ASSOCIATING LIVER PARTITION AND PORTAL VEIN LIGATION (ALPPS) FOR COLORECTAL LIVER METASTASIS: REVIEW & SINGLE-CENTER STUDY

ASSOCIAÇÃO DA PARTIÇÃO HEPÁTICA À LAQUEAÇÃO DA VEIA PORTA NO TRATAMENTO DE METÁSTASES HEPÁTICAS POR CANCRO COLORECTAL: REVISÃO DO TEMA E RESULTADOS DE UM CENTRO

ANA RUIVO[1], RODRIGO NEMÉSIO[1], RICARDO MARTINS[1], JOSÉ GUILHERME TRALHÃO[2]

[1] General Surgery department, Centro Hospitalar e Universitário de Coimbra, Portugal
Faculty of Medicine University of Coimbra, Portugal

[2] General Surgery department, Centro Hospitalar e Universitário de Coimbra, Portugal
Faculty of Medicine University of Coimbra, Portugal
CIMAGO – Centro de Investigação em Meio Ambiente, Genética e Oncobiologia
iCBR – Coimbra Institute for Clinical and Biomedical Research

ABSTRACT

The associating liver partitioning and portal vein ligation for staged hepatectomy has gained interest in the treatment of unresectable colorectal liver metastases as it has allowed to expand the limits of oncological resectability. Despite the initial poor outcomes associated to this procedure, recent reports have showed reduced morbimortality in well selected patients. The current study evaluates the outcomes of ALPPS procedure in treatment of colorectal liver metastasis at our department and identify morbimortality and survival prognostic factors. A retrospective cohort study was performed, all consecutive patients submitted to ALPPS procedure between 2015 and 2020 were included. Twenty-one patients with 61,8±10,8 (37-78), 76,2% were male, with 12,05±6,34 (5-30) hepatic nodules, whose largest size was 42.3 ± 17, 5 (18-75) mm. Among these, 71.4% underwent induction chemotherapy with FOLFIRI and 61,9% with plus Cetuximab, mean of 10,9±5,6 (4-24) cycles. At ALPPS stage 1, 6±4 (1-18) nodules were resected, 19% with concomitant splenic artery occlusion and a mean Pringle Maneuver of 33±26 (0-94) minutes. All patients did adjuvant CT. We report a global mortality of 9,6% and a major morbidity (MMb) of 28,6%. The multivariable analysis identified as risk factor for MMb: more than 10 nodules, size>38mm, interstage interval> 14 days and the resection of more than 4 lesions at stage 1. The overall survival and disease-free survival rates were 25,9± 4,2 (17,6- 34,1), 17,64 ±3,95 (9,9-25,4) moths, respectively. Age >56 years and size >38mm were identified as risk factor for poor outcome. More than 10 cycles of neoadjuvant chemotherapy were identified as risk factor for poor outcome at 2 years. Our results are similar to the recently established reference values.

Keywords: *Colorectal Neoplasms; Neoplasm Metastasis; hepatectomy; Portal Vein / surgery; Treatment Outcome.*

INTRODUCTION

Colorectal cancer (CRC) is a common and lethal disease. It is estimated that approximately 1 354 000 new cases of CRC cancer are diagnosed annually worldwide and it still remains the third most common cause of cancer death in the world.[1]

Approximately 20 percent of patients have distant metastatic disease at the time of presentation while another 20% to 25% patients will develop metastasis during the natural history of the disease.[2,3]

Patients with metastatic CRC face poor prognosis in general, with a relative 5-year survival rate of 12%.[4] However, improvements in CRC treatment have led to decreases in CRC mortality even in the face of increased incidence.[5,3]

Actually, for patients with CRC liver metastasis (CRLM), multidisciplinary approach with radical surgery represents the most effective strategy, which could markedly improve prognosis and provide a potentially curative opportunity with a relative 5-year survival rate up to 50%[6,3]

However, using standard parameters, only about 20–30% of CRLM patients are deemed resectable. [7]The most common reason for irresectability is the high tumor burden with multiple bilobar liver metastasis and insufficient estimated future liver remnant (FLR)[8].

