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Changing outlook for colorectal liver metastasis resection in the elderly

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ABSTRACT

Background: This study sought to evaluate the impact of the advancements in clinical care, obtained over the last 20 years, for patients aged 70 and older undergoing liver resection for colorectal liver metastases (CRLM).
Methods: Consecutive patients age 70 or older who underwent liver resection for CRLM at Aintree University Hospital (Liverpool, UK) between May 2008 and May 2015 were compared to a dataset of consecutive patients, meeting the same criteria, between 1990 and 2007. An enhanced recovery programme after surgery (ERAS) combined with cardiopulmonary exercise testing (CPET) was introduced in January 2008.
Results: The proportion of patients over 70 years undergoing liver resection for CRLM increased over the study period (6% in 1990, 16.3% in 2000, 26.5% in 2005 and 25.8% in 2007). The patients in the later group were more often treated with neoadjuvant chemotherapy (58 *vs* 34, $p = 0.006$) and underwent parenchymal sparing surgery, resulting in fewer major hepatectomies (51 *vs* 111, $p < 0.001$) and less perioperative morbidity (49 *vs* 70, $p = 0.043$) and mortality (3 *vs* 9, $p = 0.229$). Although there was shorter disease free survival (DFS) in the later group (DFS at 1, 3 and 5 years was 52.1%, 31.6%, 29% vs. 71.8%, 49.1%, 44.0%)($p < 0.01$), similar overall survival (OS) was achieved (OS at 1, 3 and 5 years was 85.4%, 51.6%, 32.8% vs. 81.7%, 42.1%, 27.3%)($p = 0.21$).
Conclusions: This study demonstrates that, with modern management (ERAS, CPET, neoadjuvant chemotherapy and parenchymal sparing surgery), a greater number of patients with CRLM, over the age of seventy, can undergo liver resection, with improved perioperative outcomes.

Introduction

There have been considerable advances in the perioperative and clinical care of patients undergoing liver resection for colorectal liver metastases (CRLM). These include improved radiological staging, multidisciplinary management, new systemic anti-cancer treatments, better preoperative assessment including cardiopulmonary exercise testing (CPET) [1–3], expanding operative techniques and enhanced recovery after surgery (ERAS). It has been shown that with these management strategies, excellent perioperative outcomes can be achieved with morbidity and mortality of 38.2% and 0.3% respectively [1]. Recent data suggests median survival rates for all patients undergoing CRLM resection is around 40 (20–88) months [4,5], with five-year survival rates ranging from 35% to 58% [6,7]. This is despite patients undergoing more complex treatment for more extensive disease.

Due to the aging of the world population and the increased incidence of colorectal cancer, around half of the patients presenting with CRLM are elderly. The “elderly” are not clearly defined as a homogeneous population. However, in the most recent studies, an age of seventy has been used as cut off to define the elderly populations when considering hepatectomy [8].

The older population is under-represented in the cohort of patients undergoing liver resection for CRLM [9–11]. In the majority of the studies, conducted over the last fifteen years, only 8–20% of patients undergoing liver resection belong to this population [9–11]. This likely relates to concerns regarding increased operative risk for the older patients, with expected shorter survival [8,12,13].

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However, recent outcomes have suggested patients aged over seventy undergoing liver resection for CRLM will achieve a five-year survival of 21–44%, with postoperative morbidity and mortality rates of approximately 20–40% and 0–7% respectively [8,14–19]. These studies did not employ ERAS and CPET in patient management.

This study aims to evaluate the impact of advances in clinical care for patients aged 70 and older undergoing liver resection for CRLM, to facilitate improved informed consent in patients electing to undergo resection within the modern era of ERAS, CPET and MDT management.

Methods

Study aim

The primary aim of this study was to evaluate the impact of the changes in surgical management of CRLM on aged 70 or older undergoing liver resection for CRLM.

Patients and study design

Patients aged 70 or older who underwent liver resection for CRLM at Aintree University Hospital (Liverpool, UK), between May 2008 and May 2015, were identified from a prospectively maintained cancer database. These were compared to a previously published dataset from the same institution, including consecutive patients meeting the same criteria between 1990 and 2007 [15].

Patient management

Patient management has been summarised in previously published papers [1,15]. In brief, all patients were discussed within the multi-disciplinary team meeting and considered eligible for surgery with curative intent on a case-by-case basis. Postoperative follow-up consisted of determination of carcinoembryonic antigen (CEA) and CT chest-abdomen-pelvis every 6 months for the first two years post-operatively and yearly thereafter.

