Original articles

Two decades of liver resection with a multidisciplinary approach in a single institution: What has changed? Analysis of 1409 cases

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HIGHLIGHTS

• Analysis of changes in hepatectomies during the last 2 decades.
• The surgical treatment of liver tumors needs a multidisciplinary approach.

ARTICLE INFO

Objectives: To evaluate results of patients undergoing liver resection in a single center over the past two decades with a particular look at Colorectal Liver Metastasis (CRLM) and Hepatocellular Carcinoma (HCC).

Method: Patients were divided into two eras, from 2000 to 2010 (Era 1) and 2011 to 2020 (Era 2). The most frequent diagnosis was CRLM and HCC, with 738 (52.4%) and 227 (16.1%) cases respectively. An evaluation of all liver resection cases and a subgroup analysis of both CRLM and HCC were performed. Preoperative and perioperative variables and long-term outcomes were evaluated.

Results: 1409 liver resections were performed. In Era 2 the authors observed higher BMI, more: minimally invasive surgeries, Pringle maneuvers, and minor liver resections; and less transfusion, less ICU necessity, and shorter length of hospital stay. Severe complications were observed in 14.7% of patients, and 90-day mortality was 4.2%. Morbidity and mortality between eras were not different. From 738 CRLM resections, in Era 2 there were significantly more patients submitted to neoadjuvant chemotherapy, bilateral metastases, and smaller sizes with significantly less transfusion, the necessity of ICU, and shorter length of hospital stay. More pedicle clamping, minimally invasive surgeries, and minor resections were also observed. From 227 HCC resections, in Era 2 significantly more minimally invasive surgeries, fewer transfusions, less necessity of ICU, and shorter length of hospital stay were observed. OS was not different between eras for CRLM and HCC.

Conclusions: Surgical resection in a multidisciplinary environment remains the cornerstone for the curative treatment of primary and metastatic liver tumors.

Keywords: Hepatectomy, Liver neoplasms, Hepatocellular carcinoma, Colorectal liver metastases, Morbidity

ABSTRACT

Introduction

Historically, liver resection was considered a complex procedure followed by high mortality rates. In the 1970s, mortality rates up to 10%–20% were observed. However, with the increase in experience and the formation of centers dedicated to liver surgery, a significant improvement in the safety of hepatic resection was observed. Recent series from high-volume specialized centers have reported mortality rates of <3–5%. As a result, hepatic resection has evolved into the treatment of choice for selected patients with benign and malignant hepatobiliary disease.

The main indication for liver resection in Western countries is Colorectal Cancer Liver Metastasis (CRLM). Hepatic resection is the only potentially curative therapy for selected patients with CRLM. Large single centers, as well as multi-institutional experiences, have shown 5-year overall survival rates ranging from 35% to 57% following liver resection. Better image tools for liver and extra-hepatic staging, novel surgical strategies such as parenchyma preserving resection,
selective portal vein embolization, liver venous deprivation, 2-stage hepatectomy, ALPPS, and the possibility of extrahepatic tumor eradication, have allowed patients with multiple nodules and even large tumor burden to undergo complete resection. In the last years, systemic chemotherapy new regimens could provide significant response rates in the majority of patients, including those with an initially unresectable disease which, after excellent response, became resectable (conversion therapy). In addition, response to chemotherapy treatment is a surrogate factor of better tumor biology, used for selecting patients for resection. All these strategies, associated with a better selection of patients, have led to an expansion of the indications for CRLM resection.

In Eastern countries, the main indication for liver resection is Hepatocellular Carcinoma (HCC), the most common primary liver cancer. The available curative therapies for HCC are a liver transplant, resection, and ablation. Liver transplantation is suitable for patients with impaired liver function and portal hypertension within selective criteria (Milan criteria), ablation is reserved for nodules < 2 cm in diameter, and resection is indicated for patients with preserved liver function. Resection proved to be a safe procedure in the last years with good long-term outcomes. Preoperative diagnosis for patients submitted to liver resection (2000–2020). The authors evaluated preoperative and perioperative variables and long-term outcomes. Preoperative data consisted of diagnosis (afterward confirmed by a histopathologic evaluation), sex, age, BMI, ASA status, and preoperative portal vein embolization. Perioperative variables were procedure date, open or minimally invasive surgery, type, and extension of liver resection (major resection when 3 or more contiguous segments were resected), one or two stages hepatectomy, use of Pringle maneuver, necessity and volume of transfusion, surgery time, need for ICU, length of hospital stay, postoperative morbidity according to the Dindo-Clavien classification, 90-day mortality.

Patients were followed according to the institutional protocol for each diagnosis. Overall Survival (OS) was defined as the time interval between the date of liver resection and the date of death or more recent contact during follow-up.