Several liver volume remodeling strategies have been developed to improve resectability and expanding the pool of surgical candidates.

In 2012, Schitzbauer, described a technique that consists in associating liver partitioning and portal vein ligation for staged hepatectomy (ALPPS), taking advantage of the liver's regenerative capacity for the resection of liver lesions that would otherwise be unresectable.[9] This recent technique postulated a more complete vascular occlusion that produce rapid liver hypertrophy with the possibility of performing the second resection time in a shorter time interval, during the same hospital stay, minimizing a possible tumor progression in this waiting period.[10]

The higher morbidity and mortality rates initially associated to this procedure has been reduced with the improvement of the surgical technique and with a more careful selection of patients who may benefit from this very invasive procedure.

OBJECTIVES

The purpose of the present article was to evaluated the overall survival (OS) and disease-free survival (DFS) of patients submitted to ALPPS for CRLM in our institution. The secondary endpoints were to identify possible morbidity and mortality factors.

PATIENTS AND METHODS

Between 2015 and 2020, two hundred and fifteen patients were submitted to surgical intervention at our department for CRLM but only 21 underwent ALPPS procedure and were included in this study.

Twenty-one patients with 61,8 ± 10,8 (37-78) years were studied, 76,2% were male, with 12,05 ± 6,34 (5-30) hepatic nodules, whose largest size was 42.3 ± 17, 5 (18-75) mm. Among these, 71.4% underwent induction chemotherapy (CT) with FOLFIRI and 61,9% with plus Cetuximab, mean of 10,9 ± 5,6 (4-24) cycles.

At ALPPS stage 1 (T1), after 7 (6-8,5) weeks of the end of CT, 6 ± 4 (1-18) nodules were resected, 19% with concomitant splenic artery occlusion and a mean Pringle Maneuver of 33 ± 26 (0-94) minutes. ALPPS stage 2 (T2) took place 14 (7,5-21) days later. All patients did adjuvant CT (Table 1)

Following surgery all of the patients were followed up regularly and prospectively monitored for recurrence with serum laboratory tests, CT-scan, MRI or US every 3 months up to 2 years and then every 6 months thereafter.

Volumetric data were acquired by contrasted computed tomography performed before and at a median of 9±5(3-19) days after T1 and processed

using image software (Osirix, Pixmeo, Geneva, Switzerland).

The standardized volume of the future liver remaining (sFLR) and the kinetic growth ratio (KGR) were calculated based on methods validated in previous studies.[11,12]

Morbidity was defined according to Clavien-Dindo (CD) Classification and "Major morbidity" was defined by CD ≥ *III*. Post-hepatectomy liver failure (PHLF) and biliary leakage after hepatectomy was classified according International Study Group of Liver Surgery (ISGLS).[13,14]

