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Original article

Liver transplantation increases R0 resection and survival of patients with a non-disseminated unresectable Klatskin tumour

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ARTICLE INFORMATION

ABSTRACT

Introduction: There are no established indications for liver transplant (LT) in patients with a Klatskin tumour (KT) due to the differences in the published results.

Objective: To report on our patients who have non-disseminated unresectable KT and who were given a LT, and to compare results with those of patients who have had tumour resection and those who have not.

Patients and method: We have treated 75 patients diagnosed with KT. The mean age was 62 (11) years (range, 38–88 years) and 50 were males (66%). Twenty patients were inoperable. Of the 55 patients who underwent surgery: tumour resection (TR) was performed in 29 cases; there was no tumour dissemination in 11 unresectable cases and therefore these patients were added to the LT waiting list and the remaining 15 unresectable cases had tumour dissemination and remained on palliative treatment.

Results: In the LT group there was no postoperative mortality (during the first month) and the survival rate was 95%, 59%, and 36% with a disease-free survival of 75%, 40%, and 20%; whereas the patients given RT had a survival rate of 80%, 52%, and 38% at 1, 3, and 5 years, with a disease-free survival of 65%, 35%, and 19%, without any differences compared to the LT group. Patients with unresectable tumour left on palliative therapy had a lower survival than the unresectable who underwent LT (P<.001).

Conclusions: In patients with non-disseminated unresectable KT, LT has a similar survival to that obtained in cases with resectable R0 liver resection. LT improves the survival rate achieved using palliative treatment in patients with non-disseminated unresectable KT.

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El trasplante hepático aumenta la resecabilidad R0 y la supervivencia de los pacientes con tumor de Klatskin irresecable no diseminado

R E S U M E N

Palabras clave:
Tumores hepáticos
Tumor de Klatskin
Trasplante hepático
Cirugía hepática

Introducción: La indicación de trasplante hepático (TH) en el tumor de Klatskin (TK) no está establecida debido a la discrepancia en los resultados de las series publicadas.

Objetivo: Presentar los resultados del TH en pacientes con TK irresecable no diseminado y compararlos con los obtenidos en los pacientes no resecados y con resección del tumor.

Pacientes y método: Hemos tratado 75 pacientes con TK. La edad media fue de 62±11 años (rango: 38–88) y 50 fueron varones (66%). Veinte pacientes se consideraron inoperables. Se realizó resección del tumor (RT) en 29 de los 55 pacientes operados, TH en 11 casos (en tumores irresecables no diseminados) y tratamiento paliativo en los 15 pacientes con TK irresecables diseminados.

Resultados: En el grupo TH no hubo mortalidad postoperatoria (primer mes) y presentaron una supervivencia a 1, 3 y 5 años del 95, el 59 y el 36% con una supervivencia libre de enfermedad (SLE) del 75, el 40 y el 20%. Los pacientes con RT presentaron una supervivencia del 80, el 52 y el 38%, con una SLE del 65, el 35 y el 19%, sin diferencias respecto al grupo TH. Los pacientes con tumor irresecable que quedaron con tratamientos paliativos presentaron una supervivencia inferior a la de los pacientes con tumores irresecables que recibieron TH (p < 0,001).

Conclusiones: En pacientes con TK irresecable no diseminado, el TH consigue una supervivencia similar a la obtenida en los casos resecables con la resección hepática R0, y mejora claramente la esperanza de vida de estos pacientes con tratamientos paliativos.

Introduction

The most accepted treatment for hilar cholangiocarcinoma (Klatskin tumour, KT) is R0 liver resection, which presents a 5-year survival for between 20% and 45%[1-16] of cases. In inoperable patients, survival is 0 to 5 years, and in patients whose tumour is unresectable without dissemination (due to the extension of the tumour to the intra-hepatic biliary radicals, bilaterally), the prognosis is similar to inoperable patients. In these cases, some authors propose a liver transplantation (LT),[17-26] although some groups considered this contraindicated due to the shortage of organs. In 1993, the Mayo Clinic group launched a chemo-radiotherapy protocol prior to LT in these same patients, presenting good results after 5 years.[27-31]

Our goal is to present the results obtained in our patients with KT, which in the course of the laparotomy were considered unresectable due to infiltration of the intra-hepatic bile duct in the absence of extra-hepatic disease, who subsequently received LT. The results of this group of patients are compared with those obtained in patients who could undergo a resection without LT and with those of patients without resection either because they were inoperable or because the disease was found to be disseminated during the laparotomy.

