EUROPEAN JOURNAL OF CANCER 47 (2011) 2291–2298

available at www.sciencedirect.com

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journal homepage: www.ejconline.com

Effectiveness and cost-effectiveness of peri-operative versus post-operative chemotherapy for resectable colorectal liver metastases

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ARTICLE INFO

Article history:
Available online 7 June 2011

Keywords:
Liver metastases
Colorectal cancer
Cost-effectiveness
Partial hepatectomy
Chemotherapy
Adjuvant
Neoadjuvant

ABSTRACT

Background: The role of neo-adjuvant chemotherapy prior to hepatectomy in patients with resectable colorectal liver metastases is currently a matter of debate. The aim of the present study was to analyse life-expectancy, quality adjusted life-expectancy and cost-effectiveness of the two chemotherapeutic strategies.

Methods: A Markov decision model was developed, on the basis of parameters derived from an extensive literature search of the last ten years, to compare outcomes of peri-operative versus post-operative chemotherapy.

Results: Life-expectancy observed for peri-operative chemotherapy was 54.56 months and 52.62 months with post-operative chemotherapy only; the quality-adjusted life-expectancy with peri-operative chemotherapy was 39.33 quality-adjusted life-months (QALMs) and 37.84 QALMs with post-operative chemotherapy. Peri-operative chemotherapy results in an increase in total costs of 1180 € over ten years and in an incremental cost-effectiveness ratio (ICER) of 791.9 €/QALM. The model was more sensitive to the expected 3-year recurrence-free survival (RFS) and cost of hepatic resection: with respect to an expected 3-year RFS $\leqslant$ 25% the peri-operative approach was more cost-effective than post-operative strategy but differences in average cost-effectiveness were small. The relationship between ICER and cost of hepatic resection was inverse because the higher the cost of hepatic resection, the higher the cost saving due to patients becoming unresectable during neo-adjuvant therapy.

Conclusions: In the treatment of resectable colorectal liver metastases, the addition of neo-adjuvant chemotherapy could be cost-effective because it makes it possible to avoid hepatic resection in patients who do not respond to the neo-adjuvant approach; however, the life-expectancy of the two strategies is very similar.

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.05.014

1. Introduction

The liver is the most common site of colorectal metastases. At diagnosis, 15–20% of patients will have synchronous liver metastases and among those who develop metachronous metastases (more than 50% of stage III cases) would develop these within 3 years after primary colon surgery.[1,2] Surgical resection of liver metastases offers the hope of cure and is currently recognised as the only treatment that offers the chance of long-term survival. The use of neo-adjuvant chemotherapy was first indicated for patients with initially unresectable metastases, with the aim of downstaging the tumour spread and making surgical removal technically feasible.[3] In recent years, administering neo-adjuvant chemotherapy, followed by post-operative treatment, has been increasingly adopted also in patients with resectable colorectal liver metastases; however, there is no universal agreement about the oncologic benefits of such approach and some perplexities were raised regarding the parenchymal injury that can be caused by preoperative chemotherapy which may increase morbidity after surgery.[4] At present, studies both on neo-adjuvant chemotherapy and adjuvant chemotherapy only include patients undergoing surgery alone as their control arm and, to the best of our knowledge, there are no studies regarding the comparison of the two approaches. A randomised controlled trial comparing neo-adjuvant chemotherapy with adjuvant therapy after liver resection is advocated to definitively elucidate the relative risk–benefit ratios of these approaches.[4] The first aim of the present study was to develop a Markov decision model, built on the basis of the available literature data, in order to compare the effectiveness of these two treatment strategies and to investigate which clinical and tumoural variables would be able to define the best strategy to adopt. Neo-adjuvant chemotherapy introduces a new drug schedule in the treatment strategy of resectable colorectal liver metastases: cost-effectiveness analysis is thus mandatory to assess the efficacy of such an approach.[5] The second aim of the present study was to analyse the cost-effectiveness of peri-operative chemotherapy and adjuvant therapy after liver resection.

2. Methods

2.1. Structure of the model

We developed a Markov decision model using TreeAge Pro 2008 (TreeAge Software Inc., Williamstown, MA, USA) that follows a hypothetical cohort of adult patients with resectable colorectal liver metastases over 10 years as they move between different states of health, before and after hepatic resection, until death. In the model, patients were divided into two groups: patients receiving chemotherapy prior to and after hepatectomy (peri-operative chemotherapy group) and patients receiving the same regimen only after hepatectomy (post-operative chemotherapy group). The chemotherapy employed in the present model consists of a FOLFOX4-based regimen.[4] A schematic representation of the present Markov model is depicted in Fig. 1.

