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Original article

Major hepatectomies are safe in patients with cholangiocarcinoma and jaundice

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A B S T R A C T

Background: Surgical resection is the only possibility of long term survival in patients with Klatskin tumours. However, surgical resection is a challenging problem and hepatic resection is often necessary.

Objective: The aim of our study was to assess the need for biliary drainage, resection rate and outcome of hilar cholangiocarcinoma in a single tertiary referral centre.

Patients and methods: From 2005 to 2008, 26 patients with Klatskin tumours were identified and assessed prospectively with multidetector CT and MR cholangiography in special cases. Seven patients (27%) were deemed to be unresectable in pre-operative staging. A total of 19 surgical procedures were performed, 8 left hepatectomies, 5 right hepatectomies, and 6 resections exclusively of the biliary tree.

Results: Resection rate was 73%, transfusion rate 53% and preoperative biliary drainage was performed only in 7 cases (37%). Major complications occurred in 11 (58%), including 2 post-operative deaths (10%).

There were no differences in the epidemiological data, when we separately analysed the outcomes of the 9 patients with bilirubin <15 mg/dL and the 10 patients with bilirubin >15 mg/dL. Biliary drainage was required in 6 (67%) patients in the group with low bilirubin levels versus 1 (10%) in the other group ($P=.02$). The mean bilirubin level in the jaundiced group was 22.1 (3.9) versus 4.7 (4.3) ($P<.001$) in the other group. There were no differences in the postoperative outcome between both groups.

Conclusion: Resection and survival rates have increased recently but still carries the risk of significant morbidity and mortality. Major hepatectomies in selected patients without percutaneous biliary drainage are safe.

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Las hepatectomías mayores en pacientes con colangiocarcinoma e ictericia son seguras

R E S U M E N

Palabras clave:

Colangiocarcinoma hiliar
Tumor de Klatskin
Drenaje biliar
Enfermedad
Tratamiento
Hepatectomía
Resultados

Introducción: En el tumor de Klatskin la única posibilidad de cura es la extirpación quirúrgica radical. No obstante, la resección quirúrgica es difícil.

Objetivo: El objetivo de este trabajo es valorar la necesidad de drenaje biliar preoperatorio, el índice de resecabilidad, el porcentaje de hepatectomías, la morbilidad y la supervivencia a largo plazo.

Material y métodos: Desde el año 2005 hasta el año 2008, se estudió a 26 pacientes con tumor de Klatskin mediante tomografía computarizada helicoidal con multidetectores y colangiografía por resonancia magnética en casos especiales. Siete pacientes se consideraron irresecables (27%). A los restantes 19 pacientes se les realizaron 8 hepatectomías izquierdas, 5 derechas y 6 resecciones exclusivamente de la vía biliar con linfadenectomía y hepático yeyunostomía a todos ellos.

Resultados: La resecabilidad fue del 73%, la transfusión del 53% y el drenaje biliar preoperatorio se utilizó en 7 casos (37%). La morbilidad fue del 58% y la mortalidad del 10%. La supervivencia y la recidiva a los 48 meses fueron respectivamente del 63 y del 37%.

Al comparar la evolución de los 9 pacientes con bilirrubina inferior a 15 mg/dl y los 10 pacientes con bilirrubina superior a 15 mg/dl, no hubo diferencias en los datos epidemiológicos. Seis pacientes (67%) con bilirrubina baja frente a un paciente (10%) del grupo de bilirrubina alta habían recibido un drenaje biliar preoperatorio ($p=0,02$). La bilirrubina del grupo no icterico era de $4,7\pm 4,3$ frente a $22,1\pm 3,9$ del grupo con ictericia ($p<0,001$). No hubo diferencias en la evolución postoperatoria.

Conclusión: La resecabilidad y la supervivencia postoperatoria de los pacientes con tumor de Klatskin han mejorado sensiblemente en los últimos años. En casos seleccionados, las hepatectomías mayores en pacientes con ictericia sin desnutrición ni colangitis preoperatoria son seguras.

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Introduction

Hilar cholangiocarcinoma or Klatskin tumour¹ is a rare tumour occurring at the confluence of the right and left bile ducts; it is associated with a poor prognosis. The only possible means of curing this tumour is radical surgical resection.² However, surgical resection is difficult due to the tumour's anatomical position close to major vascular structures surrounding the bile duct. There is therefore little knowledge of this type of surgical treatment in some medical environments and many of these patients receive palliative treatment via a prosthesis positioned by means of endoscopy or interventional radiology. One of the most significant prognostic factors following radical surgical removal is that this is done with negative surgical margins.³ It has recently been shown that if surgical resection is performed along with a hepatectomy with resection of the caudate lobe, the percentage of margins invaded and tumour recurrence are lower and survival longer.⁴ As a result, nowadays these patients tend to be referred to reference centres with greater casuistics to increase the possibilities of resection and to improve the outcome.

