Systematic review of surgical management of synchronous colorectal liver metastases

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Background: The optimal management of colorectal cancer with synchronous liver metastases has not yet been elucidated. The aim of the present study was systematically to review current evidence concerning the timing and sequence of surgical interventions: colon first, liver first or simultaneous.

Methods: A systematic literature review was performed of clinical studies comparing the timing and sequence of surgical interventions in patients with synchronous liver metastases. Retrospective studies were included but case reports and small case series were excluded. Preoperative and intraoperative data, length of hospital stay, perioperative mortality and morbidity, and 1-, 3- and 5-year survival rates were compared. The studies were evaluated according to a modification of the methodological index for non-randomized studies (MINORS) criteria.

Results: Eighteen papers were included and 21 entries analysed. Five entries favoured the simultaneous approach regarding duration of procedure, whereas three showed no difference; five entries favoured simultaneous treatment in terms of blood loss, whereas in four there was no difference; and all studies comparing length of hospital stay favoured the simultaneous approach. Five studies favoured the simultaneous approach in terms of morbidity and eight found no difference, and no study demonstrated a difference in perioperative mortality. One study suggested a better 5-year survival rate after staged procedures, and another suggested worse 1-year but better 3- and 5-year survival rates following the simultaneous approach. The median MINORS score was 10, with incomplete follow-up and outcome reporting accounting primarily for low scores.

Conclusion: None of the three surgical strategies for synchronous colorectal liver metastases appeared inferior to the others.

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Introduction

Colorectal cancer remains the fourth most common malignancy in the UK and USA, being the third commonest cancer in both men and women\(^1\)\(^,\)\(^2\). Approximately 15–25 per cent of these patients present with synchronous colorectal liver metastases (CLM)\(^3\)\(^–\)\(^6\), that is metastases detected either before operation or during the first surgical procedure\(^7\). As with metachronous CLM, surgical resection of synchronous CLM is the best treatment option, when feasible\(^8\)\(^,\)\(^9\).

The management of colorectal cancer with synchronous metastases is multimodal, including chemotherapy, radiotherapy for rectal primaries, minimally invasive techniques such as radiofrequency ablation, and surgery. The need for surgical management of the two different sites renders the combination of these modalities particularly complex regarding sequencing. Three approaches have been shaped in relevant literature regarding appropriate timing of surgical resection of primary and metastatic tumours: the classical approach, whereby the primary is resected first and liver metastases in a second operation; the simultaneous approach in which both resections are done in the same procedure\(^10\); and the liver-first approach where resection of liver metastases precedes that of the primary tumour\(^11\)\(^,\)\(^12\).

The present study aimed to review systematically all published comparative studies on the timing of surgical approaches in treatment of synchronous CLM and to evaluate the current evidence for any of the three strategies: colon first, liver first or simultaneous.
Table 1  Modified MINORS criteria used for evaluation of included studies

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
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</thead>
<tbody>
<tr>
<td>Study aim</td>
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<tr>
<td>Consecutive patients</td>
<td>0</td>
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<tr>
<td>Data collection methodology</td>
<td>0</td>
</tr>
<tr>
<td>Reported endpoints</td>
<td>0</td>
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<td>Outcome evaluation bias</td>
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<td>Equivalent groups</td>
<td>0</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>0</td>
</tr>
<tr>
<td>Follow-up period</td>
<td>0</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
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<td></td>
<td>2</td>
</tr>
</tbody>
</table>

- 0: Not reported
- 1: Reported but not clear
- 2: Clearly reported
- 0: Not reported
- 1: Not consecutive patients
- 2: Consecutive patients
- 0: Not reported
- 1: Retrospective collection
- 2: Prospective collection
- 0: Not reported
- 1: Incomplete endpoints
- 2: Complete endpoints
- 0: Not reported
- 1: Incomplete protocol
- 2: Complete protocol
- 0: No perioperative protocol
- 1: Incomplete matching
- 2: Complete matching
- 0: No matching analysis
- 1: Inappropriate statistical methods
- 2: Appropriate statistical methods
- 0: Not reported
- 1: < 5 years
- 2: ≥ 5 years
- 0: Not reported
- 1: Stated > 5% or expected < 5% according to methodology
- 2: Stated < 5%

*Modification of the original methodological index for non-randomized studies (MINORS) definition.

Methods

Literature search

The search words for the literature review were arranged in four groups: the first group contained the keywords ‘liver’ and ‘hepatic’; the second group comprised the keywords ‘colorectal’, ‘colon’, ‘colonic’, ‘rectal’ and ‘rectum’; the third group consisted of the words ‘metastasis’ and ‘metastases’; and the fourth included ‘synchronous’ and ‘simultaneous’. The search terms were structured by combining one word from each group, so that all possible combinations were employed. This process yielded 40 search terms, all of which were sought in titles and/or abstracts of English- or French-language papers appearing in any of four databases: PubMed (National Library of Medicine), Embase, ISI Web of Knowledge, and Library, Information Science and Technology Abstracts (LISTA) (EBSCO). References from relevant papers were also included to form the initial pool of articles. The last search was performed on 31 August 2013. Abstracts were reviewed independently by two authors and the full text of relevant studies considered for inclusion.