2.2. Literature search strategy and selection criteria

Model probability parameters were derived from the literature: a systematic search of MEDLINE and EMBASE databases was independently conducted by two investigators (M.C. and G.E.), and was narrowed to English-language publications from the last ten years. The following Medical Subject Headings (MeSH) terms were used for the bibliographic search: 'colorectal cancer', 'liver metastases', 'hepatic resection', 'neo-adjuvant', 'adjuvant', 'drug therapy', 'hepatectomy'. Inclusion or exclusion of studies was performed hierarchically based on the title of the report first, followed by the abstract, and then by the full text. If the initial study was followed by a more complete study or studies that included the original dataset, the most recent and complete report was chosen. Such linked studies were identified on the grounds of authorship, institutions, design, length of follow-up, and study populations. We finally reviewed the reference lists of all selected studies for additional citations; disagreement on study selection was resolved by consulting a third investigator (A.C.). Publications where systemic chemotherapy was used in patients with resectable liver metastases prior to and/or after hepatectomy were identified for inclusion: this included the use of chemotherapy drugs comprising 5-FU, leucovorin, oxaliplatin or irinotecan; studies that included the use of bevacizumab or cetuximab prior to hepatectomy were excluded since they represented a small proportion of all studies examined and the question as to whether their use prior to hepatectomy can reduce hepatic regeneration and thus increase post-operative mortality is still under investigation.[4,6–8] Studies were selected for evaluation on the basis of their level of evidence as described by the US Preventive Services Task force. Probabilities were directly derived from the literature or calculated following the DEALE method.[9] according to the formula $(\ln S)/t$ where t is the time at which the survival S is measured; the summary of probabilities was reported in pooled estimates obtained by combining information from independent samples taken from populations believed to have the same distribution; plausible ranges were extracted from the literature or calculated assuming a beta-distribution (95% confidence interval).

2.3. Model probabilities and utilities used in the model

Probabilities and ranges extracted and used in the present Markov model are reported in Table 1. The median number of cycles of neo-adjuvant chemotherapy administered was 6, ranging from 3 to 11; tumour progression was calculated to be 15.5% but only 31.9% of these patients became unresectable[10–25]; the time interval assumed in the present model between end of neo-adjuvant chemotherapy and surgery was 5 weeks. Post-operative mortality and morbidity after neo-adjuvant chemotherapy were calculated to be 1.5% and 29.1%, respectively, resulting in a median in-hospital stay of 10 days. The 3-year recurrence-free survival (RFS) of patients undergoing peri-operative chemotherapy was calculated to be 34.1% and the patient survival 62.1%.[10–25,8,7] The impact of response to neo-adjuvant chemotherapy in determining 3-year RFS after hepatectomy was also considered: taking the available studies together, a hazard ratio of 2.13 was calculated

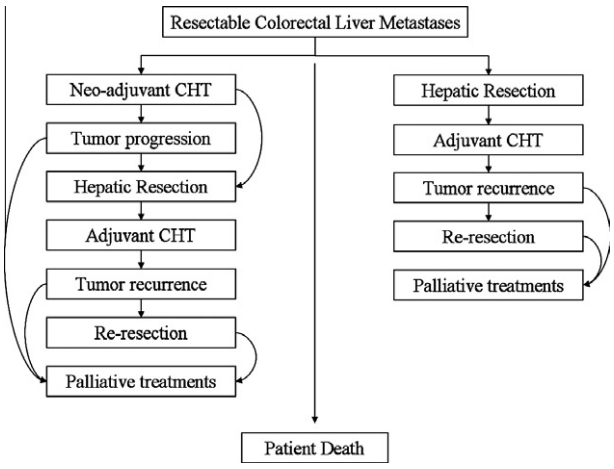

Fig. 1 – Schematic representation of the Markov model built in the present analysis. All health states included quality-of-life utilities and can proceed directly to death, arrows are omitted for simplicity.

and applied for 3-year RFS after hepatectomy in patients who experienced tumour progression during neo-adjuvant chemotherapy and a hazard ratio of 0.90 in patients who remained stable or showed a clinical response.[11,14,15,19] Regarding data about post-operative chemotherapy only, mortality and morbidity were calculated to be 1.7% and 24.3%, respectively, resulting in a median in-hospital stay of 8.5 days; the pooled 3-year RFS was 33.4% and the patient survival was 60.5%.[26–35] For both groups, tumour recurrence was assumed to be confined to the liver in 44.8% of cases; of these, 59.6% were submitted to a second hepatectomy. The mortality rate calculated for the second resection was 1.0% and the 3-year patient survival 58.2%.[36–48] Complications after surgery were estimated to add 3 days of hospitalisation, as already reported in previous simulation models.[49,50] The median survival following tumour not suitable for curative treatments assumed in the present model was 20 months, ranging from 10 to 30 months.[49–51]

Utilities were scaled from 0 (dead) to 1 (perfect health). Quality-adjusted life-expectancy is the measure that combines an estimate of the life years gained from an intervention with a judgment on the quality of these life years. Utilities extracted from the literature regard both quality of life during chemotherapy and their related adverse events and post-operative outcome, and are detailed in Table 2; ranges were assumed to be within 20% of the base-case value.

2.4. Costs

Base-case estimates for all costs are summarised in Table 2. Costs were estimated from a social perspective. Estimates of annual direct costs for each health state included the frequency and costs for inpatient and outpatient visits, diagnostic and laboratory testing, medications, and procedures. Costs were extracted from the data on current payments within the Italian public health care system, converted to 2010 Euro (€),

Table 1 – Variables calculated from the literature and used in the present Markov model.

