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ORIGINAL ARTICLE

Optimal management of colorectal liver metastases in older patients: a decision analysis

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Abstract

Background: Comparative trials evaluating management strategies for colorectal cancer liver metastases (CLM) are lacking, especially for older patients. This study developed a decision-analytic model to quantify outcomes associated with treatment strategies for CLM in older patients.

Methods: A Markov-decision model was built to examine the effect on life expectancy (LE) and quality-adjusted life expectancy (QALE) for best supportive care (BSC), systemic chemotherapy (SC), radiofrequency ablation (RFA) and hepatic resection (HR). The baseline patient cohort assumptions included healthy 70-year-old CLM patients after a primary cancer resection. Event and transition probabilities and utilities were derived from a literature review. Deterministic and probabilistic sensitivity analyses were performed on all study parameters.

Results: In base case analysis, BSC, SC, RFA and HR yielded LEs of 11.9, 23.1, 34.8 and 37.0 months, and QALEs of 7.8, 13.2, 22.0 and 25.0 months, respectively. Model results were sensitive to age, comorbidity, length of model simulation and utility after HR. Probabilistic sensitivity analysis showed increasing preference for RFA over HR with increasing patient age.

Conclusions: HR may be optimal for healthy 70-year-old patients with CLM. In older patients with comorbidities, RFA may provide better LE and QALE. Treatment decisions in older cancer patients should account for patient age, comorbidities, local expertise and individual values.

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Introduction

There are over 39 million people in the US over the age of 65 years, an increase of 13.2% since 2000.[1] Furthermore, 54.7% of cancer cases are diagnosed in patients over 65 years.[2] Age-related increases in cancer incidence and the growing geriatric population is leading to increased numbers of older patients with cancer, the second most deadly being colorectal carcinoma (CRC).

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Colorectal liver metastases (CLM) develop in 50–60% of CRC patients and are responsible for two-thirds of mortalities.[3,4] Metachronous CLM represent approximately 71% of disease recurrence in patients who underwent CRC resection, and are the most frequent initial recurrence site.[5,6] Survival with untreated CLM is dismal and most patients die within a year after diagnosis.[7–10] Surgery offers the highest cure rate, approximately 40% at 5 years;[11–15] however, novel strategies such as ablative therapies and evolving chemotherapy agents are also effective.[16]

Primary modalities for CLM management include best supportive care (BSC), systemic chemotherapy (SC), radiofrequency ablation (RFA) and hepatic resection (HR). For older patients, non-surgical therapies are often favoured, with the assumption that surgical morbidity and mortality are unacceptable owing to

comorbidities or advanced age. Safety and success of HR has improved in the past two decades with careful patient selection, advances in anaesthesia and better post-operative care,[17] prompting investigations into HR in older patients;[18–31] however, all studies are single-centre retrospective studies with limited numbers.

Management decisions for older patients with CLM is further complicated by balancing comorbidities, which increased treatment-related toxicity and competing causes of mortality, quality of life (QoL) and risks of therapy. As there are no clear guidelines and a randomized trial to examine this issue is unlikely, we chose to assess the relative efficacies utilizing a Markov decision analysis (DA) methodology. The objective of this study was to determine, from a patient perspective, the optimal strategy for the management of older patients (age ≥ 70 years) who present with liver metastases after primary CRC surgery. This study evaluated commonly used strategies for treating older patients with CLM using a decision-analytic model to determine gains in life expectancy (LE) and quality-adjusted life expectancy (QALE). No other study has focused on exploring treatment strategies specifically for the elderly. As this question may never be answered with randomized trials, this DA serves as a comprehensive synthesis of the current available evidence.

