Approach to synchronous liver metastases from colorectal carcinoma - results from a Portuguese reference center

Abordagem das metástases hepáticas síncronas de carcinoma colorretal – resultados de um centro de referência

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ABSTRACT
About 15%-25% of patients with colorectal cancer, have synchronous liver metastases. The best surgical approach for the patients with asymptomatic primary colorectal tumor and

synchronous liver metastases is still the subject of much debate. We aimed to evaluate the perioperative and long-term results as well as to identify possible prognostic factors of the two strategies: liver- first and synchronous resection. Observational, retrospective study, which included patients with synchronous liver metastases from colorectal cancer, who underwent liver surgery between January 2016 and December 2021, in a Portuguese reference center. Patients were divided into two groups according to the therapeutic approach (synchronous resections vs Liver First) and into three groups according to the hepatic tumor burden (single liver lesion versus more than three liver lesions versus bilobar lesions). To determine the overall and disease-free survival, Kaplan-Meier curves and the log-rank test were performed and, to identify factors with an impact on the prognosis, a univariate and multivariate analysis were performed with the application of Cox regression (significance of 5%). Among the 46 patients included, 54,4% underwent the liver-first approach and 21 patients (45.7%) underwent simultaneous resection. The liver-first group had a greater number of patients with primary rectal tumor (84% vs.14.3%; p<0.001), with more than 3 hepatic lesions (56% vs.14%; p=0.004) and with more extensive hepatic resection. As for postoperative morbimortality, no statistically significant difference was observed between the two approaches (*p*=0.514). The median overall survival was similar even when considering the hepatic tumor burden (35.0 months (95%CI 15.91- 54.09) in the liver-first group vs. 48.0 months (95%CI 21.69-74.96) in the synchronous resection group; p=0.145). The same was observed for the median disease-free survival (16.0 months (95% CI 0-32.7) vs. 23.0 months (95% CI 16.3-29.7) p=0.651, respectively). The two strategies showed similar morbidity. No statistically significant difference was observed with regard to overall and disease-free survival even when the hepatic tumor burden was considered. One-year and three-year survival were also similar. However, it should be stressed that, the choice of the surgical approach for each group did not took into account the hepatic tumor burden, which we believe it is essential in choosing the best surgical approach.The existence of a multidisciplinary team is fundamental for the therapeutic success of these patients.

Keywords: colorectal neoplasm, neoplasm metastasis, surgical oncology.

RESUMO

Cerca de 15% a 25% dos pacientes com câncer colorretal apresentam metástases hepáticas sincrônicas. A melhor abordagem cirúrgica para os pacientes com tumor colorretal primário assintomático e metástases hepáticas sincrônicas ainda é objeto de muito debate. Nosso objetivo foi avaliar os resultados perioperatórios e de longo prazo, bem como identificar possíveis fatores prognósticos das duas estratégias: ressecção do fígado primeiro e ressecção sincrônica. Estudo observacional, retrospectivo, que incluiu pacientes com metástases hepáticas sincrônicas de câncer colorretal, submetidos à cirurgia hepática entre janeiro de 2016 e dezembro de 2021, em um centro de referência português. Os pacientes foram divididos em dois grupos de acordo com a abordagem terapêutica (ressecções síncronas vs Liver First) e em três grupos de acordo com a carga tumoral hepática (lesão hepática única versus mais de três lesões hepáticas versus lesões bilobares). Para determinar a sobrevida global e livre de doença, foram realizadas curvas de Kaplan-Meier e o teste log-rank e, para identificar fatores com impacto no prognóstico, foi realizada uma análise univariada e multivariada com a aplicação da regressão de Cox (significância de 5%). Entre os 46 pacientes incluídos, 54,4% foram submetidos à abordagem do fígado primeiro e 21 pacientes (45,7%) foram submetidos à ressecção simultânea. O grupo fígado-primeiro teve um número maior de pacientes com tumor retal primário (84% vs. 14,3%; p<0,001), com mais de três lesões hepáticas (56% vs. 14%; p=0,004) e com ressecção hepática mais extensa. Quanto à morbimortalidade pós-operatória, não foi observada diferença estatisticamente significativa entre as duas abordagens (p=0,514).

A sobrevida global mediana foi semelhante mesmo quando se considerou a carga tumoral hepática (35,0 meses (IC95% 15,91-54,09) no grupo fígado-primeiro vs. 48,0 meses (IC95% 21,69-74,96) no grupo ressecção sincrônica; p=0,145). O mesmo foi observado para a mediana da sobrevida livre de doença (16,0 meses (IC 95% 0-32,7) vs. 23,0 meses (IC 95% 16,3-29,7) p=0,651, respectivamente). As duas estratégias apresentaram morbidade semelhante. Não foi observada diferença estatisticamente significativa com relação à sobrevida global e livre de doença, mesmo quando a carga tumoral hepática foi considerada. A sobrevida em um ano e em três anos também foi semelhante. No entanto, vale ressaltar que a escolha da abordagem cirúrgica para cada grupo não levou em consideração a carga tumoral hepática, o que acreditamos ser essencial para a escolha da melhor abordagem cirúrgica, sendo fundamental a existência de uma equipe multidisciplinar para o sucesso terapêutico desses pacientes.

Palavras-chave: neoplasia colorretal, metástase de neoplasia, oncologia cirúrgica.