Survival was assessed using the Kaplan-Meier method and a comparison between the curves was performed with the log-rank test. Qualitative variables are presented as frequencies and percentages. Univariate associations between clinicopathologic qualitative variables and eras were examined using the x² test and/or Fisher’s exact test. Quantitative variables are shown in mean values, median values, standard deviations, and ranges (minimum and maximum values). Data normality was evaluated using the Kolmogorov-Smirnov non-parametric test for quantitative variables. Comparison between the distribution of the quantitative variables between treatment groups was then completed using the Student’s t-test (data with normal distribution) or Mann-Whitney test (data

Methods

A retrospective study of all consecutive patients who underwent liver resection at our institution between 2000 and 2020 was performed. Data was collected using REDCap electronic database. This study was approved by the institutional Ethics Committee. Exclusion criteria were patients subjected to first-step liver resection for staged hepatectomy that did not reach the second step; liver cysts defenestration.

In order to evaluate what has changed over the past 20 years, patients were divided according to two different eras, from 2000 to 2010 (Era 1), and from 2011 to 2020 (Era 2). The most frequent diagnosis in all series was Colorectal Liver Metastasis (CRLM) and Hepatocellular Carcinoma (HCC), with 738 (52.4%) and 227 (16.1%) cases respectively. An evaluation of all liver resection cases and a subgroup analysis of both diagnoses, CRLM and HCC was then performed.

All cases were previously discussed at a multidisciplinary meeting where surgery was indicated. For CRLM the inclusion criteria were complete resection of all hepatic lesions, liver remnant > 25% in healthy livers and > 30% after long-term chemotherapy, and limited resectable extra-hepatic disease. All patients with CRLM were submitted to perioperative chemotherapy. For HCC the inclusion criteria were uni or oligo-nodular disease (up to 3 nodules), absence of extrahepatic disease, Child-Pugh A (or B when minor peripheral resection was required), and Model of End-Stage Liver Disease (MELD) ≤ 10, without clinically significant portal hypertension (small caliber esophageal varices and platelets > 100.000 mL), and future liver remnant ≥ 40%.

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![Fig. 1. Preoperative diagnosis for patients submitted to liver resection (2000–2020).](image)
Results

During the study period, 1409 liver resections were performed. Indications for liver resection are shown in Fig. 1. More than half (52.4%) of all liver resections were for CRLM, 16.1% for HCC, 6.4% for liver cell adenoma, and 3.4% for intrahepatic cholangiocarcinoma. 3.3% for non-colorectal non-neuroendocrine liver metastasis, 2.6% for intrahepatic lithiasis, 2.1% for mucinous cystic neoplasia. Table 1 summarizes preoperative and postoperative patients' characteristics.

When patients from the two Eras were compared, the authors observed on Era 2 a higher BMI, and significantly more patients with bilateral metastases, but with smaller sizes. Regarding the number of metastatic nodules, the authors observed more multinodular cases in Era 2 (26.3% vs. 19.9%) however the difference was not significant (p = 0.103). Moreover, patients received more neoadjuvant chemotherapy in Era 2.

A comparison between eras was made showing in Era 2 significantly less transfusion, the necessity of ICU, and a shorter length of hospital stay. From a technical point of view, in Era 2 the authors observed less pedicle clamping maneuvers, minimally invasive surgeries and fewer transfusions, less necessity of ICU, and a shorter length of hospital stay (Table 4).

Colorectal liver metastases

Seven hundred thirty-eight liver resections for Colorectal Liver Metastasis (CRLM) in 708 patients were performed. In Era 2 there were significantly more patients with bilateral metastases, but with smaller sizes. Regarding the number of metastatic nodules, the authors observed more multinodular cases in Era 2 (26.3% vs. 19.9%) however the difference was not significant (p = 0.103). Moreover, patients received more neoadjuvant chemotherapy in Era 2.

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Hepatocellular carcinoma

Two hundred twenty-seven resections for Hepatocellular Carcinoma (HCC) were performed. In the HCC group, a comparison between eras was made showing in Era 2 significantly more minimally invasive surgeries and fewer transfusions, less necessity of ICU, and a shorter length of hospital stay (Table 4).

OS was 83.9%, 68.7%, and 52.8% at 1, 3, and 5 years, respectively. When comparing both eras, OS at 1, 3, and 5 years in Era 1 was 86.3%, 58.4%, and 40.7%, respectively; and in Era 2 OS was 90.4%, 67.9%, and 51.5% at 1, 3, and 5 years, respectively. OS was not different between eras (p = 0.069) (Fig. 3A).

