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Liver transplantation for hilar cholangiocarcinoma

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Core tip: The most appropriate treatment for Klatskin tumor (KT) with a curative intention is multimodal therapy based on achieving R0 resection combined with other types of neoadjuvant or adjuvant treatment. In irresectable non-disseminated KT patients, using liver transplantation without neoadjuvant treatment, the 5-year survival rate increase to 38%, reaching 50% survival in early stage. In selected cases, with liver transplantation and neoadjuvant treatment (chemotherapy and radiotherapy), the actuarial survival rate is 65% at 5 years and 59% at 10 years. In conclusion, correct staging, neoadjuvant treatment, living donor and priority on the LT waiting list may lead to improved results.

Abstract

The most appropriate treatment for Klatskin tumor (KT) with a curative intention is multimodal therapy based on achieving resection with tumour-free margins (R0 resections) combined with other types of neoadjuvant or adjuvant treatment (the most important factor affecting KT survival is the possibility of R0 resections, achieving 5-year survival rate of 40%-50%). Thirty to forty percent of patients with KT are inoperable and present a 5-year survival rate of 0%. In irresectable non-disseminated KT patients, using liver transplantation without neoadjuvant treatment, the 5-year survival rate increase to 38%, reaching 50% survival in early stage. In selected cases, with liver transplantation and neoadjuvant treatment (chemotherapy and radiotherapy), the actuarial survival rate is 65% at 5 years and 59% at 10 years. In conclusion, correct staging, neoadjuvant treatment, living donor and priority on the liver transplant waiting list may lead to improved results.

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INTRODUCTION

The most appropriate treatment for cholangiocarcinoma (CC) with a curative intention is multimodal therapy based on achieving R0 resection combined with other types of neoadjuvant or adjuvant treatment such as external radiation therapy or brachytherapy, systemic or arterial chemotherapy, chemoradiation therapy and photodynamic therapy^[1-10].

Thirty to forty per cent of patients with Klatskin tumour (KT) are inoperable and present a 5-year survival rate of 0%. The other 60%-70% of patients may be eligible for surgery, although some 15%-50% are non-resectable and have an identical prognosis to inoperable

patients. In these non-resectable cases (due to spread to the second-generation intrahepatic radicals), and providing there is no lymph node dissemination, liver metastases or extrahepatic spread, some authors classically have proposed liver transplant (LT)^[9]. The most important factor affecting KT survival is the possibility of tumour resection with tumour-free margins (R0 resections)^[9,11-15]. The rate of resectability has increased over the last 20 years^[16-22] as a result of several factors: (1) extending tumour resection to the hepatic parenchyma, especially caudate lobe resection^[16-18], since bile drainage occurs at the bifurcation of the hepatic ducts, performing extended right-sided resections also increases resectability^[9] and it is often necessary to increase the residual liver volume with portal vein^[23,24] or arterial^[16] embolization; (2) extending tumour resection to the pancreatic head, associating a cephalic duodenopancreatectomy (CDP) to the liver resection^[16,25-30]. This technique has been used when performing both liver resection and LT^[16,25-30]. Most authors generally only consider CDP for KT when there is invasion of the lower biliary resection margin; (3) performing vascular resections has led to higher rates of morbidity and mortality, although it increases the possibility of resection and also of performing R0 resections^[16]. Portal vein resection does seem to increase the 5-year survival rate, whereas hepatic artery resection does not appear to increase survival but does increase postoperative morbidity and mortality; and (4) performing a lymphadenectomy appears to be fundamental for achieving an R0 resection by removing the lymphatic pathways of dissemination and eliminating the frequent perineural dissemination through the periduodenal and peripancreatic elements of the hepatic hilum^[31].