Patients and method

From May 1988 (start date of our LT program) until October 2008, we treated 75 patients with the diagnosis of KT. The median age was 62 (11) years (range, 38-88 years) and 50 were males (66%). In 69 patients, the symptoms were secondary to cholestasis and the total bilirubin (TB) level was 14 (11) mg/dL (range, 5-44), in 6 cases (8%) there was no jaundice and one dissociated cholestasis was found in the analytical tests.

Eleven patients (14%) presented renal failure with creatinine levels greater than 3. All patients underwent ultrasound and triple-phase hepatic CT, looking for dilated intrahepatic biliary radicals, a tumour mass in the porta, liver metastases, retroperitoneal or hepatic hilum lymphadenopathy and portal or arterial invasion. Since 1998 we have been performing systematic cholangio-MR (50 patients). In 63 patients (84%), all with TB levels above 10 ng/mL, a percutaneous transhepatic cholangiography was performed by placing an external supratumoural intrahepatic biliary drain to avoid manipulating the tumour. When we considered the patient to be inoperable,[32] we inserted an internal-external guide or permanent transtumoural prosthesis.

To determine the location of the tumour, we used the classification of Bismuth-Corlette[33]: five cases of type I (6.6%), 4 cases type II (5.3%), 22 type III cases (29.3%), and 44 type IV cases (58.6%). For the final staging of the tumour, we used the TNM classification of the international union against cancer (UICC).[34]

Twenty patients were considered inoperable (inoperable criteria in Table 1). Tumour resection (TR) was performed in 29 of the 55 patients who underwent surgery, 11 were unresectable tumours without dissemination, and they were therefore included on the waiting list for LT, and 15 patients with unresectable tumours with dissemination were given palliative treatment (Table 1).

Table 1 – Inoperability (n=20) and unresectability (n=15) criteria in Klatskin's tumour

Inoperable (20 patients)

Older age and functional defects of the patient	8 cases
Multi-organ failure	4 cases
Distant metastasis	4 cases
Gastrointestinal haemorrhage[a]	1 case
Complications: radiological drainage[b]	2 cases
Refusal of treatment by patient	1 case

Unresectable (15 patients). Consideration of locally advanced disease by the surgeon

Arterial and portal invasion	4 cases
Mesenteric and retroperitoneal lymph node	5 cases
Bilateral liver metastases	3 cases
Carcinomatosis	3 cases

[a]The patient had hemorrhagic gastritis, renal failure, worsening of liver function, and multi-organ failure.
[b]After percutaneous drainage, one patient had biliary peritonitis and sepsis, and the other presented a large subcapsular haematoma. Both suffered deteriorated liver function and developed multi-organ failure.

The group of patients who did not undergo tumour resection was composed of 35 patients (20 inoperable and 15 unresectable), and the group of patients whose tumour could be resected consisted of 40 patients: twenty-nine with TR and 11 with LT.

Statistical method. Rates and survival curves were calculated using the Kaplan-Meier method and log-rank test. Survival data of each group are summarized by their survival rates at 1, 3, and 5 years with 95% of confidence intervals. Potential prognostic factors for survival were evaluated with the Cox proportional hazards regression model. We present the results of the prognostic factors for survival, selected with the risk ratio for each category (odds ratio) and its 95% of confidence interval a $P<.05$ was considered statistically significant.

Results

Patients without tumour resection (n=35)

In inoperable cases (n=20), half-life was 6 (2) months (range, 1-14 months). In the first month of admission 7 patients died (35%) from complications and the 13 remaining patients died of advanced neoplastic disease. No patient received chemoradiotherapy. In the cases considered unresectable (n=15), half-life was 9 (2) months (range, 1-30 months), 2 patients died after surgery due to multi-organ failure. Five patients received chemotherapy (gemcitabine), of which only 2 patients lived for 16 and 30 months.

Patients with tumour resection (n=40)

LT group (n=11). All had undergone a laparotomy with attempted resection, and the surgeon did not feel capable of achieving an R0 resection from the intrahepatic bile extension. Tumour dissemination was not found in any case. The average waiting time was 2 months (range, 1-4 months) and 2 patients received chemotherapy with gemcitabine during the waiting period. The technique consisted of a block resection of the entire bile duct until it entered the pancreas, a distal resection of the tumour of the portal vein and hepatic artery. We performed extensive lymphadenectomy of the portal vein and the hepatic artery. In all cases, intraoperative biopsies of the distal bile duct and glands in the portal vein were negative. There were no cases of invasion of the inferior vena cava, and thus the classical technique was performed in 2 patients and the piggy-back technique was used in the remaining 9 patients. The biliary reconstruction was performed by Roux-Y hepaticojejunostomy. Two patients had positive nodal disease (N1) in the final anatomical pathology (Table 2). No patients received postoperative chemotherapy or radiotherapy. There was no postoperative mortality (first month). R0 resection was achieved in all cases. The half-life was 60 (17) months (range, 12-122 months) and 7 patients died in follow-up, all from tumour disease: five recurring abdominal tumours (at 12, 16, 19, 43, and 46 months), one from lung metastases (12 months) and one for a de novo abdominal tumour (undifferentiated tumour with a lymphomatous origin at 122 months). Four patients lived for 96, 72, 39, and 12 months, respectively.