Consequently, the current standards for surgical treatment are resectability in 50% of patients, a hepatectomy in the majority of cases, with operative mortality lower than 10%,

post-operative morbidity of 50% and 50% and 30% survival rate in resected patients at 3 and 5 years, respectively.⁵

Nevertheless, there are still some unresolved questions regarding the pre-operative study and surgical preparation. Klatskin tumour is characterised as often presenting with jaundice. The jaundice is accompanied by malnutrition, increased enteric permeability and bacterial translocation, renal insufficiency and greater risk of post-operative hepatic insufficiency. Therefore, for Eastern authors, pre-operative biliary drainage is therefore obligatory.⁶ Some Western authors have already shown that it is possible to perform major hepatectomies in patients with jaundice without prior biliary drainage with acceptable mortality rates; however their work has not generally had much follow-up.⁷

For the authors of this article, the study policy for such patients is based on non-invasive examinations, such as computerised tomography (CT) with multidetectors and magnetic resonance cholangiography (MRC). With respect to pre-operative biliary drainage, this is reserved for patients with high bilirubin levels, pre-operative cholangitis and significant malnutrition.⁸ The aim of this study is to analyse the most recent experiences in the surgical treatment of Klatskin tumour and focus on the need for pre-operative biliary drainage, the resection index, the percentage of hepatectomies, morbidity and mortality and long-term survival.

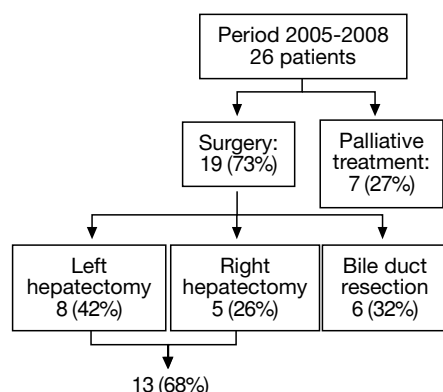


Figure 1 - Clinical evolution and treatment of 26 patients with hilar cholangiocarcinoma.

Material and methods

From January 2005 to September 2008, 26 patients with hilar cholangiocarcinoma or Klatskin tumour were referred to this centre (Figure 1).

All patients were first of all examined by means of an ultrasound to diagnose the degree of obstruction and rule out other causes of jaundice. To determine the tumour stage, helical CT with 10 slice multidetectors were used (16 since 2007) and efforts were made to rule out vascular variations, tumour invasion of the arterial or portal vein, the presence of adenopathy with the suspicion of tumour metastasis and the presence of hepatic metastasis.⁸ MRC was used to study the degree of bile duct obstruction in more detail, however only in special cases.

Radiological studies were reviewed in a weekly meeting with radiologists, oncologists and surgeons and surgical resection was indicated if this was considered appropriate for the patient. The radiological criteria for excluding resection included: bilateral occlusion of the portal vein trunk or the hepatic arteries, the presence of hepatic metastasis or adenopathy at the celiac artery region or the intraaortocaval region and significant spread to the secondary branches of the bile ducts. An exploratory laparotomy was performed on all patients with no anaesthetic or radiological contraindications.

The Bismuth-Corlette classification was used to stage patients; this is based on the extent of the proximal spread of the tumour.⁹ Pre-operative biliary drainage was indicated for patients with plasma bilirubin levels greater than 15 mg/dL, if they presented pre-operative cholangitis or if jaundice was accompanied with significant malnutrition and serum albumin levels lower than 3 mg/dL¹¹. Portal vein embolisation was indicated for those patients who were candidates for a right hepatectomy in which the remnant liver volume, calculated via CT-based volumetric analysis, was lower than 40% of the parenchyma.

