Original article

Propensity score-matched outcomes analysis of the liver-first approach for synchronous colorectal liver metastases

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Background: **Liver resection before primary cancer resection is a novel strategy advocated for selected patients with synchronous colorectal liver metastases (sCRLM). This study measured outcomes in patients with sCRLM following a liver-first or classical approach, and used a validated propensity score.**

Methods: **Clinical, pathological and follow-up data were collected prospectively from consecutive patients undergoing hepatic resection for sCRLM at a single centre (2004–2014). Cumulative disease-free survival (DFS), cancer-specific survival (CSS) and overall survival (OS) were calculated by means of Kaplan–Meier analysis. Survival differences were analysed in the whole cohort and in subgroups matched according to Basingstoke Predictive Index (BPI).**

Results: **Of 582 patients, 98 had a liver-first and 467 a classical approach to treatment; 17 patients undergoing simultaneous bowel and liver resection were excluded. The median (i.q.r.) BPI was significantly higher in the liver-first compared with the classical group: 8·5 (5–10) *versus* 8 (4–9) ($P = 0·030$). Median follow-up was 34 months. The 5-year DFS rate was lower in the liver-first group than in the classical group (23 *versus* 45·6 per cent; $P = 0·001$), but there was no difference in 5-year CSS (51 *versus* 53·8 per cent; $P = 0·379$) or OS (44 *versus* 49·6 per cent; $P = 0·305$). After matching for preoperative BPI, there was no difference in 5-year DFS (37 *versus* 41·2 per cent for liver-first *versus* classical approach; $P = 0·083$), CSS (51 *versus* 53·2 per cent; $P = 0·616$) or OS (47 *versus* 49·1 per cent; $P = 0·846$) rates.**

Conclusion: **Patients with sCRLM selected for a liver-first approach had more oncologically advanced disease and a poorer prognosis. They had inferior cumulative DFS than those undergoing a classical approach, a difference negated by matching preoperative BPI.**

Presented to the Digestive Disorders Federation meeting, London, UK, June 2015; published in abstract form as *Gut* 2015; **64**(Suppl 1): A178

Paper accepted 2 December 2015
Published online 10 February 2016 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.10099

Introduction

Colorectal cancer is the fourth commonest malignancy in the UK, with an incidence of 41 581 in 2011[1]. Approximately 15–25 per cent of these patients have liver metastases at diagnosis, so-called synchronous metastases[2,3]. The classical approach has been to resect the primary tumour, followed by resection of liver metastases, with the potential addition of either neoadjuvant or adjuvant chemotherapy. Some patients are suitable for a combined bowel and liver resection, with the theoretical advantage of a single operation and shorter overall length of hospital stay, balanced against potentially increased mortality[4,5].

In 2006, Mentha and colleagues[6] advocated the 'liver-first' approach for patients with synchronous colorectal liver metastases (sCRLM). It was argued that, for patients with multiple or large liver metastases, the liver disease may progress and become inoperable during the time the primary is treated and preclude treatment with curative intent. Neoadjuvant chemotherapy followed by liver resection and then primary tumour resection provided a median survival of 46 months and a 4-year overall survival (OS) rate of 51 per cent in 20 patients with advanced sCRLM. Currently there are no randomized clinical trials to compare these approaches, and the evidence suggests that neither one offers a survival advantage[7].

The authors' unit has used the liver-first approach in selected patients with sCRLM since 2004. This study reviewed the management of patients presenting with sCRLM and compared the long-term outcomes of a liver-first *versus* a classical approach. The Basingstoke Predictive Index (BPI)[8], a multifactorial risk stratification

index that provides risk estimates for cancer-specific survival (CSS) in patients undergoing hepatic resection for colorectal liver metastases, was used to determine the predicted survival for each group. Cumulative disease-free survival (DFS), CSS and OS were compared in case-matched groups.

Methods

Patients presenting with sCRLM were identified from a contemporaneously collected database of patients undergoing hepatic resection for colorectal metastases at a single institution between 1 April 2004 and 31 March 2014, and grouped according to treatment approach (classical or liver-first). Patients undergoing synchronous bowel and liver resections were excluded.