Variable	Base case value	Plausible range	References
Patients receiving neo-adjuvant therapy			
No. of cycles of neo-adjuvant CHT	6	3–11	Table 1S
Tumour progression after neo-adjuvant	15.5%	12.9–18.2%	Table 1S
Tumour progression – unresectable	31.9%	22.3–41.4%	Table 1S
Post-operative mortality (within 30 days)	1.5%	0.8–2.0%	Table 2S
Post-operative morbidity	29.1%	26.8–31.4%	Table 2S
Median in-hospital stay (days)	10	8–13	Table 2S
3-Year recurrence free survival (RFS)	34.1%	31.5–36.8%	Table 2S
RFS Odds Ratio for tumour progression	2.13	1.00–6.83	11,14,15,19
RFS Odds Ratio for tumour response/stability	0.90	0.31–1.00	11,14,15,19
3-Year patient survival	62.1%	59.4–64.8%	Table 2S
HR for progression free for surgery alone	1.37	1.03–1.81	13
Patients not receiving neo-adjuvant therapy			
Post-operative mortality (within 30 days)	1.7%	1.3–2.2%	Table 3S
Post-operative morbidity	24.3%	22.7–25.9%	Table 3S
Median in-hospital stay (days)	8.5	7–10	Table 3S
3-Year recurrence free survival (RFS)	33.4%	30.7–36.1%	Table 3S
3-Year patient survival	60.5%	59.0–62.0%	Table 3S
Tumour recurrence			
Recurrence confined to the liver only	44.8%	42.4–47.2%	Table 4S
Re-resection of liver metastases	59.6%	56.1–63.1%	Table 4S
Post-operative mortality (within 30 days)	1.0%	0.3–1.5%	Table 4S
3-Year patient survival	58.2%	55.1–61.3%	Table 4S
Median survival of palliative (months)	20	10–30	51–53
Side-effects during chemotherapy			
Grade 3–4 neutropenia	1.3%	1.0–4.0%	51–53
Febrile neutropenia requiring hospitalisation	1.0%	0.1–2.0%	51–53
Grade 3–4 diarrhoea	0.7%	0.1–2.0%	51–53

HR = hazard ratio.

Table 2 – Utilities and costs assumed in the present Markov model.

Variable	Base case value	Plausible range	References
Utilities			
During chemotherapy	0.68	0.54–0.82	[51–53]
Post-resection without morbidity (first month)	0.69	0.55–0.83	[51–53]
Post-resection with morbidity (first month)	0.65	0.52–0.78	[51–53]
End of chemotherapy recurrence-free	0.78	0.62–0.94	[51–53]
Neutropenic fever	0.47	0.38–0.56	[51–53]
Grade 3–4 diarrhoea	0.32	0.26–0.38	[51–53]
Palliative treatments	0.63	0.50–0.76	[51–53]
Costs (€ 2010)			
Central venous system costs	250	200–300	NHS; [54]
Pump costs (pump)	40	32–48	NHS; [54]
Antiemetic prophylactic therapy	200	160–240	NHS; [54]
Cost of chemotherapy per cycle	250	200–300	NHS; [54]
Cost of staging (CT scan or RMN)	350	280–420	NHS; [54]
Hepatic resection	15,000	10,000–20,000	NHS; [54]
Daily cost after hepatectomy	150	120–180	NHS; [54]
Therapy of grade 3–4 diarrhoea	150	120–180	NHS; [54]
Therapy of grade 3–4 neutropenia (CSF)	240	192–288	NHS; [54]
Cost of febrile neutropenia	3500	2800–4200	NHS; [54]
Daily cost of palliative therapy	250	200–300	NHS; [54]

NHS = national healthcare system.

and compared with the previous cost-effectiveness reports in order to validate cost assumption; ranges were assumed to be within 20% of the base-case value. As is recommended for pharmaco-economic analysis,[53] drug costs were based on average wholesale costs, in particular: 5-FU, 5 g/100 ml fl. = 12.70 €; oxaliplatin, 200 mg fl. = 380 €; leucovorin, 100 mg fl. = 10.28 €. All costs included in the present analysis were discounted at a real annual rate of 3% to adjust for the relative value of the Euro at present. The willingness-to-pay (WTP) is defined as the maximum amount of money that may be contributed by an individual to equalise a utility change; in other words, how much you would pay for a specific increase in time-span: the WTP threshold was set at 3000 €/QALM that corresponds to about 50,000 $ per quality-adjusted life-year (QALY) reported in the literature[54]; for sensitivity analysis, WTP was ranged between 2500 and 3500 €/QALM.