Table 1 – **Demographic characteristics and outcomes of intervention**

PATIENT CHARACTERISTICS	
Male, n (%)	16 (76,2)
Age, yrs, mean ± SD, (min-max)	61,8± 10,8 (37-78)
ASA ≥ III, n (%)	6 (29)
PREOPERATIVE ONCOLOGICAL TREATMENT	
FOLFIRI, n (%)	15 (71)
FOLFOX, n (%)	4 (19)
FOLFOXIRI, n (%)	2(10)
Plus Bevacizumab, n (%)	38%
Plus Cetuximab, n (%)	65%
Number of cycles, mean ± SD, (min-max)	10,9 ± 5,6 (4 – 24)
Interval between end of CT and surgery (Weeks), median [IQR]	7 [4 – 17]
VOLUMETRIC DATA	
FLR volume before T1(cm^3), mean ± SD, (min-max)	512 ± 290 (222 – 1568)
FLR volume before T2(cm^3), mean ± SD, (min-max)	638 ± 317 (340 – 1706)
Time interval to volumetric evaluation after T1, days, mean ± SD, (min-max)	9 ± 5 (3 – 19)
Kinetic Growth Rate, %/day, mean ± SD, (min-max)	3,7% ± 3,3 (0,1-10)
Degree of Liver hypertrophy, %, median [IQR]	24,66 [0,6-64]
SURGERY CHARACTERISTICS	
Number of metastasis, mean ± SD, (min-max)	12,1± 6,34 (5 – 30)
Number of metastasis resected at T1, mean ± SD, (min-max)	6±4 (1-18)
Size of the largest metastasis (mm), mean ± SD, (min-max)	42,3±17,5(18-75)
Pringle maneuver (minutes), mean ± SD, (min-max)	33 ± 26 (0-94)
Splenic artery occlusion, n (%)	4 (19)
Concomitant colorectal resection stage 1, n (%)	1(4,8)
Interstage interval, days, median [IQR]	14 [8 – 21]
Drop-out, n (%)	0
Morbidity and Mortality	
90-day mortality, n (%)	2(9,5)
Complications ≥3b stage 1, n (%)	1(4,8)
Complications ≥3b stage 2, n (%)	6 (28,6)

Survival was estimated using the Kaplan-Meier method and a multivariate logistic regression model was used for the risk factor analysis using IBM SPSS® Statistics (version 27). Values were considered statistically significant when *p* was <0,5.

RESULTS

Of all patients studied, only 1 (4,8%) did not complete both stages of the procedure due to an acute renal failure that led to dead.

After Stage 2, global morbidity was 47,6%, being major in 6 patients (28,6%) due to: four cases of abscesses requiring percutaneous drainage;one case of nosocomial pneumonia with severe respiratory failure and one patient with PHLF grade C. This patient was carrying HBsAg and was transplanted from a marginal donor.

In-house mortality after stage 2 was 4,8% due to isolated respiratory failure on the 87th postoperative day.

Regarding volumetric data, the volume of the future remaining liver increased by a median of 512 ± 290 (222 – 1568) cm^3 to 638 ± 317 (340 – 1706) cm^3 in a median of 9 ± 5 (3 – 19) days, which represents an increase in the sFLR from 31 to 36% with a kinetic growth rate (KGR) mean of 3,7% ± 3,3 (0,1-10) /day and an degree of hypertrophy median of 24,66 [0,6-64] %

The mean overall survival (OS) and disease-free survival (SLD) was 25.9 ± 4.2 (17.6-34.1) and 17.64 ± 3.95 (9.9-25.4) months, respectively. (Fig 1 and 2)

Several potential risk factors for major morbidity after ALPPS were analyzed in our serie (Table 2): an interval between the two times superior to two weeks; age ≥65 years; a median of hepatic nodules greater than 10.5mm; the size of the largest nodule

Table 2 – **Risk factors for morbidity after ALPPS**

VARIABLE	*P* (T1)	*P* (T2)
Age > 65 years	0,331	n.s
Number of metastasis **> 10**	**<0,001**	**0,017**
Size of the largest metastasis > 38mm	**0,002**	n.s.
Number of CT cycles >10	0,331	n.s
Resection of >4 lesions at T1	**0,022**	n.s
Pringle maneuver >30 minutes	0,96	n.s
Interstage interval > 14 days	**0,022**	n.s

