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Liver transplantation for unresectable malignancies: Beyond hepatocellular carcinoma

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ABSTRACT

Indications for liver transplantation have expanded over the past few decades owing to improved outcomes and better understanding of underlying pathologies. In particular, there has been a growing interest in the field of transplant oncology in recent years that has led to considerable developments which have pushed the boundaries of malignant indications for liver transplantation beyond hepatocellular carcinoma (HCC). In this article, we review and summarise the published evidence for liver transplantation in non-HCC primary and metastatic liver malignancies and highlight ongoing clinical trials that address unresolved questions therein. We also examine the current technical, immunological and oncological challenges that face liver transplantation in this growing field and explore potential approaches to overcome these barriers.

Introduction

Outcomes following liver transplantation have improved significantly over the past few decades owing largely to advances in surgical techniques, immunosuppression and management of underlying pathologies [1]. Five-year overall patient survival rates exceed 70% globally for adult first transplants from deceased donors based on recently published figures worldwide [2–4]. Indications for transplantation are gradually expanding as a result of these outcomes which act as benchmarks for the efficacy of newer indications [5].

Non-resectable primary and secondary liver malignancies are examples of emerging indications for liver transplantation that pose unique technical, immunological and oncological challenges within the developing field of transplant oncology [6]. Interestingly, the first successful liver transplant carried out by Thomas Starzl in 1967 was for a patient with hepatoblastoma, who died 18 months later with metastatic disease [7]. In fact, outcomes from transplantation for various liver malignancies in the decades that followed including hepatocellular carcinoma (HCC) were unsatisfactory and therefore were not widely accepted indications for transplantation [8,9].

It was not until the post-transplant disease-free survival rates for HCC improved following the introduction of the Milan criteria in 1996 that transplantation became an established treatment option for HCC [10]. Since then, the boundaries for transplantation for HCC have been pushed even further [11,12]. In addition, a renewed interest in liver transplantation as a treatment option for other primary and secondary liver malignancies has grown owing to improved results over the past 15 years [13,14] coupled with modest survival outcomes with current standard therapeutic options including surgical resection and minimally invasive local therapies [15]. Nevertheless, transplantation for many non-resectable liver malignancies remains investigational at this current stage [6].

The aim of this review is to summarise the current evidence for liver transplantation in unresectable primary and secondary liver malignancies beyond HCC.

Primary liver malignancies

Cholangiocarcinomas

Cholangiocarcinomas (CCA) are a heterogeneous group of malignancies characterised by biliary epithelial differentiation [16]. These are divided based on location into intrahepatic (i-CCA), perihilar (h-CCA) and distal cholangiocarcinomas (d-CCA). Although partial hepatectomy remains the standard potentially curative

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treatment option for CCA, less than 40% of patients in the western hemisphere have a resectable tumour on presentations and 5-year survival rates for R0 resections for CCA are between 20 and 40% [17–20]. Historical attempts at liver transplantation alone for i-CCA and h-CCA have been met with unacceptable rates of disease recurrence even in cases of incidental CCA identified in explants [21–26]. Survival outcomes did not improve when transplantation was combined with pancreaticoduodenectomy (extended bile duct resection) despite higher rates of surgical clearance [27,28]. Three-year survival rates in studies published up until 2005 ranged between 8 and 65% (Supplementary Table 1). Such poor results may have been related to limitations in the design of these earlier studies. Survival outcomes from hilar and intrahepatic CCA were combined in a number of reports which most likely confounded the results in these distinct groups [21,22,24–26,29–32]. In addition, significant heterogeneity is evident in many of these cohorts in relation to disease extent, underlying pathology (primary sclerosing cholangitis (PSC) versus de-novo CCA) and adjuvant therapy administration (Supplementary Table 1). Interestingly, several researchers at that time had identified the significance of tumour size and nodal involvement as risk factors for disease recurrence, particularly in the case of h-CCA [21,33–35].

The outlook for liver transplantation in h-CCA improved following the introduction of the Mayo protocol around the turn of this century [13,36]. The protocol involves a strict selection process where patients with radiological evidence of nodal or metastatic disease are excluded as are those with tumours that have a radial diameter greater than 3 cm. High-dose intravenous neoadjuvant chemotherapy (5-FU) is then delivered along with external beam radiotherapy followed by iridium brachytherapy. Oral capecitabine is also administered until the time of transplantation as tolerated and biliary drainage is undertaken prior to chemoradiotherapy if required. Operative staging after neoadjuvant therapy is mandatory; performed closer to the time of transplantation in most cases in order to rule out nodal or peritoneal disease and minimise organ reallocation at short notice. Staging is usually performed laparoscopically, during which hilar nodes are routinely sampled regardless of appearance [37].

