Liver Transplantation for Cholangiocarcinoma

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Abstract

The treatment of intra- and extrahepatic cholangiocarcinomas remains a medical challenge. Due to the poor efficacy of conventional chemotherapy, surgical treatment modalities represent the only chance of attaining long-term survival and cure. The introduction of new procedures, in particular extended liver resections – which were enabled by increasing surgical expertise and the implementation of multimodal treatment protocols – led to an increasing number of curatively treated patients and significant improvements in long-term results after curative resection. However, numerous patients are not suitable for radical resection because of local tumour growth, intrahepatic metastases, infiltration of main vascular and biliary structures or insufficient remnant liver function. In unresectable tumours, liver transplantation is a curative treatment option for many patients and represents the only chance to achieve long-term survival and cure. Yet, cholangiocarcinomas are not currently a standard indication for liver transplantation, because of the organ shortage and the resulting necessity to allocate available organs to patients with the best prognosis. In recent years, the results of liver transplantation for the different types of cholangiocarcinoma have improved following the application of new treatment protocols. The most promising long-term results were achieved in hilar cholangiocarcinoma by using neoadjuvant radiochemotherapy prior to transplantation. Long-term survival rates were not inferior to those seen in patients receiving a transplantation for benign liver diseases or early-stage hepatocellular carcinoma. The improved long-term outcomes of transplantation for intra- and extrahepatic cholangiocarcinomas have led to a renewed interest for liver transplantation as a treatment for these tumour entities.

Keywords

Hilar cholangiocarcinoma, intrahepatic cholangiocarcinoma, liver transplantation, results, indications

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Over the past two decades, liver transplantation for cholangiocarcinomas has been controversial. In the early era of transplantation, intrahepatic and hilar cholangiocarcinomas were considered to be ideal indications for liver transplantation. The tumours tend to remain localised within the liver and the liver hilum, respectively, until late in the course of the disease and can often be completely removed by hepatectomy and replacement of a homograft, even if curative resection is not feasible.[1,2] Therefore, liver transplantation represents a curative treatment option in patients with cholangiocarcinomas. However, despite cure obtained in a considerable proportion of patients, the long-term results of the procedure were found to be inferior to those of liver transplantation performed on patients with benign diseases or early-stage hepatocellular carcinoma.[1–4] In the early 1990s, because of the upcoming organ shortage and the resulting necessity to allocate available organs to patients with the best prospects of success in the long term, cholangiocarcinomas started to be refused as an indication for liver transplantation.[5,6]

However, numerous patients with cholangiocarcinomas are not suitable for resection due to local tumour extension or insufficient remnant liver function (see *Figure 1*). In particular, patients with an underlying liver disease, such as primary sclerosing cholangitis (PSC), frequently have unresectable cholangiocarcinomas (see *Figure 2*). A number of these patients develop cholangiocarcinoma at a younger age, which underlines the need for a curative treatment option in tumours that are not suitable for resection.[7] In this group of patients, liver transplantation remains the only chance of long-term survival and cure. Therefore, liver transplantation remains an important tool in the treatment of patients with cholangiocarcinomas.