Major changes in perioperative management were introduced since 2008. An ERAS programme combined with CPET was introduced in January 2008 and has been previously described [1]. The ERAS programme is summarised in Table 1.

There was also standardisation of preoperative staging to include CT chest-abdomen-pelvis, MRI liver and FDG PET-CT [20].

Data analysis

The following data were extracted: age, gender, ASA score, CPET

Table 1
Summary of Aintree ERAS pathway [1].

Time point	Goals
Referral	Discussion of referral and review of all imaging in MDT
First clinic appointment	Patient education initiated, discussion of the full care pathway Discussion of intended operative intervention, and the associated risks and complications
Preoperative assessment	Cardiopulmonary exercise testing Assessment in preoperative clinic Review by dedicated liver anaesthetist
Day of admission	Review of operative intervention, risks and expected outcomes Review of expectations of enhanced recovery
Surgery	Minimize use of drains No nasogastric tube use Selective critical care admission post-surgery
Postoperative Day 1	Sat out of bed at least 8 h 4 walks of 30 m or more Respiratory physiotherapy review Review by acute pain team Commence full diet as tolerated Discharge planning meeting
Postoperative Day 2	Maintain oral intake If epidural in use place Fentanyl patch (25 mcg/hr) at 22:00 If PCA aim to convert to oral analgesia Sat out of bed at least 8 h 4 walks of 40 m or more
Postoperative Day 3	Removal of epidural analgesia Discontinue supplemental oxygen if saturations within normal range Maintain oral intake Sat out of bed at least 8 h 4 walks of 60 m or more Plan discharge
Postoperative Day 4–6	Maintain oral intake Sat out of bed at least 8 h 4 walks of 60 m or more Discharge if: Tolerating full oral intake Pain adequately controlled Passing Flatus and urine normally Normal routine observations Independently mobile and deemed safe for discharge Patient and family happy for discharge
Day 1 post discharge	Phone review with cancer specialist nurse (CNS)

test results [Oxygen uptake at the anaerobic threshold (AT) and peak exercise ($ml.kg^{-1}.min^{-1}$)], presentation (synchronous or metachronous), primary tumour characteristics (location, pT, pN), distribution (unilobar/bilobar), number and maximum size of liver metastases, extent of liver resection, neoadjuvant chemotherapy use, radicality of the surgery (R0, R1, R2), Pringle time (in minutes). Carcinoembryonic antigen (CEA) was not routinely collected preoperatively, as such this could not be included in any analysis.

The primary tumour stage was defined according to the 7th edition of the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) Tumour Node Metastasis (TNM) staging system. The extent of the liver resection was classified according to Goldsmith and Woodburne (major *i.e.*≥3 segments *versus* minor *i.e.*<3 segments). Ablations were considered as minor procedures.

Resection margins were considered R1 if the resection margin was less than 1 mm, or where there was tumour exposure to the resection margin.

Postoperative mortality and morbidity included deaths and complications recorded in hospital or within 90 days post-surgery. The severity of complications was defined by the Clavien-Dindo classification [21]. Major complications were considered as all complications of Clavien-Dindo grade 3 or greater.

Follow-up was considered closed at the time of death or the last follow-up visit. Overall survival (OS) and Disease-free survival (DFS) were calculated from the day of surgery.

Statistical analysis

Statistical analysis was carried out using SPSS version 25.0 (IBM, Armonk, New York, USA). Categorical data was analysed using the χ [2] test, Mann-Whitney *U* test for continuous non-normally distributed variables. Logistic regression was carried out to identify the variables associated with complications. Factors with $p \leq 0.10$ at the univariate analysis were compared in a multivariate analysis. DFS and OS were estimated with the Kaplan-Meier method. Log-rank test was used to evaluate the influence of individual variables on survival. A multivariate analysis was performed using Cox regression to identify independent prognostic factors for survival.

Results

Patient demographics

In the historical pre ERAS cohort, between August 1990 and April 2007, there were 654 liver resections for CRLM, with 181 performed in those over 70 years old. There was a median of 8 resections per year in this group of patients.

In comparison, between May 2008 and May 2015, 471 patients underwent liver resection for CRLM. There were 172 resections performed on 161 patients over the age of 70. This was a median of 20 per year, significantly more than in the prior cohort ($p < 0.01$).

