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After laparoscopic liver resection for colorectal liver metastases, age does not influence morbi-mortality

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Abstract

Background Hepatectomy remains the only curative option in patients presenting with colorectal liver metastases (CLM). Although laparoscopic approach has improved postoperative morbidity and mortality rates, its suitability for patients of all age groups has yet to be confirmed. The aim of this study was to analyze postoperative outcomes following laparoscopic liver resection (LLR) in different age groups of patients presenting with CLM.

Methods All patients who underwent LLR for CLM from 2008 to 2017 were reviewed. Patients were divided into four age groups: < 55, 55–65 years, 65–75 and > 75 years. Baseline and intraoperative characteristics as well as postoperative morbidity and mortality were compared between all four groups.

Results Overall, 335 patients were included with 34 (10%), 113 (34%), 136 (41%) and 52 (15%) in < 55, 55–65, 65–75 and > 75 years subgroups. Baseline characteristics were similar between all four groups except for elevated pressure, dyslipidemia and ASA score which were higher in older patients. Regarding surgical procedures, major hepatectomy, uni- or bisegmentectomy and wedge resection were performed in 122 (36%), 87 (26%) and 126 (38%) patients, respectively, with no significant differences between age groups. Overall, 90-day postoperative mortality rate was nil and postoperative morbidity was similar between all four groups except for biliary fistula occurrence, which was higher in < 55 years patients ($p = 0.006$).

Conclusion Short-term postoperative outcome following LLR for CLM does not seem to be affected by age. Curative laparoscopic treatment should therefore be considered whenever possible, regardless of patient age.

Keywords Liver resection · Hepatectomy · Laparoscopy · Colorectal metastasis · Age · Elderly · Morbi-mortality

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Abbreviations

CLM Colorectal liver metastases
CRC Colorectal cancer
LLR Laparoscopic liver resection
ASA American Society of Anesthesiologists
BMI Body mass index
CT Computed tomography;

In colorectal cancer (CRC), up to 70% of patients develop at some point colorectal liver metastases (CLM) [1], with synchronous occurrence ranging between 14 and 18% [2]. In these patients, treatment with curative intent can be considered provided complete surgical resection is achievable, with a 5-year survival of 30% [3] and a median survival of 3.5 years [4]. Still, parenchymal-sparing oncological hepatectomy is a demanding procedure requiring expertise, adequate tumor location and appropriate underlying hepatic function; unfortunately, a minority of patients is suitable for liver resection with curative intent [3]. Ranking third in incidence and fourth in associated mortality worldwide [5], CRC increasingly occurs in older patients [6, 7]. As a consequence of improved overall life expectancy [8], an increasing number of elderly candidates for liver resection with CLM should be expected.

Increasing age has been traditionally associated with adverse outcomes following liver resection [9–15], especially in patients considered at high risk in terms of anesthetic procedures (ASA ≥ 3) [16, 17], leading some teams to contraindicate liver resection in elderly patients. However, with the increasingly improved perioperative management [18–27], this assessment becomes debatable. Among main advances in liver surgery, laparoscopic liver resection (LLR) has witnessed a widespread use. Compared to open approach, benefits of LLR include decreased major [20, 24, 26, 27] and pulmonary complication rates [21], reduced intraoperative blood loss [20, 24–26] and shorter hospital stay [21, 24–27]. So far, laparoscopic approach has been described for most liver resections [27–29] with respect to oncological principles [22, 24–27] and has also been associated with a decreased morbi-mortality in the elderly [23, 30].

As evidence of improved postoperative outcomes has been strengthened, determining precisely the influence of age on postoperative outcomes after LLR for CLM should further improve candidate selection for this surgical technique in this setting. The aim of the present study was to analyze postoperative outcomes in different age groups in order to clarify this debate and potentially improve decision-making for CLM during multidisciplinary team meetings.

Materials and methods

Patients' selection

Patients were retrospectively retrieved from a prospectively collected database. From January 2008 to December 2017, all consecutive patients who underwent LLR for CLM with curative intent (R0 or R1) at Institute Mutualiste Montsouris (Paris, France) were identified. Laparoscopic approach was considered for liver resection only when adequate surgical margins could be achieved without total vascular exclusion, liver cooling or major vascular reconstruction (portal vein/branch or hepatic vein/inferior vena cava). Previous abdominal surgery, obesity, underlying cirrhosis, bilobar disease and previous portal vein embolization were not considered as contraindications for a laparoscopic approach. Patients who underwent concomitantly hollow viscus resection were excluded. This study was approved by the local review board.