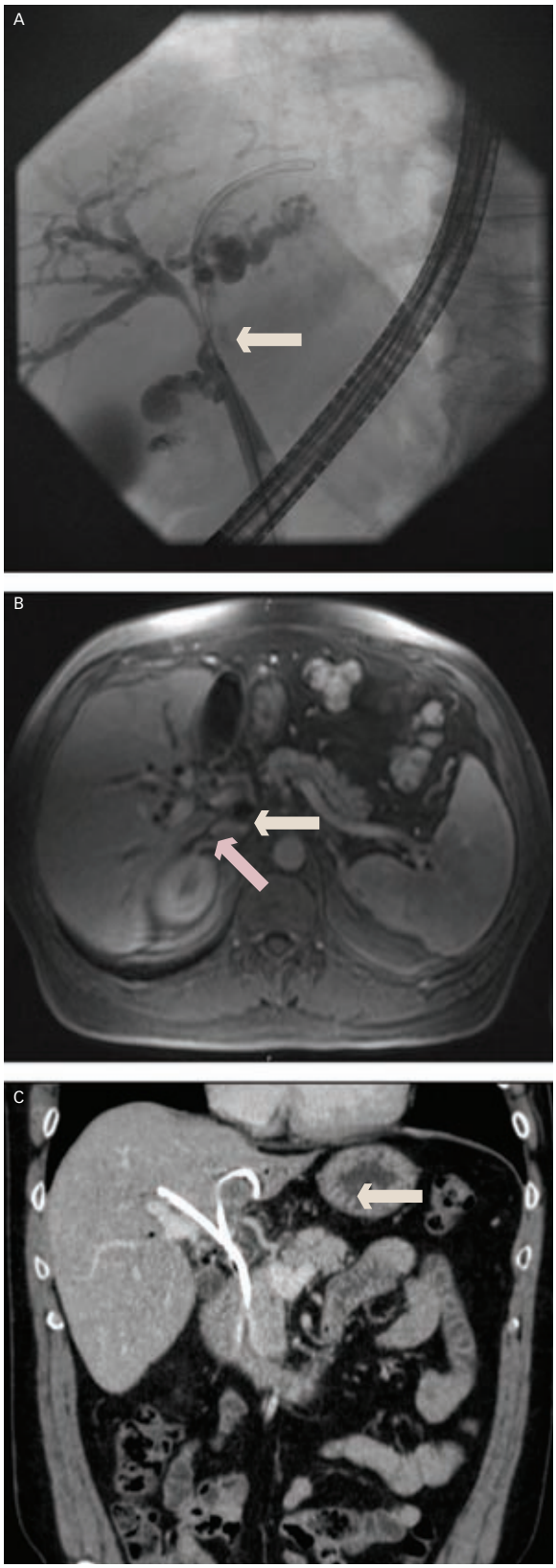
In recent years, new treatment approaches have markedly improved patient outcomes. However, liver transplantation used in the treatment of cholangiocarcinomas remains complex and the indication needs to take into account the different biological behaviours, the availability of effective alternative treatment modalities, the current transplant allocation criteria and the individual prognosis.

Hilar Cholangiocarcinoma

The Mayo Clinic Experience

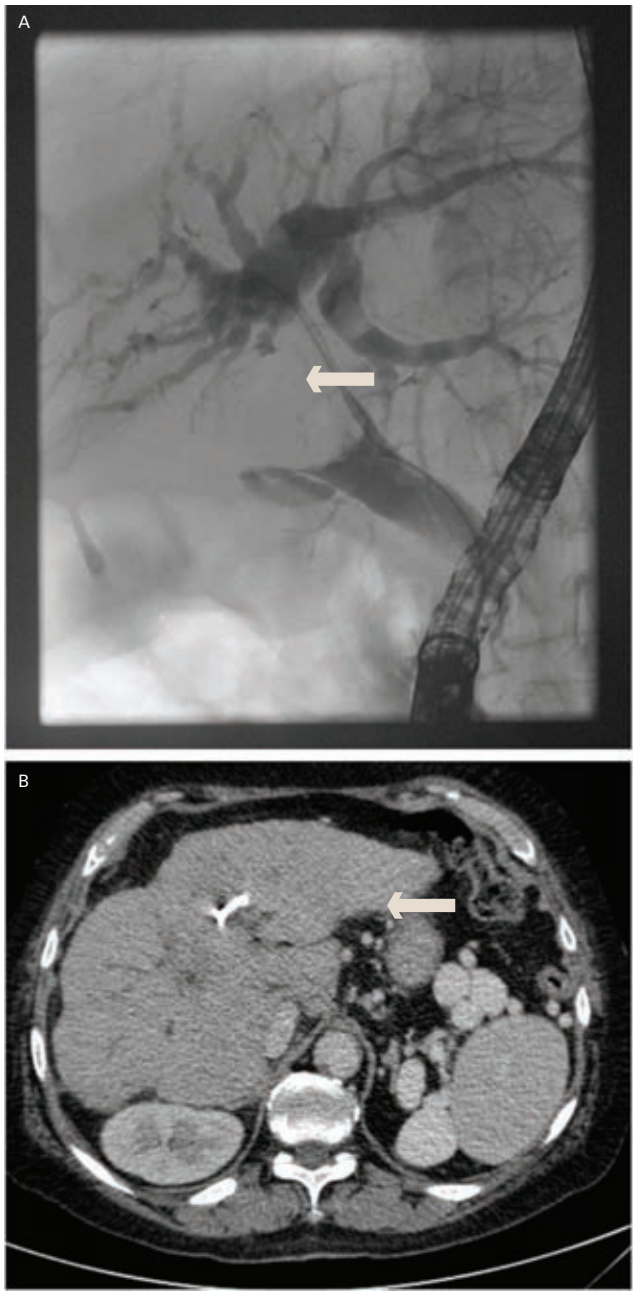
In patients with hilar cholangiocarcinoma, the most promising results of liver transplantation were reported by the Mayo Clinic group in the US, with a protocol that included radiochemotherapy prior to transplantation. In the most recent evaluation of its results, the Mayo Clinic group reported a five-year survival rate of 73 % in 120 patients who finished a treatment protocol of liver transplantation after neoadjuvant radiochemotherapy.[8] In the