There was a rising proportion of those over 70 within the last 20 years. Only 6% of patients were over 70 in 1990, increasing to 16.3% in 2000, 26.5% in 2005, 25.8% in 2007 and 35.1% in 2015.

The patient demographics are summarised in Table 2.

The patients in the later group were older, with 161 patients aged between 70 and 87 years (Median 75 years, Interquartile range (IQR = 73–79) *vs* 178 patients aged between 70 and 82 years (Median 74 years, Interquartile range (IQR = 71–76) in the earlier group at the time of surgery ($p < 0.01$).

The ASA status was available for all patients in the later cohort, but not recorded routinely in the early cohort. There were 117 ASA 1–2 and 55 ASA 3 patients. CPET was performed in 146 of 161 in the later cohort with a median VO_2 at AT of 11.3 $ml\ kg^{-1}.min^{-1}$ (Range 4.9–21.8 $ml\ kg^{-1}.min^{-1}$), and a median VO_2^{peak} of 17.1 $ml\ kg^{-1}.min^{-1}$ (Range 9.2–35.1 $ml\ kg^{-1}.min^{-1}$).

Table 2
Patients and lesion characteristics.

Variable	1990–2007	2008–2015	p
Patients	178	161	
Age*	74 (70–82)	75 (70–87)	**0.001**
Sex M/F	115 (64.6)/63 (35.4)	113 (70.1)/48 (29.9)	0.274
Presentation			
Synchronous	66 (36.5)	62 (36.0)	0.778
Metachronous	110 (60.7)	97 (56.4)	
Recurrence	3 (1.7)	13 (7.6)	
Unknown	2 (1.1)	0 (0.0)	
Primary tumour			
Colon	92 (51.7)	103 (63.9)	0.101
Rectum	75 (42.1)	58 (36.1)	
Unknown	11 (6.2)	0 (0.0)	
pT1-2	51 (28.7)	23 (14.2)	**0.001**
pT3-4	116 (65.2)	127 (78.8)	
Unknown	11 (6.1)	11 (7.0)	
pN0	164 (92.1)	72 (44.7)	**0.001**
pN+	9 (5.1)	75 (46.7)	
Unknown	5 (2.8)	14 (8.7)	
Liver metastases			
1-3	149 (88.7)	148 (86.0)	0.463
>3	19 (11.3)	24 (14.0)	
Unilobar	137 (75.6)	129 (75.0)	0.880
Bilobar	44 (24.4)	43 (25.0)	
Size (Range)*	50 mm(10–190)	40 mm(3–130)	**0.001**
Neoadjuvant Chemotherapy	34 of 181(18.8)	58 of 172 (33.7)	**0.006**

Shown as absolute number (percentage), except * where it is median (range).

In both groups the primary tumour was more often colonic, rather than rectal. In the later group the patients had more advanced primary tumours, with 127 patients with pT3-T4 tumour ($p < 0.01$) and 75 with pN + disease ($p < 0.01$).

The majority of patients in both cohorts presented metachronously with liver metastases. In both groups the majority of patients had 3 or fewer liver metastases in a unilobar distribution.

The size of the metastases in the earlier group was larger compared to the later group (median diameter of 50 mm in the early group vs. 40 mm in the later group, $p < 0.01$).

Neoadjuvant chemotherapy

Neoadjuvant chemotherapy was given to 34 (18.8%) patients in the earlier group and 58 (33.7%) in the later group ($p < 0.01$). No patient underwent neoadjuvant chemotherapy before 2000.

Oxaliplatin formed the basis of most chemotherapy regimens, with all patients in the earlier cohort receiving it. In the later cohort, 43 of 58 patients received oxaliplatin based regimes.

Operative and perioperative data

The operative and perioperative outcome data are summarised in Table 3.

In both groups, the most frequent treatment was liver resection alone. Synchronous resection of the primary tumour was undertaken in 2 patients in the earlier group, compared to 5 in the later group ($p = 0.20$). Two-stage liver resection was undertaken in 2 patients in the later cohort.

Ablation was combined with liver resection in 21 patients in the later cohort and only five in the earlier cohort ($p < 0.01$).

In the later group, the majority of the patients underwent a minor liver resection (121 of 172) with the use of the Pringle

Table 3
Operative and perioperative factors.