Preoperative assessment and surgical procedure

For all patients, preoperative investigations included complete blood and liver function tests, physical examination, assessment of comorbidities as well as routine cardiopulmonary evaluation. Pulmonary comorbidity was defined as chronic and severe limitation of mobility (obstructive, restrictive, and vascular) and inability to perform household chores, whereas cardiovascular comorbidity was defined as symptomatic coronary heart disease with New York Heart Association stage 2 and 3 clinical limitations or myocardial infarction during the previous 6 months. An echocardiogram and lung function test were performed when occult cardiopulmonary disease was suspected. Chronic kidney disease was defined as either kidney damage or a decreased glomerular filtration rate of less than 60 mL/min/1.73 m^2 for ≥ 3 months. Surgical risk was assessed using the criteria of the American Society of Anesthesiologists (ASA), and liver resection was contraindicated for patients with a score > 3. Specific geriatric evaluation for patients aged ≥ 75 years was not routinely performed. Computed tomography (CT) and/or magnetic resonance imaging were performed to assess tumor characteristics. The decision for hepatectomy was taken by a multidisciplinary board that included surgeons, medical oncologists gastroenterologists and radiologists. All resections were performed with curative intent.

Surgical technique was described in a previous report [31]. Briefly, LLR was performed using three to six trocars, depending on the surgical procedure and operator preference. Laparoscopic ultrasonography was routinely

used. Tissue dissection and hemostasis were performed using ultrasonic dissector, bipolar forceps and harmonic scalpel. Pringle maneuver was used in case of bleeding only. The resected specimen was placed in a plastic bag and removed through a 5- to 8-cm suprapubic incision without muscle section or through a trocar incision (in case of small lesion resection). This incision was immediately closed and the abdomen reinsufflated to confirm hemostasis and absence of bile leaks. Methylene blue or air injection through the cystic drain was not routinely performed. Abdominal drainage was only used if there was concern about intraoperative bile control or the adequacy of hemostasis. All intraoperative parameters, including blood loss with subsequent red cell transfusion, duration of surgery, Pringle maneuver and duration of the maneuver, were recorded. Extent of liver resection was classified according to Brisbane 2000 classification [32]; accordingly, for the purpose of the study, major liver resection was described as any resection of ≥ three contiguous segments, minor resection as any resection of ≤ two contiguous segments, and wedge resection as any non-anatomical resection extending to less than one segment. Surgical procedure was designed in respect of parenchyma-sparing strategy [33].

Postoperative course

Postoperative complications were assessed using Clavien–Dindo classification [34]. Minor and severe postoperative complications were defined as Clavien–Dindo I–II and III–IV, respectively. Postoperative hepatocellular insufficiency was diagnosed using the "50–50" criteria (prothrombin time < 50% and serum bilirubin > 50 µmL/L i.e., 2.9 mg/dL) on postoperative day 5 [35]; ascites was defined as a postoperative daily drain output of ascitic fluid exceeding 10 mL/kg (according to preoperative body weight) [36]. Postoperative hemorrhage was diagnosed if hemoglobin level dropped more than 3 g/dL compared to preoperative baseline value, if red blood cells transfusion was required and/or if invasive redo surgery was necessary [37]. Biliary leakage was diagnosed when bilirubin concentration in the drainage fluid was more than three times higher than serum value [38]. Postoperative morbidity and mortality were assessed at 90 days after surgery.

Statistical analysis

Patients were divided into four distinct age groups: < 55 years, 55–65 years, 65–75 years, and > 75 years. Baseline and intraoperative characteristics as well as postoperative outcome were analyzed. Quantitative variables were presented as median (range) and categorical variables as frequencies (percentage). Categorical variables were compared using the χ^2 test with Bonferroni's correction whenever necessary. Quantitative variables were compared using ANOVA test. A p value of 0.05 was considered statistically significant. All statistical analyses were performed with PASW (SPSS) 18.0 (SPSS Inc, Chicago, IL).

