, CH

15.00
SATELLITE SYMPOSIUM
OLYMPUS

15.45
COFFEE BREAK

16.15
Reoperative pelvic floor surgery – dealing with perineal hernia, reoperations, and complex reconstructions
Guillaume Meurette, Nantes, FR

16.45
Salvage strategies for rectal neoplasia
Roel Hompes, Amsterdam, NL

17.15
Beyond TME – technique and results of pelvic exenteration and sacrectomy
Paris Tekkis, London, UK

19.30
FESTIVE EVENING

Information & Registration **www.colorectalsurgery.eu**