Study types

All clinical studies comparing at least two groups (classical approach, simultaneous approach, liver-first approach) were considered. Based on the authors’ knowledge, no randomized clinical trials (RCTs) were expected, so comparative cohort studies were accepted. Single-case reports and case series were excluded. Studies with fewer than ten patients in each group were excluded, as were those that presented fewer than two clinical outcomes (see below). Data collection methodology (prospective or retrospective) was not used as an exclusion criterion, but was used as an evaluation criterion.

Data collection

Data collected were arranged in three groups. The first included preoperative information, such as type of study, number of patients, median age, sex, site of primary lesion (colon or rectum), pathological tumour (T) category (T1 and T2, or T3 and T4), number of metastases (1 or 2, or more than 2) and the presence of bilobar disease. The second group included operative data such as duration of surgery (by stage as well as total for staged procedures), blood loss and number of patients who had a transfusion. The third group included clinical outcome data, including length of hospital stay, perioperative mortality and morbidity, and 1-, 3- and 5-year survival. The data were extracted independently by two reviewers and cross-checked.

Evaluation of studies and statistical analysis

For quality assessment, two reviewers independently evaluated the included studies according to the methodological index for non-randomized studies (MINORS) criteria, an established method for evaluating non-RCTs. However, for the purposes of this study three items were omitted. That referring to sample size was excluded, because all authors agreed that cut-off values to stratify the studies would be totally arbitrary. Two items pertaining to appropriate controls and contemporary groups were also omitted as this study was designed to include only directly comparative reports. Consequently, nine items were finally used with a maximum score of 18 (Table 1).

As no RCTs were expected, no meta-analysis of extracted data was planned; although such analysis of non-RCTs can be considered, it is of questionable value. However, basic descriptive statistical analysis was conducted to give a hint of the overall quality of contemporary literature on the studied subject, in an effort to investigate the power of the conclusions to follow.
Results

The literature search yielded 818 papers, excluding duplicates. After screening for relevance, a pool of 129 papers was created. Review of the references of these articles did not identify any further articles. After reading the full texts, 103 of the 129 papers were excluded as they were not original papers, or did not compare at least two of the examined groups. Two papers were excluded because they had groups with fewer than ten patients, three because they did not provide comparative data in a clear and usable way, and three because they presented only one clinical outcome (Fig. 1). Eighteen papers were finally included in this analysis. In three of these, grouping and comparison was conducted in two different ways, so a total of 21 entries were assessed.

Quality assessment

Table 2 summarizes the quality assessment of the 21 included entries, according to the modified MINORS criteria. Scores ranged from 7 to 15, with a median value of 10; six studies were in the top quartile (score above 13) and five were in the bottom quartile (score below 9). The most common problem was the retrospective design of the studies. Two more items that accounted for low scores were the failure to report completeness of follow-up, as well as an inadequate follow-up period (less than 5 years). None of the included studies reported all outcomes specified for review in this analysis. Finally, regarding equivalence of groups, there were only two case-matched studies; two studies did not provide enough preoperative data to assess equivalence.

Study characteristics and outcomes

Only comparative cohort studies were found; there were no RCTs. Patient and disease characteristics in the included studies are shown in Table S1 (supporting information). Intraoperative data and short-term outcomes are summarized in Table 3 and Table S2 (supporting information). Five entries favoured the simultaneous approach in terms of cumulative duration of procedure, whereas in three there was no difference. Five entries favoured the simultaneous approach as regards blood loss and four found no significant difference. All studies that compared length of hospital stay favoured the simultaneous approach. Five entries favoured the simultaneous approach in terms of morbidity, whereas the remaining eight did not detect a significant difference. No study demonstrated any difference in mortality. One study favoured the staged approach in terms of total blood transfusion.
Table 2 Modified MINORS evaluation of included studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study aim</th>
<th>Consecutive patients</th>
<th>Data collection methodology</th>
<th>Reported endpoints</th>
<th>Outcome evaluation bias</th>
<th>Equivalent groups</th>
<th>Statistical methods</th>
<th>Follow-up period</th>
<th>Follow-up loss</th>
<th>Overall score</th>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>10</td>
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<tr>
<td>Martin et al.</td>
<td>6, 16</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
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<td>1</td>
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<td>Chua et al.</td>
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<td>2</td>
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<td>1</td>
<td>1</td>
<td>n.s.</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>8</td>
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<tr>
<td>de Haas et al.</td>
<td>29</td>
<td>1</td>
<td>1</td>
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<td>n.s.</td>
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<td>de Haas et al.</td>
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<td>1</td>
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<td>1</td>
<td>10</td>
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<tr>
<td>Brouquet et al.</td>
<td>28</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>n.s.</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>13</td>
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<tr>
<td>Luo et al.</td>
<td>31</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>n.s.</td>
<td>2</td>
<td>1</td>
<td>1</td>
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<td>9</td>
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<tr>
<td>Moug et al.</td>
<td>32</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>13</td>
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<tr>
<td>Mayo et al.</td>
<td>33</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>13</td>
</tr>
</tbody>
</table>