In accordance with technical standards, the same surgical team operated on all patients. A thorough examination was performed shortly after the laparotomy. The extent of hepatic

infiltration was studied via intra-operative ultrasound to confirm the size of the lesion, its relation to the vascular structures and to rule out the presence of carcinomatosis or hepatic metastasis. After confirming resectability, a block dissection of the tumour was performed, including the biliary tree, all the ganglions and the fibroadipose tissue of the pedicle up to the celiac artery and retropancreatic region, with or without hepatectomy. The common bile duct was cut at the intra-pancreatic portion with intra-operative examination of the distal margin. If vascular invasion was suspected, resection of the portal or artery vein was performed. Proximal biliary resection was always performed in the right or left secondary branches. Biliary continuity was re-established by means of hepatic jejunal anastomosis with Roux-en-Y reconstruction. An intra-operative biopsy of the distal resection margin was always performed; if this was positive a cephalic pancreaticoduodenectomy would need to be performed or at least an assessment conducted to establish whether this could be done during a second intervention. Intra-operative biopsy of the proximal resection margins was not performed systematically due to its low profitability, false negatives and false positives, in particular, if the patient has an intraductal catheter, which always shows signs of inflammation.

The surgical specimen was examined jointly by the pathologist and the surgeon. The TNM (tumour, node, metastasis) classification was followed in accordance with the guidelines of the International Union Against Cancer.¹⁰

Pre-operative nutrition was enteral or oral for all patients along with prebiotics (Actimel® Danone, Belgium) and probiotics (Impact oral® Nestle Healthcare, Esplugues de Llobregat, Barcelona).

The following were prospectively entered into a Microsoft Access® 2003 database: demographic data, radiology results, pre-operative biliary drainage, histopathological data, duration of the intervention, haemorrhage, transfusion, morbidity and mortality (defined as death within 30 days or before discharge), tumour recurrence, and survival. Patients were followed up every 3 months during the first year and every 6 months after that. Statistical analysis was performed using the SPSS program for Windows (version 10.0, Chicago, IL). Continuous variables were compared using the Student *t* test and categorical variables with the χ^2 test. Survival was calculated using the Kaplan-Meier method and compared using the log rank test. *P* < .05 was considered statistically significant.

Results

Seven patients (27%) out of the 26 assessed were considered unresectable or as having medical contraindications for the intervention, according to the pre-operative studies; these patients were given palliative treatment straight away. The remaining 19 patients were operated on and resection was performed on all of them as a curative measure; these patients comprised the study group (Figure 1).

There were 11 males and 8 females. The average age was 63 and pre-operative bilirubin levels were 15 mg/dL (nominal value, 1.2). According to the Bismuth classification, the

majority of tumours were type III, followed by type I, II, and IV. Four patients were referred to the centre having already undergone pre-operative biliary drainage. Pre-operative drainage was indicated in another 3 patients (37%) due to bilirubin levels greater than 15 mg/dL along with hypoalbuminemia (Table 1). A hepatectomy was performed in 13 patients (68%): eight left hepatectomies and 5 right hepatectomies. Resection of the caudate lobe was also performed in all patients (100%) and of the portal vein in 1 case (5%). In 6 patients (32%) with tumours with a low proximal tumour margin (Bismuth I) or contraindications for a hepatectomy, the bile duct was removed and a lymphadenectomy performed. In all patients the bile duct was reconstructed via Roux en Y hepaticojejunostomy (range, 2-6 cuts) (Figure 1).

Figure 2 shows the distribution of the casuistics of this study according to the Bismuth-Corlette classification and the type of surgical resection with or without hepatectomy.

Table 1 – Epidemiological variables and type of surgical treatment

Variable		
Age, mean (SD), y	63 (9)	Range, 46-75
Gender, M/F (%)	11/8	(58/42)
Bilirubin, mg/dL	14.6 (9.6)	Range, 1-27
Albumin, mg/dL	3.55 (0.44)	Range, 2.9-4.6
Bismuth classification, I/II/III/IV	6/4/7/2	
Pre-operative biliary drainage, n (%)	7	(37)
Resectability n (%)	19/26	(73)
Hepatectomy n (%)	13/19	(68)
Resection of the caudate lobe, n (%)	13/13	(100)
Resection of the portal vein, n (%)	1/19	(5)

F indicates female; M, male.