3. Results

In the intention-to-treat analysis, the 10-year life-expectancy that could be obtained with peri-operative chemotherapy in the base-case scenario was 54.56 months, slightly higher than the life-expectancy that could be obtained with post-operative chemotherapy of 52.62 months (incremental life-expectancy = +1.94 months). The corresponding 1, 3 and 5-year survival rates were 91%, 62% and 38% for peri-operative chemotherapy patients, and 88%, 59% and 36% for post-operative chemotherapy patients (Fig. 2). These results were consistent with the data reported in the literature and the model thus appears to be well calibrated. Considering utilities, the quality-adjusted life-expectancy with peri-operative chemotherapy was 39.33 quality-adjusted life-months (QALMs) whereas the quality-adjusted life-expectancy with post-operative chemotherapy was 37.84 QALMs (incremental = 1.49 QALMs). The total costs for patients submitted to peri-operative chemotherapy was 27,054 €, whereas the total costs for

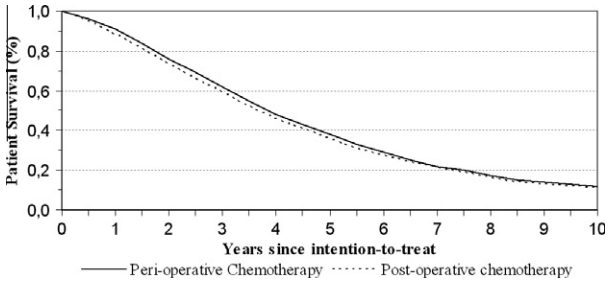

Fig. 2 – Survival curves of peri-operative and post-operative chemotherapy strategies since intention-to-treat.

patients submitted to post-operative chemotherapy was 25,874 €; thus, peri-operative chemotherapy resulted in an overall increase of the total costs of only 1180 € over ten years. The cost per life-month saved was 495.9 €/month for peri-operative chemotherapy and 491.7 €/month for postoperative chemotherapy only. The cost-effectiveness was 687.9 €/QALM for peri-operative chemotherapy and 683.8 €/QALM for post-operative chemotherapy; thus, the incremental cost-effectiveness ratio (ICER) was 791.9 €/QALM, quite lower than the threshold for the willingness-to-pay of 3000 €/QALM assumed in the present model. Surgery alone led to a 5-year life-expectancy of 46.36 months corresponding to 1-, 3- and 5-year survival rates of 84%, 51% and 29%, respectively, and a quality-adjusted life-expectancy of 33.26 QALMs. The total cost for patients submitted to surgery alone was 24,809 €, thus, the cost-effectiveness was 745.9 €/QALM higher than both peri-operative and post-operative strategies.

3.1. *Sensitivity analysis on life-expectancy*

Univariate sensitivity analysis on the crude life-expectancy is depicted in Fig. 3. This graph reports changes in the incre-

mental life-expectancy observed for peri-operative chemotherapy on variation of the variables considered in the present model (base case = +1.94 months). It should be noted that 3-year recurrence-free survival was the main determinant of life-expectancy, whereas tumour progression under neo-adjuvant therapy, un-resectability of tumour progression and post-operative mortality play minor roles; the remaining variables have a minimal impact on the overall results of the present model. Two-way sensitivity analysis was performed on simultaneous variation of the expected 3-year RFS of both chemotherapy approaches: in a range of 3-year RFS between 20% and 40%, the incremental life-expectancy of peri-operative approach remains stable at 1.94 months over ten years following intention-to-treat.

3.2. *Sensitivity analysis on cost-effectiveness*

Univariate sensitivity analysis showed that the expected 3-year recurrence-free survival and costs of hepatic resection were the main determinants of the cost-effectiveness of the two strategies. Regarding the 3-year recurrence-free survival expected from the peri-operative chemotherapy approach, the ICER ranged from 448.1 €/QALM when 3-year RFS was 36.8% up to 8075 €/QALM when 3-year RFS was 31.5%; the ICER was higher than the assumed WTP of 3000 €/QALM when the 3-year RFS was lower than 32.0%. The expected 3-year RFS after post-operative chemotherapy strategy also had a strong impact on the cost-effectiveness of the peri-operative approach: in fact, the ICER of peri-operative chemotherapy was 661.9 €/QALM when 3-year RFS was 30.1%, it was higher than the assumed WTP when the 3-year RFS was above 35.0%, and when the 3-year RFS was higher than 36.0%, post-operative chemotherapy alone was the best strategy to adopt, because of lower costs and higher survivals in comparison to peri-operative chemotherapy (dominated). The 3-year RFS rates after peri-operative and post-operative chemotherapy strategies are summarised in the two-way sensitivity analysis of Table 3. With respect to an expected 3-year RFS $\leqslant$ 25% the neo-adjuvant strategy should be considered as cost-effective; whereas by increasing the 3-year RFS the neo-adjuvant approach resulted in an incremental average cost-effectiveness.

The cost variable that most affected the ICER was the cost of hepatic resection; however, the relationship was inverse and with respect to a cost of hepatic resection of 10,000 €, the ICER of peri-operative chemotherapy was 1099 €/QALM whereas with respect to a cost of 20,000 €, the ICER fell to 487.3 €/QALM. This is because the higher the cost of hepatic resection, the higher the saving due to patients becoming unresectable during neo-adjuvant therapy. The impact of the remaining costs considered in the present analysis was minimal (data not reported).