*Major hepatectomy subseries; †case-matched subseries. MINORS, methodological index for non-randomized studies.

Table 3 Details of outcomes where statistically significant differences were reported

<table>
<thead>
<tr>
<th>Reference</th>
<th>Duration of operation (min)*</th>
<th>Blood loss (ml)*</th>
<th>Transfused patients (%)</th>
<th>Hospital stay (days)*</th>
<th>Morbidity (%)</th>
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<tr>
<td>Martin et al.</td>
<td>235</td>
<td>550</td>
<td>31</td>
<td>10</td>
<td>48</td>
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<td>Chua et al.</td>
<td>370</td>
<td>600</td>
<td>n.s.</td>
<td>10</td>
<td>53</td>
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<tr>
<td>Capussotti et al.</td>
<td>325</td>
<td>600</td>
<td>n.s.</td>
<td>18</td>
<td>21</td>
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<tr>
<td>Thelen et al.</td>
<td>260</td>
<td>35</td>
<td>n.s.</td>
<td>20</td>
<td>18</td>
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<tr>
<td>Turini et al.</td>
<td>325</td>
<td>350</td>
<td>n.s.</td>
<td>18</td>
<td>21</td>
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<td>Vassiliou et al.</td>
<td>260</td>
<td>12</td>
<td>n.s.</td>
<td>12</td>
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<td>180</td>
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<td>50</td>
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<td>250</td>
<td>950</td>
<td>n.s.</td>
<td>12</td>
<td>25</td>
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<tr>
<td>de Haas et al.</td>
<td>180</td>
<td>300</td>
<td>16</td>
<td>n.s.</td>
<td>19</td>
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<td>17</td>
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<td>Mayo et al.</td>
<td>290</td>
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<td>n.s.</td>
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<td>Capussotti et al.</td>
<td>330</td>
<td>n.s.</td>
<td>42</td>
<td>14</td>
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<td>Reddy et al.</td>
<td>202</td>
<td>268</td>
<td>n.s.</td>
<td>12</td>
<td>60</td>
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<tr>
<td>de Haas et al.</td>
<td>202</td>
<td>450</td>
<td>n.s.</td>
<td>12</td>
<td>31</td>
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</table>

*Values are median, except †mean. ‡Major hepatectomy subseries; §case-matched subseries. n.s., Not stated. ¶Statistical significance favouring simultaneous procedure; #statistical significance favouring staged procedure (classical approach, primary first).
One study suggested a better 5-year survival rate after staged procedures (60 per cent versus 43 per cent for simultaneous procedures), and another suggested worse 1-year but better 3- and 5-year survival rates after a simultaneous approach (78, 70 and 45 per cent respectively versus 88, 55 and 38 per cent following staged procedures) (Table S3, supporting information).

Among the 21 included entries, only two studies included a group of patients operated on by a liver-first approach. In these studies, clinical outcomes did not differ significantly between groups, apart from lower estimated blood loss in the combined-approach group.

**Discussion**

The present systematic review suggests that none of the three surgical strategies (primary first, liver first or simultaneous resection) is inferior to the others. All of them should be considered for patients with synchronous CLM, with the exception of those with symptomatic primaries, in whom the liver-first approach is not suitable. None of the approaches demonstrated better short- or long-term outcomes, and no subgroups of patients who would clearly benefit from a particular approach were recognized.

Since the early 1990s, when resection of CLM was adopted widely as a standard approach, the view of synchronous CLM has gradually been shaped by two concepts. The first is that simultaneous surgical management of the primary and metastatic site is an approach with considerable potential benefits. The second is that synchronous CLM comprise a special subgroup of CLM, with particular biology and prognosis, and require specifically tailored studies to evaluate the various therapeutic strategies. Several strategies have been devised over the past 20 years to combine the various treatment modalities required for the management of synchronous CLM. The present study concentrated on the three principal approaches described for ordering the surgical element of this process.