Figure 1: Cholangiocarcinoma with Insufficient Remnant Liver Function



Endoscopic retrograde cholangiography (A), angiomagnetic resonance imaging (B) and computed tomography scan (C) of a patient with hilar cholangiocarcinoma Bismuth-Corlette type IV, with infiltration of right portal vein and atrophy of left liver lobe. Arrows show the hilar stenosis (A); the main portal vein (white arrow) and tumour infiltration of the right portal vein (pink arrow) (B); and the atrophy of the left liver lobe (C). Right-sided hemihepatectomy is prevented due to insufficient remnant liver volume and left-sided hemihepatectomy is prevented due to tumour infiltration of the right portal vein.

Figure 2: Cholangiocarcinoma with Underlying Liver Disease



Endoscopic retrograde cholangiography (A) and computed tomography scan (B) of a patient with hilar cholangiocarcinoma Bismuth-Corlette type II, with liver cirrhosis due to primary sclerosing cholangitis. Arrows show the hilar stenosis caused by local tumour growth at the bile duct bifurcation (A) and the cirrhotic transformed liver (B). Liver resection is prevented due to insufficient remnant liver function.

group's first study, the results were even better, with five-year survival rates exceeding 80 %.[9] These long-term results are not inferior to those obtained by liver transplantation in patients with benign liver disease or hepatocellular carcinoma selected according to the Milan criteria, and thus invalidate the assumption that, because of organ shortage, patients with hilar cholangiocarcinomas are not suitable transplant candidates.[10] A five-year survival rate of more than 70 % represents an outstanding success – a success that cannot be achieved through any other treatment modality – and was considered to be completely unrealistic for this type of tumour some years ago.

However, despite the fact that the number of patients who are treated according to the Mayo Clinic protocol is continuously increasing, it is probably still too early to designate neoadjuvant radiochemotherapy and subsequent liver transplantation as the treatment of choice in patients with hilar cholangiocarcinomas. This circumspection is not only due to concerns regarding the validity, but also to concerns regarding the safety of the treatment protocol.

As regards the validity of the protocol, it must be critically noted that the long-term survival rate in the intention-to-treat population is very high. In the first Mayo Clinic study, the five-year survival rate in the intention-to-treat population was 58 %; the figure decreased to 54 % in the most recent study, which is still extremely good.[8,9] In the first study, the intention-to-treat population comprised 71 patients, of whom only 38 finished the treatment protocol (including liver transplantation); in the most recent study, 184 patients started neoadjuvant radiochemotherapy and 120 finished the treatment protocol (including liver transplantation).[8,9] The outstanding five-year survival rates even in patients who, for various reasons, were excluded from liver transplantation during the neoadjuvant phase of the treatment, suggest that at least some of these patients may have been originally incorrectly diagnosed with hilar cholangiocarcinoma. In fact, the Mayo Clinic protocol allows other inclusion criteria than a positive histology, including positive brush cytology, endoscopic biopsy or a carbohydrate antigen (CA) 19-9 level exceeding 100 ng/ml if patients have a morphological visualisation of a malignant stricture without signs of cholangitis.[11] Although, in principle, we accept this as justified and corresponding to general practice, there are doubts regarding the accuracy of the diagnosis.