4. Discussion

Current recommendations from a European expert panel of hepatobiliary surgeons and medical oncologists suggest that the majority of patients with colorectal liver metastases should be treated upfront with systemic chemotherapy, irrespective of the resectability status of their metastases based on the results of the Nordlinger trial.[4,13] The control arm of this trial was represented by patients submitted to surgery alone and comparative data between peri-operative and post-operative chemo therapy strategies are currently lacking in the literature.[13] In addition, neo-adjuvant chemotherapy introduces a new drug schedule in the treatment strategy of resectable colorectal liver metastases and cost-effectiveness analysis is, therefore, necessary to assess the efficacy of such an approach before becoming routine. Results from the present model showed that peri-operative chemotherapy could lead to a very modest incremental life-expectancy in comparison to post-operative strategy. This is probably the consequence of the small differences observed in the recurrence rate and in patient survival reported in the literature but can also be the result of the exclusion from resection of patients who experienced tumour progression leading to un-resectability of metastases. Consequently, survival after hepatectomy was affected by the selection of patients who responded to the neo-adjuvant approach. Even if the incremental life-expectancy was quite small, the additional costs related to the neo-adjuvant chemotherapy, in comparison to immediate surgery, were also small and the incremental cost-effectiveness ratio was below the willingness-to-pay suggested by the literature[54]; thus, the peri-opera-

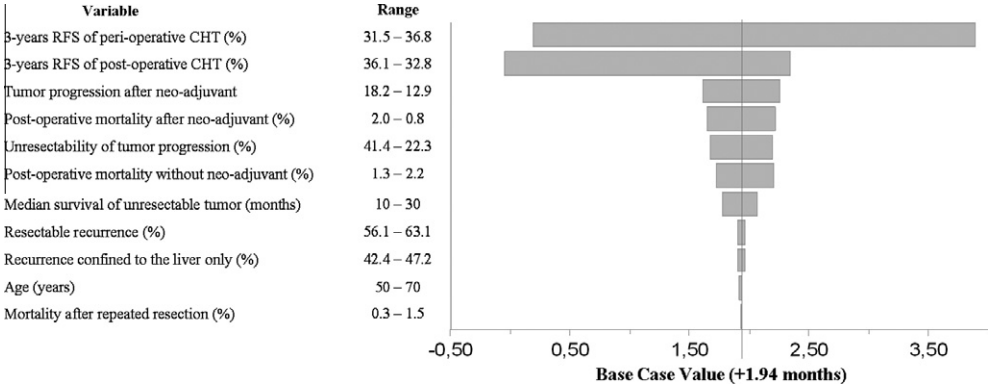

Fig. 3 – Univariate sensitivity analysis that shows how the incremental life-expectancy, observed with peri-operative chemotherapy in the base case scenario, changes in relationship with changing of the variables assumed in the present model.

Table 3 – Two-way sensitivity analysis at simultaneous variation of 3-year RFS of both strategies. Based on an expected 3-year RFS ⩽ 25%, the average cost-effectiveness value of peri-operative strategy was lower than that of post-operative strategy. Ranges were enlarged to cover different clinical scenarios.

Expected 3-year RFS (%)	Cost-effectiveness (€/QALM)		Delta
	Peri-operative (95% CI)	Post-operative (95% CI)	
20	796.3 (816.3–776.1)	803.1 (826.8–779.3)	−6.8
25	758.7 (779.1–737.9)	759.0 (782.9–734.9)	−0.3
30	720.2 (741.1–699.0)	714.4 (738.5–690.1)	+5.8
35	680.8 (702.2–659.2)	669.3 (693.7–644.9)	+11.5
40	640.7 (662.4–618.8)	624.1 (648.5–599.6)	+16.6
45	600.0 (622.0–577.9)	578.8 (603.2–554.4)	+21.2
50	559.1 (581.2–536.9)	533.8 (558.0–509.8)	+25.3

tive approach could be considered cost-effective, and the present study explains the reason for this result.

The increase in costs of the peri-operative strategy is the result of two main features: the additional costs of neo-adjuvant chemotherapy by itself and the costs related to the higher morbidity and prolonged in-hospital stay of these patients; on the contrary, patients becoming unresectable during neo-adjuvant therapy will lead to cost saving. It should be noted, in fact, that the costs of neo-adjuvant chemotherapy were relatively lower in comparison to the cost of hepatic resection, the exclusion from surgery of those patients who became unresectable during neo-adjuvant chemotherapy will consequently be cost-saving. Most concerns about the safety and feasibility of neo-adjuvant chemotherapy regard the reported increase in post-operative adverse events. Pooled literature estimates of morbidity confirmed post-operative complications to be more frequent after neo-adjuvant chemotherapy. Morbidity occurrence and post-operative in-hospital stay were included in the present model; thus, part of the increased costs of neo-adjuvant chemotherapy were represented by increased costs of hospitalisation. Similarly, the decreased utilities related to neo-adjuvant chemotherapy and post-operative morbidity can explain the difference observed in the quality-adjusted life-expectancy and in the ICER. To give an estimation of the impact of neo-adjuvant strategy on the national healthcare system, about 40,000 patients/year were diagnosed with colorectal tumour in Italy in the last decade[55] and approximately 4500 patients would be potential candidates for hepatic resection each year.[56] If all physicians selected the neo-adjuvant approach, it would result in an increase in costs, for the Italian national healthcare system, of 531,000 € each year.