Results

Studied population

A total of 335 patients underwent LLR for CLM. Patients' characteristics and co-morbidities are reported in Table 1. Overall, 217 (64.8%) patients were male, with a median age of 66.6 years (range 27.7–88.8) and a median body mass index (BMI) of 25.7 kg/m² (range: 15.9–41.5). Age groups were composed as follows: < 55 years ($n = 34$,

Table 1 Demographic characteristics

	< 55 years ($n = 34$)	55–65 years ($n = 113$)	65–75 years ($n = 136$)	> 75 years ($n = 52$)	p
Male gender (%)	23 (67.6%)	76 (67.3%)	87 (64%)	31 (59.6%)	0.784
Age (years), mean (range)*	49.5 (27.7–54.9)	60.5 (55.2–64.9)	69.8 (65.1–74.9)	79.3 (75.4–88.8)	< 0.001
BMI (kg/m^2), mean (range)	25.3 (20.1–32)	26.2 (15.9–38.6)	26 (18.3–41.5)	26.8 (18.1–31.2)	0.537
ASA score > 2 (%)	1 (2.9%)	21 (18.6%)	13 (9.6%)	11 (21.1%)	0.041
Diabetes mellitus (%)	0 (0%)	8 (7.1%)	15 (11%)	4 (7.7%)	0.191
Cardiac comorbidity disease (%)	0 (0%)	7 (6.2%)	10 (7.3%)	5 (9.6%)	0.342
Liver comorbidity (%)	1 (2.9%)	1 (0.9%)	0 (0%)	1 (1.9%)	0.585
Pulmonary comorbidity (%)	0 (0%)	3 (2.7%)	9 (6.6%)	5 (9.6%)	0.107
Alcohol (%)	3 (8.8%)	17 (15%)	20 (14.7%)	9 (17.3%)	0.745
Elevated blood pressure (%)	7 (20.6%)	21 (18.6%)	38 (27.9%)	20 (38.5%)	0.041
Dyslipidemia (%)	0 (0%)	21 (18.6%)	25 (18.4%)	11 (21.2%)	0.046
Tobacco (%)	2 (5.9%)	21 (18.6%)	27 (19.8%)	5 (9.6%)	0.109

ASA American Society of Anesthesiologists, *COPD* Chronic Obstructive Pulmonary Disease

10.1%), 55–65 years ($n = 113$, 33.7%), 65–75 years ($n = 136$, 40.6%) and > 75 years ($n = 52$, 15.5%). Overall, 46 (13.7%) patients were classified as ASA = 3 and 52 (15.5%) had previously undergone liver resection.

Liver metastases were described as synchronous in 154 (46%) patients and bilobar in 107 (31.9%). There were 19 (5.7%) who presented with more than 5 CLMs. Neoadjuvant chemotherapy was recorded in 159 (47.5%) patients, including 18 (11.3%) patients who presented with tumor progression following chemotherapy. Nineteen (5.7%) patients underwent portal embolization in order to enable major hepatectomy and 45 (13.4%) underwent two-stage hepatectomy.

Patients' characteristics in all four groups are shown in Table 1; ASA > 2, dyslipidemia, elevated blood pressure, and neoadjuvant chemotherapy (associated with younger age) were significantly different between groups; otherwise, no statistical difference was found between groups.

Surgical procedure

No significant differences were found between all four groups regarding intraoperative characteristics (results reported in Table 2); overall, major resection, uni- or bisegmentectomy and wedge resection were performed in 122 (36.4%), 87 (26%) and 126 (37.6%) patients, respectively. Fourteen patients (4.2%) underwent complementary radiofrequency ablation during LLR. Intermittent Pringle maneuver was required in 25 (7.5%) patients, with a median duration of 16 min (range 3–64 min). Median blood loss reached 150 mL (range 0–3000 mL) and perioperative red blood cells transfusion was required in 16 (4.8%) patients. Median operative time reached 210 min (range 60–600 min). Conversion to laparotomy was reported in 17 (5.1%) patients.

Postoperative outcomes

Postoperative outcomes are detailed in Table 3. Overall, 227 (67.8%) patients presented with any postoperative complication, with minor and severe complications occurring in 192