Variable	1990–2007	2008–2015	p
Number of liver resections	181 (27.6)	172 (35.1)	0.060
Type of resection			
liver resection alone	174 (96.1)	146 (84.9)	
liver resection + ablation	5 (2.8)	21 (12.2)	**0.001**
synchronous primary resection	2 (1.1)	5 (2.9)	
Two stage hepatectomy	0 (0.0)	2 (1.1)	
Repeat Liver resection			
Yes	3 (1.6)	178 (98.4)	**0.022**
No	11 (6.4)	161 (93.6)	
Extent of the liver resection*			
Minor	71 (39.2)	121 (70.3)	<**0.001**
Major	110 (60.7)	51 (29.7)	
Pringle			
No	77 (42.6)	46 (26.7)	
Yes	69 (38.1)	126 (73.3)	<**0.001**
Unknown	35 (19.3)	0 (0.0)	
Pringle time (min)*	30 (0–60)	22 (0–90)	
Radicality			
R0	166 (91.7)	101 (58.7)	<**0.001**
R1	15 (8.3)	71 (41.3)	
Hospital stay (days)*	13 (6–60)	6 (1–64)	**0.004**
Post-operative Complications			
Yes	70 (38.5)	49 (28.4)	**0.043**
No	111 (61.5)	123 (71.6)	
Clavien-Dindo			
<3	47	28	0.373
≥3	23	21	
Post-operative Mortality	9 (5)	3 (1.9)	0.229
Recurrence			
No	97 (53.6)	64 (37.2)	**0.002**
Yes	84 (46.4)	108 (62.8)	
Localisation of the recurrence			
Liver	36 (42.9)	43 (39.8)	
Extrahepatic	30 (35.7)	41 (38.0)	**0.003**
Diffuse	16 (19.0)	24 (22.2)	
Unknown	2 (2.4)	0 (0.0)	

Shown as absolute number (percentage), except * where it is median (range).

manoeuvre (126 of 172 patients). In the early group most patients underwent major liver resection (110 of 181) without the use of the Pringle manoeuvre (69 of 172 patients, $p < 0.01$).

Perioperative outcomes

R0 resection was achieved in most of the resections in both groups (166 in the early group vs 101 in the later group). However, more patients in the later group had R1 resection ($p < 0.01$).

The median in hospital stay was 6 days (IQR = 5–8) in the later group vs. 13 days (IQR = 10–18) in the early group ($p < 0.01$).

Postoperative morbidity was 49 of 172 liver resections in the later group and 70 of 181 liver resections in the earlier group ($p = 0.04$). There was no significant difference in the distribution of postoperative complications Clavien-Dindo grade ($p = 0.37$). Post-operative complications are summarised in Table 4.

A major liver resection was associated with an increased risk of complications in both univariate ($p < 0.01$) and multivariate analysis (HR 1.4, IC 95% 1.3–2.0, $p = 0.04$) in the later group. This was not seen in the earlier group, where there was no significant difference in postoperative complications between patients who underwent minor or major liver resections ($p = 0.38$).

In patients following minor hepatectomy there was a reduction in the rate of postoperative complications in the later cohort (27 of 71 in the earlier group vs. 27 of 121 in the later group, $p = 0.019$).

In the later group, on univariate analysis, neither neoadjuvant chemotherapy or a low VO_2 at ATml.kg.min^{-1} were associated with an increased complication rate.

Postoperative mortality within 90 days of liver surgery occurred in the 1.9% of the patients in the later group, compared with the 5.0% in the earlier group ($p = 0.22$). Major liver resection was associated with a trend towards increased mortality in the earlier group (8 of 110 major vs. 1 of 71 minor) ($p = 0.09$). All the post-operative deaths occurred in patients following a major liver resection in the later group.

Recurrence

After a median follow-up of 50 months (range 0–91 months), 108 patients within the later group developed tumour recurrence compared with 84 in the earlier group, after a median follow-up of 164 months (range 0–210 months) ($p < 0.01$).

In the later group, the median DFS was 13 months and the DFS at 1, 3 and 5 years was 52.1%, 31.6% and 29% respectively (Fig. 1). In comparison the earlier group had median DFS of 35 months and DFS at 1, 3 and 5 years of 71.8%, 49.1% and 44.0% respectively (HR 3.7, IC 95% 14.6–29.4, $p < 0.01$).