The initial published results from the Mayo clinic group were very promising, with overall 5-year survival rates of 82% compared to 21% after partial hepatectomy in node-negative localised disease [13]. The same group subsequently reported somewhat lower 5-year survival rates (71%) using the same protocol in a larger cohort in 2008. It is worth noting that histological confirmation of malignancy was lacking in one in five patients pre- and post-transplantation in the initial report by the Mayo clinic group. Although it is possible that the inclusion of these patients may have contributed to the superior early results, survival rates were only marginally reduced when this subgroup was excluded. A recently, published meta-analysis of retrospective data for h-CCA from the US Extrahepatic Biliary Malignancy Consortium (USEBMC) demonstrated comparable results with overall 5-year survival rates of 64% following transplantation based on the Mayo protocol versus 31% following partial hepatectomy for node negative tumours less than 3 cm in size [38]. Both patient selection and neoadjuvant therapy appear to play significant roles in the improved survival using this protocol [39–41]. Encouraging early results have also been obtained when the Mayo regime was substituted with stereotactic body radiation therapy (SBRT) and capecitabine, with acceptable tolerability, in a pilot study by researchers at the University of Michigan [42]. The use of neoadjuvant radiotherapy for h-CCA has been associated with higher rates of delayed vascular complications. However, this has not been found to have a significant impact on graft or patient survival [43].

The Mayo protocol has mostly been applied to h-CCA with underlying PSC and unresectable de-novo h-CCA. The former group is typically unsuitable for resection due to the strong association between PSC and multifocal CCA and therefore, if eligible, transplantation is a more acceptable option in such patients. Indeed, survival outcomes following transplantation have been shown to be somewhat more favourable in this cohort in comparison to patients with unresectable de-novo h-CCA [38,44,45]. Some recent retrospective studies suggest a role for transplantation in potentially-resectable h-CCA although the survival difference between transplantation and resection in these cases is not thought to be large enough to justify transplantation [38,46,47]. The question of whether transplantation after neoadjuvant chemoradiotherapy is superior to resection in resectable de-novo h-CCA is currently being addressed in the French TRANSPHIL trial (NCT02232932) which is expected to be completed in 2021.

Based on the growing body of evidence in favour of transplantation, standardised MELD exception scores have been approved by UNOS/OPTN since 2009 for qualifying patients with unresectable h-CCA [48]. Outside the US, transplantation for h-CCA is mainly considered in the context of clinical research [49]. Current evidence on the role of liver transplantation in h-CCA is summarised in Supplementary Table 2.

In contrast to h-CCA, i-CCA is still widely viewed as a contraindication for liver transplantation based on poor historic results (Supplementary Table 3). However, the recent encouraging results with h-CCA have sparked a renewed interest in transplantation of non-resectable i-CCA. A Spanish multicentre study in 2014 examined the outcomes following liver transplantation in cirrhotic patients with incidental i-CCA misdiagnosed preoperatively as HCC. The study demonstrated 5-year survival figures comparable to HCC controls in a subgroup of i-CCA patients with unifocal tumours measuring 2 cm or less [50]. A subsequent international multicentre study in 2016 set out to validate the results from the preceding Spanish study and further confirmed low recurrence rates and acceptable 5-year actuarial survival rates of 65% in incidental small unifocal tumours [51]. Moreover, a retrospective comparison of matched HCC and incidental i-CCA within Milan criteria in 2015 showed no difference in overall survival or recurrence rate [52]. In addition to tumour size and number, there is evidence to suggest that node negative [53]and well differentiated [54] i-CCA lesions may also be associated with improved post-transplant survival outcomes.