1 INTRODUCTION

Colorectal carcinoma (CRC) represents the fourth most common neoplasm in the world, with an incidence of 19.5% and a mortality of 9%. (1) About 15%-25% of patients have synchronous liver metastases from colorectal carcinoma (CRCLM), (2–6) and 50% develop CRCLM over the natural history of the disease. The management of patients with CRCLM requires a multidisciplinary team that includes radiologists, oncologists, surgeons and anatomopathologists. (3,6,7) Currently, several therapeutic strategies are available (3,6,8–11) for the management of patients with isolated CRCLM, among which locoregional approaches are included, which can be considered an alternative to systemic or carried out in combination with the same. (9,10)

Locoregional treatments include surgical resection, local tumor ablation (6,8–12) (currently, radiofrequency ablation (RFA) is performed more frequently due to its greater efficacy in treating a small number of liver metastases (LM) , up to five metastases, and of smaller size (up to 3 cm), with fewer post-intervention complications and with excellent local tumor control), chemoembolization (9,10) the combination of ablation interventions with surgical resection (which can be carried out to preserve the liver parenchyma) and either internal radiotherapy, selective internal radiotherapy (SIRT), or external, stereotactic external radiotherapy (SERT). (9,10) The latter may constitute a non-invasive treatment for LM larger than 3 cm, even in situations of higher surgical risk. In well-selected patients, liver transplantation may also be considered. (6,8–10,13) The existence of these different therapeutic modalities allows for a more personalized treatment; however, surgical resection remains the only possibility of cure in these patients. (2,3,5,8,13,14)

Regarding surgical resection, different approaches have been proposed for the treatment of patients with synchronous CRCLM (2,3,5,8-10) such as the classic or traditional approach (CA), the liver-first approach (LF) and synchronous resection (SR). (2,3,5,8,13,14) The CA involves resection of the primary colorectal tumor followed by chemotherapy (CT) and, for primary rectal tumors, radiotherapy (RT) is also associated. (5,8,14) LM resection is performed approximately three months after primary tumor resection (if they remain resectable). (5,8,14) The main arguments in favor of CA include control of the primary tumor and its possible complications (occlusion, hemorrhage, perforation and source of metastases). (5,8,14) However, the main disadvantage of this approach is the possibility that the LM may become unresectable, due to disease progression. (5) The LF approach was proposed by Mentha et al. in 2006 (5,8,15) and corresponds to an inverse strategy to CA. The LF strategy comprises three to six cycles of neoadjuvant chemotherapy (NACT) followed by liver resection. (5,8) Between the liver and primary tumor resections, CT is performed (and possibly RT for primary rectal tumors) and only later is the primary colorectal tumor resected, 8 to 12 weeks after NACT. (5.8)

In fact, the current cytotoxic drugs based on oxaliplatin and irinotecan (9,10) in combination with specific agents (against the epidermal growth factor receptor or the vascular endothelial growth factor) have improved the tumor response and the survival of patients with CRC. (5,9,10) The advantages of the LF strategy lie in the fact that it prioritizes the removal of LM, which are more relevant in terms of prognosis (3,5,14) and that it facilitates the inclusion of RT in locally and advanced primary rectal tumors. (5,14) The main argument against this approach is the possibility that, in the period of time that elapses from NACT and resection of the LM until the resection of the primary colorectal tumor, complications of the latter may arise. (5,8,14) The SR approach consists of the removal, in a single procedure or within a short period of time, of the primary colorectal tumor and the respective synchronous LM. This resection can be performed with or without inclusion of NACT, however, after it, CT is performed (with additional RT for primary rectal tumors). (5)

This approach has the main advantage of being able to simultaneously treat the primary tumor and the synchronous LM (3,5,8) and the main disadvantage of being the possibility of increasing morbidity and mortality by associating several procedures in a single operative time. (5)

However, the best surgical approach for patients with an asymptomatic primary colorectal tumor and synchronous LM is still the subject of much debate (2,5,7,16) particularly as to which of the LF versus SR approaches is the most indicated for each patient. (2,5,7,16) With this study, we intended to evaluate the results of our center, both perioperatively and in

the long term, in the approach to synchronous liver metastases in patients with asymptomatic primary tumor, comparing the two aforementioned therapeutic approaches, as well as identifying possible prognostic factors.

2 METHODS

2.1 STUDY DESIGN AND SETTING

This is a retrospective study, which included patients with synchronous CRCLM who underwent liver surgery with curative intent between 2016 and 2021 in the general surgery department of the Centro Hospitalar e Universitário de Coimbra (CHUC-6866PCA). This is one of the largest cancer centers in Portugal, serving a geographical area of about two million inhabitants

2.2 DATA SOURCE AND ETHICAL CONSIDERATIONS

We used anonymous data collected from the electronic health records since protocol implementation.

Due to the fact that there was a high mortality rate in the target population, a large number of data and an extended time interval, we requested the waiver of informed consent (according to Law no. 12/2005 of January 26 (Art. 19 nº6)) and on December 2, 2022, a favorable opinion was issued for the development of this study by the Ethics Committee of CHUC with the exemption of obtaining informed consent. This study was in compliance with ethical and legal principles, namely, with the recommendations of the Declaration of Helsinki 2013.

2.3 COHORT

Of the 788 patients with CRCLM who underwent liver surgery at the general surgery service at CHUC over the past 30 years, 229 patients underwent liver surgery between January 2016 and December 2021. The latter were subjected to inclusion and exclusion criteria in order to constitute the sample of this study.

Patients were included in this study: 1) synchronous CRCLM, that is, with a maximum of 6 months of interval between the diagnosis of the primary tumor and the detection of LM and 2) submitted to the LF approach or SR, between January 2016 and December 2021, at the general surgery department of CHUC. Patients were excluded from this study: 1) who underwent liver resection for metachronous CRCLM, ie, with an interval greater than 6 months

between the diagnosis of the primary tumor and the detection of LM; 2) submitted to CA; 3) patients with incomplete information in the clinical file.