The main determinant of the best strategy to adopt was the expected 3-year recurrence-free survival with or without neo-adjuvant chemotherapy. The results of the present model show that the gain in life-expectancy that could be obtained with neo-adjuvant chemotherapy remains stable on variation of RFS, but the cost-effectiveness changes. In patients with favourable tumour features, where the expected 3-year RFS is high, neo-adjuvant chemotherapy should be avoided because of the limited gain in survival that could be obtained with respect to higher costs in comparison to post-operative chemotherapy alone; conversely, the cost-effectiveness of peri-operative chemotherapy was more clear with respect to low expected 3-year RFS. Thus, the main suggestion that could be extrapolated from the present analysis is that the indication for neo-adjuvant chemotherapy should be guided by the predicted risk of recurrence after hepatic resection in order to be cost-effective. On the basis of the Memorial Sloan-Kettering Cancer Center (MSKCC) clinical risk score (CRS),[57] patients should be grouped into 2 categories: low CRS and high CRS. It has been reported that in patients with a low CRS, a 3-year RFS above 40% should be expected whereas in patients with a high CRS, the 3-year RFS drops below 20%.[58] Consequently, it seems reasonable to offer immediate surgery and post-operative chemotherapy to those patients with a low CRS and, on the contrary, to offer neo-adjuvant chemotherapy to patients with a high CRS. This approach could lead to both the cost-effectiveness of peri-operative chemotherapy and the possibility of observing the clinical response prior to hepatectomy in order to better define prognosis and the subsequent therapeutic schedule. The idea to treat only those patients with unfavourable tumour characteristics with neo-adjuvant chemo therapy is well in keeping with the suggested benefit of such an approach by excluding patients who do not respond to treatment, in whom surgery would be inappropriate.[4,59] However, the question remains whether the response to chemotherapy simply identifies patients who have a predetermined prognosis or whether the response is able to modify the course of the disease.

The present model has at least two limitations that could be taken into consideration. The first limitation is that, as with any modelling study, our findings are limited by the quality of the available literature, and the second regards costs considered for the cost-effectiveness analysis that can vary on the basis of geographical area, clinical management and cost definitions. Regarding this last issue it should be noted, however, that since the same costs were considered for peri-operative and post-operative patients, the ICER was substantially unaffected. The present model is not aimed at replacing randomised controlled trials; on the contrary, we believe that it could be helpful in constructing protocols for further RCTs aimed at assessing the benefit of neo-adjuvant chemotherapy for resectable colorectal liver metastases. The possibility of estimating the effect of several covariates could be of great help in selecting the population for an RCT. In addition, the cost analysis could be used to estimate the total cost of an RCT that remains the best technique for clinical research.

In conclusion, the addition of neo-adjuvant chemotherapy to the treatment of resectable colorectal liver metastases

could be cost-effective because it can save patients who do not respond to neo-adjuvant approach from hepatic resection, although the life-expectancy of the two strategies is very similar. The strategy of the neo-adjuvant approach could be more cost-effective in those patients with unfavourable tumour features by excluding patients who do not respond to treatment, in whom surgery would be inappropriate. Conversely, for patients with favourable tumour characteristics the utility of adding neo-adjuvant chemotherapy to the treatment schedule remains to be established.

Contributors

GE and AC equally contributed to the manuscript preparation. GE developed the protocol, coordinated the study and wrote the manuscript. AC coordinated the study, performed the statistical analysis and wrote the manuscript. MC and EP performed the literature review. All the investigators were involved in the writing of the report, and reviewed and approved the final version.

Conflict of interest statement

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2011.05.014.