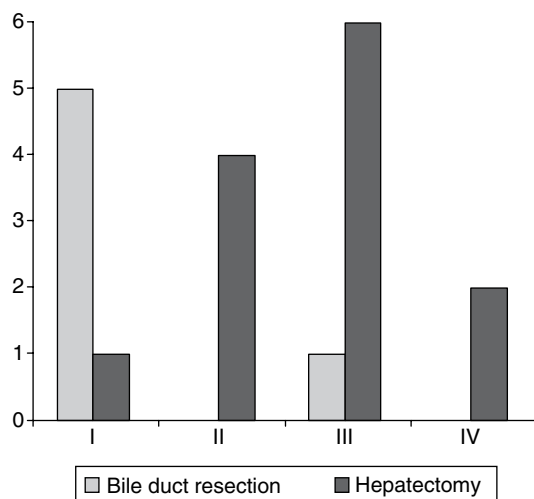


Figure 2 - Distribution of patients according to the Bismuth-Corlette classification and type of surgery performed: resection of the bile duct in blue (or black) and hepatectomy in red (or white).

Clearly, there was greater need for a hepatectomy the higher the upper limit of the tumour.

Blood loss was approximately 900 mL. However, 2 patients required intra-operative transfusion and 9 post-operative transfusions due to chronic anaemia, post-operative haemorrhage, and re-interventions. The post-operative stay was more than 3 weeks due to complications, such as biliary fistula (47%) or abdominal abscess (26%). There were 2 re-interventions due to haemoperitoneum and failure of the Y-de-Roux anastomosis. Operative mortality was 10% (2 cases) (Table 2).

The histopathological study showed invasion of the surgical margin in 7 patients (37%). The distribution of the post-surgical TNM classification showed pT1 in 1 case, pT2 in 2 cases, pT3 in 10 cases, and pT4 in 1 case. The average number of ganglions resected per patient was 9.8 (4.6) of which 1.1 (1.8) were positive. Ten patients had negative ganglions pN0, 7 had negative ganglions pN1, and 1 patient had negative ganglions pN2.

All patients with stage pT3 or higher, margins in contact with the tumour or positive ganglions, underwent a regime of 45 Gy post-operative radiotherapy and chemosensitization with intravenous 5-fluorouracil.

Tumour recurrence rate was 35% at 48 months (Figure 3) and actuarial survival at 48 months was 63% (Figure 4).

In order to study the impact of the degree of jaundice on the post-operative evolution of the hepatectomies, the patients were divided into those in which bilirubin levels immediately before the intervention were lower or higher than the average (15 mg/dL). The results are shown in Table 3 and Table 4.

No differences were found in the epidemiological data. The majority of patients with low bilirubin levels had underwent pre-operative biliary drainage ($P=0.02$), although biliary drainage was unsuccessful in one patient with high pre-operative jaundice levels. Bilirubin levels among the jaundiced group were four times higher than that of the group with no jaundice ($P<0.001$). The distribution of the Bismuth staging was practically identical among both groups. There were no differences in the type of intervention or type of hepatectomy.

Table 2 – Intra-operative and post-operative evolution of surgical patients (n=19)

Variable	No. (%)	
Post-operative stay, days average (SD)	24.8 (21)	
Post-operative mortality	2	10
Blood loss, average (SD), mL	870 (537)	
Transfusion (pre-operative and post-operative)	10	53
Reoperation	2	10
Complications (patients)	11	58
Biliary fistula	9	47
Deep abscess	5	26
Infection of the superficial wound	5	26
Haemoperitoneum	1	5
Hepatic insufficiency	3	16

SD indicates standard deviation.

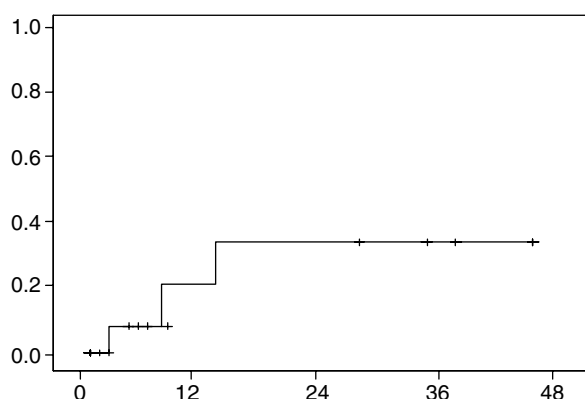


Figure 3 - Rate of tumour recurrence in the 19 surgery patients. Recurrence at 48 months (37%).