Within the later group, univariate analysis identified that performing a major liver resection ($p<0.01$), >3 metastases ($p < 0.01$) and bilobar metastases ($p = 0.04$) were predictors of inferior disease free survival (DFS) (Table 5). Multivariate analysis identified performing a major liver resection (HR 1.7, IC 95% 1.1–2.5, $p = 0.01$) and >3 metastases (HR 1.4, IC 95% 1.2–1.8, $p = 0.01$) as predictors of poorer DFS.

In the earlier group, >3 metastases ($p < 0.01$), bilobar metastases ($p = 0.03$) and R1 resection ($p < 0.01$) were predictors of inferior disease free survival. Multivariate analysis identified R1 resection (HR 3.3, IC 95% 1.6–6.8, $p < 0.01$) as predictors of poorer DFS (Table 6).

Survival

The OS at 1, 3 and 5 years was respectively 85.4%, 51.6% and 32.8% in the later group compared to 81.7%, 42.1% and 27.3% in the earlier group (Fig. 2). Median survival was 39 months in the later group vs. 33 months in the earlier group (HR 2.0, IC 95% 29.0–37.0, $p = 0.21$).

In the later group, on univariate analysis, maximum diameter of the metastases >50 mm ($p = 0.04$) and performing a major liver resection ($p = 0.01$) were predictors of poor survival (Table 7). On multivariate analysis, only the need for a major liver resection (HR 1.9, IC 95% 1.2–3.1, $p < 0.01$) predicted poorer survival.

In the earlier group, >3 metastases ($p = 0.01$), bilobar metastases ($p = 0.02$) and size of metastases >50 mm ($p = 0.01$) were predictors of inferior overall survival. On multivariate analysis, only a metastases >50 mm (HR 1.5, IC 95% 1.0–2.2, $p = 0.03$) was a predictor of poorer OS (Table 8).

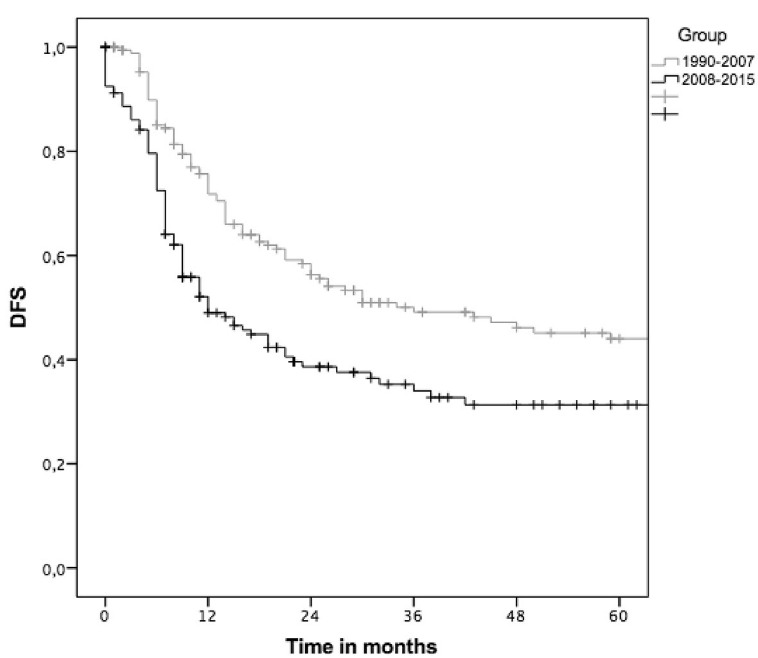
Discussion

This study demonstrates that, with modern management, a greater number of patients over the age of seventy with CRLM can undergo liver resection, with improved postoperative outcomes. There have been reductions in hospital morbidity and length of stay when managed within an established ERAS programme, utilising CPET.

The progressive rise in the percentage of patients, over the age of 70, undergoing liver resection is in keeping with previously

Table 4
(Supplemental data).