Discussion

In the last two decades, liver resection has evolved from a high mortality complex procedure to a routine standardized operation increasingly employed. Liver resection is now established as the most effective treatment for selected patients with primary and secondary hepatic malignancy and benign diseases. This evolution is a result of the spreading of dedicated liver surgery units in a multidisciplinary environment with improvements in perioperative care leading to lower morbidity and mortality rates. The mortality decrease associated with the significant decrease in blood transfusion in oncologic liver surgery represents an advance in surgical care and impacts the indications for liver resection.25,26

In the last 20 years, the present group has performed 1409 liver resections experiencing the evolution of liver surgery. The main indications for liver resection were CRLM, HCC, liver cell adenoma, and intrahepatic cholangiocarcinoma. The authors have looked at the entire cohort of patients to evaluate the changes in the last two decades, and therefore as a subgroup analysis, we evaluated the most frequent indications for liver resection, CRLM, and HCC.

Looking at the present data, patients in Era 2 presented a higher BMI, and significantly more patients with bilateral metastases, but with smaller sizes. Regarding the number of metastatic nodules, the authors observed more multinodular cases in Era 2 (26.3% vs. 19.9%) however the difference was not significant (p = 0.103). Moreover, patients received more neoadjuvant chemotherapy in Era 2.

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Looking at the present data, patients in Era 2 presented a higher BMI, reflecting a world tendency. In fact, since 1980 the prevalence of obesity has increased twofold in more than 70 countries and has risen in most other countries.

Table 1
Preoperative and postoperative study population characteristics for patients submitted to liver resection (2000–2020).

| Variable                  | Characteristic | n (%)       |
|---------------------------|----------------|-------------|
| Sex                       | Female         | 737 (52.3)  |
|                           | Male           | 672 (47.7)  |
| Age                       | <70 years      | 1159 (82.3) |
|                           | ≥70 years      | 250 (17.7)  |
| BMI (Kg/m²)               | Mean (SD)      | 26.2 (4.6)  |
|                           | Median (min-max) | 25.6 (15.0–45.7) |
| ASA status                | I              | 293 (20.8)  |
|                           | II             | 984 (69.8)  |
|                           | III            | 129 (9.2)   |
|                           | IV             | 3 (0.2)     |
| Preoperative portal vein  | No             | 1372 (97.4) |
|                           | Yes            | 37 (2.6)    |
| Era                       | Era 1          | 333 (23.6)  |
|                           | Era 2          | 1076 (76.4) |
| Diagnosis                 | Colorectal liver metastases | 738 (52.4) |
|                           | Hepatocellular carcinoma | 227 (16.1) |
|                           | Other          | 444 (31.5)  |
| Surgical approach         | Open           | 986 (70.0)  |
|                           | Minimally invasive resection | 432 (30.0) |
| Type of resection         | Right hepatectomy | 277 (19.7) |
|                           | Left hepatectomy    | 143 (10.1)  |
|                           | Bisegmentectomy 2–3 | 154 (10.9) |
|                           | Bisegmentectomy 6–7 | 66 (4.7)   |
|                           | Right extended   | 30 (2.1)    |
|                           | Left extended    | 4 (0.3)     |
|                           | Other anatomical resections | 187 (13.3) |
|                           | Wedge resections  | 548 (38.9)  |
| Extension of resection    | Major          | 473 (33.6)  |
|                           | Minor          | 936 (66.4)  |
| Two-stage hepatectomy     | Yes            | 37 (2.6)    |
| Pringle maneuver          | No             | 878 (64.0)  |
|                           | Half-Pringle    | 198 (14.4)  |
|                           | Pringle        | 296 (21.6)  |
| Blood transfusion         | No             | 1156 (82.0) |
|                           | Yes            | 253 (18)    |
| Need for postoperative ICU| No             | 244 (17.3)  |
|                           | Yes            | 1165 (82.7) |
| Length of hospital stay   | Mean (SD)      | 8.9 (9.3)   |
|                           | Median (min-max) | 6 (0–99)   |
| Perioperative morbidity    | 0–II           | 1202 (85.4) |
|                           | III–IV         | 148 (10.5)  |
| Clavien                   | V              | 59 (4.2)    |

SD, Standard Deviation; BMI, Body Mass Index; ASA, American Society of Anesthesiologists classification; Era 1 (2000–2010); Era 2 (2011–2020); ICU, Intensive Care Unit.