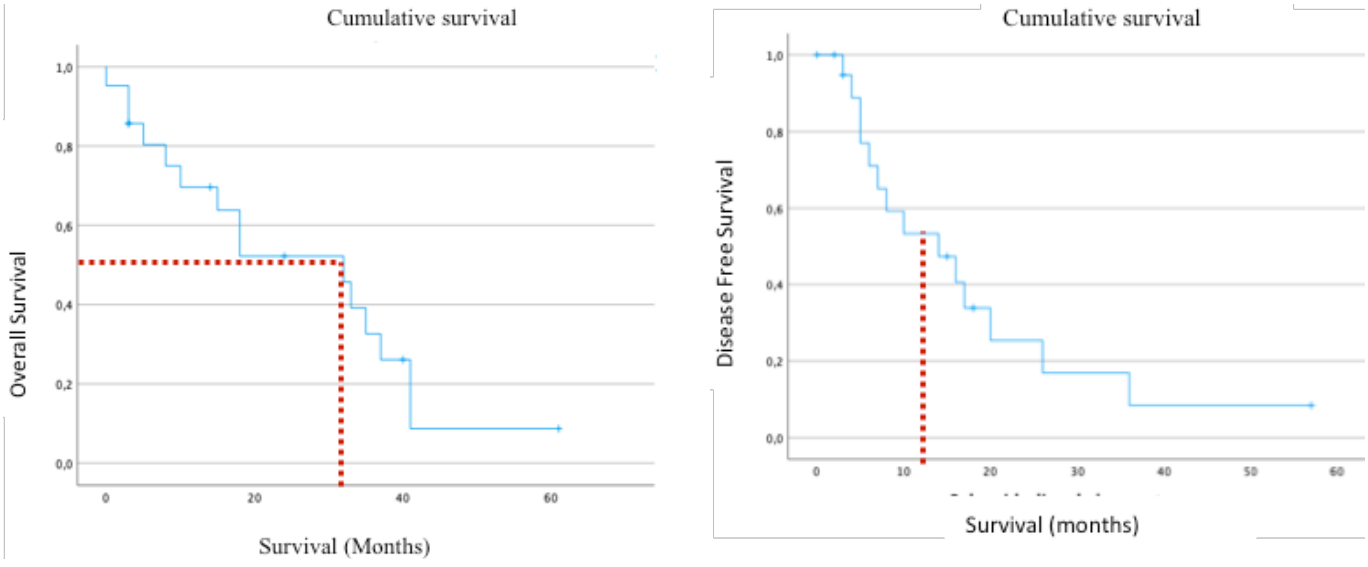

Figure 1 and 2 – **Overall Survival and Disease-Free survival**

≥38mm; more than 10 cycles of induction CT; more than 4 nodules resected in T1; Pringle maneuver greater than 30 minutes in T1.

A multivariate analysis revealed an increased risk of MbM with statistical significance after stage 1 for patients with more than 10 lesions, size of the largest nodule>38mm, interval between T1-T2>14 days and resection of more than 4 lesions in T1. (p=0.001, 0.002, 0.022 and 0.022 respectively). The same analisys for Mbm after stage 2 revealed an increased risk of MbM with statistical significance for patients with more than 10 lesions (p=0.017)

The Age >65 years and the nodule diameter>38mm were identified as poor prognostic factors for OS in the first and second year. More than 10 cycles of preoperative CT was also identified as a poor prognostic factor for OS at 2 years. With the exception of the age at surgery, no predictors of SLD were identified. (Table 3 and 4)

DISCUSSION

The serie we present has a total of 21 patients with a 95.2% conclusion rate, which is close to the reference value defined in the 2019 publication based on the results of the ALPPS registry[15], which is of 96%. The described mortality is within the values reported in other studies, which is between 8.8 and 15%[9,16,17], even though it is above the delineated reference value (5% at 90 days)[15].

Also the percentage of major complications observed (28.6%), is lower than in other published series,(40-44%)[16,17] and within the limit values defined in the 2019 study of 38%.[15] On the other hand, the percentage of cases of liver failure after T2 (4.8%) is close to the limit defined in this study, of 5%.

Our study also highlighted as risk factors for morbidity patients with a greater number of metastatic nodules, size of the largest nodule>38mm, interval between T1-T2>14 days and resection of more than 4 lesions in T1probably suggesting that they will be patients with greater impairment of liver function in the postoperative period. New studies will allow the direct association of perioperative liver cell function with the surgical results obtained.

Most of the studies published to date report on average survivals for periods of 2 years, with values between 42 and 62% and and DFS up to 67%.[18-21]

In our serie, a mean survival at 2 years of 42,9%, although this value decreased to 32% at the 3rd year after surgery. The DFS results (61,9%) are in agreement with other studies.