2.4 DATA COLLECTION AND SAMPLE SUBDIVISION

Data collection was carried out by consulting the CHUC general surgery department database and the patients' electronic and/or physical files. The respective data of interest for the study were entered into a Microsoft Excel sheet (version 2208) irreversibly anonymized, using an identification code generated for the purpose through sequential numbering.

The variables considered were age (in years), gender, location of the primary tumor (rectum, right colon, left colon), CEA value at diagnosis (cutoff of 200 ng/mL), postoperative complications (Clavien-Dindo classification), the TN staging / AJCC classification, 8th edition, the presence of mutation in the *KRAS* gene, the characterization of the LM (single or multiple, the size of the largest lesion, the lobar distribution (uni or bilobar) and the margin of surgical resection), the presence of extrahepatic disease at the time of diagnosis (lung and lymph nodes). The use of neoadjuvant therapies (CT, CRT and/or RT) and adjuvants, immunotherapy with monoclonal antibodies, the date of the patient's last contact with healthcare or the date of death) and the date of diagnosis of the recurrence were also considered (if applicable).

With these data, the 46 patients included in the study were divided into two groups according to the therapeutic approach to which they were submitted (LF or SR) and into three groups according to liver tumor burden (single liver lesion versus more than three liver lesions, regardless of whether they were unilobar or bilobar, versus bilobar lesions). Synchronous resection was considered whenever the primary tumor and the liver lesion were excised in the same operative time.

2.5 STATISTICAL ANALYSIS

Qualitative variables were described through their absolute and relative frequency and compared between groups using Fisher's exact test. Quantitative variables were described by mean and standard deviation and compared by Student's t-test for 2 independent samples after verification of normality or symmetry of distributions. The Shapiro-Wilk test was applied to assess the adjustment to a normal distribution in relation to the variables age and number of cycles, always verifying the adjustment of the sample distribution to a normal distribution, with the exception of the number of cycles in the LF group. However, this variable was symmetric in this group, so the t-Student test was applied.

The determination of the Overall Survival (OS), defined as the time, in months, elapsed between the surgical intervention and the death of the patient and the Disease-Free Survival (DFS), defined as the time, in months, elapsed between the surgical intervention and detection of tumor recurrence was performed using Kaplan-Meier curves and the log-rank test for comparison between different therapeutic approaches (LF versus RS). To identify possible factors with an impact on the prognosis, a univariate and multivariate analysis was carried out with the application of Cox regression. The analysis was performed using SPSS, version 27, and analyzed at a significance level of 5%.

3 RESULTS

3.1 COHORT CHARACTERISTICS

We included 46 patients in this study, 25 patients (54.3%) were part of the LF group and 21 patients (45.7%) were part of the SR group. In both groups, the male gender represented the majority of patients operated (19 patients (76%) in the LF group vs. 16 patients (76.2%) in the SR group; p=1.000). The two groups showed a statistically significant difference regarding mean age (60.7 + 8.6 years for the LF group vs. 67.7 + 10.0 years for the SR group; p=0.014).

3.2 PRIMARY TUMOR LOCATION, TN/AJCC STAGING, EXTRAHEPATIC DISEASE AT DIAGNOSIS, AND CEA VALUE

Regarding the location of the primary tumor, the LF group had a greater number of patients with a primary rectal tumor (21 patients (84%) vs. 3 patients (14.3%); p<0.001), a smaller number of patients with left colon cancer (4 patients (16%) vs. 10 patients (47.6%); p<0.001) and no patients with right colon tumor (0 patients vs. 8 patients (38.1%); p <0.001).

The two groups were similar in terms of TN staging, with most of the sample being classified as T3 and T4 (p=0.625). Forty-eight percent of each group had N+ lymph nodes disease (p=0.123). Regarding the presence of extrahepatic disease at the time of diagnosis and, regarding the detection of positive lymph nodes, the groups were similar (p=1,000). However, there was a statistically significant difference in the presence of lung metastases at diagnosis (9 patients (36%) in the LF group vs. 2 patients (9.5%) in the SR group; p=0.045).

With regard to the presence of a CEA value greater than 200 ng/mL at diagnosis, no statistically significant difference was observed between the 2 groups (p=0.614).

3.3 HEPATIC TUMOR BURDEN

Regarding to hepatic tumor burden, it was found that the LF group had a higher number of patients with more than three liver lesions compared to the SR group (Table 1). However, no statistically significant difference was observed between the two groups regarding the number of patients with a single lesion and with bilobar lesions (Table 1).

Table 1- Sample characterization according to the liver tumor burden

Hepatic Tumor Burden	***Liver-First* (n=25)**	**Synchronous resection (n=21)**	***p***
Single lesion, n (%)	5 (20%)	8 (38%)	0,205
Single lesion with > 3cm, n (%)	3 (12%)	2 (9,5%)	0,200
More than 3 lesions, n (%)	14 (56%)	3 (14%)	**0,004**
Bilobar lesions, n (%)	12 (48%)	5 (24%)	0,128

Source: Prepared by the authors, with data from the clinical files of patients at the CHUC General Surgery service, collected in December 2022.

3.4 FIRST INTERVENTION, POSTOPERATIVE MORBIDITY AND MORTALITY, SURGICAL RESECTION MARGINS, *KRAS* MUTATION, NEOADJUVANT AND ADJUVANT THERAPY

Patients in the LF group underwent more extensive liver resection compared to patients in the SR group ($p< 0.001$) (Table 2).

Regarding to postoperative morbidity and mortality, and taking into account the Clavien-Dindo classification, there was no statistically significant difference between the 2 groups ($p=0.514$) (Table 2).