Criteria for resectability and surgical strategy

All patients were staged with CT of the chest, abdomen and pelvis, and liver-specific MRI using a Symphony™ 1·5-T scanner (Siemens, Munich, Germany) supplemented by intravenous contrast agents: Resovist® (Schering, Baar, Switzerland) and gadodiamide (Omniscan™; Amersham Health, Oslo, Norway) before 2010, and gadoxetate sodium (Primovist®; Bayer, Leverkusen, Germany) alone from 2010. Patients with rectal cancer underwent pelvic MRI. PET–CT was used selectively. Criteria for resectability were the predicted ability to resect all primary and metastatic disease with clear margins (at least 1 mm), while leaving sufficient functioning liver (25–30 per cent)[9].

All patients were discussed at a colorectal multidisciplinary team (MDT) meeting and a specialist hepatobiliary MDT meeting to formulate an individualized treatment plan. The indications for a liver-first approach are summarized in *Table 1*. Patients with inoperable liver metastases were offered conversion chemotherapy. Those who responded were offered a liver-first approach, as were patients with operable but advanced or critically placed liver metastases, which might progress and become inoperable if the primary were resected first. This borderline operable group included patients with four or more metastases, one metastasis larger than 5 cm in diameter, or metastases close to the portal inflow or main hepatic veins. Parenchyma-sparing liver surgery was performed where possible.

Table 1 Indications for a liver-first approach

	No. of patients
Inoperable sCRLM, requiring conversion chemotherapy	56
Borderline resectable sCRLM, requiring neoadjuvant chemotherapy	26
Borderline resectable sCRLM, no chemotherapy	11
Following long-course chemoradiotherapy to rectal primary + borderline resectable sCRLM	15
Following long-course chemoradiotherapy to rectal primary – opportunistic only	4
Planned combined liver/bowel resection aborted after liver resection due to cardiac arrhythmia	1

Some patients had more than one indication. sCRLM, synchronous colorectal liver metastases.

Operative details and follow-up

The anaesthetic and surgical techniques specific to hepatic resection have been described previously[8–11]. The nomenclature and extent of hepatic resection were recorded according to Couinaud[12] and the Terminology Committee of the International Hepato-Pancreato-Biliary Association[13]. Major liver resection was defined as resection of three or more hepatic segments.

Morbidity was classified using the Clavien–Demartines–Dindo system[14]. Postoperative bile leakage[15], hepatic insufficiency[16] and postoperative haemorrhage[17] were defined according to the International Study Group of Liver Surgery criteria. Perioperative mortality was defined as death during the same hospital admission or within 30 days of hepatic resection. The follow-up protocol consisted of clinical examination, measurement of serum carcinoembryonic antigen (CEA) level and contrast-enhanced CT every 6 months for 3 years and annually thereafter. Data relating to the patient's health and oncological status were pursued until tumour recurrence, CSS or OS had been established.

Basingstoke Predictive Index and patient matching

The BPI is an internally and externally validated prognostic scoring system that provides risk estimates of CSS for patients undergoing resection of colorectal liver metastases[8]. It identifies seven independent predictors of poor survival: more than three hepatic metastases, node-positive primary, poorly differentiated primary, extrahepatic disease, tumour diameter at least 5 cm, CEA level over 60 ng/ml and a positive resection margin. The first six criteria are used in the preoperative scoring system and the last six in the postoperative score. Matching patients using a propensity score such as the BPI allows comparison in observational studies, by adjusting for the selection bias that occurs owing to lack of randomization[18].

Study endpoints

The primary endpoints of the study were cumulative DFS, CSS and OS. Patients were case-matched according to

preoperative BPI, and DFS, CSS and OS then recalculated for the matched groups. Secondary endpoints were the time to complete all planned treatment (time of diagnosis to the last operation) and reintervention (surgery, ablation, cryotherapy) for recurrent intrahepatic or extrahepatic metastatic disease.

Statistical analysis

Continuous variables are presented as median (i.q.r.), with analysis by means of the Mann–Whitney *U* test. Pearson's χ^2 test or Fisher's exact test was used for comparison of categorical data. The primary endpoints DFS, CSS and OS were regarded as time-dependent variables calculated from the time of diagnosis of colorectal cancer with sCRLM. Kaplan–Meier curves were plotted to determine survival outcomes, expressed as median with 95 per cent c.i., and statistical differences were calculated using the log rank (Mantel–Cox) test. $P < 0{\cdot}050$ was considered significant. Data were analysed using SPSS® version 22 (IBM, Armonk, New York, USA).