The restriction concerns also pertain to the selection of patients. In the first Mayo Clinic study, outstanding survival rates were achieved in a highly selected group of younger male patients who had developed hilar cholangiocarcinoma in the context of an underlying PSC.[9] However, the positive effect of the neoadjuvant treatment is not restricted to patients with underlying PSC, but can also be seen in patients without underlying PSC, yet the long-term results of the latter are inferior. In the most recent Mayo Clinic study, in which 120 patients received liver transplantation after neoadjuvant radiochemotherapy, the five-year survival rate was 79 % in patients with underlying PSC, but only 63 % in patients without underlying PSC.[8]

Concerns regarding the safety of the treatment protocol are conceded by the Mayo Clinic group itself, who described the toxicity of the neoadjuvant radiochemotherapy as significant.[11,12] Cholangitis and septicaemia were early complications that can be mainly considered to be consequences of the radiation. Liver transplantation after neoadjuvant treatment provides the advantage that early complications such as cholangitis can be completely eliminated by the removal of the damaged organ. Late complications are the dose-limiting factors of any radiation treatment. In the case of liver transplantation following neoadjuvant perihilar radiochemotherapy, they will most likely manifest within the direct surrounding area of the radiation field – i.e., the vascular structures in the lower parts of the hepatoduodenal ligament.

Although radiation damages affect lymph vessels, veins and arteries in decreasing frequency, the Mayo Clinic group reported an unusually high rate of vascular complications after liver transplantation.[12] In the most recent Mayo Clinic report, portal vein stenosis with or without thrombosis – mostly detected on a follow-up computed tomography scan performed four months after transplantation – occurred in 20 % of transplanted patients.[8] Furthermore, late stenosis of the artery was observed in 20 % of the patients who had received an arterial anastomosis on the native common hepatic artery. In a previous and more detailed report about vascular complications in liver transplant patients after neoadjuvant radiochemotherapy, the Mayo Clinic group had reported that, altogether, 40 % of 68 studied patients had vascular complications and two of the seven post-operative deaths were due to arterial complications.[13] In another five patients, arterial complications lead to organ failure and re-transplantation. In contrast, portal vein complications did not cause organ failure or death and were successfully treated, percutaneous transhepatic portal angioplasty being the most frequently used intervention. These good results following portal vein angioplasty are in accordance with other reported results in the literature and show that this procedure can be performed safely after neoadjuvant radiochemotherapy.[14–17] However, it must be noted that, in all patients, multiple interventions were required and that the success over the longer term cannot yet be assessed.

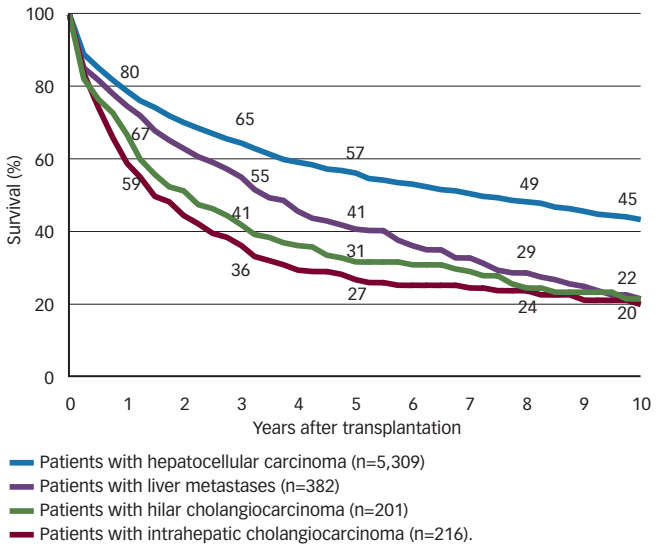
Renewed Interest for Liver Transplantation

The good long-term results of liver transplantation after neoadjuvant radiochemotherapy for the treatment of hilar cholangiocarcinoma prompted a renewed interest for transplantion in this tumour entity. The new awareness of the potential benefits of liver transplantation in this setting led to new studies, which have confirmed the improvement in long-term outcomes after liver transplantation also without neoadjuvant radiochemotherapy.