RESULTS OF LIVER TRANSPLANTATION WITHOUT NEOADJUVANCY

The indications for LT in KT patients were not well established due to the poor results reported in the literature, and each case needs to be analysed separately. When the tumour was non-resectable and not disseminated, palliative treatment obtains a zero 5-year survival rate but LT may achieve complete R0 resection of the tumour^[16]. Some authors associated a CDP to the LT^[16,25-30] and Starzl *et al.*^[32] and Alessiani *et al.*^[33] even extended the resection to neighbouring organs (cluster transplantation). The drawback with LT is immunosuppression, which favours the dissemination of tumour remains that might have gone unnoticed, which is why the fundamental cause of death following LT is usually abdominal tumour recurrence (occurring in 56%-96% of cases)^[34-39]. The 5-year survival rate in LT series for KT is 0%-38%^[34-39] and did not exceed 38% when it was more aggressive (cluster transplantation)^[32]. An example of these poor results was published by the Cincinnati Transplant Tumour Registry in 2000^[36] in an analysis of 207 cases of LT for CC, with a 23% 5-year survival rate, a 51% rate of early tumour recurrence and a 10% rate of postoperative mortality.

The survival rate was lower than with LT for other indications, and because of the scarcity of organs many centres considered LT contraindicated for KT. These poor results have been related to three factors: (1) poor patient selection, LT being indicated in patients with non-resectable tumours with biliary, portal and arterial invasion; (2) not performing a preoperative exploratory laparotomy and therefore many patients undergoing transplantation with disseminated peritoneal disease (16% of the cases) and affected regional lymph nodes; and (3) none of the patients receiving neoadjuvant therapy.

The Spanish series^[40] reported 36 LTs for KT over a period of 18 years [3 of them associated with primary sclerosing cholangitis (PSC)], with 52.7% recurrence and 8.3% postoperative mortality and 30% and 18% survival at 5 and 10 years, respectively. In the early stages (stages I - II) the survival rate was suitable for indicating LT (47% at 5 years), whereas in very advanced stages (III-IV) it was only 15%. Despite the bad results (30% survival at 5 years) we showed that a small group of patients undergoing LT with negative lymph nodes had prolonged survival rates and that LT might therefore be an option in carefully selected cases. Subsequently Kaiser *et al.*^[41], in a similar study, presented their experience in Germany and reported 47 patients undergoing transplantation for KT, with a higher postoperative mortality rate (20%) and a 5-year survival rate of 22%. As with the Spanish series, when the selection criteria were strict (from 1998 onwards) the 5-year survival rate of the 15 transplant patients was 48% ($P < 0.014$). Friman *et al.*^[42] have reported the Scandinavian experience with LT for CC and 20 of the 53 patients in the series were KT. The same results were reported as for the Spanish and German series, with a 48% 5-year survival rate in patients with tumor node metastasis (TNM) stages ≤ 2 who received transplantation from 1995 onwards (the rate of PSC in this series was 64%, compared to 8% in the Spanish series). As Friman *et al.*^[42] state, this survival rate was similar to that obtained in some series with LT for hepatic cirrhosis secondary to C virus.

Some authors have compared resection with LT without neoadjuvant. Hidalgo *et al.*^[43] have reported 106 patients with KT, managing resection in 44 cases and performing LT in 12. There were no differences between resection and LT for sex, early stages, tumour size, lymph node invasion (7 from the LT group were N1), differentiation grade, perineural invasion and vascular invasion. There were also no differences for 5-year survival (28% with resection *vs* 20% with LT). As in our series, the patients undergoing LT were much younger than those with resection ($P < 0.012$). Factors of poor prognosis were stages III-IV, R1-2 resections, presence of lymph node invasion and liver metastases, undifferentiated tumours and vascular invasion. The Mayo Clinic in Rochester, in a study published in 2005^[44], compared 38 LTs selected among 71 patients with the neoadjuvant protocol and 26 patients with liver resection from a total of 54 patients in whom it was attempted (48% resectability). The authors

concluded that transplantation may be the ideal treatment for KT due to a better 5-year survival rate (82% *vs* 21%) and lower rates of recurrence (13% *vs* 27% with resection), but the drawback with the study was that the two series were not homogeneous. The age of the LT group was 48 years, compared to 63 years in the resection group, and they were all stages I - II whereas 14% of the resection group had hepatic metastases, 39% vascular invasion, 25% positive lymph nodes in the hepatic hilum and 18% peritoneal metastases. They also performed just 38% of caudate lobe resections in the resection group, a technique which all authors currently claimed to be fundamental for preventing KT recurrence. They also selected PSC patients with an early diagnosis for the transplant group, as 58% of the transplanted patients had a Klatskin tumour besides PSC, compared to 8% of the resected patients. These results were in contrast to those published by Iwatsuki *et al.*^[45], who found no differences between LT and resection, in this case without neoadjuvant. When we have compared^[46] 11 LTs and 29 KT resections without neoadjuvant, we also found no differences for 5-year survival (38% with LT and 36% with resection), and in no case was PSC associated.