The 2 groups were similar regarding the presence of mutation in the *KRAS* gene ($p=1.000$) and the same was verified regarding the number of patients with surgical resection margins classified as R1 ($p= 1.000$).

As for the neoadjuvant therapies performed, and in particular regarding the performance of NACT, the LF group had a greater number of patients undergoing NACT (23 patients (92%) vs. 6 patients (28.6%) in the SR group; $p<0.001$) although without statistically significant difference regarding the number of NACT regimens ($p=0.553$). As for performing NART on rectal tumors, there was also no statistically significant difference between the 2 groups ($p=1.000$).

The 2 groups did not show statistically significant difference with regard to performing ACT (14 patients (63.6%) in the LF group vs. 15 patients (75%) in the SR group; $p=0.514$), the number of cycles of ACT ($p=0.145$) and the ACT schemes performed ($p=0.452$). Likewise, the 2 groups did not show a statistically significant difference regarding adjuvant therapy with

monoclonal antibody (MAb) (5 patients (22.7%) in the LF group vs. 5 patients (25%) in the SR group; p= 1,000).

Table 2- Sample characterization according to the first intervention and posoperative morbimortality. (ALPPS- Associating Liver Partition and Portal vein ligation for Staged hepatectomy)

Variable	***Liver-First*** **(n=25)**	**Synchronous resection (n=21)**	***p***
First Surgery, n (%): 1=Hepatic subsegmentectomy/Segmentectomy 2=Major Hepatectomy; 3=ALPPS; 4=Right Hemicolectomy + hepatic subsegmentectomy; 5=Sigmoidectomy+ hepatic subsegmentectomy; 6=Rectal anterior ressection + hepatic subsegmentectomy; 8= Sub/Total Colectomy + hepatic subsegmentectomy.	1- 12 (48%) 2- 8 (32%) 3- 5 (20%)	4- 7 (33,3%) 5- 9 (42,9%) 6- 3 (14,3%) 7- 2 (9,5%)	< **0,001**
Pos-operative complications, n (%)	4 (16%)	3 (14,3%)	1,000
Morbimortality - Clavien-Dindo Classification, n (%)	**3a –** Percutaneous drainage of abscess, 1 (25%) **3b –** Pulmonary embolism submitted to trombectomy , 1 (25%) **5 –** Acute Liver Failure, 2 (50%) Morbidity: 12% Mortality: 4% 2 *dropouts* due to: -Pulmonary and liver relapse -Primary tumor progression	**1-** Hepatic hematoma, 3 (33,3%) **1-** Pelvic abscess, 3 (33,3%) **3b –** Anastomotic leak– colostomy, 3 (33,3%) Morbidity :14% e Mortality: 0%	0,514

Source: Prepared by the authors, with data from the clinical files of patients at the CHUC General Surgery service, collected in December 2022.

3.5 LIVER-FIRST GROUP AND SECOND INTERVENTION: POSTOPERATIVE MORBIDITY AND MORTALITY, CLAVIEN-DINDO CLASSIFICATION AND ADJUVANT THERAPY

In this group, it was found that 18 patients (72%) underwent a second intervention, and 2 of them (11.1%) had postoperative complications (1 patient with Clavien-Dindo classification 3a due to the need for percutaneous abscess drainage and another patient with Clavien-Dindo classification 3b due to Pulmonary embolism requiring thrombectomy). After the second surgery, 7 patients (38.9%) were still submitted to ACT and 4 patients (22.2%) still underwent adjuvant therapy with Mab.