REFERENCES

1. Tjandra JJ, Chan MK. Follow-up after curative resection of colorectal cancer: a meta-analysis. *Dis Colon Rectum* 2007;**50**:1783–99.
2. Fong Y, Kemeny N, Paty P, Blumgart LH, Cohen AM. Treatment of colorectal cancer: hepatic metastasis. *Semin Surg Oncol* 1996;**12**:219–52.
3. Leonard GD, Brenner B, Kemeny NE. Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2005;**23**:2038–48.
4. Chua TC, Saxena A, Liauw W, et al. Systematic review of randomized and nonrandomized trials of the clinical response and outcomes of neoadjuvant systemic chemotherapy for resectable colorectal liver metastases. *Ann Surg Oncol* 2010;**17**:492–501.
5. Mark DB. Economic analysis: methods and end-points. In: Califf RM, Mark DB, Wagner G, editors. *Acute coronary care*. 2nd ed. St. Louis: Mosby-Year Book; 1995. p. 167–82.
6. Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 2006;**24**:2065–72.
7. Welsh FK, Tilney HS, Tekkis PP, et al. Safe liver resection following chemotherapy for colorectal metastases is a matter of timing. *Br J Cancer* 2007;**96**:1037–42.
8. Nakano H, Oussoultzoglou E, Rosso E, et al. Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy. *Ann Surg* 2008;**247**:118–24.
9. Beck JR, Kassirer JP, Pauker SG. A convenient approximation of life expectancy (the "DEALE"). I. Validation of the method. *Am J Med* 1982;**73**:883–8.
10. Lubezky N, Geva R, Shmueli E, et al. Is there a survival benefit to neoadjuvant versus adjuvant chemotherapy, combined with surgery for resectable colorectal liver metastases? *World J Surg* 2009;**33**:1028–34.
11. Bathe OF, Ernst S, Sutherland FR, et al. A phase II experience with neoadjuvant irinotecan (CPT-11), 5-fluorouracil (5-FU) and leucovorin (LV) for colorectal liver metastases. *BMC Cancer* 2009;**9**:156–8.
12. Gallagher DJ, Zheng J, Capanu M, et al. Response to neoadjuvant chemotherapy does not predict overall survival for patients with synchronous colorectal hepatic metastases. *Ann Surg Oncol* 2009;**16**:1844–51.
13. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008;**371**:1007–16.
14. Adam R, Wicherts DA, de Haas RJ, et al. Complete pathologic response after preoperative chemotherapy for colorectal liver metastases: myth or reality? *J Clin Oncol* 2008;**26**: 1635–41.
15. Gruenberger B, Scheithauer W, Punzengruber R, et al. Importance of response to neoadjuvant chemotherapy in potentially curable colorectal cancer liver metastases. *BMC Cancer* 2000;**8**:120.
16. Chun YS, Vauthey JN, Ribero D, et al. Systemic chemotherapy and two-stage hepatectomy for extensive bilateral colorectal liver metastases: perioperative safety and survival. *J Gastrointest Surg* 2007;**11**:1498–504.
17. Hewes JC, Dighe S, Morris RW, et al. Preoperative chemotherapy and the outcome of liver resection for colorectal metastases. *World J Surg* 2007;**31**:353–64.
18. Aloysius MM, Zaitoun AM, Beckingham IJ, et al. The pathological response to neoadjuvant chemotherapy with FOLFOX-4 for colorectal liver metastases: a comparative study. *Virchows Arch* 2007;**451**:943–8.
19. Tamandl D, Gruenberger B, Herberger B, et al. Selective resection of colorectal liver metastases. *Eur J Surg Oncol* 2007;**33**:174–82.
20. Malik HZ, Farid S, Al-Mukthar A, et al. A critical appraisal of the role of neoadjuvant chemotherapy for colorectal liver metastases: a case-controlled study. *Ann Surg Oncol* 2007;**14**(12):3519–26.
21. Sperti E, Faggiuolo R, Gerbino A, et al. Outcome of metastatic colorectal cancer: analysis of a consecutive series of 229 patients. The impact of a multidisciplinary approach. *Dis Colon Rectum* 2006;**49**:1596–601.
22. Zaniboni A, Torri V, Tinazzi A, et al. Neoadjuvant oxaliplatin-based chemotherapy for liver metastases from colorectal cancer. An Italian survey. *Tumori* 2005;**91**:383–7.
23. Wein A, Riedel C, Brückl W, et al. Neoadjuvant treatment with weekly high-dose 5-fluorouracil as 24-h infusion, folinic acid and oxaliplatin in patients with primary resectable liver metastases of colorectal cancer. *Oncology* 2003;**64**:131–8.
24. Allen PJ, Kemeny N, Jarnagin W, et al. Importance of response to neoadjuvant chemotherapy in patients undergoing resection of synchronous colorectal liver metastases. *J Gastrointest Surg* 2003;**7**:109–15.
25. Tanaka K, Adam R, Shimada H, et al. Role of neoadjuvant chemotherapy in the treatment of multiple colorectal metastases to the liver. *Br J Surg* 2003;**90**:963–9.
26. Rees M, Tekkis PP, Welsh FK, et al. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. *Ann Surg* 2008;**247**:125–35.