Results

A total of 1171 patients underwent resection of colorectal liver metastases in the study interval (2004–2014), of whom 582 had sCRLM. Of these, 98 (16·8 per cent) underwent a liver-first approach and 467 (80·2 per cent) a classical approach. Seventeen patients (2·9 per cent) who had a simultaneous bowel and liver resection were excluded. Four patients (4 per cent) in the liver-first group and 12 (2·6 per cent) in the classical group underwent staged liver resections[19]. The indications for a liver-first approach are detailed in *Table 1*. Eighty-two patients (84 per cent) treated by a liver-first strategy had either conversion or neoadjuvant chemotherapy before liver resection, compared with 279 (59·7 per cent) of those who had a classical approach. Nineteen patients underwent a liver-first approach after chemoradiotherapy to a rectal primary in the post-treatment interval before rectal resection (*Table 1*).

Patients in the liver-first group were significantly younger, with more associated liver disease, rectal primaries, poorly differentiated primaries, and a greater number of and larger metastases, than those in the classical group (*Table 2*). This was reflected in their preoperative BPI, which was significantly higher than that in the classical group: median 8·5 (5–10) *versus* 8 (4–9) respectively ($P = 0{\cdot}030$). Sixteen patients in the liver-first group did not undergo a subsequent bowel resection, 12 because of disease progression, one in whom the primary tumour showed a complete radiological response to chemoradiotherapy, one who developed a new primary lung cancer and two patients who died after liver surgery.

Table 2 Patient demographics, tumour characteristics and Basingstoke Predictive Index

	Liver-first ($n = 98$)	Classical ($n = 467$)	P†
Age (years)*	61·0 (50·0–70·1)	64·5 (57·1–71·0)	0·007‡
Sex ratio (M : F)	60 : 38	277 : 190	0·729
ASA grade			0·105§
I	0 (0)	0 (0)	
II	85 (87)	372 (79·7)	
III	13 (13)	92 (19·7)	
IV	0 (0)	3 (0·6)	
Associated liver disease	80 (82)	236 (50·5)	0·001
Site of colorectal primary			0·001
Colon	54 (55)	337 (72·2)	
Rectum	44 (45)	130 (27·8)	
AJCC/UICC stage of primary tumour			0·873§
I	4 (4)	18 (3·9)	
II	21 (21)	114 (24·4)	
III	57 (58)	335 (71·1)	
Unknown	16 (16)		
Differentiation			0·001§
Well	0 (0)	15 (3·2)	
Moderate	65 (66)	410 (87·8)	
Poor	17 (17)	42 (9·0)	
Unknown	16 (16)		
No. of CRLM*	3 (1–5)	2 (1–3)	0·007†
Size of CRLM (mm)*	30 (15–50)	25 (17–40)	0·035†
Preoperative BPI*	8·5 (5–10)	8 (4–9)	0·030†

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). ASA, American Society of Anesthesiologists; AJCC/UICC, American Joint Committee on Cancer/International Union Against Cancer; CRLM, colorectal liver metastases; BPI, Basingstoke Predictive Index. †Pearson's χ^2 test, except ‡Mann–Whitney *U* test and §Fisher's exact test.

Liver surgery

Details of the liver surgery are described in *Table 3*. There were more major resections in the liver-first group (69 *versus* 56·5 per cent; $P = 0{\cdot}018$), with longer Pringle clamp times. There was no difference in the overall duration of surgery, length of stay, morbidity, mortality or resection margin status.

Duration of treatment

The median overall duration of treatment from the time of diagnosis to the time of the second operation (liver or bowel, depending on approach) was significantly longer in the liver-first group than in the classical group: 9 (7–11) *versus* 7 (4–9) months ($P = 0{\cdot}005$).