RESULTS OF LIVER TRANSPLANTATION WITH NEOADJUVANCY

In 1987 the University of Nebraska initiated a protocol of brachytherapy and chemotherapy with fluorouracil (5-FU) up until transplantation and in 2002^[47] published a series of 11 patients showing prolonged survival rates for a select group of patients with non-resectable KT who received neoadjuvant internal radiation therapy alone or with chemotherapy with 5-FU (external radiation therapy was associated in 2 patients). Of these, 45% were alive and disease-free between 2.8 and 15.5 years after the transplant. The authors reported a high postoperative mortality rate of 27% and a low recurrence rate of 18%.

Subsequently in 1993 the Mayo Clinic initiated a protocol^[26,44,48-53] of neoadjuvant treatment with external radiation therapy, chemotherapy with 5-FU for three days and internal radiation therapy, followed by capecitabine up until transplantation. All the patients were considered non-resectable by an experienced group of hepatobiliary surgeons and all the patients had to belong to stages I and II of the TNM classification^[54]. For this they established an exhaustive selection process, performing exploratory laparotomy 2 mo after the end of radiation therapy and excluding the patient from the study if the tumour was disseminated. In 2008^[50] they reported 148 patients (90 having completed neoadjuvant and LT), of whom 71 were alive, 19 died (8 due to tumour recurrence), 19 were awaiting LT and 39 failed to complete neoadjuvant due to progression of the disease. The 5-year survival rate in the group was 55%, and 71% among the transplant patients. The good results with this protocol were related to several factors: external and internal radiation therapy (useful for controlling wall and perineural

invasion); strict patient selection, as all were stages I - II, unlike other series in which stages III-IV exceed 40%, and most were young patients; and lastly the significant rate of PSC (65%). The neoadjuvant treatment was so effective that no tumour was found in the explanted liver (even though cytology prior to LT had been positive). Factors of poor prognosis in their series were age > 45 years, carbohydrate antigen [carbohydrate antigen (CA) 19-9] < 100, previous cholecystectomy, residual tumour of > 2 cm, perineural invasion, and waiting time > 100 d, hence the importance of living donor LT and application of a scoring system besides the Model for End-Stage Liver Disease (MELD) system. The drawback of this protocol were a higher rate of late vascular complications and a greater need for the use of grafts^[55], especially when living donor LT was used. This greater difficulty was related to the significant fibrosis encountered during the transplant as a result of radiation therapy, although it does not affect patient or organ survival.

Results after acknowledgement of LT for KT by UNOS

The good results reported by the Mayo Clinic in Rochester lead to United Network Organ Sharing (UNOS) adopting this protocol on 17 November 2009 and beginning to allow priority MELD exception scores for CC patients who have completed the neoadjuvant chemotherapy protocol and for whom staging laparotomy was negative^[26,50]. Darwish Murad *et al.*^[26] re-published the results of the Mayo Clinic in Rochester, including 199 patients in the protocol, both intrahepatic CCs and KTs. Twenty patients did not reach the staging laparotomy, due in 15 cases to progression of the disease and to 4 dying from causes unrelated to the disease and 1 from intolerance to the treatment. An exploratory laparotomy was performed in 179 at the end of the protocol and 42 patients were excluded: 36 for metastases, 40 for progression of the disease and 2 who died without progression prior to transplantation. One hundred and thirty-seven patients underwent transplantation: 131 in their hospital (66%) and 6 in other hospitals. Thirty-six patients died (27%): 24 due to recurrence and 12 from other causes. The actuarial 5-year survival rate was 71%, with tumour recurrence in 26 patients, of whom 24 died as a result.