TR group (n=29). Four of them (13%) underwent local tumour resection, all Bismuth I, with complete resection of the bile duct and Roux-Y hepaticojejunostomy (Table 2). In 25 cases (87%) hepatectomy was associated with resection of the caudate: left in 18 cases, right in 4 cases, and broadened right in 3 cases. In all cases, reconstruction was performed on 2 or 3 biliary radicals, all guided. In all patients, lymphadenectomy of the hepatic hilum and the celiac axis was associated, and in 2 cases, retroperitoneal lymphadenectomy. Seven patients had hilar lymph node invasion, 3 patients had retroperitoneal lymph node invasion, and 2 patients had liver metastases in the left lobe that was resected (Table 2). In 5 patients, with invasion of the portal vein, resection was performed of the entire circumference of the portal vein with end-to-end anastomosis or partial resection with its removal. Five patients received postoperative chemotherapy (5-fluorouracil) plus external radiotherapy. The half-life was 49 (8) months (range, 1-78 months). One patient (3.4%) died at 2 months due to biliary sepsis and multi-organ failure.

At follow up, 13 patients have died of tumour recurrence (44%) (4 with local tumour resection and 9 of the 25 remaining patients with liver resection). Therefore, 16 patients are still alive, 2 with disease relapse in current treatment with chemotherapy.

Comparisons between groups

In the LT group, the mean age was lower ($P<.02$), the TB was higher ($P<.003$), and the Bismuth IV was more frequent ($P<.05$) than in the TR group (Table 2).

Inoperable patients (n=20) had a 1-year survival rate of 27% and 0% at 2 years. Those unresectable patients with dissemination who did not receive LT (n=15) had a survival rate of 28% per year and 12% at 2 years, much lower than that obtained for unresectable patients receiving LT ($P<.001$). Patients with LT had a survival of 95%, 59%, and 36% with a

Table 2 – Characteristics of patients with tumour resection and liver transplantation			
Variables	Resection (n=29)	Transplant (n= 1)	P
Age	64 (10)	51 (10)	.02
Sex: males	14 (48%)	10 (91%)	.036
TB	6.9 (6.3)	12.8 (4)	.003
Ca 19/9	382 (197)	371 (197)	.385
Renal failure	1 (3.4%)	1 (9%)	.792
Bismuth			
I	4 (13.8%)	1 (9%)	.05
II	1 (3.4%)	10 (91%)	
III	17 (58.6%)		
IV	7 (24%)		
LM	2 (6.8%)	1 (9%)	.527
TNM			
T1N0M0	2 (6.9%)	1 (9%)	
T2N0M0	6 (20.6%)	3 (27%)	.380
T3N0M0	11 (37.9%)	4 (6%)	
T2N1M0	1 (3.4%)	0	
T3N1M0	4 (13.8%)	2 (18%)	
T3N2M0	3 (10.3%)	0	
T3N0M1	0	1 (9%)	
T3N1M1	1 (3.4%)	0	
T3N2M1	1 (3.4%)	0	
Stages			
I-II	8 (27%)	4 (36%)	.391
III-V	21 (73%)	7 (64%)	
Histological type			.269
Scirrhous	22 (75%)	10 (91%)	
Non scirrhous	7 (25%)	1 (9%)	
Invasive margin	5 (17%)	0%	.127
Vascular invasion	5 (17%)	1 (9%)	.475
Parenchyma invasion	20 (68%)	7 (63%)	.497
Lymph node invasion	10 (34%)	2 (18%)	.285
Peri-neural invasion	20 (68%)	10 (91%)	.05
Adjuvant treatment	5 (17%)	0%	.182
Mortality 1st month	1 (3.4%)	0%	.358
Survival at 1, 3, and 5 years (DFS)	80%, 52%, and 38% (65%, 35%, and 19%)	95%, 59%, and 36% (75%, 40%, and 20%)	.727
DFS indicates disease-free survival; LM, liver metastases; TB, total bilirubin.			

disease-free survival of 75%, 40%, and 20%, and patients with TR (n=29) had a survival of 80%, 52%, and 38% at 1, 3, and 5 years with a disease-free survival of 65%, 35%, and 19%, without significant differences regarding the LT group (Figure).