Methods

Model design

A Markov state transition model was developed using TreeAge Pro software (v2009; TreeAge Software, Inc., Williamstown, MA, USA) to evaluate the effectiveness of BSC, SC, RFA and HR for treating CLM in older patients. A Markov DA allows modelling outcomes for clinical problems associated with continuous (e.g. risk of recurrence/progression) as opposed to a one-time risk (e.g. risk of peri-operative mortality). Furthermore, it allows for modelling outcomes when the timing of events is important and when these events may happen multiple times.[32] The Markov DA assumes that a patient is always in one of a finite number of health states and that events are represented as transitions from one state to another. A utility value, which is a QOL value on a 0–1 scale, is assigned to each health state. The overall QALE is the sum of time spent in each health state multiplied by the utility assigned to that health state.[32]

In our model, it is assumed that all patients present with CLM after a resection of the primary colorectal lesion. This represents the majority of patients who present with resectable CLMs.[4,33] We also assumed that patients entering the analysis have CLMs that are amenable to all treatment options. This assumption allows fair comparison between strategies as the invasive strategies each have their own limitations such as the size of lesions for RFA and the distribution of lesions for HR. In reality, patients who are not amenable to all treatment options at presentation represent a heterogeneous group for whom therapeutic choices are often limited. A simulated patient is randomly allocated to one of four different treatment options: (1) BSC; (2) SC; (3) RFA; or (4) HR. Within a given treatment option, patients can only transition from one health state to another once per cycle. The model was simulated for 5 years using one-month cycle lengths with the assumption that tumour recurrence will not be detected before 1 month.[34]

For the Markov DA model, several health states were defined for the four different treatment modalities. All events of interest were modelled as transitions between health states (Fig. 1). In the BSC arm, all CRC liver metastases are left untreated and patients are provided supportive care only. SC was defined as 5-FU, leucovorin and irinotecan, currently the standard regimen for CLM, which has established safety and efficacy in older patients.[35–38] Severe toxicity was defined as grade ≥ 3 toxicity according to the Common Terminology Criteria for Adverse Events scale.[39,40] An assumption of our model is that chemotherapy is halted if a patient develops severe toxicity and therefore there is no transition from severe to no/mild toxicity. With each cycle, there is also a probability that a patient transitions from no/mild toxicity to severe toxicity. RFA and HR were built with a similar structure to ensure model balance according to good modelling practice.[41–45] Peri-procedural chemotherapy was not modelled as separate strategies and was included in the analysis as part of RFA or HR. Recurrence was defined as any local or metastatic disease progression and resulted in patients receiving non-invasive treatments (i.e. BSC or SC) without repeat ablation or surgery. The choice of entering the BSC or SC treatment arms after either RFA or HR was related to the patient's baseline co-morbidity (see below). A number of patients entering our model were defined to have RFA that was ineffective (inability to obtain complete oncologic clearance and therefore was not performed) and thus proceeded to receive BSC or SC. The effective and ineffective arms for RFA were to reflect clinical practice and create a balance with the HR arms of resectable and unresectable, respectively. Similarly, patients determined at the time of HR to have unresectable disease also preceded to BSC or SC. Treatment complications could impact outcomes in two ways: they impart a disutility (i.e. loss of health-related QoL) in the short term (3 months) and increase baseline mortality in the long term (up to 24 months). At the start of each simulated cycle, the patient can stay in their current treatment modality or move to another, depending on transitional probability (derived from probability of recurrence of 50% over 10 months), age and comorbidity.

The model was run until one of four conditions was met: (1) all simulated patients have died; (2) all simulated patients reach 100 years of age, (3) incremental benefits gained per cycle have become <0.001/cycle, or (4) 60 cycles (5 years) have passed. The upper age limit of 100 years was necessary given the paucity of reliable mortality data for patients older than 100 years. An incremental utility gain of less than 0.001 per cycle was defined as negligible in order to improve model efficiency. The 60-cycle (5-year) limit was placed on our model in order to enhance clinical relevance, as the lack of recurrence by 5 years after treatment generally defines a cure.[46] Another reason for this limit is the scarcity of data on survival and recurrence rates after 5 years after