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Running title: Dorsal sector anatomy and transplantation

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ABSTRACT

Introduction: Recipient hepatectomy is a challenging liver transplantation (LT) procedure that has life-threatening complications. The current predictive mortality clinic-biological scores (Child/MELD) do not take into consideration the recipient liver anatomy. The aim of this study was to evaluate the impact of the dorsal sector anatomy of a cirrhotic liver on the morbidity/mortality rates of hepatectomy. **Methods:** A multicenter retrospective study (clinic-biological and morphologic) was performed from 2013 to 2014. The degree of encirclement of the inferior vena cava (IVC) by the dorsal sector of the liver was measured. **Results:** The study population included 320 patients. Seventy-four (23%) patients had complete IVC encirclement. A correlation (p=0.01) has been reported between the existence of a circular dorsal sector and the number of transfusions during LT (4 PRC in the group without IVC *vs* 7 PRC in the other group). The existence of such anatomy increases the relative risk of early reoperation for IVC bleeding by 31% (p=0.05). There is a correlation between alcoholic cirrhosis and dorsal-sector hypertrophy (126 cc *vs* 147.5 cc, p=0.05). Concerning surgical time, we found no significant between-group differences. Compared to the severity of cirrhosis, an inverse correlation was observed between the MELD and Child scores and the dorsal sector hypertrophy (p=<0.001). No significant difference in terms of transfusion was found between the temporary portocaval shunt group (n=168) and the other group (n=152). **Conclusion:** The presence of a circular sector is associated with an increased risk of hemorrhage during hepatectomy, as well as an immediate postoperative risk of reoperation.

Keywords: dorsal sector, hepatectomy, vena cava preservation, bleeding, transplantation

INTRODUCTION

The first step in liver transplantation (LT) consists of a full hepatectomy. Initial liver transplantation techniques are required to replace the recipient's inferior vena cava (IVC) at the retrohepatic part(1). Reconstruction techniques allowing for the preservation of the IVC have been described(2). The hepatectomy represents the most difficult time during surgery, with life-threatening complications related to the risk of massive hemorrhage. In addition, the difficulty of hepatectomy is hard to define and to anticipate. There is no preoperative score that considers the morphological data of the native liver to anticipate hepatectomy difficulty; the existence of hypertrophy in the dorsal sector has been quoted by many authors, but there are few analyses of the surgical impact. The difficulty of hepatectomy seems to be related to the release of the IVC, and, thus, it depends on the hepatic segment in contact with the vein: the involved segments are I and IX, according to Couinaud(3), and anatomical variations of this hepatic sector are important. Both segments are linked in the back of the IVC by the IVC ligament(4). This dorsal sector of the liver is enlarged in the evolution of chronic liver disease into cirrhosis. There is a calculated caudate-right lobe ratio(5) defining cirrhosis, and this ratio changes in cirrhotic livers due to an enlarged the caudate lobe(6). In some cases, a caudate lobe entirely encircling the IVC in its retrohepatic portion can be observed in preoperative imaging. In the Rashi et al.(7) study, an analysis of 95 patients, the existence of a circular segment I appeared to be linked to an increased difficulty of the hepatectomy and to an increased risk of IVC clamping. Pre-transplant examination, including imagery, is systematic and primarily involves scanner-provided accessibility and improved identification of the vascular elements necessary to plan the surgery(8). To date, there are no pre-surgical predictive morphological criteria defining a difficult

hepatectomy. For the anesthesiologist, it could be of great interest to prepare and to manage a patient during the transplantation. At this stage, such anticipation is mainly based on the cirrhosis severity scores, which are predictive mortality scores: the CHILD and MELD (Model for End-Stage Liver Disease) scores. When the liver vena cava cannot be dissected, it may be necessary to resect the inferior vena cava in its retro hepatic portion and to perform a so-called "classic" liver transplant, with replacement of the vena cava. Current reconstruction techniques (piggyback) lead to the preservation of the recipient's vena cava, thereby avoiding complete vena cava exclusion. This technique should be favored because of its reduced ischemia time, its reduced blood loss and the decreased risk of renal failure(9).

The primary endpoint of our study was to determine whether the degree of encirclement of the vena cava is linked to an increase in intra-operative morbidity and mortality. The secondary endpoints were to find a correlation between hypertrophy and/or the degree of encirclement of the vena cava and liver disease or the severity of liver disease.