* 37 missing patients.
Table 2
Liver resections (n = 1409): comparison between eras.

| Variable                        | Total     | Era 1 n = 333 | Era 2 n = 1076 | p-value |
|---------------------------------|-----------|---------------|----------------|---------|
| Sex                             |           | n (%)         | n (%)          |         |
| Female                          | 737       | 184 (55.3)    | 553 (51.4)     | 0.218   |
| Male                            | 672       | 149 (44.7)    | 523 (48.6)     |         |
| Age                             |           |               | n (%)          |         |
| < 70 years                      | 1159      | 274 (82.3)    | 885 (82.2)     | 0.989   |
| ≥ 70 years                      | 250       | 59 (17.7)     | 191 (17.8)     |         |
| BMI (Kg/m²)                     |           |               | n (%)          |         |
| Mean (min–max)                  | 25.6 (15.6–41.2) | 25.4 (15.0–45.7) | 0.013   |
| Median (SD)                     | 25.1 (4.67) | 25.9 (4.65)   |               |         |
| ASA status                      |           | n (%)         | n (%)          |         |
| I                               | 293       | 72 (24.2)     | 221 (20.5)     | 0.939   |
| II                              | 984       | 237 (75.8)    | 747 (70.8)     |         |
| III                             | 129       | 22 (6.6)      | 107 (9.9)      |         |
| IV                              | 3         | 2 (0.6)       | 1 (0.1)        |         |
| Prooperative portal vein embolization |           | n (%)         | n (%)          |         |
| No                              | 1372      | 330 (99.1)    | 1042 (96.8)    | 0.029   |
| Yes                             | 37        | 3 (0.9)       | 34 (3.2)       |         |
| Diagnosis                       |           | n (%)         | n (%)          |         |
| Colorectal metastases           | 738       | 167 (50.2)    | 571 (53.1)     | 0.095   |
| Hepatocellular carcinoma        | 227       | 67 (20.1)     | 160 (14.9)     |         |
| Other                           | 444       | 99 (29.7)     | 345 (32.0)     |         |
| Surgical approach               |           | n (%)         | n (%)          |         |
| Open                            | 986       | 250 (81.7)    | 696 (64.7)     | <0.001  |
| Minimally invasive              | 423       | 132 (41.9)    | 380 (35.3)     | <0.001  |
| Right hepatectomy               | 277       | 95 (26.8)     | 182 (16.9)     | <0.001  |
| Left hepatectomy                | 143       | 36 (10.8)     | 107 (9.9)      |         |
| Bisegmentectomy 2–3             | 154       | 36 (10.8)     | 118 (11.0)     |         |
| Bisegmentectomy 6–7             | 66        | 14 (4.2)      | 52 (4.8)       |         |
| Other anatomical resections      | 221       | 68 (20.5)     | 153 (10.9)     |         |
| Wedge resection                 | 548       | 84 (25.2)     | 464 (43.1)     |         |
| Extension of resection          |           | n (%)         | n (%)          |         |
| Major                           | 473       | 149 (44.7)    | 324 (30.1)     | <0.001  |
| Minor                           | 936       | 184 (55.3)    | 752 (69.9)     |         |
| Two-stage hepatectomy           |           | n (%)         | n (%)          |         |
| No                              | 1372      | 322 (96.7)    | 1050 (97.6)    | 0.376   |
| Yes                             | 37        | 11 (3.3)      | 26 (2.4)       |         |
| Use of Pringle maneuver<sup>a</sup> |       | n (%)         | n (%)          |         |
| No                              | 878       | 230 (74.2)    | 648 (61.0)     | <0.001  |
| Half-Pringle                    | 198       | 36 (11.6)     | 162 (15.3)     |         |
| Pringle                         | 296       | 44 (14.2)     | 252 (23.7)     |         |
| Blood transfusion               |           | n (%)         | n (%)          |         |
| No                              | 1156      | 227 (68.2)    | 929 (86.3)     | <0.001  |
| Yes                             | 253       | 106 (31.8)    | 147 (13.7)     |         |
| Need for ICU                    |           | n (%)         | n (%)          |         |
| No                              | 244       | 27 (8.1)      | 217 (20.2)     | <0.001  |
| Yes                             | 1165      | 306 (91.9)    | 859 (79.8)     |         |

(continued)
In Era 2, more parenchyma-sparing resections were employed. These techniques are an important advance in oncologic liver surgery because they improve the safety of the procedure by decreasing the risk of postoperative liver failure. Moreover, in patients with CRLM, it allows a novel resection in cases of recurrence. In this context, the authors have performed significantly fewer major liver resections, especially fewer right hepatectomies in Era 2.

After the beginning of the quality program in liver surgery, the authors noticed that patients with CRLM submitted to neoadjuvant oxaliplatin-based chemotherapy needed more blood transfusions. This fact

| Variable                             | Era 1 (n = 167) | Era 2 (n = 571) | p-value |
|--------------------------------------|-----------------|-----------------|---------|
| Length of hospital stay Mean (min-max) | 9.7 (0.71)      | 8.7 (0.99)      | <0.001  |
| Perioperative morbidity Severe        | 207 (17.1)      | 150 (13.9)      | 0.152   |
| Perioperative mortality Yes           | 1350 (96.1)     | 1030 (95.7)     | 0.768   |

SD, Standard Deviation; BMI, Body Mass Index; ASA, American Society of Anesthesiologists classification; Era 1 (2000–2010); Era 2 (2011–2020); ICU, Intensive Care Unit.