3.6 OVERALL SURVIVAL ANALYSIS: GLOBAL SAMPLE, LF GROUP VERSUS SR GROUP, FACTORS IMPACTING OS AND HEPATIC TUMOR BURDEN

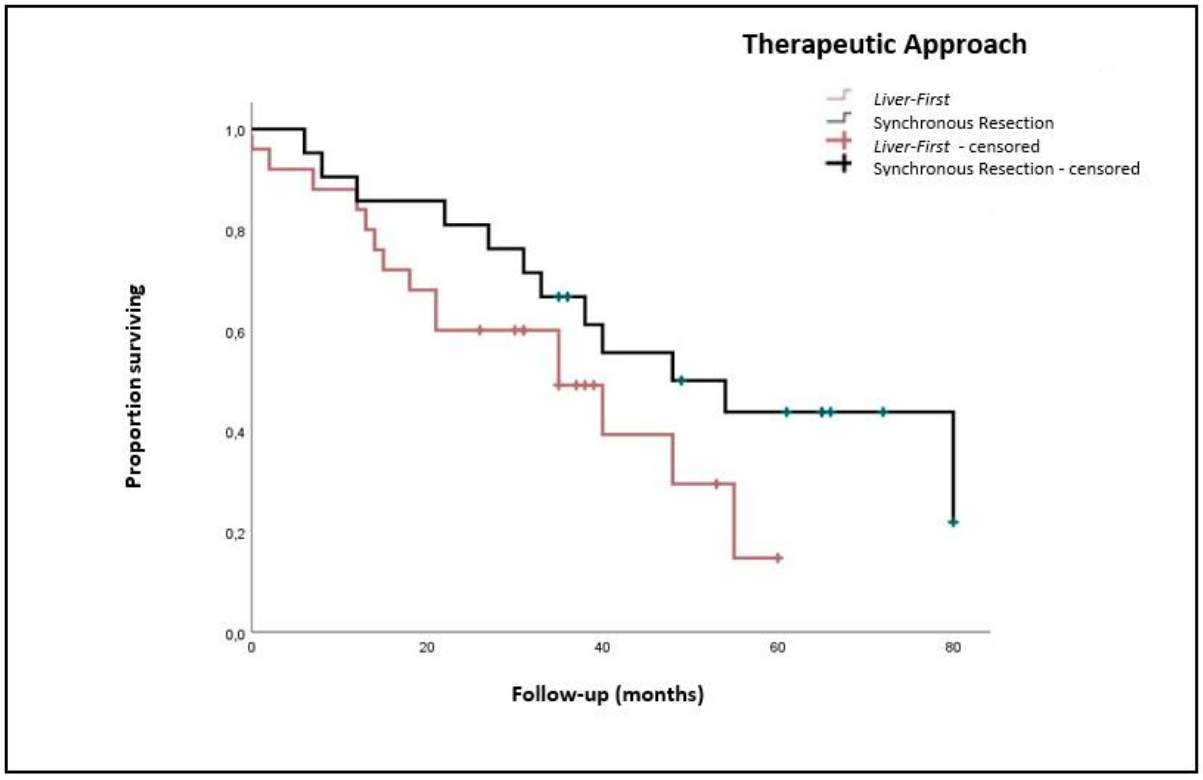
3.6.1 Global Cohort

The median follow-up time was 36 months (95%CI 0-80) and the median OS of the sample, regardless of the therapeutic strategy used was 40 months (95%CI 27.6-52 ,4). The one-year and three-year survivals for the overall sample were 89.1 ± 4.6% and 57.5% ± 7.5%, respectively.

3.6.2 LF Group Versus SR Group

Median OS was similar for both groups (35.0 months (95%CI 15.91 – 54.09) in the LF group vs. 48.0 months (95%CI 21.7-75.0) in the SR group; p =0.145) (Fig.1). Likewise, these groups showed similarities in one-year survival (84.0% + 7.3% in the LF group vs. 85.7% + 7.6% in the SR group; p=0.145) and in three-year survival (49.1% + 10.6% in the LF group vs. 66.7% +10.3% in the SR group).

Figure 1: Overall survival according to the therapeutic approach (*Liver-First* versus Synchronous Resection)



Source: Prepared by the authors, with data from the clinical files of patients at the CHUC General Surgery service, collected in December 2022.

3.6.3 Factors With an Impact on Overall Survival

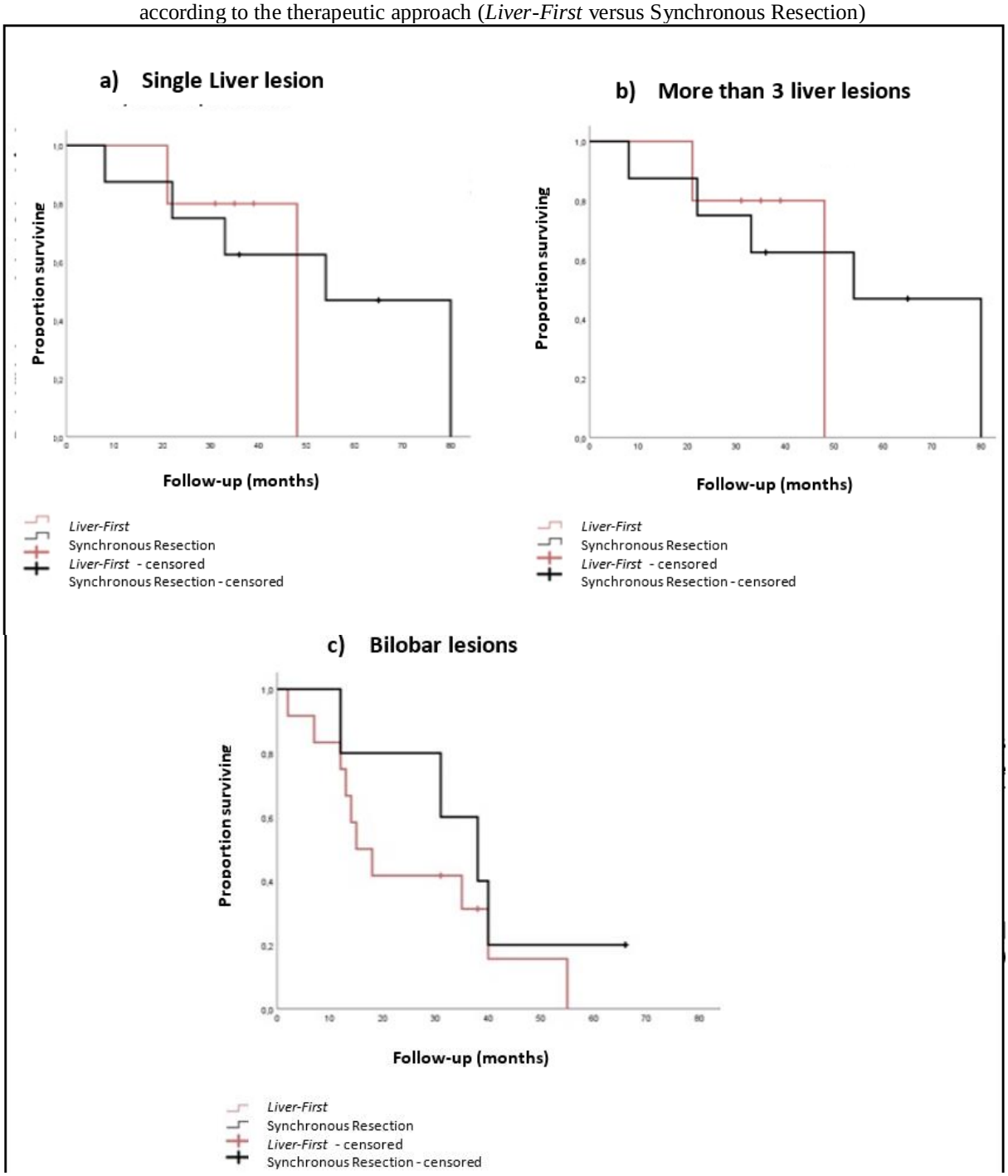
In the multivariate analysis, neoplasms of the right colon (HR = 0.21; CI 95% 0.04 – 1.07; p=0.061) and more than three liver lesions (HR = 4.33; CI 95% 1 .30 – 14.43; p=0.017) had an negative impact on OS. On the contrary, the variables age (HR=1.02; 95% CI 0.97-1.08; p=0.412), NACT (HR=1.64; 95% CI 0.32-8.30; p=0.550), surgical approach (HR=0.25; CI 95% 0.04-1.77; p=0.165) and presence of lung metastases at diagnosis (HR=1.62; CI 95% 0.04-1.77; p=0.350) had no impact on OS.