Table 2 Intraoperative characteristics

	< 55 years ($n = 34$)	55–65 years ($n = 113$)	65–75 years ($n = 136$)	> 75 years ($n = 52$)	p
Conversion rate	1 (2.9%)	2 (1.8%)	11 (8.1%)	3 (5.8%)	0.194
Major hepatectomy	10 (29.4%)	45 (39.8%)	51 (37.5%)	16 (30.8%)	0.558
Uni- or bisegmentectomy	7 (20.6%)	23 (20.4%)	43 (31.6%)	14 (26.9%)	0.200
Wedge resection	17 (50%)	45 (39.8%)	42 (30.9%)	22 (42.3%)	0.134
Minor or wedge resection	24 (70.6%)	68 (60.2%)	85 (62.5%)	36 (69.2%)	0.558
Pringle maneuver	3 (8.8%)	10 (8.8%)	8 (5.9%)	4 (7.7%)	0.355
Mean Pringle maneuver duration (min)	12.3	22.6	28.4	13.3	0.883
Mean surgery duration (min)*	231.0	217.9	234.5	214.7	0.643
Mean blood loss (mL)*	225.3	251.7	345.5	241.4	0.242
Intraoperative blood unit transfusion	2 (5.9%)	4 (3.5%)	8 (5.9%)	2 (3.8%)	0.449

Table 3 Postoperative outcomes

	< 55 years ($n = 34$)	55–65 years ($n = 113$)	65–75 years ($n = 136$)	> 75 years ($n = 52$)	p
Postoperative complications (%)	23 (67.6%)	76 (67.3%)	90 (66.1%)	38 (73.1%)	0.839
Clavien I–II complications (%)	17 (50.0%)	62 (54.9%)	80 (58.8%)	33 (63.5%)	0.583
Clavien III–IV complications (%)	6 (17.6%)	14 (12.4%)	10 (7.4%)	5 (9.6%)	0.287
Postoperative mortality (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	–
Liver failure (%)	2 (5.9%)	9 (8.4%)	4 (3.1%)	3 (6.1%)	0.372
Ascites	2 (6.2%)	2 (1.8%)	4 (2.9%)	1 (2.0%)	0.602
Hemorrhage (%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	–
Biliary fistula (%)	5 (16.1%)	5 (4.7%)	2 (1.6%)	2 (4.1%)	0.006
Intra-abdominal collection	6 (18.8%)	12 (11.2%)	8 (6.2%)	5 (10.2%)	0.168
Pulmonary complications (%)	0 (0%)	9 (8.4%)	5 (3.9%)	3 (6.1%)	0.222
Reoperation (%)	0 (0%)	4 (3.5%)	3 (2.2%)	2 (3.8%)	0.650
Hospital stay (days), median	7	6.5	6.5	6	0.872

(57.3%) and 35 (10.4%) patients, respectively. Postoperative mortality rate was nil.

Specific hepatic complications such as liver failure, biliary leakage and ascites were observed in 18 (5.4%), 14 (4.2%) and nine (2.7%) patients, respectively. Thirty-one (9.3%) patients were diagnosed with intra-abdominal collections and one (0.3%) with intra-abdominal hemorrhage. In 9 (2.7%) patients, redo surgery was required due to the occurrence of postoperative complications. Median length of hospital stay reached 7 days (range 2–55). Pulmonary complications such as pulmonary embolism, pleural effusion and pleural infection related to damaged thoracic tube were observed in three (0.9%), one (0.3%) and one (0.3%) patients, respectively. Also, deep venous thrombosis (without pulmonary embolism), central line sepsis and transient ischemic attack (with right hemiplegia) were observed in three (0.9%), two (0.6%) and one (0.3%) patients, respectively.

No differences were found between all four groups in term of morbi-mortality, intra-abdominal collections, pulmonary complications and length of hospital stay. Regarding specific liver complications, no differences were found other than biliary fistula occurrence, which was highest in <55 years group ($p=0.006$).

Discussion

Decision to treat with curative intent results from a complex equation that takes into consideration (1°) expected life expectancy without treatment, (2°) treatment benefit in terms of life expectancy and (3°) morbi-mortality related to the treatment. If life expectancy is lower in elderly patients who present with CLM compared to their younger counterparts and the benefit of complete surgical resection of CLM is well determined [4], morbi-mortality related to hepatectomy in this specific population has yet to be precisely assessed.

In current literature, reported short-term postoperative outcomes following hepatectomy for CLM in elderly patients are heterogeneous [9–19, 23]; some authors have reported increased morbi-mortality, while others consider that an appropriate patients' selection leads to acceptable short-term results. However, differences in terms of perioperative management and surgical approach (open versus laparoscopy) between these studies were probably responsible for these discrepancies. Indeed, many authors have already reported the benefits of laparoscopy compared with the open approach: reduced intraoperative blood loss [20, 24–26], decreased complication rate [20, 21, 24, 26, 27] and hospital stay [21, 24–27]. In the elderly, LLR is associated with decreased morbi-mortality [23, 30]. These different reports suggest that elderly patients present with a better tolerance of liver resection when performed using a laparoscopic approach.