The role of neoadjuvant therapy for i-CCA prior to transplantation remains to be clarified. In 2011, researchers at UCLA demonstrated that patients with locally advanced i-CCA and h-CCA who received neoadjuvant and adjuvant therapies in conjunction with liver transplantation had significantly improved recurrence-free survival in comparison to those who received no therapy or adjuvant therapy alone [39]. However, the authors pooled both i-CCA and h-CCA in their analysis and included a range of historic adjunctive therapy protocols used during the duration of the study (1985–2009) which limits the interpretation of these results. Nonetheless, in 2010, the Methodist-MD Anderson Joint Cholangiocarcinoma Collaborative Committee (MMAJCCC) established a liver transplantation protocol for biopsy-proven locally advanced node-negative unresectable intrahepatic cholangiocarcinoma with a sustained biological response or stability for at least 6 months after gemcitabine-based neoadjuvant chemotherapy. Their results were published in 2018 in a case series of 6 patients where a 5-year overall survival rate of 83.3% was reported [55]. Despite the small sample size in this study, it suggests a role for neoadjuvant therapy in identifying patients with i-CCA that may benefit from transplantation and implies that such benefit may extend beyond incidental lesions. A recently commenced single arm trial by the Toronto group might shed further light on the role of liver

transplantation in early biopsy-proven i-CCA in cirrhotic patients in the near future (NCT02878473).

In essence, published research in recent years has demonstrated excellent survival rates following transplantation for certain subgroups of i-CCA with favourable characteristics [56]. Therefore, the diagnosis of i-CCA should not necessarily disqualify patients from transplantation. However, excellent outcomes for early i-CCA have also been demonstrated following liver resection recently [57] and the lack of data comparing resection with transplantation in this subgroup should be addressed in future research before further recommendations can be made on the role of transplantation for i-CCA.

Evidence for the role of liver transplantation in combined HCC-CCA remains scanty and is largely based on retrospective analyses of retrospectively-diagnosed lesions (Supplementary Table 3). Although recurrence rates have been shown to be higher than in HCC in the past [58], promising results on the role of transplantation in this group of tumours were demonstrated by Sapisochin et al., in 2014 where 5-year survival figures were shown to be comparable to a matched cohort of patients transplanted for HCC [59]. A more recent analysis of recipients with retrospectively-diagnosed HCC-CCA on explants demonstrated a trend towards inferior survival and recurrence rates in this group compared to recipients with HCC. However, comparable overall and disease-free survival rates were shown when both groups were matched on pathological features (size, differentiation and vascular invasion) [60]. In addition, node negativity has been shown to be associated with improved survival outcomes [61].

Hepatoblastoma

Hepatoblastoma is the most common paediatric primary liver tumour with a rising incidence of 1–2 per million. The peak age at presentation is within the first two years of life [62,63]. Children typically present with weight loss and anorexia and serum α-fetoprotein is raised in the majority of cases [63]. Hepatoblastoma is a chemoresponsive tumour and the prognosis has markedly improved with the introduction of cisplatin-based chemotherapy in the 1980s which to date remains a central treatment for this tumour [64–66]. Nevertheless, in order to achieve cure, complete surgical resection is key. In European centres, surgical intervention is performed after neoadjuvant chemotherapy in all cases irrespective of tumour stage based on guidelines issued by the International Childhood Liver Tumour Strategy Group (SIOPEL) [66]. However, the type of resection required does depend on the tumour stage which is outlined in the PRETEXT (Pre-Treatment Tumour Extent) staging system contrived during early SIOPEL clinical trials [63]. Four tumour stages are identified based on the number of adjacent Couinaud sections that are tumour-free. While PRETEXT stages I-III can be treated with liver resection (limited or extended), children with PRETEXT IV or central POSTTEXT III (post chemotherapy) with portal or hepatic venous involvement will likely require complete hepatectomy and transplantation [63]. With current neoadjuvant chemotherapy regimens, liver resection is possible in around 85% of cases negating the need for transplantation, and 5-year survival rates in such cases is above 80% [67,68]. However, early referral for transplant assessment is recommended for the remainder of cases according to most current treatment protocols [69,70].