Table 3
Comparison between eras (colorectal liver metastases).

| Variable                                | Era 1 (n = 167) | Era 2 (n = 571) | p-value |
|-----------------------------------------|-----------------|-----------------|---------|
| Sex                                     |                 |                 |         |
| Female                                  | 80 (47.9%)      | 269 (47.1%)     | 0.856   |
| Male                                    | 87 (52.1%)      | 302 (52.9%)     |         |
| Age                                      |                 |                 |         |
| < 70 years                               | 130 (77.8%)     | 475 (83.2%)     | 0.114   |
| ≥ 70 years                               | 37 (22.2%)      | 96 (16.8%)      |         |
| BMI (Kg/m²) Mean (min-max)               | 25.6 (16.9–37.3)| 26.3 (15–41.8) | 0.107   |
| BMI (Kg/m²) Median (SD)                  | 25 (4.25)       | 25.0 (4.47)     |         |
| ASA status I                            | 29 (17.4%)      | 95 (16.6%)      | 0.058   |
| ASA status II                           | 133 (79.6%)     | 428 (75.0%)     |         |
| ASA status III                          | 5 (3.0%)        | 48 (8.4%)       |         |
| Largest tumor size Mean (min-max)        | 4.67 (0.40–23.5)| 3.29 (0.2–16.1)| <0.001  |
| Neoadjuvant chemotherapy No              | 82 (51.6%)      | 125 (22.8%)     | <0.001  |
| Neoadjuvant chemotherapy Yes             | 77 (48.4%)      | 424 (77.2%)     |         |
| Preoperative portal vein embolization No | 165 (98.8%)     | 549 (96.1%)     | 0.133   |
| Surgical approach Open                  | 157 (94.0%)     | 429 (75.1%)     | <0.001  |
| Surgical approach Minimally invasive    | 10 (6.0%)       | 142 (24.9%)     |         |
| Type of resection Right hepatectomy     | 56 (33.5%)      | 96 (16.8%)      | <0.001  |
| Left hepatectomy                        | 19 (11.4%)      | 41 (7.2%)       |         |
| Bisegmentectomy 1–3                     | 14 (08.4%)      | 43 (07.5%)      |         |
| Bisegmentectomy 4–7                     | 8 (04.8%)       | 29 (05.1%)      |         |
| Other anatomical resections             | 34 (20.3%)      | 83 (14.5%)      |         |
| Wedge resection                         | 36 (21.6%)      | 279 (48.9%)     |         |
| Extension of resection Major            | 85 (50.9%)      | 157 (27.5%)     | <0.001  |
| Extension of resection Minor            | 82 (49.1%)      | 414 (72.5%)     |         |
| Two-stage hepatectomy No                | 157 (94.0%)     | 546 (95.6%)     | 0.408   |
| Two-stage hepatectomy Yes               | 10 (06.0%)      | 25 (04.4%)      |         |
| Use of Pringle maneuver No              | 111 (73.0%)     | 348 (62.1%)     | 0.035   |
| Use of Pringle maneuver Yes             | 12 (07.9%)      | 76 (13.6%)      |         |
| Blood transfusion No                    | 109 (65.3%)     | 504 (88.3%)     | <0.001  |
| Blood transfusion Yes                   | 58 (34.7%)      | 67 (11.7%)      |         |
| Need for ICU No                         | 12 (07.2%)      | 126 (22.1%)     | <0.001  |
| Need for ICU Yes                        | 155 (92.8%)     | 445 (77.9%)     |         |
| Perioperative morbidity Severe          | 23 (13.8%)      | 74 (13.0%)      | 0.784   |
| Perioperative morbidity Yes             | 144 (86.2%)     | 497 (87.0%)     |         |
| Perioperative mortality Yes             | 161 (96.4%)     | 547 (95.8%)     | 0.725   |

SD, Standard Deviation; BMI, Body Mass Index; ASA, American Society of Anesthesiologists classification; Era 1 (2000–2010); Era 2 (2011–2020); ICU, Intensive Care Unit.