PATIENT and METHODS

Patient selection:

This retrospective two-center study (Montpellier and Rennes) included all LTs performed in 2013 and 2014. In our study, IVC conservation was attempted for all patients, according to the piggyback technique. In 51 of 320 cases, the reconstruction technique was piggyback; in 266 of 320 cases, it was anastomosis side-to-side (m-piggyback). Three patients required a "standard" reconstruction. To reduce bias, we excluded patients with previous LTs, patients with auxiliary liver transplantation, patients with liver polycystosis, and patients with left or right

hepatectomy in their medical histories. In total, 320 patients were included in the final group (82% men [n = 264/320]; mean age, 55 years; 70% of patients had alcoholic cirrhosis [n = 224/320]; and 10% [n = 32/320] had mixed cirrhosis).

Imaging review:

Data collection of the preoperative imaging was performed. All patients underwent preoperative imaging 109 days (on average) before transplantation. In 90% of cases, the preoperative imaging was contrast-enhanced (CT), and liver magnetic resonance imaging (MRI) was performed in the remaining cases (Table 1).

All preoperative imaging from the scanners or MRI was analyzed by the same operator using Intrasense Myrian Xp Liver ® software (approval by the American FDA 2012; ISO 9001 and ISO13485 since 2006) (Figure 1). Total liver and dorsal area volume measurements were performed, as well as a measurement of the posterior liberty degree of IVC. The existence of a circular caudate lobe (posterior liberty degree 0°) was observed in 74 patients (23%).

Reviews of patient records:

The medical records of the patients were analyzed by compiling data from the operative reports and intensive care and anesthesia records. We collected the number of packed red blood cells (PRC) and fresh frozen plasma (FFP) transfused per procedure, IVC injuries on operating and anesthesia reports, and hepatectomy and operating times. Postoperative data were also analyzed, focusing on IVC complications, with early surgical revisions (i.e., between postoperative day [POD] 0 and POD 7 following OLT) related to bleeding from the vena cava, or hematoma in contact with cavocaval anastomosis. For the PRC transfusions, we corrected data compared with pre-transplant hemoglobin administration. The anesthesiology policy

of the two centers is to transfuse 2 PRC units before surgery in patients with a starting hemoglobin level of less than < 8 g/dl.

Aims of the study:

The primary endpoint of this study was to find a correlation between the degree of encirclement of the IVC by the hepatic parenchyma and the intra and postoperative outcomes.

The secondary endpoints were to correlate hypertrophy in this dorsal sector with the etiology of cirrhosis. For all patients, the total liver volume and dorsal sector were measured. We analyzed the main causes of cirrhosis: alcoholic cirrhosis and viral cirrhosis. We also sought to establish a link between the existence of hepatocellular carcinoma (HCC) and hypertrophy in this segment. Then, we studied the possibility of a correlation between the severity of cirrhotic disease and this hypertrophy. To minimize the variability of volumes depending on the individual body, the ratio dorsal sector volume/liver volume was also studied.

Statistical analysis:

Statistical analyses were performed by the Department of Medical Information, using R 3.2.1 software. The significance threshold was set at 95% or corresponding to a p-value of < 0.05. Therefore, between-group comparisons were performed using the non-parametric Wilcoxon test. Comparisons between two quantitative variables were made using Spearman's correlation coefficient. Linear regression was performed for the continuous criteria to characterize differences, and binary criteria were analyzed using logistic regression. The stepwise selection method was used in the context of the variables explaining the revision surgery between POD 0 and POD 7. These variables were selected from those with a p-value of < 0.15 in the univariate analysis.

RESULTS

Circular dorsal sector:

In our study, 23% of the patients (n = 74/320) had complete IVC encirclement. In our population, we had to replace the IVC during the LT for 3 patients; 2 of these patients had a circular dorsal sector. We found a correlation between the existence of a paracaval circular sector and a significant increase in the number of transfusion of per operative PRCs, with an average of 4 PRCs in the group without circular segment and 7 PRCs in the group with circular segment (p = 0.01); the same result was observed after correcting the starting hemoglobin level (Table 2). Surgical revision due to anastomotic bleeding or hematoma in contact with the IVC between POD 0 and 7 post LT occurred 15 times: 8/246 times (3.3%) in the group without circular segment and 7/74 times (9.5%) in the group with a circular segment. In the circular segment group, the causes of reoperation were short hepatic veins bleeding in 3 cases and collateral vessels of retroperitoneum behind IVC dissected during the hepatectomy in 3 cases, as well as 1 case of anastomotic bleeding. In the non-circular group, the causes were short hepatic veins in 3 cases, anastomotic bleeding in 3 cases and retroperitoneal tissues in 2 cases. In the group with the circular segment, the difference was significant (p=0.05), and the relative risk of revision surgery increased by 31% when there was a circular dorsal sector. Concerning surgical time, we found no significant between-group difference in the operative time (360 vs 364 minutes) or in the hepatectomy time (124 vs 121 minutes). Even the impact of hepatectomy on the intervention (time of hepatectomy on operating time ratio) which could decrease the effect of the surgeons' speed differences. This ratio was not affected by the existence of a circular dorsal sector (the hepatectomy time represented 35% of the surgical time in the group without circular segment and 34%