The evidence for the role of liver transplantation in the treatment of hepatoblastoma is outlined in Supplementary Table 4. It is unsurprising that 5-year survival rates have drastically improved from 50% in the pre-cisplatin era to over 75% in recent times [31,71,72]. In 2004, Otte and colleagues reported the outcomes of twelve liver transplants for hepatoblastoma from the first collaborative SIOPEL trial conducted between 1990 and 1994 [73]. This was the first collaborative study to include liver transplantation for unresectable disease as a suggested treatment option in its protocol. Patients were deemed suitable for transplantation when tumours remained unresectable after six cycles of cisplatin-based neoadjuvant chemotherapy (i.e. PRETEXT IV or proximity to main portal or hepatic venous branches) provided that some response to chemotherapy was evident and that extrahepatic disease was completely cleared. In addition, patients who experienced relapse after resection or underwent incomplete resection were eligible for “rescue” transplantation. Despite 58% of transplanted cases demonstrating gross vascular invasion and 42% presenting with lung metastases on initial diagnosis, an overall 5-year post-transplant survival rate of 75% was achieved in this trial. Interestingly, long-term survival rates for primary transplants were considerably higher than those for rescue transplants in this cohort (85% versus 40% 10-year overall survival respectively). Although the number of transplanted patients was relatively low in this trial, the authors also performed a literature review of the previous transplant experience for hepatoblastoma worldwide including 147 cases and obtained similar survival results following primary and rescue transplants (82% versus 30% 6-year overall survival respectively). The authors concluded that extrahepatic disease was not necessarily a contraindication for transplantation if complete clearance can be achieved by chemotherapy with or without surgical resection, and that extended resections for large volume disease should be avoided due to the inferior results seen with rescue transplantation. However, this latter point is debatable in light of more recent studies showing promising results with extreme resections for POSTTEXT III and IV disease [74,75].

The favourable results of primary transplantation for advanced hepatoblastoma have been replicated in a number of studies over the past decade (Supplementary Table 4). The largest of these cohorts was reported by researchers from the Stanford University School of Medicine who examined hepatoblastoma patients that underwent liver transplantation after 1997, therefore only including patients treated under SIOPEL or Children's Oncology Group (COG) neoadjuvant chemotherapy protocols [72]. The group observed a 10-year overall and disease-free survival rate of 84% and 82% respectively in this cohort, results that are comparable to those achieved in resectable disease. The group also identified a number of risk factors associated with recurrence after transplantation including PRETEXT IV disease, tumour rupture and being diagnosed at a relatively older age. In fact, numerous risk factors for recurrence have been identified through various studied series although many of these could not be confirmed in others (Table 1).

Although the evidence for neoadjuvant chemotherapy for hepatoblastoma is clear, data regarding the role of adjuvant chemotherapy post transplantation is lacking. Improved outcomes with the use of adjuvant chemotherapy have been reported in some small series on the one hand [76,77], but Otte et al. found no survival benefit with or without adjuvant chemotherapy in their systematic review of global data, bearing in mind the potential heterogeneity in chemotherapy regimens delivered [78]. Current COG and SIOPEL protocols recommend that transplanted patients receive the same neoadjuvant and adjuvant chemotherapy that patients undergoing conventional resection receive [79]. With regards to immunosuppression, the use of a tacrolimus-based regime and early steroid withdrawal is recommended in paediatric recipients [78].

Where, available, the utilisation of living donor transplants in this setting has the advantage that transplantation is timed with the completion of neoadjuvant chemotherapy in addition to the improved long-term survival outcomes observed with these grafts [78].

Table 1
Reported risk factors for recurrence following liver transplantation for hepatoblastoma.

Risk factor	Reference
Tumour factors	
Vascular invasion	Czauderna 2016 [166]; Umeda 2018 [167]
Extrahepatic extension	Czauderna 2016 [166]
Lung/LN metastasis at diagnosis (not a risk for recurrence after LT according to Pham 2015)	Uchida 2018 [168]; Brown 2000 [169]; Cruz 2013 [170]; Zsiros 2010 [171]; Czauderna 2016 [166]
Tumour rupture	Czauderna 2016 [166]; Pham 2015 [72]
PRETEXT stage	Uchida 2018 [168]; Brown 2000 [169]; Czauderna 2016 [166]; Pham 2015 [72]
Tumour size	Uchida 2018 [168]
Tumour histology	Uchida 2018 [168]
Multifocal tumour at diagnosis	Uchida 2018 [168]; Czauderna 2016 [166]
Extent of tumour necrosis	Uchida 2018 [168]
High or low AFP on presentation (<100 or >1,000,000)	Czauderna 2016 [166]; Uchida 2018 [168]; Sakamoto 2014 [172]
Patient factors	
Age >8	Czauderna 2016 [166]; Pham 2015 [72]
Low birth weight <1.5 kg	Czauderna 2016 [166]
Prematurity	Czauderna 2016 [166]
Comorbidities eg BWS	Czauderna 2016 [166]
Treatment factors	
Response to chemotherapy	Browne 2008 [76]; Umeda 2018 [167]; Pimpalawar 2002 [173]; Isono 2018 [174]
Non-anatomical resection	Uchida 2018 [168]
Longer time on waiting list	Pham 2015 [72]