* 26 missing patients.
As a result of a better follow-up and surveillance for patients with oxaliplatin,29 leading to more bleeding during liver transection. Consequently, in the last years (Era 2), the authors have employed more intermittent pedicle clamping (Pringle maneuver) during parenchyma transaction resulting in lower transfusion rates. For non-anatomical resections, especially on the right lobe of the liver, the authors employed a selective pedicle clamping (half-Pringle) as reported elsewhere.30 From an oncological point of view, the avoidance of blood transfusion impacts positively because many studies showed a negative impact on survival for patients who received a transfusion.25,31

Laparoscopic liver resections have reached increasing acceptance for the treatment of benign and malignant liver lesions over the last two decades.32,33 It offers better perioperative outcomes with less intraoperative bleeding and lower rates of postoperative complications without compromising oncologic results. Moreover, due to the low invasiveness, results in better recovery and shortening of hospital stay.32 In the present series, the rate of minimally invasive surgeries in the last era presented a threefold increase (12.9% to 35.3%). Most specialized hepatobiliary centers adopted the minimally invasive approach as reported in recent South American and European surveys where the proportion between minimally invasive and open liver resection ranged from 10% to 29%.34,35

In this series, a decrease in ICU needs and a shorter hospital stay are a result of multiple factors such as better patient selection and perioperative care, a parenchyma sparing approach, and the increasing use of minimally invasive surgery. These factors, associated with a lower bleeding rate observed in the last decade, can also lead to a cost reduction. The mortality rate (4.2%) observed in the present study did not change between eras and is in accordance with other large series worldwide.2,6

In this study, the authors focused on CRLM and HCC, the main indications for liver resection in our experience and worldwide. All CRLM cases were discussed in a multidisciplinary meeting, and almost all patients were subjected to perioperative oxaliplatin-based systemic chemotherapy. In Era 1 chemotherapy was preferably delivered after liver resection. Neoadjuvant chemotherapy is mostly employed in patients with unfavorable prognostic factors to eliminate micrometastatic disease and understand tumor biology by evaluating response rates.36,37 In Era 2 when more patients with multiple (not significantly different) and bilateral diseases were treated, 77.2% were submitted to preoperative chemotherapy, significantly more than in Era 1 (48.4%). As a result of a better follow-up and surveillance for patients with colorectal cancer, and the use of preoperative systemic treatment, the authors observed in Era 2 patients with smaller tumor sizes.

In the last years (Era 2), the authors adopted the concept of parenchyma sparing resection for CRLM with significantly more minor and wedge resections. Mise et al.38 and Torzilli39 have shown that preserving liver parenchyma does not increase local recurrence. Moreover, an increase in survival was observed in patients submitted to parenchyma sparing resection due to the possibility of performing new treatments in case of recurrence (re-hepatectomy or ablation).

There was a significant increase in minimally invasive procedures when comparing Eras. For CRLM this increase was from 6% to 24.9% in Era 1 and Era 2, respectively. Indeed, the Oslo group has reported the first prospective randomized trial comparing open and laparoscopic resection of CRLM and showed less postoperative complications and shorter hospital stay in the laparoscopic group.40

The 5-year survival following CRLM resection was 40.7% in Era 1 and 51.5% in Era 2. This increase, despite not being significant, reflects a better staging, the evolution of chemotherapy regimens, and the use of modern surgical strategies (parenchyma sparing, staged liver resections, portal vein embolization, ALPPS). It should be noted that in Era 2 the authors operated on patients with more advanced disease (more nodules and bilateral disease), and despite this, the results improved, showing an advance in the selection and treatment strategies for CRLM.

Despite the debate between resection versus liver transplantation, in the present context of a lack of donors and a long waiting list time, HCC resection became an excellent curative option, especially in patients with preserved liver function. Moreover, resection can provide treatment for patients not candidates for transplant. All cases were discussed in a multidisciplinary meeting with hepatologists, oncologists, transplant surgeons, radiologists, and liver surgeons to define the best treatment strategy.

From all indications of laparoscopic liver resection, patients with HCC are those who benefit most from the minimally invasive approach.41-43 In addition to the benefits already mentioned, a lower incidence of postoperative ascites was consistently observed following the minimally invasive resection in patients with chronic liver disease.19-44 This is probably a consequence of the preservation of the abdominal wall and umbilical ligament collateral venous circulation. Moreover, in cases of recurrence, salvage transplantation can be more easily performed following laparoscopic liver resection when compared to open surgery due to fewer adhesions.45
There was also a significant increase in minimally invasive procedures for HCC, from 20.9% to 63% in Era 1 and Era 2, respectively. The increase in the minimally invasive approach resulted in fewer transfusions, a lower necessity of ICU, and shorter hospital stay.

The 5-year survival following HCC resection was 47.4% in Era 1 and 56.8% in Era 2. Despite not being significant, the improvement in survival rates was probably due to a better staging (modern imaging techniques), and a rigorous selection of patients.

The present study’s results are in accordance with the most important specialized hepatobiliary groups in the world. The multidisciplinary approach has provided much better results than those observed in the past, allowing an expansion of the limits both in the indication and in liver surgery itself. In the last decade, significantly more minimally invasive surgeries were done, and less bleeding and better perioperative results were observed.