in the group with; NS). There was no significant between-group difference in the incidence of IVC injuries during LT (N=5/274 (2%) vs N3/74 (4%). Furthermore, in our series, we reported no intraoperative stenosis of the cava due to stitches, which may occur when excessive stitches are placed particularly towards the hepatic veins, where the intrahepatic cava tends to be smaller. There was no significant between-group difference (Table 3).

Degree of IVC encirclement:

Spearman's correlation analysis showed a weak link between the degree of encirclement of the IVC and the operative time: a larger "free angle" of the IVC encirclement was associated with shorter operative time, but with a low level of significance (p= 0.07 [< 0.1]). In the linear regression model, the trend appeared to be identical, with a p= 0.08. The variability, however, remained low. Preoperative transfusions also seemed to indicate a connection between the increase of "the free angle" and the decrease of PRC transfusions after correction upon starting hemoglobin (p= 0.05). This result was noted without significant difference in the linear regression model (p=0.3). However, no link was established in our study between the degree of encirclement of the IVC and the incidence of IVC injuries (p=0.2) or early revision surgery (p=0.06).

Association liver disease/hypertrophy in the dorsal sector:

The secondary objective of our study was to identify an association between the underling liver disease and the hypertrophy in the dorsal sector. Regarding the dorsal sector volume, there was a correlation between alcoholic cirrhosis and hypertrophy in

this segment: 126 cc in the non-alcoholic cirrhosis group and 147.5 cc in patients suffering from alcoholic cirrhosis (p=0.05). Similarly, the presence of HCC seems to be linked to hypertrophy in the dorsal area; in this study, 137/320 patients had an HCC and in 104/137 of these patients, the liver disease was alcoholic. Compared to the severity of cirrhosis, a link appeared between the MELD and Child scores and the dorsal sector hypertrophy: lower scores aligned with a higher volume of the paracaval segment. Thus, for Child A patients, the dorsal sector volume was approximately 180 cc compared to 134 cc for the other stages (p=<0.01). Analysis of the dorsal sector/liver ratio seemed to reveal the same correlations between alcoholic cirrhosis and hypertrophy in the dorsal segment; in alcoholic cirrhosis, the dorsal sector represented 11% of hepatic volume compared with 8% in the other etiologies of cirrhosis (p=<0.01). This result was similar in the linear regression model, with a p-value =0.01. For the MELD score, the relationship between a low score and hypertrophy in the dorsal segment appears to be confirmed (p=0.02).

Analysis of portocaval shunts:

For policy, all transplant patients 168/320 performed at Rennes underwent a temporary (end-to-side) portocaval shunt. No significant difference in terms of PRC transfusion was found between the portocaval group and the other group. We observed a significant difference in the duration of hepatectomy, with a duration increased to approximately 18 minutes in shunt cases (p=< 0.01), but there was no impact on the total operating time. No significant difference was observed in either the number of IVC injuries or early re-operation cases (Table 4).

DISCUSSION

The existence of a circular dorsal sector influenced hepatectomy during LT, with increased bleeding and, therefore, PRBC transfusions. Similarly, the presence of one such segment enhanced postoperative outcomes, with a significant increase in the relative risk of early revision surgery due to bleeding around the IVC. When there is a circular segment, the relative risk of re-operation increased by 31% due to bleeding in contact with the IVC. To manage this bleeding and to avoid re-operation, we must accurately control hemostasis during the vena cava dissection, particularly in cases of circular segment (short hepatic and collaterals vessels of the retroperitoneum behind the IVC). Therefore, sometimes it may be helpful to temporarily clamp the IVC to expedite the hepatectomy and to better expose the dorsal area of the IVC. Polypropylene stitches are preferable than clips to control short hepatic vessels of the IVC. In fact, during the vena cava clamping, which is necessary for the anastomosis, the applied clips (metallic or not) may accidentally be removed or dislocated, causing severe bleeding. Finally, we recommended avoiding all clips to control the short hepatic or retroperitoneal vessel of the IVC, particularly when close to the clamping site.