Table 3 Details of liver surgery

	Liver-first ($n = 98$)	Classical ($n = 467$)	P†
Major resection (≥ 3 segments)	68 (69)	264 (56·5)	0·018
Pringle time (min)*	42 (31–54)	37 (28–49)	0·018‡
Blood loss (ml)*	285 (190–410)	245 (147–430)	0·393‡
Duration of surgery (min)*	245 (210–290)	240 (210–270)	0·067‡
Length of hospital stay (days)*	6 (4–9)	6 (5–8)	0·835‡
No. of patients with grade III or IV complications	10 (10)	33 (7·1)	0·392
30-day mortality	2 (2)	1 (0·2)	0·079§
No. of patients with clear margin	91 (93)	443 (94·9)	0·136

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †Pearson's χ^2 test, except ‡Mann–Whitney U test and §Fisher's exact test.

Disease-free, cancer-specific and overall survival

Median follow-up from the time of diagnosis was 34 (18–61) months. No patient was lost to follow-up. The median DFS was significantly lower in the liver-first group than in the classical group (36·4 (95 per cent c.i. 27·9 to 44·9) and 53·3 (46·4 to 60·6) months respectively; $P = 0·001$) (*Fig. 1a*). Five-year DFS rates were 23 *versus* 45·6 per cent. There was no difference in either median CSS (59·8 (48·2 to 70·0) *versus* 67·0 (53·7 to 80·3) months; $P = 0·379$) or OS (49·5 (30·4 to 68·6) *versus* 59·7 (51·0 and 63·1) months; $P = 0·305$) (*Fig. 2a*) between the liver-first and classical groups. Five-year CSS and OS rates were 51 *versus* 53·8 per cent and 44 *versus* 49·6 per cent respectively.

Case-matched survival analysis

When patients were matched using preoperative BPI, there were 56 patients in the liver-first group and 234 in the classical group. There was no difference in DFS between the matched groups, with a median DFS of 41·4 (95 per cent c.i. 35·5 to 47·3) months in the liver-first group and 51·3 (44·5 to 58·1) months in the classical group ($P = 0·083$) (*Fig. 1b*). Similarly, there was no difference between the matched groups in either median CSS (60·8 (40·7 to 76·9) *versus* 63·1 (47·1 to 73·4) months; $P = 0·616$) or OS (59·8 (39·7 to 79·9) *versus* 59·7 (49·3 and 70·1) months; $P = 0·846$) (*Fig. 2b*). Five-year DFS, CSS and OS rates for the liver-first *versus* classical approach were 37 *versus* 41·2 per cent, 51 *versus* 53·2 per cent, and 47 *versus* 49·1 per cent respectively.

Further intervention for metastatic disease

Thirty (37 per cent) of the 82 patients who completed a liver-first approach underwent subsequent reintervention (resection, ablation or cyberknife) for intrahepatic or extrahepatic metastatic disease during follow-up, compared with 126 (27·0 per cent) of the 466 patients who survived a classical approach ($P = 0·077$).