Clavien-Dindo	1990–2007	2008–2015
Grade 1	4 urinary retention 3 wound infection 2 post-operative ileus	4 urinary retention 3 transient liver failure 3 bile leak1 post-operative ileus
Grade 2	11 pneumonia 4 bile leak 3 abdominal collection 3 ileus 3 atrial fibrillation 2 transient liver failure 2 pressure sore 1 TIA 1 anaemia 1 ascites 1 bleeding from the drain site 1 confusion 1 duodenal ulcer + ileus 1 pneumothorax 1 fever 1 intraoperative bleeding 1 decompensate diabetes	7 pneumonia 3 acute kidney injury 1 atrial fibrillation 1 heart failure 1 hypertension 1 bile leak + pulmonary embolism 1 wound dehiscence 1 liver failure + post-operative ileus 1 bile leak + wound dehiscence
Grade 3	4 bile leak 2 intestinal obstruction 1 oesophageal ulcer	4 intestinal anastomotic leak 2 bile leak 3 intestinal obstruction 2 wound dehiscence 2 intra-abdominal abscess 1 ARDS 1 duodenal ulcer
Grade 4	4 transient liver failure 1 renal failure - hypotension 1 heart failure – renal failure 1 heart failure – sepsis	1 SIRS – liver and kidney failure 1 bile leak – intestinal ischemia – liver and kidney failure 1 acute kidney injury
Grade 5	5 liver failure 2 hepato-renal syndrome 1 cardiac arrest 1 sepsis	1 post-operative bleeding Stroke 1 aspiration pneumonia, MOF 1 cardiac arrest



No at risk

1990-2007	179	168	156	144	132	120
2008-2015	159	148	136	124	112	100

Fig. 1. Disease free survival.

Table 5
Univariate and multivariate analysis of predictors of disease free survival ERAS group.

		N°	Univariate	Multivariate	p
			p	HR(95% CI)	
Sex	F	50	0.170		
	M	122			
Age	70–80	137	0.838		
	>80	35			
	>1	83			
ASA	<3	117	0.972		
	≥3	55			
Primary tumour	Colon	112	0.867		
	Rectum	60			
Presentation	Synchronous	70	0.186		
	Metachronous	102			
Distribution	Unilobar	129	**0.048**	0.8(0.4–1.5)	0.539
	Bilobar	43			
No. of metastases	<3	146	**0.000**	**1.4(1.2–1.8)**	**0.014**
	>3	26			
Maximum diameter (mm)	<50	125	0.230		
	>50	45			
Neoadjuvant chemotherapy	Yes	118	0.100		
	No	54			
Extent of the liver resection	Minor	121	**0.001**	**1.7(1.1–2.5)**	**0.019**
	Major	51			
R0 resection		101	0.144		
R1 resection		64			
Complications	No	123	0.143		
	Yes	49			
Major complications	Yes	21	0.312		
	No	28			

Table 6
Univariate and multivariate analysis of predictors of disease free survival Historical group.

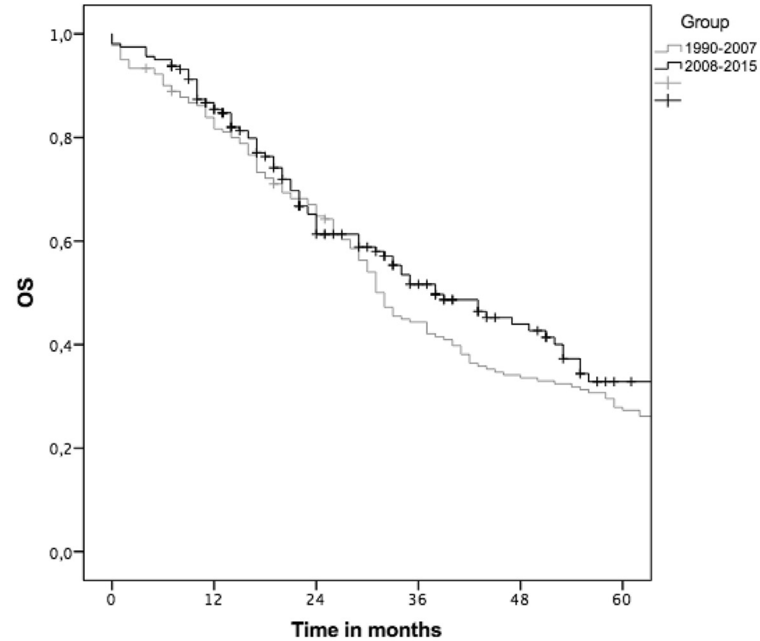
		N°	Univariate	Multivariate	p
			p	HR(95% CI)	
Sex	F	115	0.720		
	M	63			
Age	70–80	174	0.631		
	>80	7			
Primary tumour	Colon	92	0.785		
	Rectum	75			
Presentation	Synchronous	66	0.292		
	Metachronous	110			
Distribution	Unilobar	137	**0.032**	1.1(0.6–2.0)	0.649
	Bilobar	44			
No. of metastases	<3	149	**0.007**	1.7(0.9–3.2)	0.065
	>3	19			
Maximum diameter (mm)	<50	63	0.116		
	>50	81			
Neoadjuvant chemotherapy	Yes	34	0.191		
	No	147			
Extent of the liver resection	Minor	71	0.460		
	Major	110			
R0 resection		166	**0.005**	**3.3(1.6–6.8)**	**0.001**
R1 resection		15			
Complications	No	70	0.472		
	Yes	111			

published series and the globally aging population [22].