The original strategy is often referred to as the ‘classical’ approach to synchronous CLM. It involves resection of the primary site and adjuvant chemotherapy (plus radiotherapy for rectal primaries when indicated), followed by resection of liver metastases 3–6 months after the first procedure, with consideration of continuation of adjuvant chemotherapy. The second strategy, involving simultaneous resection of primary and metastatic foci, potentially with neoadjuvant chemotherapy and followed by adjuvant chemotherapy, was suggested as soon as surgical management of CLM had been accepted. The intended benefits and possible risks have already been clearly presented. The third option, suggested in 2008, involves initial resection of intrahepatic disease, followed by surgical management of the primary site. Chemotherapy may be employed before liver resection as neoadjuvant treatment, between the two procedures and after the colorectal resection. The aim is to avoid the possible risks of a combined procedure, at the same time avoiding the risks of delayed liver resection. However, such a strategy can be applied only for primary tumours without symptoms that render the surgical management of this site urgent (for example obstruction and perforation).

The major question arising from the otherwise equivalent outcomes of different strategies is whether subgroups exist that could benefit from a specific strategy. Some patient-related factors seem to favour a staged approach (either classical or liver first according to symptoms) in terms of postoperative outcomes, including age above 70 years, poorer physical performance (either expressed as American Society of Anesthesiologists fitness grade or pulmonary disease) and previous abdominal surgery. Despite a general perception of incompatibility between low anterior resection and major hepatectomy, this has not been confirmed beyond doubt in relevant studies, so scepticism remains.

Despite the relatively large number of published studies on surgical management of synchronous CLM, there are no RCTs and all published studies are observational, usually retrospective and often non-comparative. This review was designed particularly to include comparative studies, and the comments that follow concern only these. Several weaknesses, repeatedly detected, render the literature on this subject inadequate to provide a solid basis for conclusions. First, it should be mentioned that there are discrepancies concerning the definition of synchronous CLM. Some studies considered as synchronous CLM those detected within 6 months of the surgical procedure for the primary tumour. Such an assumption defines a subgroup of patients with synchronous CLM who cannot possibly be managed by the simultaneous or liver-first approach, so including such patients in these studies is inappropriate. Another nearly universal issue concerns reporting of follow-up. Most of the included studies did not clearly state how many patients were lost to follow-up, which is important in terms of evaluation. This parameter does not require modification of methodology or special design, and it is thus considered an avoidable disadvantage that accounts for low scores. A third point concerns discrepancies in the way data were reported. Variables with more than two possible values (such as T category) should be reported according to a universally agreed grouping system, in order to facilitate presentation.
and statistical analysis. In the example of T category, some authors grouped T1 with T2 and T3 with T4, whereas others\textsuperscript{20,25} discriminated between T1–T3 and T4. Consequently it is impossible to create a single pool of patients to examine the impact of this parameter on outcomes. Data regarding duration of surgery and hospital stay for staged procedures are often presented for liver resection only, making comparison with total duration of simultaneous procedures impossible\textsuperscript{23}. Ideally, data should be presented for each stage of the classical and liver-first approaches, or at least cumulative times from both procedures. The liver-first approach may be particularly suitable for rectal primaries with liver metastases. Thus, the indications for the approach may be completely different and so comparison is difficult. Finally, data regarding chemotherapeutic regimens are often missing or inadequate, and evaluation of long-term oncological outcomes is clearly difficult without this information.

Overall, a strict definition of high-quality papers should include those in the top quartile of the total range (0–18 points), that is papers with a score above 14. Accordingly, only one study\textsuperscript{25} in the present review can be considered of high quality, and this did not report any statistically significant differences in short- and long-term outcomes between the different approaches. The present data were based on non-RCTs suffering from several weaknesses and statistical analysis. In the example of T category, guidelines regarding timing of surgical management of synchronous CLM are not feasible. Treatment plans should therefore be defined in a single-centre experience. The liver-first approach for synchronous colorectal liver metastasis: a 5-year single-centre experience. HPB (Oxford) 2011; 13: 745–752.

The authors declare no conflict of interest.

Disclosure

The authors declare no conflict of interest.

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45 van der Pool AE, de Wilt JH, Lalmahomed ZS, Eggermont AM, Ijzermans JN, Verhoef C. Optimizing the outcome of

Supporting information
Additional supporting information may be found in the online version of this article:
Table S1 Patient and disease characteristics in included papers (Word document)
Table S2 Intraoperative data and short-term outcomes (Word document)
Table S3 Long-term outcomes (Word document)

Snapshot quiz 14/7

Question: A 77-year-old man with chronic obstructive pulmonary disease presented with an uncomfortable bulge in his upper abdomen. There was no history of trauma. The lump had the characteristics of a hernia in an unusual place as shown on computed tomography. What is the diagnosis?

The answer to the above question is found on p. 652 of this issue of BJSS.
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