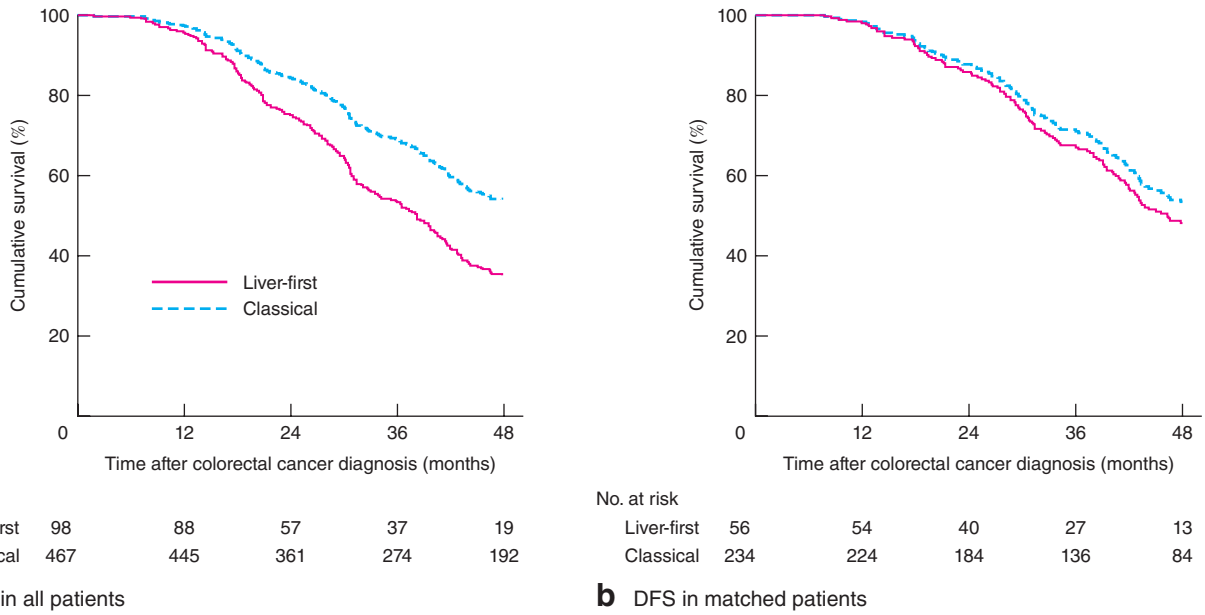

Fig. 1 Disease-free survival (DFS) after diagnosis of synchronous colorectal liver metastases according to surgical strategy: **a** in all patients and **b** in patients matched for preoperative Basingstoke Predictive Index. **a** $P = 0·001$, **b** $P = 0·083$ (log rank test)

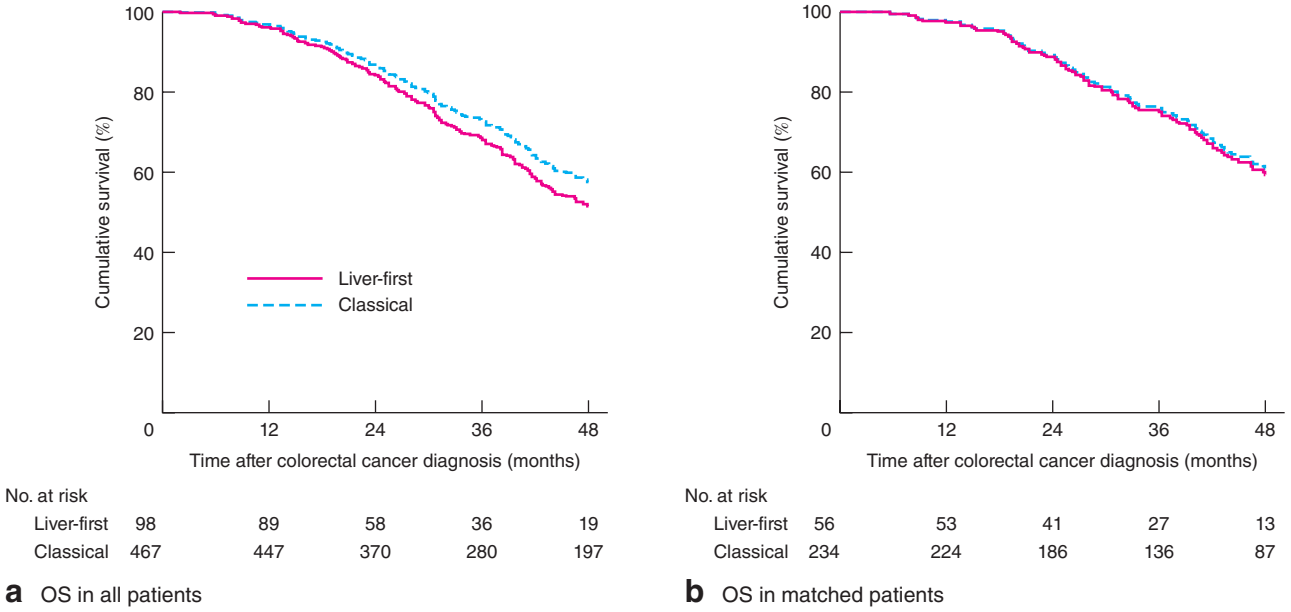

Fig. 2 Overall survival (OS) after diagnosis of synchronous colorectal liver metastases according to surgical strategy: **a** in all patients and **b** in patients matched for preoperative Basingstoke Predictive Index. **a** $P = 0{\cdot}305$, **b** $P = 0{\cdot}846$ (log rank test)