Results from present series are in accordance with these conclusions. No significant differences were found between all four groups in terms of postoperative morbi-mortality including overall complication rate (67.8%), minor and major postoperative complications (57.3% and 10.4%, respectively) and postoperative mortality (0%). No significant differences were found in terms of specific complications related to liver function such as ascites (2.7%) and liver failure (5.4%). Also, there were no differences in terms of pulmonary complications (5.1%) and complications related to surgery [hemorrhage (0.3%), abdominal collections (9.3%) and redo surgery (2.7%)]. Only biliary fistula was significantly higher in younger patients (16.1% in patients younger than 55 years old versus 3% in patients who were older, $p=0.006$). Consequently, current results suggest that age does not influence postoperative outcomes after LLR for CLM; advanced age should therefore not be considered as a contraindication to perform LLR for CLM.

In current study, patients were divided into four different age groups including a group of patients <55 years and one with patients >75 years, respectively. Unlike most studies, we sought to compare patients based on four age categories instead only two (cutoff set at 70, 75 or 80 years in most studies) [9–19, 23], in order to better observe subtle differences that might appear with increasing age.

Current results showed that patients' baseline and intraoperative characteristics were very similar; although elderly patients presented more often with elevated blood pressure, dyslipidemia and ASA score >2, these factors have not been reported as prognostic factors of postoperative outcome following hepatectomy. Performed surgical procedures were not significantly different between groups (extent of liver resection, Pringle maneuver, blood loss and operative duration). Consequently, the lack of difference in in terms of postoperative morbi-mortality did not result from highly selected patients and/or less aggressive surgical procedures in older patients.

Furthermore, current results seem to support the assumption that liver function is not impaired by increased age [39]. Indeed, there were no significant differences in terms of liver-specific complications (such as postoperative liver failure and ascites) after LLR with comparable surgical resection. Even though the rate of major hepatectomy was scarce in elderly patients and none presented with liver cirrhosis, increasing experience with elderly donors in liver transplantation, without increased biliary, vascular and graft functional-related complications may result from the same mechanism and also support this assumption [40]. It seems therefore that short-term outcomes following LLR may depend more on co-morbidities and surgical procedure than age.

This conclusion should also lead to consider consequences of laparotomy in the elderly. In order to improve

postoperative outcomes, enhanced recovery programs should be pursued in elderly patients as well. These programs aim to decrease pain, improve mobility, reduce fasting and institutionalization, as well as overall in-hospital stay; all of the objectives mentioned above are benefits associated with laparoscopy. However, the conclusion that age does not influence postoperative outcomes after LLR for CLM should not lead to think that risk is decreased in elderly patients. When laparoscopic approach has been reported as the best approach for major liver resection in elderly patients [23, 30], some hepatectomies remain technically challenging: major, superior and posterior resections. In current results, mortality rate was nil and severe postoperative complication rate was 10.4% but these good outcomes resulted from a specific perioperative management that has now been established for a decade. Indeed during these past years we have developed and promoted minimally invasive techniques for hepatectomy [31] and complied with sparing-parenchyma principles in more than 500 cases [33].

Obviously, this study may be criticized owing to methods and usual flaws associated with retrospective reports (length of the study, different surgeons, various management protocols, etc.). Also, as this report is based on patients who underwent surgery, a selection bias was probably caused as frail (potentially elderly) patients may have been refused for liver resection. Also, a complete geriatric assessment in all patients > 65 years might have led to identify subgroups with different outcomes. Nonetheless, we believe that despite its retrospective design, this report showing age group analysis in a large series (335 patients) should be an asset in daily decision-making for CLM.

In conclusion, this study contributes to increase evidence that, in patients presenting with CLM, age does not influence short-term morbi-mortality following LLR. Therefore, patients' selection should be based on technical feasibility and usual prognostic factors including co-morbidities and liver function, regardless of age.

Compliance with ethical standards

Disclosure Regarding current study, Alban Zarzavadjian Le Bian, Nicolas Tabchouri, Mostefa Bennamoun, Christophe Louvet, Candice Tubbax, Anthony Sarran, Marine Lefevre, Marc Beaussier, Frédéric Pamoukdjian, Philippe Wind, Brice Gayet and David FUKS have no conflict of interest to declare.

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