The rate of liver resection in patients over the age of seventy in this study has progressively increased. This may be related to an increasing age of the general population considered for surgery, however it could also represent greater willingness to offer liver resection to these patients. The percentage of patients over 70 within the later cohort of this study (35.1%) is higher than in the Liver Met Survey international registry, where 1624 of 7764 (20.9%) patients undergoing liver resection for CRLM were over 70 years old [18].

The advent of parenchymal preserving surgery and the increased use of thermal ablation in combination with resection is likely to have contributed to the rising rate of resections and the reduced postoperative morbidity, and for the decreasing number of major liver resections. Parenchymal sparing liver surgery has been shown to be associated with less surgical stress, fewer post-operative complications, uncompromised cancer-related outcomes and higher feasibility of future resections [23]. It has also recently been associated with better postoperative and long-term outcomes than “not parenchymal sparing resection” [24,25].

A major contributor to the low mortality seen in the later cohort of our study is the reduction in major liver resections. All the



No at risk						
1990-2007	180	169	157	145	133	121
2008-2015	160	149	137	125	113	101

Fig. 2. Overall survival.

Table 7
Univariate and multivariate analysis of predictors of overall survival ERAS group.

		N°	Univariate	Multivariate	p
			p	HR (95% CI)	
Sex	F	48	**0.072**	2.8 (0.7–10.2)	0.114
	M	113			
Age	70–80	127	0.127		
	>80	34			
ASA	<3	109	0.695		
	≥3	52			
Primary tumour	Colon	103	0.370		
	Rectum	58			
Presentation	Synchronous	63	0.506		
	Metachronous	98			
Distribution	Unilobar	122	0.790		
	Bilobar	39			
No. of metastases	<3	137	0.131		
	>3	24			
Maximum diameter (mm)	<50	116	**0.047**	1.6(0.4–6.8)	0.473
	>50	43			
Neoadjuvant chemotherapy	Yes	102	**0.091**	1.1(0.7–1.8)	0.573
	No	59			
Extent of the liver resection	Minor	113	**0.011**	**1.9(1.2–3.1)**	**0.019**
	Major	48			
R0 resection		96	**0.052**	1.5(0.3–6.7)	0.597
R1 resection		59			
Complications	No	123	0.531		
	Yes	49			
Major complications	Yes	21	0.289		
	No	151			

postoperative deaths in the earlier group happened in patients who underwent major liver resection and in the later group this type of resection was the only factor associated with an increased risk of morbidity, mortality and worse long term outcomes. This is in keeping with previous publications where Reddy et al. found that increasing patient age was independently associated with postoperative mortality following major hepatic resection [26]. Indeed, in the multicentre study of Adam, postoperative morbidity and mortality were more common in patients 70 years and older undergoing major liver resections [18].

Table 8
Univariate and multivariate analysis of predictors of overall survival Historical group.

		N°	Univariate	Multivariate	p
			p	HR(95% CI)	
Sex	F	115	0.767		
	M	63			
Age	70–80	174	0.183		
	>80	7			
Primary tumour	Colon	92	0.906		
	Rectum	75			
Presentation	Synchronous	66	0.957		
	Metachronous	110			
Distribution	Unilobar	137	**0.024**	1.3(0.7–2.2)	0.300
	Bilobar	44			
No. of metastases	<3	149	**0.012**	1.2(0.7–2.0)	0.480
	>3	19			
Maximum diameter (mm)	<50	63	**0.010**	**1.5(1.0–2.2)**	**0.031**
	>50	81			
Neoadjuvant chemotherapy	Yes	34	0.829		
	No	147			
Extent of the liver resection	Minor	71	**0.090**	1.0(0.6–1.5)	0.936
	Major	110			
R0 resection		166	**0.065**	1.6(0.8–3.2)	0.132
R1 resection		15			
Complications	No	70	**0.058**	1.4(0.9–2.1)	0.056
	Yes	111			

Parenchymal preserving surgery may have contributed to the rise in the R1 resection rate in the later group. However, an R1 resection was not statistically associated with worse DFS on univariate or multivariate analysis. In addition, it has been shown that the width of a negative margin does not affect the disease-free survival or the site of recurrence [27].