Table 3 and 4 – **Mortality at first and second year**

VARIABLE	HR	*p*
Age > 65 years	1,2	**0,004**
Interstage interval > 14 days	-	1
Number of metastasis > 10	-	1
Size of the largest metastasis> 38mm	2,4	**0,019**
Number of CT cycles >10	1,2	**0,005**
Pringle maneuver >30 minutes	-	1
Splenic artery occlusion	-	1
DHsFLR < 30%	-	1

VARIABLE	HR	*p*
Age > 65 years	1,2	**0,004**
Interstage interval > 14 days	-	1
Number of metastasis > 10	-	1
Size of the largest metastasis > 38mm	2,4	**0,019**
Number of CT cycles >10	-	1
Pringle maneuver >30 minutes	-	1
Splenic artery occlusion	-	1
DHsFLR < 30%	-	1

In addition to size of biggest nodule and more than 10 cycles of preoperative CT, age>65 years was also identified as poor prognostic factor for OS in our serie. Age was previous mentioned as risk factor for perioperative mortality[22,23] However, more recent studies do not corroborate this conclusion.[21,24] Similarly, the role of preoperative chemotherapy has not been clearly associated to an increased risk of mortality. However, it has been reported that extended preoperative chemotherapy may cause steatotic changes and sinusoidal injury of the liver parenchyma without improving the pathologic response which may impair hepatic regeneration and increase major morbidity.[23,25]

It must be kept in mind when we are comparing the results of ALPPS that these patients represent a subgroup with a burden liver load that approaches the palliative situation.[21] Until recently we only had two-stage hepatectomy (TSH) with portal vein embolization (PVE) or portal vein ligation (PVL) as surgical treatment option for this patients.[21]

More recently, beside ALPPS, parenchyma-sparing surgery has been introduced by relying on intraoperative ultrasound (IOUS) guidance.[26]

The major reported advantage of ALPPS, that was responsible for de initial interest in the technique comparative to TSH, was the enhanced hypertrophy and the shortening of the interstage interval with less drop-outs reported.[27]

However, even knowing that about one third of patients does not undergo stage 2 hepatectomy[28,29], that if the stage 2 cannot be performed then patients' prognosis is poor, even worse than with CT only [28] and that ALPPS has a significant higher conclusion rate (92–100%)[29,30,31,21], it is still not clear if ALPPS is friend or foe.

If on the one hand, the tumor progression and the insufficient hypertrophy of the FLR are the main reasons for failure of TSH. On the other hand, there are also good arguments that make ALPPS less interesting like the rapid hypertrophy rate may be harmful, mainly because of the assumed bigger stimulus on tumor growth but also because hardly opens a window for biological selection.[32,33,28,34]

Regarding OS, the results do not agree between the series: some authors defend that ALPPS improves survival (OS about 46 moths versus 26moths)[35] while others, despite a higher resectability rate in ALPPS, the DFS is the same in both groups.[36]

Recently, another approach has become more advocated as an alternative to TSH and just recently, also to ALPPS: the parenchymal preserving one-stage ultrasound-guided hepatectomy (e-OSH)[26,37,38].

This technic combines a solution for the main problems of the previous mentioned approaches: it has a significantly lower drop-out rate than TSH (0% versus 40.5%) and a lower overall, lower severe and also lower liver-specific morbidity than ALPPS. However, despite the lower morbidity in multiple bilateral CRLM and the low R0-resection rate, the OS and DFS is similar to ALPPS and TSH (5-year-survival of 38.2%).[37,38]

Thus, ALPPS has to be seen as a last resort at the end of the spectrum in the treatment of CRLM, and here, where patients have no surgical alternative to ALPPS, its oncological outcome needs to be compared to that of palliative treatment options such as chemotherapy or loco-regional therapies.