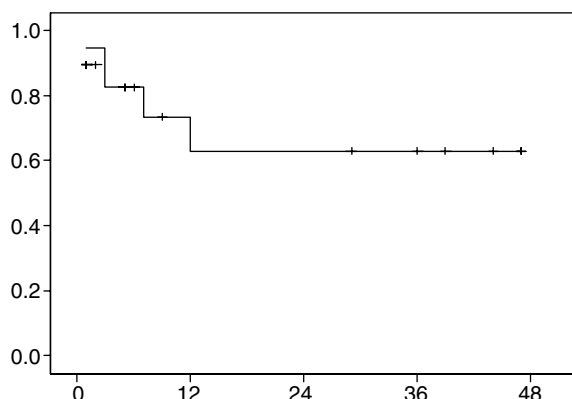


Figure 4 - Actuarial survival of the 19 surgical patients. Survival at 48 months (63%).

However, in all cases there were more hepatic resections among jaundiced patients. There were no differences in terms of blood loss or the duration of the intervention.

Nor were there any significant differences in the post-operative evolution (Table 4). Morbidity and type of complications were similar. Nor were there any differences found in terms of transfusions, re-admission and mortality between both groups.

Discussion

This study, like other studies conducted by Eastern groups,^{6,11,12} shows that the resection index of patients with Klatskin tumour in specialist surgical centres can be high (73% in this group). Although bias cannot be excluded due to the fact that the most serious or oldest patients do not attend these centres; if the region's healthcare structure is taken into account, this is of little significance. The healthcare region includes seven district hospitals and this hospital is the reference centre for high technology, both in terms of endoscopy and high technology oncological surgical resources. Traditionally, in Western centres the resection index is much lower (between 30% and 50%).^{2,4,11,13} However, more recent studies from Europe, America, and Asia confirm these results with an increased resection index of 50% to 70%.^{14,15}

Pre-operative biliary drainage is not exempt from risks itself: it could cause cholangitis, extend the pre-operative stay, fail to improve the nutritional state and or the immunological status and increase post-operative complications due to infection. According to surgeons at Nagoya University,¹¹ biliary drainage must be bilateral or of all of the affected segments, while for other authors,¹⁶⁻¹⁸ unilateral biliary drainage on the remnant only, which is not going to be resected, presents advantages in terms of hepatocyte regeneration and lower morbidity. In this study, only 37% of patients required

Table 3 – Epidemiological variables and type of surgical treatment in patients with pre-operative bilirubin greater or less than 15 mg/dL

Variable	Bilirubin		P
	<15 mg/dL (n=9)	>15 mg/dL (n=10)	
Male, n (%)	4 (44)	7 (70)	.26
Age, mean (SD), y	61 (10)	64 (7.8)	.53
Pre-operative biliary drainage, n (%)	6 (67)	1 (10)	.02
Pre-operative bilirubin, mg/dL	4.7 (4.3)	22.1 (3.9)	<.001
Albumin, mg/dL	3.68 (0.49)	3.39 (0.32)	.17
Bismuth classification, I/II/III/IV	3/2/3/1	3/2/4/1	.93
Hepatectomy, n (%)	6 (67)	8 (80)	.38
Right hepatectomy n (%)	2 (25)	3 (30)	
Left hepatectomy n (%)	4 (44)	4 (40)	
Resection of bile duct only, n (%)	3 (38)	3 (30)	.94
Blood loss, mean (SD), mL	800 (440)	916 (613)	.69
Intervention duration, mean (SD), min	298 (77)	321 (67)	.50

SD indicates standard deviation.

Table 4 – Intra-operative and post-operative evolution of patients with pre-operative bilirubin levels greater or lower than 15 mg/dL

Variable	Bilirubin		P
	<15 mg/dL (n=9), No. (%)	>15 mg/dL (n=10), No. (%)	
Mortality	1 (10)	1 (10)	.71
Patient morbidity	5 (63)	6 (60)	.65
Biliary fistula	4 (44)	5 (50)	.59
Deep abscess	3 (33)	2 (20)	.44
Infection of the superficial wound	3 (33)	2 (20)	.44
Hepatic insufficiency	1 (11)	2 (20)	.54
Ascites	1 (14)	3 (30)	.44
Post-operative stay, mean (SD), d	29 (10)	22 (12)	.51
Readmission	2 (25)	1 (10)	.41
Transfusion (pre-operative and post-operative)	5 (56)	5 (50)	.59