Darwish Murad *et al.*^[26] analysed pre-LT dropout factors and found that 62 of the 199 patients (31%) abandon the waiting list, their mean survival being just 3.6 mo. Statistically significant factors of poor prognosis in the univariate analysis were presentation with painless jaundice, weight loss, visible tumour mass of ≥ 3 cm, positive or suspicious intraluminal brushing or biopsy, high CA 19-9 (> 500) and higher MELD score. Statistically significant in the multivariate analysis were mass size of ≥ 3 cm, positive or suspicious intraluminal brushing or biopsy, high CA 19-9 and higher MELD score.

Darwish Murad *et al.*^[26] also analysed the prognostic factors related to tumour recurrence following liver transplantation. Statistically significant in the univariate analysis were age over 50 years, size ≥ 3 cm, CA 19-9 over

500 and vascular encasement. Statistically significant in the multivariate analysis were high CA 19-9 and complete portal vein encasement, perineural invasion and tumour persistence in the explant. In the multivariate study tumour persistence in the explanted liver was exclusively significant. It is worth noting in this series that the patients undergoing transplantation for KT associated with PSC had a lower risk of recurrence than the patients with the *novus* KT.

In 2012, after approving the neoadjuvant protocol in 2009 in the United States, Darwish Murad *et al.*^[50] send a survey to 50 American centres to collect their experience in LT for cholangiocarcinoma between 1993 and July 2010 and received 30 responses (8 of the 20 non-respondents were because they did not apply the neoadjuvant protocol). Selection for transplantation from the waiting list was done with a MELD score of 22 points and with the same criteria as with hepatocarcinoma: every 3 months 10% drop off the waiting list. The objectives have been: (1) to assess the efficacy of neoadjuvant for KT; (2) to analyse the intercentre impact of neoadjuvant; and (3) to evaluate whether the MELD system applied is appropriate. They included 287 patients, of whom 22 were excluded (16 due to progression, 3 who died of causes unrelated to cancer, and 3 who did not tolerate the treatment). Staging laparotomy was performed in 229 patients and extrahepatic disease detected in 40, who were also excluded. Nine patients were excluded after the laparotomy (7 for tumour progression and 2 who died of non-tumour-related causes). Transplantation was done in 184 cases following staging and in another 30 who underwent transplantation without staging after neoadjuvant (214 liver transplants in total).

Of the 287 patients included in the study 193 belonged to the Mayo Clinic in Rochester and 94 to other centres (between 2 and 12 transplants). A CDP was associated in 22 cases. One hundred and twenty-two patients died: 60 prior to liver transplantation and 62 after transplantation (22%). There was a post-transplant recurrence in 43 patients (20%), of whom 40 died. The actuarial survival rate was 65% at 5 years and 59% at 10 years. They analysed the prognostic factors and found no differences between living and deceased donor transplantation or between KT associated with PSC and the *novus* KT; there were also no differences between patients with and without exploratory laparotomy: 36/184 recurrences (20%) *vs* 7/30 recurrences (23%), respectively. A poorer prognosis was shown by patients who do not fulfil UNOS criteria for MELD exception: existence of a mass of > 3 cm (21 patients), with a 5-year survival rate of 32%, *vs* 69% for < 3 cm masses; those with liver metastases (4 patients); and when a percutaneous biopsy was done for tumour diagnosis (16 cases). As in previous series there was a group of patients with no preoperative biopsy for diagnosis, no tumour in the explanted specimen and whose deaths were not tumour-related. Of 87 patients with no reliable preoperative tumour diagnosis 55 did have a tumour in the explant and another 17 presented with tumour recur-

rence during evolution. The remaining 15 cases (5%) had no tumour in the preoperative period or in the explant and the authors claim that even if they had been excluded the 5-year survival rate was 50% in the other 272. They concluded that neoadjuvant was effective, there were no inter-centre differences and that the MELD system was valid for waiting list selection.