3.6.4 Hepatic Tumor Burden: Single Lesion, More Than Three Uni and/or Bilobar Lesions and Bilobar Lesions

3.6.4.1 Patients With Single Hepatic Lesion

In this group of patients, the median OS, regardless of the therapeutic approach, was 54.0 months (95% CI 28.5-79.5). When considering the therapeutic strategy performed, it was found that the mean OS was similar (42.6 months (95%CI 29.2-56.0) in the LF approach vs. 53.8 months (CI 95% 32.1-75.5) in the SR approach; p=0.773) (Fig.2).

Figure 2: Overall survival of the groups: a) single liver lesion b) more than 3 liver lesions c) Bilobar lesions according to the therapeutic approach (*Liver-First* versus Synchronous Resection)



Source: Prepared by the authors, with data from the clinical files of patients at the CHUC General Surgery service, collected in December 2022.

3.6.4.2 Patients With More than Three Uni and/or Bilobar Hepatic Lesions

In this group of patients, the median OS, regardless of the therapeutic approach, was 35.0 months (95% CI 10.0-60.0) When considering the therapeutic strategy to which these patients were submitted, the median OS was found to be similar (18.0 months (95% CI 0-40.0) for the LF approach vs. 38.0 months (95% CI 0-79.6) for the SR approach; p = 0.929) (Fig.2).

3.6.4.3 Patients With Bilobar Liver Metastasis

The median OS, regardless of the therapeutic approach, was 31.0 months (95% CI 5.3-56.7). When considering the therapeutic strategy to which these patients were submitted, it was found that the median OS was similar (15.0 months (95%CI 8.2-21.8) in the LF approach vs. 38 .0 months (95% CI 23.0-53.0) in the SR approach; p=0.376) (Fig.2).

4 DISEASE-FREE SURVIVAL (DFS) ANALYSIS: GLOBAL SAMPLE; LF VERSUS SR GROUP; PROGNOSTIC FACTORS AND HEPATIC TUMOR BURDEN

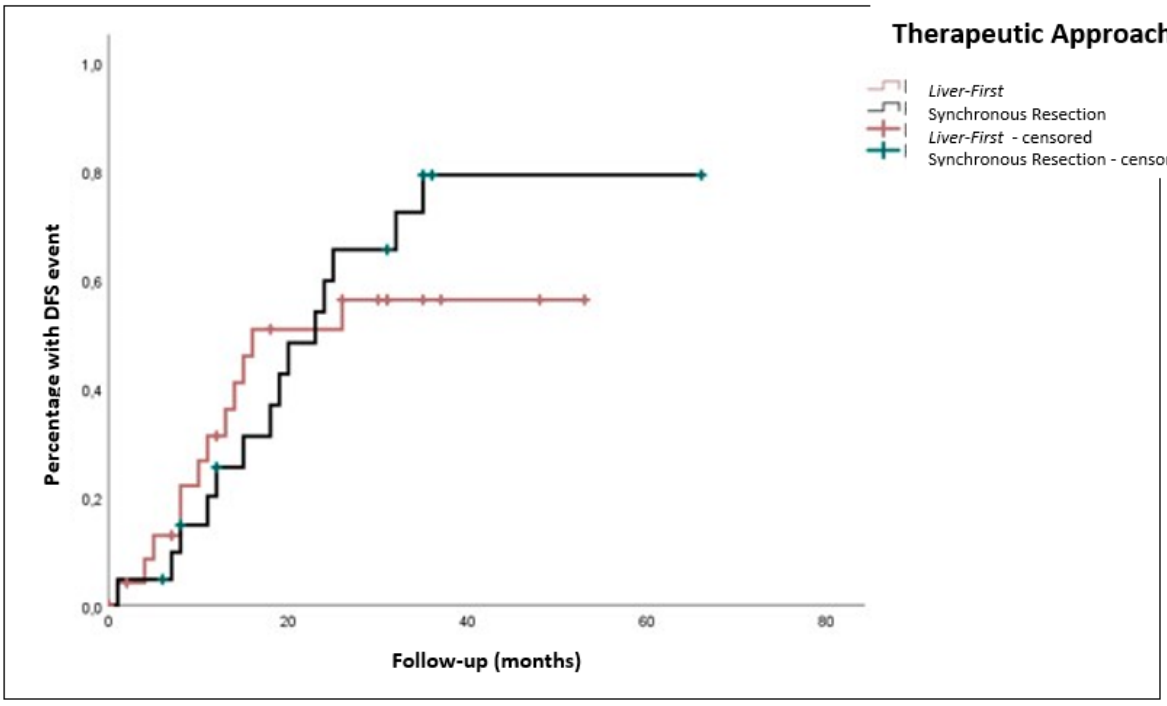
4.1 GLOBAL SAMPLE

The median follow-up time was 36 months (95%CI 0-80) and the median DFS of the overall sample, regardless of the type of therapeutic strategy, was 23.0 months (95%CI 14.5-31.4). The one-year and three-year DFS for the sample was 71.6% + 7.0% and 30.3% + 8.2% for the LF and SR group, respectively.