Alcoholic etiology is a factor for abnormal development of the caudate lobe and for hypertrophy in this part of the liver. It is difficult in surgery to estimate blood loss per procedure, particularly in long surgeries, such as liver transplantation, in which the average duration is approximately 6 hours, as it was in our population (average, 377±115.6 minutes). In the 2007 R.S. Mangus et al study (10), the predictive factors for transfusion during the LT in the piggyback technique were the MELD score, surgical history, and operative time. In addition, several studies have demonstrated the negative impact of PRC transfusions on patients and graft survival (11). The

impact of the portocaval shunt on blood loss during a transplant remains unclear, however, the impact of a derivation would be most important for platelet transfusions (12). In the 2015 J.D. Kim et al study (13), the aim was to compare the incidence of portocaval shunts in cases of difficult hepatectomy. The authors performed a bypass in patients with previous upper abdominal surgery, acute liver failure, or large caudate lobes. The analysis found no significant difference in terms of the number of transfusions per procedure or perioperative outcomes. In our population, we found no significant between-group difference in terms of PRC transfusion. In the Navarro et al study (14), which focused on vascular complications in the reconstruction of the piggyback technique, IVC conservation was found to be the best technique to reduce vascular outcomes. The author questioned the relevance of achieving a “standard transplantation" in cases of circular dorsal sector. In our series, only 3 patients benefited from this type of reconstruction. The disadvantages of this technique in intra and post-operation (e.g., hemodynamic instability, kidney dysfunction and increase warm ischemia)(15) suggest that the choice of this technique should depend not only on the anatomical factor of native liver but also on several elements that define “difficult hepatectomy”, with important risks that include intraoperative bleeding, increased hepatectomy time, and difficulty reconstructing the IVC. Most studies that have investigated the predictors of the number of PRC transfusions, such as Ramos et al (16) 2003, have not considered the anatomical variables of the recipient liver patient. Regarding the analysis of the association between underling liver disease and hypertrophy in the dorsal sector, our study found a correlation between hypertrophy and alcoholic cirrhosis, which seems to correspond to the data reported in the literature (17). The caudate lobe hypertrophy is more important in alcoholic cirrhosis than in viral cirrhosis (18). The natural progression of cirrhosis

moves to right lobe atrophy, as well as enlargement of the caudate lobe and the side of the left lobe. Thus, advanced cirrhosis can be diagnosed by the caudate right lobe ratio. Early cirrhosis radiological signs are less specific, except for the enlargement of the periportal space (19-21). Our study observed this correlation between hypertrophy in the dorsal sector and alcoholic cirrhosis; however, it appears that the the development of cirrhosis evolves towards liver atrophy because the correlation with the MELD score seems to indicate that the as the severity of cirrhosis increases, the more paracaval segment volume decreases. This trend is consistent with the results in the 2007 study by Xiang-ping Zhou et al (20), which described a similar progression of the volume of the caudate lobe, depending on the severity of viral cirrhosis; however, our study did not observe this correlation for viral cirrhosis.

Several limitations to our study must be acknowledged, including its retrospective nature and use of two centers with different surgical technique patterns (realization of the portocaval shunt is systematic in Rennes). In addition, when measuring volumes, the dorsal sector of the liver has no anatomical landmarks on its right side.

In conclusion, the existence of a circular dorsal sector increases intraoperative bleeding and the number of PRC transfusions. Similarly, according to linear regression analysis, it seems that the degree of encirclement of the vena cava correlated with the number of transfusions. When there is a circular segment, the relative risk of re-operation increased by 31% due to bleeding in contact with the IVC.