Prognostic factors for survival in resected patients (n=40) (Table 3)

Bismuth I and II patients (P<.005) and vascular invasion (P<.02) were factors for a poor prognosis of survival (the Bismuth I-II, possibly related to the performance of local tumour resection). Advanced stages were near the statistical significance of a poor prognosis because they showed worse survival at 5 years than early cases (19% vs 38%), scirrhous histologic types (23% vs 58%), and peri-neural invasion (31% vs 50%).

Discussion

Most authors consider the LT contraindicated in KT due to poor published results, despite getting more resecability,[18] which in our series[35,36] was 100%, while the number found in the series by Hidalgo et al[37] was 75%. Some authors, by seeking a higher R0 resection, associate the DPC[18] to the LT, and even Starlz et al[19,20] extend the resection to adjacent organs (cluster transplantation).

The poor results are associated with high tumour relapse, which occurs between 56% and 96% of patients,[21-26,35-37] usually in the abdomen, which is related to the immunosuppression that favours the spread of the tumour remains that may go undetected. These results are also related with a poor selection of patients, as LT was indicated for tumours that
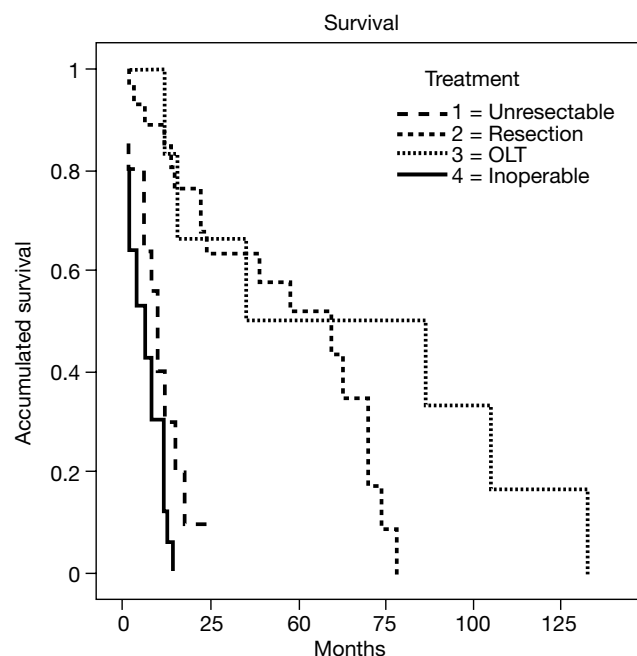
Figure – Survival curves of patients with liver transplantation, resection, unresectable with palliative treatments and inoperable patients.

Table 3 – Univariate analysis of prognostic factors for survival in patients with tumour resection (resected and transplanted) (n=40)

Variables: 40 cases	5-Year survival	P
Age		
<60 y	39%	.301
>60 y	33%	
Sex		
Males (n=24)	29%	.282
Women (n=16)	48%	
Bismuth		
I-II (n=5)	0%[a]	.005
III-IV (n=35)	44%	
Stages		
I-II (n=12)	38%	
III-IV (n=28)	19%	.09
Histological type		
Scirrhous (n=32)	23%	.08
Non scirrhous (n=8)	58%	
Invasive margin		
Yes (n=5)	39%	.307
No (n=35)	38%	
Vascular invasion		
Yes (n=6)	0%	.02
No (n=34)	44%	
Parenchyma invasion		
Yes (n=27)	40%	.656
No (n=13)	31%	
Lymph node invasion		
Yes (n=12)	32%	.651
No (n=28)	44%	
Peri-neural invasion		
Yes (n=30)	31%	.08
No (n=10)	50%	
Adjuvant treatment		
Yes (n=5)	40%	.384
No (n=35)	37%	

[a]In all cases there had been local tumour resection.

were considered non-disseminated, however in the explant histological study there was ganglion, arterial and portal invasion as well as peritoneal dissemination. As a result, in the series of LT in KT, 5-year survival ranges between 0% and 38%[21-26,35-37] and, with greater intensity (cluster transplantation), it does not exceed 38%.[19,20]

Despite the poor results, it was demonstrated that some patients with HT showed prolonged survival. Therefore, in the Spanish series[35] with a postoperative mortality of 8.3%, we collected 36 HT from KT with a 5-year survival of 30%. However, in the early stages (stages I-II) the rate was 47%, whereas in stages III-IV the rate was only 15%, results similar to those obtained in this study. In a similar study, Kaiser et al[38] (experience in Germany) reported 47 patients transplanted from KT, with a higher postoperative mortality (20%), and a survival rate of 22% at 5 years. When the selection criteria were more strict (since 1998) survival of 15 transplanted patients was 48% at 5 years (P<.014).