4.2 LF GROUP VERSUS SR GROUP

Median DFS was similar for both groups (16.0 months (95%CI 0-32.7) in the LF group vs. 23.0 months (95%CI16.3-29.7) in the SR group; p=0.651) (Fig. 3), as well as the one-year DFS (68.8% + 9.8% in the LF group vs. 74.6% + 9.9% in the SR group; p=0.651) and the DFS at three years (43.7% + 10.9% in the LF group vs. 20.6% + 10.1%; p=0.651).

Figure 3: Overall disease-free survivall according to the therapeutic approach (*Liver-First* versus Synchronous Resection)



Source: Prepared by the authors, with data from the clinical files of patients at the CHUC General Surgery service, collected in December 2022.

4.3 FACTORS WITH DISEASE-FREE SURVIVAL IMPACT

In the multivariate analysis, age (HR=0.98; CI 95% 0.93-1.03; p=0.292), location of the primary tumor in the right colon (HR = 0.70; CI 95% 0 .19-2.64; p=0.603), the location of the primary tumor in the left colon (HR=1.03; 95%CI 0.20-5.25; p=0.976), the hepatic tumor burden, namely more than three liver lesions (HR = 1.76; 95%CI 0.66-4.69; p=0.256), NACT (HR=1.68; 95%CI 0.45-6.32; p=0.444),presence of lung metastases at diagnosis (HR=0.59; 95% CI 0.19-1.83; p=0.364) and the therapeutic approach (HR=0.40; 95% CI 0.12-1.37 ; p=0.144) had no impact on DFS.

4.4 HEPATIC TUMOR BURDEN: SINGLE HEPATIC LESION; MORE THAN THREE UNI AND/OR BILOBAR LESIONS; BILOBAR LESIONS

4.4.1 Patients With a Single Hepatic Lesion

The mean DFS, regardless of the therapeutic approach, was 27.1 months (95% CI 18.3-36.0). When the therapeutic strategy was considered, it was found that the mean DFS was similar (34.0 months (95%CI 18.9-49.1) in the LF approach vs. 20.6 months (95%CI 14.1-27, 0) in the SR approach; p=0.221) (Fig.4).

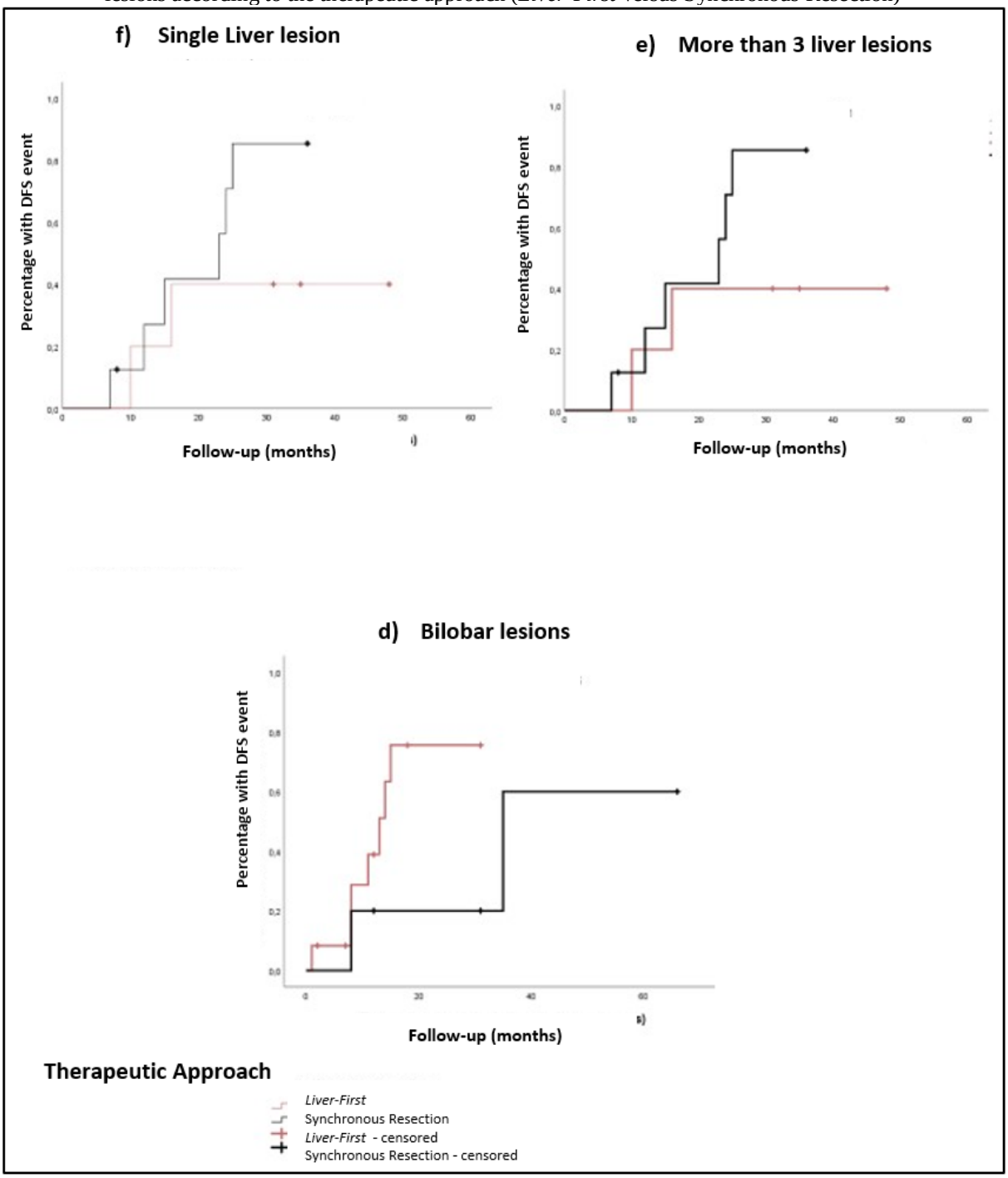
4.4.2 Patients With More Than 3 Lesions, uni and/or Bilobar