27. Viganò L, Ferrero A, Lo Tesoriere R, et al. Liver surgery for colorectal metastases: results after 10 years of follow-up. Long-term survivors, late recurrences, and prognostic role of morbidity. *Ann Surg Oncol* 2008;**15**:2458–64.
28. de Haas RJ, Wicherts DA, Flores E, et al. R1 resection by necessity for colorectal liver metastases: is it still a contraindication to surgery? *Ann Surg* 2008;**248**:626–37.
29. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007;**25**:4575–80.
30. Connor S, Hart MG, Redhead DN, et al. Follow-up and outcomes for resection of colorectal liver metastases in Edinburgh. *Eur J Surg Oncol* 2007;**33**:55–60.
31. Niu R, Yan TD, Zhu JC, et al. Recurrence and survival outcomes after hepatic resection with or without cryotherapy for liver metastases from colorectal carcinoma. *Ann Surg Oncol* 2007;**14**:2078–87.
32. Malik HZ, Prasad KR, Halazun KJ, et al. Preoperative prognostic score for predicting survival after hepatic resection for colorectal liver metastases. *Ann Surg* 2007;**246**:806–14.
33. Wei AC, Greig PD, Grant D, et al. Survival after hepatic resection for colorectal metastases: a 10-year experience. *Ann Surg Oncol* 2006;**13**:668–76.
34. Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg* 2005;**241**:715–22.
35. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg* 2002;**235**:759–66.
36. de Jong MC, Mayo SC, Pulitano C, et al. Repeat curative intent liver surgery is safe and effective for recurrent colorectal liver metastasis: results from an international multi-institutional analysis. *J Gastrointest Surg* 2009;**13**:2141–51.
37. Assumpcao L, Choti MA, Gleisner AL, et al. Patterns of recurrence following liver resection for colorectal metastases: effect of primary rectal tumor site. *Arch Surg* 2008;**143**:743–9.
38. Pessaux P, Lermite E, Brehant O, et al. Repeat hepatectomy for recurrent colorectal liver metastases. *J Surg Oncol* 2006;**93**:1–7.
39. Shaw IM, Rees M, Welsh FK, et al. Repeat hepatic resection for recurrent colorectal liver metastases is associated with favourable long-term survival. *Br J Surg* 2006;**93**:457–64.
40. Yan TD, Lian KQ, Chang D, et al. Management of intrahepatic recurrence after curative treatment of colorectal liver metastases. *Br J Surg* 2006;**93**:854–9.
41. Ishiguro S, Akasu T, Fujimoto Y, et al. Second hepatectomy for recurrent colorectal liver metastasis: analysis of preoperative prognostic factors. *Ann Surg Oncol* 2006;**13**:1579–87.
42. Sugawara G, Isogai M, Kaneoka Y, et al. Repeat hepatectomy for recurrent colorectal metastases. *Surg Today* 2005;**35**:282–9.
43. Tanaka K, Shimada H, Ohta M, et al. Procedures of choice for resection of primary and recurrent liver metastases from colorectal cancer. *World J Surg* 2004;**28**:482–7.
44. Adam R, Pascal G, Azoulay D, et al. Liver resection for colorectal metastases: the third hepatectomy. *Ann Surg* 2003;**238**:871–83.
45. Takahashi S, Inoue K, Konishi M, et al. Prognostic factors for poor survival after repeat hepatectomy in patients with colorectal liver metastases. *Surgery* 2003;**133**:627–34.
46. Petrowsky H, Gonen M, Jarnagin W, et al. Second liver resections are safe and effective treatment for recurrent hepatic metastases from colorectal cancer: a bi-institutional analysis. *Ann Surg* 2002;**235**:863–71.
47. Suzuki S, Sakaguchi T, Yokoi Y, et al. Impact of repeat hepatectomy on recurrent colorectal liver metastases. *Surgery* 2001;**129**:421–8.
48. Muratore A, Polastri R, Bouzari H, et al. Repeat hepatectomy for colorectal liver metastases: a worthwhile operation? *J Surg Oncol* 2001;**76**:127–32.
49. Karuna ST, Thirlby R, Biehl T, et al. Cost-effectiveness of laparoscopy versus laparotomy for initial surgical evaluation and treatment of potentially resectable hepatic colorectal metastases: a decision analysis. *J Surg Oncol* 2008;**97**:396–403.
50. Gazelle GS, Hunink MG, Kuntz KM, et al. Cost-effectiveness of hepatic metastasectomy in patients with metastatic colorectal carcinoma: a state-transition Monte Carlo decision analysis. *Ann Surg* 2003;**237**:544–55.
51. Tumeh JW, Shenoy PJ, Moore SG, et al. A Markov model assessing the effectiveness and cost-effectiveness of FOLFOX compared with FOLFIRI for the initial treatment of metastatic colorectal cancer. *Am J Clin Oncol* 2009;**32**:49–55.
52. Tampellini M, Bitossi R, Brizzi MP, et al. Pharmacoeconomica comparison between chronochemotherapy and FOLFOX regimen in the treatment of patients with metastatic colorectal carcinoma: a cost-minimization study. *Tumori* 2004;**90**:44–9.
53. Gold MR, Siegel JE, Russell LB, et al. *Cost-effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.
54. Russell LB, Gold MR, Siegel JE, et al. The role of cost-effectiveness analysis in health and medicine. Panel on cost-effectiveness in health and medicine. *JAMA* 1996;**276**:1172–7.
55. De Angelis R, Grande E, Inghelmann R, et al. Cancer prevalence estimates in Italy from 1970 to 2010. *Tumori* 2007;**93**:392–7.
56. Garden OJ, Rees M, Poston GJ, et al. Guidelines for resection of colorectal cancer liver metastases. *Gut* 2006;**55**(S3):1–8.
57. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999;**230**(3):309–18.
58. House MG, Ito H, Gönen M, et al. Survival after hepatic resection for metastatic colorectal cancer: trends in outcomes for 1600 patients during two decades at a single institution. *J Am Coll Surg* 2010;**210**:744–52.
59. Power DG, Kenteny NE. Role of adjuvant therapy after resection of colorectal cancer liver metastases. *J Clin Oncol* 2010;**28**:2300–9.