However, despite of all these possible approaches, some metastases remain technically inaccessible to liver resection, mainly because of anticipated insufficient future liver remnant volume. This peculiar situation is the starting point of the concept of Liver Transplant (LT) for CRLM: resecting all metastases (R0) by total hepatectomy.[39]

In the 90's, the Vienna experience with 17 patients that were submitted to LT for CRLM showed a 5-year survival of 12% with a recurrence rate over 60%[40]. These disappointing results were corroborated by North American data[41] and it was admitted that the results did not justify using a limited pool of liver grafts.

Until 2013, with the exception of few case reports, no further data in this field were published. The SECA-I study (for SEcondary CAncer) published

by the Oslo group reported the results of the first 21 LT for non-resectable CRLM: OS at 1, 3 and 5 years were 95%, 68% and 60% respectively. The DFS was 35% at 1 year and 0% at 2 years.[42]

There is no unanimous definition of the minimal survival requirements after a LT: ranges between 50% and 70% have been suggested[43]. Comparing the results of LT for other common accepted indications: the publication that has set the gold standard of transplantation for Hepatocellular carcinoma, was reported a survival of 70% at 5 years.[44] In the 2018 report of the SRTR, the mean graft survival was approximately 75% at 5 years.[45]

The second SECA study with patients with more extensive nonresectable disease with median of 12 liver metastases with a median size of 45 mm and more than 50% have started second or later lines of chemotherapy at time of LT. Despite the extensive disease burden, the KM-estimated 5-year OS was 83%.[46]

Although these promising results, the major challenge is, unlike the peculiar situation of Norway, the limited number of donors. The long waiting time for LT and the high mortality on the waiting list associated to a new indication for LT that certainly will introduce many potentially eligible patients to the waiting list will obviously make this harder to handle.

An attempt to overcome this problem as led to the emergence of other solutions like: the RAPID concept, that takes the advantage of the normal function of the non-tumor parenchyma[47]; the auxiliary grafts from living donors (ongoing LIVERT(W) OHEAL study-NCT03488953), this alternative allows transplanting patients with CRLM without prejudice to other candidates for LT;

the use of marginal grafts for these recipients, since they probably tolerate better transplantation with extended criteria donor grafts.

The SECA study still has multiple ongoing trials and together with the LIVERT(W)OHEAL trial and the TRANSMET (NCT02597348) trial that will assess the efficacy of LT versus other therapies or associated to other therapies, might elucidate us in a near future.

The recommendations published last year by International Liver Transplantation Society Transplant Oncology (ILTS) Consensus Conference state that LT can have a role in select patients with unresectable CRLM: only liver involvement, a maximum tumor diameter ≤ 5.5 cm, pre-LT carcinoembryonic antigen (CEA) ≤ 80 μg/L, response to chemotherapy, and time interval from diagnosis to LT ≥ 2 years.[48] These criteria were similar to the Oslo score previous associated to OS in the 2013 SECA study.[42]

In a multicenter study published in 2017, the authors also identified the time between colorectal surgery and transplantation (with a cut-off at 24 months) as a predictor of DFS, while tumor diameter (<5.5 cm), the last CEA level (80 μg/l) and cancer progression could not be validated as risk factors. However, this cohort, for which we contributed with two patients, combined planned surgery and salvage procedures as well as different types of liver grafts (non-marginal donors after brain-death, domino donors with familial amyloid polyneuropathy, and living-related donor).[49]

One of our patients mentioned here were submitted to LT due to PHLF after ALPPS procedure. He was transplanted from a marginal donor and died 18 months after the transplant with liver, lung and bone metastasis.

In oncologic surgery, the main criteria for success is survival, especially disease-free survival. So far, for ALPPS long-term oncologic data are almost missing.

Aside from the limited size of our sample, coming from only one center, the results obtained have been encouraging and are approaching the recently established reference values. It will be important to continue to consolidate the experience obtained, continuing to adjust the parameters for selecting the patients who will benefit most from this procedure, namely through the study of biological factors for the prognosis of the disease.

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Correspondência:
ANA RUIVO
e-mail: ruivo.ais@gmail.com

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