Some series compare the resection with non-neoadjuvant LT. Hidalgo et al[37] collected 106 patients with KT, resection was achieved in 44 cases and LT was performed in 12 cases. There were no differences in sex, early stages, tumour size, lymph node invasion (7 of LT group were N1), degree of differentiation, peri-neural invasion, and vascular invasion when comparing resection and LT. There were no differences in survival rates at 5 years (28% with resection compared with 20% with LT). As in our series, patients who received LT were younger than patients with resection (P<.012). Stage III-IV were factors of poor prognosis along with R1-2 resections, presence of lymph node invasion, the presence of liver metastases, undifferentiated tumours and vascular invasion. Similarly,

Iwatsuki et al[39] and us[36] did not find survival rate differences between LT and TR with liver resection.

At present there are data in the medical literature indicating that non-disseminated unresectable KT is a good indication for LT. In 1993, the Mayo Clinic initiated a protocol[27-31] of neoadjuvant treatment with external radiotherapy, chemotherapy and internal radiation therapy in cholangiocarcinomas I and II of the TNM classification, which were unresectable by a first laparotomy. Two months after finishing radiotherapy, a second exploratory laparotomy was performed and, if the tumour was disseminated, the patient was excluded from the study. In 2008,[30] 148 patients were identified, of which 90 completed the neoadjuvant

therapy and the LT; of these, 71 are alive and 19 died (8 due to tumour relapse), 19 are awaiting LT and 39 failed to meet neoadjuvant therapy due to disease progression. The 5-year survival rate of the group was 55% and the transplant survival rate was 71%. The success of this protocol is related to several factors: external and internal radiotherapy (useful for controlling wall invasion and peri-neural invasion); the strict selection of patients (all were stage I-II), unlike other series in which the stages III-IV exceed 40%; most patients were young; and finally, there was a significant percentage of primary sclerosing cholangitis (PSC) (65%). Neoadjuvant therapy was so effective that in many patients, no tumour was found in the explanted liver (although the pre-LT cytology was positive). In their series, prognostic factors were age >45 years, Ca 19/9 >100, the performance of a previous cholecystectomy, the existence of a residual tumour >2 cm, peri-neural invasion and the waiting time >100 days; hence the importance of living donor LT and implementation of an additional point system aside from the MELD system. This protocol has the disadvantage that it is associated with a higher percentage of late vascular complications and an increased need for using grafts,[40] especially when using live donor LT. This increased difficulty associated with the significant fibrosis encountered during the transplant in relation to radiotherapy, although it does not affect patient or organ survival.

Other authors such as Sudan et al[41] and Wu et al[42] have partially reproduced these results. The last results reported 6 patients with PSC and cholangiocarcinoma, with a screening protocol similar to the patients of the Mayo Clinic who only received neoadjuvant radiotherapy for the LT with duodenopancreatectomy, of whom only one died of non-tumour causes and the other 5 remain alive after more than 5 years.

In the retrospective study,[28] survival at 5 years in the LT group with neoadjuvant therapy was 82% compared to 21% in the group with TR without neoadjuvant therapy. However, the 2 groups were not homogeneous, as the age in the TH[28] group was 48 years versus 63 years in the TR group and all were stage I-II, whereas in the TR group 14% had liver metastases, 39% had vascular invasion, 25% had positive lymph nodes in the portal vein, and 18% had peritoneal metastases. Furthermore, in the TR group only 38% had caudate resections performed and 58% of transplant patients had a KT on a PSC compared to 8% of the resected patients.

To conclude, we agree with other authors[43] that the LT, as indicated in very selected cases (unresectable tumours from intrahepatic biliary extension, non-disseminated, with the intervention of surgeons with experience in hepatic surgery), reach a higher survival rate than that from palliative treatment in patients with unresectable, non-disseminated KT. Neoadjuvant therapy protocols, proper staging, priority in the waiting lists for LT and LT with live donors may also contribute to the improvement of results.

Conflict of interest

The authors affirm that they have no conflicts of interest.

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