A retrospective analysis of 47 hilar cholangiocarcinoma patients who underwent liver transplantation in different German transplant centres showed significantly better post-operative results and long-term survival rates after 1998.[18] The median survival for patients transplanted after 1998, including patients who deceased post-operatively, was 42 months, with three- and five-year survival rates of 57 % and 48 %, respectively. In a Spanish national survey, the accumulated survival of 36 hilar cholangiocarcinoma patients after liver transplantation was 55 months and the corresponding one-, three-, five- and 10-year survival rates were 82 %, 53 %, 30 % and 18 %, respectively.[19] These results are comparable with those obtained with resection and confirm the therapeutic efficacy of liver transplantation in the treatment of hilar cholangiocarcinoma.[20] However, they are still inferior to the long-term results of liver transplantation in patients with benign disease or early-stage hepatocellular carcinoma. Therefore, due to the organ shortage and the resulting necessity to allocate available organs to patients with the best prognosis, liver transplantation can still not be considered a standard treatment in hilar cholangiocarcinoma.

One of the main sources of uncertainties surrounding liver transplantation for hilar cholangiocarcinoma is the lack of suitable and generally accepted selection criteria. While generally accepted criteria allowing the selection of suitable patients could be established for hepatocellular carcinoma in cirrhosis (i.e., the Milan criteria), with subsequent good long-term outcomes and low recurrence rates, such selection criteria do not currently exist for hilar cholangiocarcinoma. This is probably due to the significantly lower incidence of hilar cholangiocarcinoma compared with hepatocellular carcinoma and the resulting smaller number of patients, which makes the scientific analysis of this group of patients

Figure 3: Cumulative Survival of Patients Receiving Liver Transplant for Malignant Liver Tumours between May 1968 and December 2004 in ELTR Countries



The numbers in the graph indicate the percentage of surviving patients. ELTR = European Liver Transplant Registry. Source: European Liver Transplant Registry, 2004.[3]

more difficult. A possible approach could be to perform liver transplantation in multicentre studies applying clearly defined selection criteria, in order to help establish hilar cholangiocarcinoma as a generally accepted indication for liver transplantation.

Extended Bile Duct Resection

It is not only liver transplantation, but also the extended resection of the whole biliary tree followed by liver transplantation, that currently attracts renewed interest for the treatment of hilar cholangiocarcinoma. New long-term results obtained with 'extended bile duct resection' have recently been published. The method was first described in 1994 and combines a hepatectomy with a Whipple procedure and subsequent liver transplantation, resulting in a complete resection of the biliary tree.[21] First experiences with the method had confirmed its efficacy in patients with hilar cholangiocarcinoma, but had failed to show a significant superiority over other treatment modalities, such as liver transplantation alone or liver resection.[22] Therefore, extended bile duct resection had not been applied to a larger number of patients.

The recent re-evaluation of the method, with five- and 10-year survival rates of 38 %, underlines its therapeutic efficacy.[23] If post-operative deaths are excluded, the five- and 10-year survival rates in patients with nodal-negative tumours even reaches 58 %, although most of these patients suffer from locally advanced hilar cholangiocarcinomas. However, a matched-pair analysis reveals that the long-term results achieved by extended bile duct resection are comparable to those obtained with liver transplantation alone, but that liver transplantation alone is accompanied by a lower post-operative mortality. The recent re-evaluation thus confirms that the efficacy of extended bile duct resection is not superior to that of liver transplantation alone. On the other hand, extended bile duct resection can achieve long-term survival and cure in a considerable proportion of patients with locally advanced hilar cholangiocarcinomas. It is therefore an option in the treatment of this tumour entity, particularly in patients with unresectable tumours who cannot be treated curatively by liver transplantation alone.

Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma is the second most frequent primary liver cancer. In Europe and North America, for unknown reasons, its incidence has been increasing over the past decades.[24–26] This rarest entity of cholangiocarcinomas arises from the small peripheral bile ducts of the liver and corresponds histologically to an adenocarcinoma.[27]

Limitations of Curative Resection

Resection represents a curative treatment option and is accompanied by a five-year survival rate of around 30 %.[28–30] Even in locally advanced and nodal disseminated tumour stages, resection can achieve long-term survival and cure.[28,30] It is currently considered to be the treatment of choice in patients with intrahepatic cholangiocarcinoma.[31]

However, the tumour tends to remain clinically inapparent until late in the course of the disease and is very frequently diagnosed at an advanced stage. As a consequence, in numerous patients, the tumour is considered unresectable due to multiple intrahepatic metastases or infiltration of main vascular and biliary structures. Furthermore, in a considerable proportion of patients, although the intrahepatic cholangiocarcinoma in itself would be suitable for resection in terms of its local extension and intrahepatic metastases, resection is prevented by an insufficient remnant liver function. Patients who develop an intrahepatic cholangiocarcinoma in the context of an underlying liver disease (such as PSC) in particular often have an insufficient remnant liver function. In this group of patients, even the pre-operative induction of hypertrophy of the remaining liver – for example, by portal vein embolisation – cannot, most of the time, achieve a sufficient remnant liver volume. Resection is therefore precluded in these patients due to the high risk of post-operative liver insufficiency.

The need for an effective treatment option in these patients is particularly urgent considering that they frequently develop cholangiocarcinomas at a younger age.[32] The response of cholangiocarcinomas to conventional chemotherapy and radiation is rather poor, thus the prognosis of patients with unresectable intrahepatic cholangiocarcinomas remains poor and long-term survival is seen in rare exceptions only.[31]

US and European Long-term Study Results

Liver transplantation, consisting of complete hepatectomy and subsequent replacement by a liver graft, is in principle a curative treatment option for patients with unresectable intrahepatic cholangiocarcinoma. Therefore, it constitutes an option to offer a curative therapy to a broader share of patients suffering from intrahepatic cholangiocarcinoma.[33]

In the early days of transplantation, intrahepatic cholangiocarcinoma, just like hilar cholangiocarcinoma, was a common and generally accepted indication for liver transplantation.[34] Survival rates after liver transplantation were not inferior to those after liver resection and were clearly better than in patients treated palliatively.

The two largest studies of liver transplantation in unresectable intrahepatic cholangiocarcinoma come from the US and Europe. In 2004, the European Liver Transplant Registry (ELTR) published a series of 216 intrahepatic cholangiocarcinoma patients who had received a liver transplantation between 1968 and 2004. These

patients represented 3.8 % of all patients with malignant primary liver tumours in Europe. The series showed one-, three-, five- and 10-year survival rates of 59 %, 36 %, 27 % and 20 %, respectively (see *Figure 3*).[3] The other large study was an analysis of data from the Cincinnati Transplant Tumour Registry that included 207 patients with unresectable tumours.[35] The survival rates in this series were comparable to those in the ELTR study, with one-, three- and five-year rates of 72 %, 48 % and 23 %, respectively.

In addition, the aforementioned Spanish national survey showed, in 23 patients with intrahepatic cholangiocarcinomas, survival rates of 77 %, 65 %, 42 % and 23 % at one, three, five and 10 years, respectively, with an accumulated survival of 66 months.[19] Furthermore, in a recently published survey from three Scandinavian countries, the five-year survival rate in patients who received liver transplantation for intrahepatic cholangiocarcinoma after 1995 was 38 %.[36]

These various studies confirmed that liver transplantation can achieve long-term survival and cure in a considerable proportion of patients with intrahepatic cholangiocarcinoma. However, when their long-term results are compared with survival rates following liver transplantation for benign disease or early-stage hepatocellular carcinoma, these results appear to be rather poor – as was the case for hilar cholangiocarcinoma. Therefore, once again, because available organs need to be allocated to the patients with the best prospects, intrahepatic cholangiocarcinoma is currently not a standard indication for liver transplantation.