pre-operative biliary drainage. This is much lower than the figure of 100% in the group described by Nimura et al¹¹ and other American, European or Eastern authors.¹³⁻¹⁵ This figure can be explained by 2 reasons: a) we are beginning to see the benefits of the efforts in the different district hospitals in this region to refer these patients early; b) our guideline for performing biliary drainage in patients is bilirubin levels greater than 15 mg/dL, unlike other centres which perform drainage on all patients or those with bilirubin levels greater than 5 mg/dL.¹⁴ Among the above-mentioned patients, pre-operative biliary drainage by means of endoscopy was performed on 4; this failed to reduce bilirubin levels in one patient. Pre-operative biliary drainage via interventional radiology was indicated in two cases and via endoscopy in another; this caused chronic cholangitis in this patient, which ruled out a hepatectomy and therefore only resection of the bile duct and a lymphadenectomy were performed. Complications inherent to biliary drainage can reach up to 25%¹³ and can contaminate the bile retained and, therefore, transform clean surgery into contaminated surgery with the accompanying septic complications. Biliary drainage was therefore avoided where possible. Pre-operative biliary drainage is mainly indicated in cases of extended hepatic resection, such a right hepatectomy or a right trisectionectomy. However, due to the small number of patients, it is not possible to draw conclusions on evolution in terms of bilirubin levels in the 5 patients who underwent a right hepatectomy. When necessary, pre-operative percutaneous biliary drainage via interventional radiology is preferred. The drainage is only positioned on the future liver remnant proximal to the tumour and the bile is collected and reinfused via a small calibre nasoenteral tube to prevent poor absorption of lipo-soluble vitamins, malnutrition, bacterial translocation and alkaline gastritis.¹⁹

As a result, the authors of this work will uphold the same policy: promote early referral of these patients, perform a rapid non-invasive study based on CT with multidetectors, pre-operative preparation based on care of the nutritional state using symbiotics¹⁰ and early intervention if the patient does not present cholangitis or hypoalbuminemia.

Achieving complete resection of the tumour with negative margins is the main objective of the surgical treatment of Klatskin tumours. Performing a hepatectomy during surgery increases resectability and the number of patients with negative margins. However, it is very important that at the end of the intervention or during consultation with the pathologist, samples are taken of the border of the proximal resection to establish whether the resection has been complete and, if not, propose chemotherapy or post-operative radiotherapy. The intra-operative study by freezing the proximal margin in this study is not very reliable, yielding false negatives and one false positive. Nor will knowing the intra-operative result of the margin status have any clinical relevance, since in this technique, the bile duct is split at the end, following the hepatic transection and it is no longer possible to extend the margins of the bile duct.

If the histopathological study is thorough unfortunately the number of cases with positive margins remains high (37% in this case). However, these figures are much lower than those of 50% to 70% published in the first series^{11,20-23} and are closer to the 20% obtained in the most recent studies.^{4,6,12,24} A significant finding in this work is the long-term survival of patients with positive margins. In this study, only 1 patient presented with macroscopic invasion and microscopic invasion presented in the other 6. This could also be explained by the beneficial effect of adjuvant chemotherapy and radiotherapy treatment.¹² Due to the small number of patients, it is not possible to draw conclusions on the significance of the hepatectomy when analysing margin invasion or tumour recurrence.

The portal vein was only resected in one patient who underwent a right hepatectomy and who presented invasion of the left portal vein. The non-touch technique proposed by Neuhaus with block resection, including the portal vein, seems appropriate.²⁴ However, the results published to date indicate that while the resection of the portal vein should not necessarily be considered as a standard part of all interventions, nor should the suspicion of tumour invasion of the portal vein be a contraindication for curative surgical resection.¹⁴

One of the most encouraging findings is the high long-term survival (63% at 48 months among the patients who underwent resection), which provides encouragement to continue with this surgical policy of radical resection based on hepatectomy of the side with vascular involvement or the secondary branches. It was not possible to identify significant factors, the presence of adenopathy or invaded margins, nor for a hepatectomy to be performed. This is most likely explained by the small number of patients.

The main objective of this work was to confirm that the performance of a major hepatectomy in these patient yields a good outcome, even if bilirubin levels are greater than 15 mg/dL.⁷ There were no differences in the pre-operative and intra-operative data or in the operative or post-operative evolution. Although infections of the surgical wound and deep abscesses were less frequent in the group with bilirubin levels lower than 15 mg/dL, this difference was not statistically significant. The performance of a greater number of pre-operative biliary drainages in the group of jaundiced patients, and the consequent septic contamination, is probably the most likely explanation for the infections.

In conclusion, the resectability and post-operative survival of patients with Klatskin tumour on whom radical resection is possible has significantly increased in recent years. In certain cases, major hepatectomies in certain patients presenting no pre-operative malnutrition or cholangitis are safe.

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