Surgery remains the cornerstone for the curative treatment of primary and metastatic liver tumors but, to achieve excellent results, it is recommended that this complex procedure should be performed in a multidisciplinary environment.

### Authors’ contributions

Paulo Herman: Conceived the idea and wrote the paper.

Gilton Marques Fonseca: Collected data, performed the statistical analysis, and helped in the paper writing.

Fabricio Ferreira Coelho: Reviewed and made suggestions during the paper writing.

Jaime Arthur Pirolla Kruger: Collected data and reviewed paper writing.

Fabio Ferrari Makdissi: Reviewed and made suggestions during the paper writing.

Vagner Birk Jeismann: Collected data, performed the statistical analysis, and helped in the paper writing.

Luiz Augusto Carneiro De Oliveira: Reviewed the paper.

Albuquerque: Reviewed the paper.

Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg 2002;236(4):397–406. discussion 7.

### Conflicts of interest

The authors declare no conflicts of interest.

### References

1. Foster JH, Berman MM. Solid liver tumors. Major Probl Clin Surg 1977;22:1–342.

2. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg 2002;236(4):397–406. discussion 7.
3. Palavecino M, Kishi Y, Chan YS, Brown DL, Gottumukkala VN, Lichtiger B, et al. Two-surgeon technique of parenchymal transection contributes to reduced transfusion rate in patients undergoing major hepatectomy: analysis of 1,557 consecutive liver resections. Surgery 2010;147(1):40–8.

4. Kamitani T, Nakanishi K, Yokoo H, Kamachi H, Tabara M, Yasamitsa K, et al. Perioperative management of hepatic resection toward zero mortality and morbidity: analysis of 793 consecutive cases in a single institution. J Am Coll Surg 2010;211(4):443–9.

5. Kruger JAP, Fonseca GM, Maddini FF, Jeismann VB, Coelho FF, Herman P. Evolution in the surgical management of colorectal liver metastases: propensity score matching analysis (PSM) on the impact of specialized multidisciplinary care across two institutional eras. J Surg Oncol 2018;118(1):50–60.

6. Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, et al. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. Ann Surg 2004;240(4):698–708, discussion 10.

7. Andres A, Majno PE, Morel P, Rubbia-Brandt L, Giostra E, Gervaz P, et al. Improved long-term outcome of surgery for advanced colorectal liver metastases: reasons and implications for management on the basis of a severity score. Ann Surg Oncol 2008;15(1):34–43.

8. Adam R, De Gramont A, Fijtenas J, Guthrie A, Kokado N, Kunstlinger F, et al. The oncysurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. Oncologist 2012;17(10):1225–39.

9. House MG, Ito H, Gonen M, Fong Y, Allen PJ, DeMatteo RP, et al. Survival after hepatic resection for metastatic colorectal cancer: trends in outcomes for 1,600 patients during two decades at a single institution. J Am Coll Surg 2010;210(5):544–52, 52-S.

10. Kopetz S, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol 2009;27(22):3677–83.

11. Jaeck D, Oussoultzoglou E, Rosso E, Greget M, Weber JC, Bachellier P. A two-stage hepatectomy procedure combined with portal vein embolization to achieve curative resection for initially unresectable multiple and bilobar colorectal liver metastases. Ann Surg 2004;240(6):1037–49, discussion 49–51.

12. Madoff DC, Ostbo BC, Schadde E, Gaba RC, Bennink RJ, van Gulik TM, et al. Improving the safety of major resection for hepatobiliary malignancy: portal vein embolization and recent innovations in liver regeneration strategies. Curr Oncol Rep 2020;22(6):59.

13. Adam R, Laurent A, Aouzoul D, Castaing D, Bismuth H. Two-stage hepatectomy: a planned strategy to treat irresectable liver tumors. Ann Surg 2000;232(6):777–85.

14. Siversgaard K, Larsen LP, Sorensen M, Kramer S, Schlander S, Amanaciuc N, et al. Diagnostic accuracy of CE-CT, MRI and FDG PET/CT for detecting colorectal cancer liver metastases in patients considered eligible for hepatic resection and/or local ablation. Eur Radiol 2018;28(11):4735–47.

15. Adam R, Delvart V, Gaba C, Aouzoul D, Cestaing D, Azoulay A, et al. Rescue surgery for unresectable colorectal liver metastases downstreamed by chemotherapy: a model to predict long-term survival. Ann Surg 2004;240(4):644–57, discussion 57–8.

16. Kawaguchi Y, Kopetz S, Panettieri E, Ihwang H, Wang X, Cao HST, et al. Improved survival over time after resection of colorectal liver metastases and clinical impact of multiple intervention tests in patients with metastatic colorectal cancer. J Gastrointest Surg 2021.