Yet, because of the urgent need for curative treatment options, liver transplantation for the treatment of intrahepatic cholangiocarcinoma has in recent years attracted renewed attention. In a recently published retrospective analysis of 10 patients who had received a liver transplant for intrahepatic cholangiocarcinoma, the one-, three- and five-year survival rates were 70 %, 50 % and 33 %, respectively, but three patients died post-operatively. All three had received the transplant before 2001.[37] Only two patients in this series developed tumour recurrence and, when the post-operatively deceased patients were excluded from the analysis, the median survival was 32.2 months. This analysis confirms that liver transplantation can achieve long-term survival and cure, and therefore represents a curative treatment option, in patients with unresectable intrahepatic cholangiocarcinoma.

Determining Suitable Selection Criteria

An crucial tool for further improving outcomes of intrahepatic cholangiocarcinoma patients after liver transplantation lies in the establishment of suitable selection criteria, which would allow clinicians to identify patients with the best prognosis prior to transplantation. In fact, some authors have already analysed patient and tumour characteristics in order to identify prognostic factors that could serve as selection criteria.

At the University of Hannover in Germany, Weimann et al. investigated 24 patients who had received a liver transplant for intrahepatic cholangiocarcinoma, and they identified pre-operative jaundice, lymph node and distant metastases as well as tumour stage as independent prognostic factors for survival after transplantation.[38] A study from the US, which included 16 patients, showed primary tumour size, intrahepatic metastases and the invasion of adjacent organs by the primary tumour as having a significant correlation with survival after liver transplantation.[39] Casavilla et al. reported that, in a series of 20 patients, multiple tumour nodes, bilobar tumour manifestation, lymph node and distant metastases, tumour-positive resection lines and advanced tumour stage had a significant correlation with prognosis.[40]

Due to the divergent results of these studies looking at possible prognostic factors, and to the relatively low number of patients with intrahepatic cholangiocarcinoma treated with liver transplantation, suitable selection criteria could not be established so far. However, the relevance of suitable prognostic factors for long-term survival after liver transplantation is reinforced by good long-term results in well selected patients.

In the series published by Casavilla et al., the five-year survival rate of patients with solitary, lymph node-negative tumours was 60 %.[40] In the aforementioned Scandinavian survey, the five-year survival rate of cholangiocarcinoma patients at TNM (tumor-node-metastasis) stage 2 or below was 48 %, with TNM stage being a significant prognostic factor.[36] Three patients who received a liver transplant for a suspected hepatocellular carcinoma within the Milan criteria, later diagnosed as intrahepatic cholangiocarcinoma in the post-operative histological examination, were alive and recurrence-free 30 months after transplantation.[37] These results indicate that, like patients with hepatocellular carcinoma, patients with intrahepatic cholangiocarcinoma can benefit from liver transplantation, particularly if performed in the early tumour stages.

Furthermore, these good results seem to show that the long-term survival of well selected patients with intrahepatic cholangiocarcinoma undergoing liver transplantation may be comparable to that of patients transplanted for early-stage hepatocellular carcinoma or benign disease. This would justify accepting selected patients with intrahepatic cholangiocarcinomas as suitable transplant candidates even in the context of an organ shortage.

The experience of using liver transplantation to treat intrahepatic cholangiocarcinomas is currently limited to a small number of patients and, from the data collected so far, it has not been possible to establish generally accepted selection criteria. To establish suitable selection criteria for this tumour entity, it would be necessary to treat and analyse patients in multicentre trials that would include all experienced centres.

Summary

Liver transplantation represents a curative treatment option for patients with unresectable cholangiocarcinomas. However, these tumours are currently not generally accepted standard indications for transplantation. New treatment approaches have brought significant improvements of the long-term results after liver transplantation for cholangiocarcinoma over the past decades. In particular, patients with nodal-negative hilar cholangiocarcinomas show excellent long-term survival rates after neoadjuvant radiochemotherapy and subsequent liver transplantation, which are not inferior to survival rates in patients transplanted for early-stage hepatocellular carcinoma or benign liver disease. For intrahepatic cholangiocarcinomas, current data also indicate improved long-term survival rates after liver transplantation. Liver transplantation therefore attracts renewed interest as a treatment in patients with

cholangiocarcinomas and is increasingly considered in patients with unresectable tumours. However, at present, the suitability of liver transplantation in patients with cholangiocarcinomas remains an individual decision, which must take into account the specific patient and tumour characteristics, potential effective treatment alternatives and individual prognosis. ■

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