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Table 1: Recipient demographic data (n=320)

Variable	Mean	Median
Gender (n)		
Male	264 (82%)	
Female	56 (18%)	
Age (yrs)	54.9±10.4	57 [50.6]
BMI (%)	26.2±5.3	25.9 [22.3]
HCC presence (n)	137 (43%)	
Alcoholic cirrhosis	224 (70%)	
Viral cirrhosis	68 (21%)	
Mixte cirrhosis	32 (10%)	
MELD score	19.1±10	18 [11.3]
Child score	8.9±2.9	9 [6-11.3]
A	87 (28)	
B	86 (27)	
C	141 (45)	
Operation time (min)	377±115	360 [283- 461]
Hepatectomy time (min)	133±58.9	122 [90-167.5]
Porto-caval shunt (n)	168 (53%)	
PRC (units)	5.9±5.3	5 [2-8]
FFP (units)	7.2±6.1	6 [3-10]

BMI: Body mass index; HCC: Hepatocellular carcinoma; RPC: Packet red cell; FFP: Fresh frozen plasma

Table 2: Effect of the existence of a circular dorsal sector

	Without circular (n=246)	**Circular (n=74)**	**P value**
Operation time (min)	360[282-460]	364[308.5-465.8]	0.42
Hepatectomy time (min)	124[90-166]	121[90.3-169]	0.87
Hepatectomy/operation time ratio (%)	35%[30-40]	34%[29-39]	0.62
Temporary IVC clamping (times)	23	12	0.23
PRC (units)	4[2-8]	7[3.3-8.8]	**0.01**
FFP (units)	6[3-10]	7[3-12]	0.51
RPC transfusion corrected (units)*	4[2-8]	7[3.3-8.8]	**0.01**
Vena cava injury (n)	5/246 (2%)	3/74 (4.1%)	0.39
Vena cava anastomosis bleeding (n)	5/246 (2 %)	4/74 (5.4%)	0.22
Vena cava haematoma (n)	7/246 (2.9%)	5/74 (6.8%)	0.16
Surgical revision between POD 0-7 (n)	8/246 (3.3%)	7/74 (9.5%)	**0.05**

*corrected on the base of the Hb level before surgery (<8 gr/dL). BMI: PRC: Packet red cell; FFP: Fresh frozen plasma. IVC: Inferior vena cava.

Table 3: Population with or without IVC encirclement

Variables	Without circular (n=246)	Circular (n=74)	P value
Gender (F)	42/246(17.1%)	14/74(18.9%)	0.85
Recipient age (yrs)	57[51-63]	56[47-62]	0.19
HCC presence (n)	101/246(41.1%)	36/74(48.7%)	0.31
Alcoholic cirrhosis (n)	173/246(70.3%)	51/74(68.9%)	0.93
Viral cirrhosis (n)	51/246(20.7%)	17/74(23%)	0.80
Mixte cirrhosis (n)	25/246 (10.2%)	7/74 (9.5%)	>0.99
MELD score	18[11-26]	19[10.1-25. 5]	0.69
Child score	9[6-11]	9[6-11.8]	0.93
Child A	66/241(27.4%)	21/74(28.4%)	0.99
Child B	67/241(27.8%)	19/74(25.7%)	0.83
Child C	108/241(44.8%)	34/74(46%)	0.97
Hb before surgery (gr/dL)	10.7[9.2-12.7]	10.85[9.7-13.3]	0.20

HCC: Hepatocellular carcinoma; PRC: Packet red cell; FFP: Fresh frozen plasma

Table 4: Comparison between porto-caval shunt group and without porto-caval shunt group (PCS = porto-caval shunt).

	Without PCS (n=152)	**With PCS (n=168)**	**Pvalue**
Operation time (min)	347.5[272.2-446.2]	372[300-472.5]	0.11
Hepatectomy time (min)	112[76.8-160.2]	129.5[93-177.5]	0.01
Hepatectomy/operation time ratio (%)	35%[28%,40%]	35%[31%,40%]	>0.99
PRC (units)	4.5[2.8-8]	5[2-8]	0.47
FFP (units)	8[4-12]	5[2-9]	0.68
PRC corrected transfusion (units)	4[2-8]	5[2-7.5]	0.48
Vena cava injuries (n)	4/152 (2.6%)	4/166 (2.4%)	>0.99
Vena cava haemorrhage (n)	5/152 (3.3%)	4/166 (2.4%)	0.74
Vena cava haematoma (n)	10/152 (6.6%)	2/166 (1.2%)	0.02
Surgical revision (between POD 0-7)	9/151 (6%)	6/161 (3.7%)	0.43

PRC: Packet red cell; FFP: Fresh frozen plasma

Figure 1 A,B,C: A) Segment I (arrow) and dorsal sector (segment IX, arrow) view of a cirrhotic native liver after a total hepatectomy. B) Posterior and anterior view of inferior vena cava and the dorsal sector. IVC= inferior vena cava; S1 = segment I; S9 = segment IX; VSH = hepatic veins. C) CT-views of the encirclement of the inferior vena cava. S1 = segment I; S9 = segment IX.