Validation of the results of other centres

These results show that LT is a valid therapeutic option for both hilar and intrahepatic cholangiocarcinoma, especially when neoadjuvant treatment is used. However, there are doubts in the literature, as not all centres reproduce these results, something which, as also claimed by Friman *et al.*^[56], may be related to the high % of patients with PSC, strict criteria for a preoperative diagnosis of malignancy and especially^[55] strict criteria for selection (performing a staging laparotomy after performing neoadjuvant). Other American centres have recently reported their results for LT for cholangiocarcinoma. Panjala *et al.*^[27], from the Mayo Clinic in Florida, reported 22 patients in whom the protocol of the Mayo Clinic in Rochester was applied between 2001 and 2008. Seventeen cases (77%) were associated with PSC and 5 were the *novus* KTs. They did not perform an exploratory laparotomy and staging was done during LT with 2 recipients. The preoperative diagnosis was certainty in 12 cases and suspicion in 10. During transplantation 3 of the 12 patients with a preoperative diagnosis of certainty presented with liver metastases in 2 cases and an intestinal implant in 1 case. Overall survival was 63%, similar to that reported by the Rochester group. As with the Rochester group there were patients with no tumour in the explant, which influenced the survival rate: there was still tumour in 77% (17 cases) but no tumour remains could be identified in 5 cases (23%), a factor with which survival was related, such that patients with tumour in the explant had a survival rate of 52% at 3 years and those with no tumour in the explant had a survival rate of 100%. Nine patients (41%) died as a result of recurrence and 3 for other non-tumour-related causes, the recurrence rate being 27% at one year, 4.5% the second year and 4.5% the third year. When the association with PSC was analysed, these patients made up 93% of the group of patients with no tumour recurrence, whereas it constituted 50% of the patients who did have tumour recurrence, which implies that patients with *de novo* KT carry a higher risk of recurrence than those associated with PSC: of the 17 with PSC there were 4 recurrences and 1 with visceral metastases, whereas in the 5 *de novo* KTs there were 4 recurrences and 2 visceral metastases.

Of a total of 132 cholangiocarcinomas, the UCLA University^[57,58] selected 57 for surgery and perform LT in 38 of them^[57]. In a subsequent publication they reported 40 liver transplants for CC, of which 14 were for KT^[58]. Only 13 patients received neoadjuvant treatment with chemotherapy plus radiation therapy^[58] and the 5-year survival rate was 47% when neoadjuvant was applied, compared to 20% without neoadjuvant treatment and

33% when adjuvant treatment was administered. These results were lower than those reported by the Rochester group and similar to those reported for European groups without neoadjuvant on selected early cases^[40-42].

In 2012 the Anderson Cancer Center reported the efficacy of neoadjuvant treatment in patients with resection of tumours of the bile duct. Of 157 patients 94 were cholangiocarcinomas^[59]. Forty-eight point seven per cent received adjuvant chemotherapy, 17.8% had neoadjuvant chemotherapy and 15.8% had chemotherapy plus neoadjuvant radiation therapy (the latter treatment delayed surgery by 6.8 mo). The 5-year survival rate was 30.4%, and when immediate tumour resection was achieved without neoadjuvant with a margin of at least 1 cm the survival rate was 52.4%. Thus, immediate tumour resection increased survival from 42.3 to 53.5 mo. This protocol was applied to patients considered initially resectable, and not as occurs in CC patients considered non-resectable to whom the Rochester protocol was applied before transplantation.

The results for other non-American groups^[60-62] has been contradictory, with favourable^[60] and unfavourable^[61] cases, very small series and an absence of multicentric prospective studies. Wu *et al*^[62] achieved good results with the protocol. They reported 6 patients with PSC and cholangiocarcinoma, with a similar early detection protocol to that of the Mayo Clinic in Rochester; the patients only received neoadjuvant radiation therapy before LT with CDP and only 1 died from a non-tumour-related cause, the other 5 having survived more than 5 years.

In conclusion, R0 resection is the most accepted treatment of KT. In non-disseminated unresectable tumours, liver transplantation in early stages have an acceptable survival (50% at 5 years). In these same patients (KT and early stages), treatment with neoadjuvant chemoradiotherapy and very strict selection criteria achieves a 5-year survival rate of over 65%. The series with neoadjuvant treatment are not homogeneous and most tumours are associated with PSC as compared to other series where most are the novo KT. Therefore, some authors consider it necessary prospective randomized studies, comparing KT associated to PSC and the novo KT, to discover the proper role of neoadjuvant chemoradiation^[63]. Staging correct, the priority in the waiting list LT (MELD) and living donor LT may lead to better results.

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