Discussion

In this study patients selected for a liver-first approach had a significantly worse predicted survival, determined by preoperative BPI, than those treated by the classical approach. Furthermore, they were more likely to have had either conversion or neoadjuvant chemotherapy before liver resection, resulting in a longer overall length of treatment. Despite this, there was no difference in CSS or OS between patients having a liver-first or classical approach. However, DFS was significantly lower in the liver-first group. This difference was negated by matching for preoperative BPI. These findings are in contrast to the LiverMetSurvey data published in 2012 by Andres and co-workers[20]. This multicentre study (219 institutions) compared the survival of 58 patients treated by a liver-first strategy with that of 729 patients managed with the classical approach. The authors found no difference in prognostic scores based on the Fong Clinical Risk Score[21] or DFS between groups. However, the number of patients having liver surgery first in that study was smaller, the data were pooled from multiple centres, without a single MDT approach, and the Fong score was used to predict prognosis, which is a more simplistic prognostic indicator than the BPI.

In the present study, the median OS in the liver-first group was 49·5 months, which compares favourably with the median of 35·5 months in a series of 22 patients reported by De Jong and colleagues[22] and 44 months described by Mentha and co-workers[23] in a cohort of 35 patients, calculated on an intention-to-treat basis. In contrast, Brouquet *et al.*[24] reported a median OS of 50 months among 27 of 41 patients who completed a liver-first strategy, compared with 19 months in 16 of 23 patients described by Verhoef and colleagues[25]. Two groups[26,27] have published systematic reviews of the 121 patients in these four studies[22–25]. They noted that the liver-first strategy was completed in 89 (73·6 per cent) of the 121 patients, compared with 82 (84 per cent) of 98 in the present study. Both groups concluded that the liver-first strategy was safe and feasible, but with considerable variation in OS between the four studies, despite apparently similar treatment protocols. In 2013, Verhoef's group[28] published an update showing a median OS of 49 months on an intention-to-treat basis in 31 of 42 patients who completed a liver-first approach.

Here, the median OS among patients undergoing a classical approach was 59·7 months, higher than in the liver-first group, but the difference was not statistically significant. There was no difference in OS when the groups were matched for preoperative BPI. The patients in the liver-first group had a higher preoperative BPI and were therefore predicted to have worse OS and CSS (as well as poorer DFS, which the data did demonstrate). The lack of significance may be explained by a type II statistical error owing to small numbers. However, more patients underwent reintervention (resection, ablation or

cyberknife) for recurrent intrahepatic and extrahepatic disease in the liver-first group compared with the classical group, reflecting the authors' proactive approach to surveillance and treatment of recurrent disease.

These data suggest that a liver-first approach is as oncologically sound as the classical approach and that these patients with a poor prognosis are not being disadvantaged. An alternative approach with this liver-first group would have been to consider a simultaneous liver and bowel resection. Although both a meta-analysis[7] and systematic review[29] showed no difference in morbidity, mortality or long-term survival between any of the three approaches, Abbott and co-workers[5] were more cautious. They investigated 361 096 patients from the United States National Inpatient Sample who had had either a liver resection (35 185), colorectal resection (322 286) or combined colon and liver resection (3625) for colorectal cancer between 2002 and 2006. Hospital stay was significantly prolonged in patients undergoing a combined major hepatectomy and colectomy compared with that for patients having a minor liver resection with colectomy, and there was a trend towards increased mortality in patients who had undergone a major hepatectomy and a colectomy (5·9 per cent) compared with those who had a minor liver resection and colectomy (3·3 per cent). The authors thus advocated a staged approach in patients with sCRLM requiring a major hepatectomy. In the present study, significantly more patients in the liver-first group required a major hepatectomy (69 per cent compared with 56·5 per cent in the classical group). This, coupled with the increased use of conversion or neoadjuvant chemotherapy (84 *versus* 59·7 per cent), which increases the risk of postoperative complications[30,31], supports the MDT decision to adopt a liver-first rather than a combined approach in this high-risk group.

These data confirm previous findings that a liver-first approach is feasible for patients with sCRLM. After correcting for the extent of disease using the preoperative BPI, the DFS, CSS and OS rates for the liver-first strategy were comparable to those of the classical approach. These data support a MDT approach, offering an individualized treatment plan for every patient presenting with sCRLM, rather than randomizing this heterogeneous group of patients into a trial of the classical, combined or liver-first approach.

Acknowledgements

The authors acknowledge the work of V. Bonwitt and C. Murray (research assistants) in maintaining the Basingstoke liver resection database.

Disclosure: The authors declare no conflict of interest.

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