In this study, the shorter DFS in the latter cohort did not affect OS, as seen in previous studies [28,29].

Performing a major liver resection is associated with poorer survival, and it should be limited to cases where it is the only curative option. These patients may have greater tumour burden and more aggressive tumour biology. However, minimising the use of major liver resection may reduce complications, which are known to increase the rate of recurrence. Minimising major liver resection also preserves surgical options to deal with hepatic recurrence [24]. Liver limited recurrence is a frequent site of recurrent disease following CRLM resection [30]. This would be supported by the shorter DFS, without impact on the overall survival.

ERAS has been employed in this cohort and is likely responsible for much of the reduced length of stay and rate of post-operative complications. This is particularly pertinent when comparing only those patients undergoing a minor hepatectomy. This would be in keeping with other liver surgery ERAS programmes in the literature and demonstrates that ERAS is equally applicable and feasible to those patients over the age of seventy [1,31,32]. A recent meta-analysis of randomized controlled trials on the efficacy of the ERAS programme in liver surgery showed that this approach significantly reduces post-operative morbidity ($p = 0.01$), length of stay ($p < 0.01$) and accelerates functional recovery (time to first flatus $p < 0.01$) [33]. CPET has been used as part of the ERAS programme to help select patients for liver resection [2]. Careful pre-operative evaluation of the overall patient health status is very important before major liver surgery, especially in elderly patients. CPET assessed low fitness has been suggested as predicting poorer postoperative outcome following liver resection in some series [3,4]. In this study, CPET was utilised to aid in the identification of those high risk patients and help triage perioperative care. In this study a $10\ ml\ kg^{-1}.min^{-1}$ was not associated with increased morbidity on multivariate analysis. This is in keeping with prior work from our institution, where CPET is integral to perioperative management [2].

The overall survival in the later cohort did not improve as expected. This may reflect the fact patients with less favourable disease characteristics and comorbidities were being taken on for surgical intervention. This can be seen when examining the differences in the baseline characteristics including more patients with T3-4 and node positive primary tumours. Despite the less favourable disease characteristics overall survival was preserved, this may reflect greater use and improved chemotherapeutics.

Nowadays, the majority of chemotherapy regimens contain infusional fluorouracil, leucovorin, oxaliplatin and irinotecan as a combination regimen (FOLFOX, FOLFIRI or FOLFOXIRI). Those regimens are usually used in conjunction with target biologic agent (such as bevacizumab or cetuximab) to increase the possibility of converting unresectable to resectable disease [34].

The UK National Institute for Health and Care Excellence (NICE) recommends treatment with FOLFOX with or without cetuximab (depending on RAS mutational status) as first-line for patients with unresectable liver disease. FOLFIRI is considered for second-line treatment. Chemotherapy with FOLFOXIRI has also been proposed [35].

Our study suggests greater willingness to employ neoadjuvant chemotherapy to bring elderly patients to resection, where previously they would have been treated with palliative intent. Reassuringly, the increased use of chemotherapy was not associated with poorer postoperative outcome. Data on chemotherapy response rates was not available; this could have further enhanced the study.

Although these results provide an important insight into the management and outcome of colorectal liver metastases among elderly patients in routine clinical practice, this is a retrospective study. The two cohorts have differing tumour and patient characteristics and only those elderly patients who underwent liver resections have been included in the analysis. Data for those not considered for liver resection are not available. As such, the study is at risk of selection bias, and some of the differences in oncological outcomes may relate to evolution of clinical care.

Our study supports the theory that parenchymal sparing liver surgery, with or without combination with chemotherapy and ablation, should be used to avoid unnecessary major liver resection. It also supports the adoption of an ERAS protocol to optimise perioperative care.

Conclusion

This study has demonstrated that despite the aging of the population and the increased number of over 70 undergoing liver resection for CRLM over the last 10 years, with the use of enhanced recovery, neoadjuvant chemotherapy and parenchymal sparing surgery it is possible to achieve good DFS and OS with less morbidity and mortality.

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Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2018.11.024.

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