The mean DFS, regardless of therapeutic approach, was 22.6 months (95% CI 12.1-33.1). When considering the therapeutic strategy to which these patients were submitted, it was found that the mean DFS was similar (24.0 months (95%CI 11.3-36.8) in the LF approach vs. 26.0 months (95%CI) % 5.6-46.4) in the SR approach; p=0.927) (Fig.4).

4.4.3 Patients With Bilobar Hepatic Lesions

The mean DFS, regardless of therapeutic approach, was 27.2 months (95% CI 13.1-41.2). When considering the therapeutic strategy performed in this group of patients, it was found that the mean DFS was similar (15.5 months (95%CI 9.4-21.7) in the LF approach vs. 42.0 months (95%CI 19 .3-64.7) in the SR approach; p = 0.125) (Fig.4).

Figure 4- Overall disease-free survival of the groups: a) single liver lesion b) more than 3 liver lesions c) Bilobar lesions according to the therapeutic approach (*Liver-First* versus Synchronous Resection)



Source: Prepared by the authors, with data from the clinical files of patients at the CHUC General Surgery service, collected in December 2022.

5 DISCUSSION

The best surgical approach for patients with synchronous CRCLM and asymptomatic primary tumor remains controversial and complex. (2,4,7,16–18) The LF approach prioritizes the removal of LM, which are more relevant in terms of prognosis, and facilitates the inclusion of RT in primary rectal tumors. (2,3,5,14) With regard to SR, the EGOSLIM group (Expert

Group on OncoSurgery management of Liver Metastases) (18) found that, when properly evaluated by a multidisciplinary team and without increasing the operative risk, be the preferred option for these patients. (3.18)

Our study showed that the LF group had a greater number of patients with a primary tumor at the rectal level, with more than 3 liver lesions and a greater number of patients undergoing NACT compared to the SR group, which is expected taking into account the indications mentioned in the literature for each approach. (2,3,5,14) As described in the literature, (2,20) it was found that patients in the LF group underwent a more extensive hepatic resection compared to patients in the SR group.

As for postoperative complications and morbimortality, it was found that there was no statistically significant difference (p=0.514) between the two groups, similarly to what is described in most studies, (2,16,20) although another study has greater morbidity was described for the SR group. (7) However, despite not being statistically significant, it was found that the LF group had Clavien-Dindo scores 3a, 3b and 5 (the latter corresponding to acute liver failure) and, therefore, with greater severity when compared to complications postoperative conditions observed for the Sr group (classified in Clavien-Dindo 1 and 3b) similarly to what is described in the study carried out by Carbone et al. (4). It should be noted however that the LF approach includes a greater number of major interventions (in the group we have 18 patients submitted to Associating Liver Partition and Portal Vein Ligation (ALPPS) procedure).

As for prognostic factors and taking into account the variables that showed a statistically significant difference between the 2 groups (LF and SR), it was found that the hepatic burden, namely more than 3 liver metastases, was an independent factor with a negative impact on OS which is in line with the literature which states that LM are most relevant in terms of prognosis. (2,3,5,14). The location of the primary tumor and, in particular, its right colon location, represented a factor with a positive impact on OS compared to the rectal location. With regard to DFS, no impact factor was identified.

Our study demonstrated that OS and DFS were similar for both therapeutic approaches, which is in line with what is described in the literature. (2,4,7,16,20,21) This similarity was maintained for one- and three-year survival, as observed in the study by Slesser et al. (21)

The same was verified when the hepatic tumor burden was considered, in which no statistically significant difference was observed in the OS and DFS according to the hepatic tumor burden, contrary to what is described in the literature. (3,4) However, it should be noted that the choice of therapeutic approach was assessed by a multidisciplinary team, individualized

and carried out according to the hepatic tumor burden of each patient, so we believe that the lack of statistical results is due to a correct pre-selection of patients for each approach.

Finally, this study has some limitations, namely: it is a retrospective and unicentric study, so we admit a selection bias and we consider that it would be important, in future studies, to include other reference centers that perform the two types of therapeutic approach referred to in this study; it is a study with a small number of patients, so it would be pertinent, in future studies, to obtain a larger sample of patients that was representative of the various reference centers in Portugal; and it was a study that covered a relatively short period of time (5 years).

6 CONCLUSION

We found that the two therapeutic strategies LF and SR had similar postoperative morbidity and mortality. Likewise, no statistically significant difference was observed regarding OS and DFS for the two surgical approaches even when hepatic tumor burden was considered. Survival at one and three years were also similar. However, hepatic tumor burden, namely having more than 3 liver lesions, was an independent factor with a negative impact on OS, so we believe that the latter is essential in selecting the best therapeutic approach.

The choice of the best therapeutic approach for patients with synchronous CRCLM and asymptomatic primary tumor is highly complex and for the therapeutic success of these patients, it is fundamental to have a multidisciplinary team that allows a careful and individualized evaluation for the selection of the best therapeutic strategy for each patient.

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