17. Adam R, Wicherts DA, de Haan RJ, Aliaia T, Levin P, Paulus B, et al. Complete pathologic response after preoperative chemotherapy for colorectal liver metastases: myth or reality? J Clin Oncol 2008;26(10):1635–41.

18. Blazer 3rd DG, Kishi Y, Maru DM, Kopetz S, Chun YS, Overman MJ, et al. Pathologic response to preoperative chemotherapy: a new outcome end point after resection of hepatic colorectal metastases. J Clin Oncol 2008;26(3):5344–51.

19. Herman P, Lopes Fde L, Kruger JA, Fonseca GM, Jeismann VB, Perini MV, et al. Parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. Ann Surg 2008;247(1):109–17.

20. Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. Br J Surg 2007;94(3):274–86.

21. Herman P, Perini MV, Coelho F, Saad W, D’Albuquerque LA. Half-Pringle maneuver: a useful tool in laparoscopic liver resection. J Laparoendosc Adv Surg Tech A 2010;20(1):35–37.

22. Schiesser TS, Rentsch M, Kasparek MS, Frenes K, Jauch KW, Thaler WE. Impact of perioperative allogeneic red blood cell transfusion on recurrence and overall survival after resection of colorectal liver metastases. Dis Colon Rectum 2015;58(1):74–82.

23. Goelho FF, Kruger JA, Fonseca GM, Araujo RL, Jeismann VB, Perini MV, et al. Minimally invasive surgery: experience based guidelines. World J Gastrointest Surg 2016;8(1):1–26.

24. Wakabayashi G, Cherqui D, Geller DA, Buell JF, Kaneko H, Han HS, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. Ann Surg 2015;261:619–29, United States.

25. Albrecht J, Belli G, Boni L, Cillo U, Ettorre G, De Carlis L, et al. Italian experience in minimally invasive liver surgery: a national survey. Updates Surg 2015;67(2):129–40.

26. Pabol J, Clara Sanchez R, Salceda J, Mauretta I, Schelotto PB, Pierin L, et al. Laparoscopic resection of liver: a South American experience with 2887 cases. World J Surg 2020;44(11):3868–74.

27. Nordlinger B, Sorbye H, Gillemot D, Poston JG, Schlag PM, Rougier P, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (FORTIC): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 2013;14(12):1208–15.

28. Cremolini C, Schiirripa M, Antoniotti C, Moretto R, Salvatore L, Mani G, et al. First-line chemotherapy for mCRC – a review and evidence-based algorithm. Nat Rev Clin Oncol 2015;12(10):607–19.

29. Mise Y, Alobia TA, Brudvik KW, Schwarz L, Vauthey JN, Conrad C. Parenchymal-sparing hepatectomy in colorectal liver metastasis improves salvageability and survival. Ann Surg 2016;263(1):146–52.

30. Torzilli G. Parenchyma-sparing vessel-guided major hepatectomy: nonsense or new paradigm in liver surgery? Br J Surg 2021;108(2):109–11.

31. Fretland A, Dagenborg U, Bjornevold GMW, Kazaryan AM, Kristiansen R, Fagerlund MW, et al. Laparoscopic versus open resection for colorectal liver metastases: the OSLO-COMET randomized controlled trial. Ann Surg 2018;267(2):199–207.

32. Igiuchi S, Hidaka M, Kugiyama T, Suyama A, Hara T, Nakagawa K, et al. Changes in the role and mode of liver resection for hepatocellular carcinoma over 20 years: a single-center analysis. World J Surg 2021;45(1):152–8.

33. Isbellka C, Nautil JC, Barber L, Schwarz L, Lim C, Laurent A, et al. Influence of surgical approach and quality of resection on the probability of cure for early-stage HCC occurring in cirrhosis. JHEP Rep 2020;2(6):100153.

34. Tsilimigras DJ, Sahara K, Moris D, Mehta R, Paredes AZ, Ratti F, et al. Assessing textbook outcomes following liver surgery for primary liver cancer over a 12-year time period at major hepatobiliary centers. Ann Surg Oncol 2020;27(9):3318–27.

35. Famularo S, Donadon M, Cipriani F, Arditto F, Iaria M, Carisimi P, et al. The impact of postoperative ascites on survival after surgery for hepatocellular carcinoma: a national study. J Gastrointest Surg 2021.

36. Rhu J, Kim JM, Choi GS, Kwon CHD, Jo JH, Soubrane O. Laparoscopy of hepatocellular carcinoma is helpful in minimizing intra-abdominal adhesion during salvage transplantation. Ann Surg Treat Res 2018;95(5):258–65.

37. Adam R, Kitano Y. Multidisciplinary approach of liver metastases from colorectal cancer. Ann Gastroenterol Surg 2019;3(1):50–6.