Notably, prospective data continues to be collected on transplanted patients worldwide into the Paediatric Liver Unresectable Tumour Observatory (PLUTO) registry which was created in 2006 on behalf of SIOPEL. As of 2015, the registry contained data on over 200 paediatric liver transplant recipients for unresectable liver tumours in 79 centres worldwide [80]. Future data from this registry may help answer some outstanding questions pertaining to chemotherapy and immunosuppression post transplantation for hepatoblastoma.

Hepatic epitheliod haemangioendothelioma (HEHE)

First described by Weiss and Enzinger in 1982 [81], epithelioid haemangioendothelioma (EHE) is a rare vascular neoplasm with an estimated incidence of less than one per million [82]. The earliest report of hepatic occurrence (HEHE) was from a case series published in 1984 [83]. Although described as a malignant neoplasm, the clinical course of this tumour can vary from benign haemangioma-like to a rapidly progressive course similar to malignant Angiosarcomas [84]. Patients often present with multifocal disease (81%) and frequently with extrahepatic spread (37%), usually to the lungs or bone [85]. Radiologically, two distinct patterns are identified that correspond with tumour progression. Early stages are typically characterised by a peripheral pattern showing multiple nodular and usually subcapsular lesions. In latter stages, these lesions coalesce and form large confluent masses in a diffuse pattern, often with vascular invasion and parenchymal distortion [85].

Although long-term survival and even spontaneous regression has been reported [86,87], a previous literature review had shown that in the absence of treatment the 5-year survival rate is a mere 4.5% [85]. Standard chemotherapy and radiotherapy is ineffective in these tumours, and therefore surgical resection is the only curative option [88]. However, given the frequent multifocal pattern of disease, the majority of cases are not suitable candidates for surgical resection [89]. In those cases with limited disease where complete resection is possible, a 5-year survival rate of 75% has been reported [85]. A relatively recent Mayo clinic analysis has shown no survival advantage with transplantation in comparison to resection for resectable disease [90]. However, aggressive tumour recurrence has been reported following incomplete resection for more extensive disease, probably due to the expression of angiogenic signalling factors [91]. Nevertheless, some studies have reported successful salvage transplantation for post-resection recurrence [92].

Liver transplantation remains the mainstay curative option for the majority of cases where liver resection is not appropriate [93]. Despite the limited worldwide experience with transplantation due to the rarity of these tumours, reported outcomes have generally been good. Results from large case series and database studies from Europe and North America in addition to a comprehensive literature review have demonstrated 5-year overall survival rates ranging between 55 and 83% even in the presence of lymph node or vascular involvement or extrahepatic disease [49,85,92,94,95]. Nonetheless, the incidence of recurrence following transplantation is relatively high, occurring in up to 1 in 4 patients. Recurrence is often within the allograft and may occur late after transplantation. Similar to the primary lesions, the early clinical picture can be subtle and the course unpredictable, therefore routine post-transplant surveillance with cross-sectional imaging is recommended [84].

In 2017, a European collaborative published the results of a second HEH-European Liver Transplant Registry (ELTR) study building on information obtained from an initial study in 2007 [92,96]. The more recent study included data on 149 liver transplant recipients for HEHE, representing the largest published transplant series for HEHE to date. The study revealed an overall post-transplant recurrence rate of 24.8% and a 5-year disease-free survival rate of 79.4% [96]. The authors identified three risk factors for disease recurrence, namely a short pre-transplant waiting time of less than 120 days, macrovascular invasion and hilar lymph node involvement. Moreover, the study confirmed previously reported data that pre-transplant extrahepatic disease was not a significant risk factor for recurrence. The authors devised a scoring system (HEHE-LT Score) based on these risk factors in order to stratify patients according to recurrence risk. Patients with low, intermediate and high scores had disease-free survival rates of 93.9%, 76.9% and 38.5% respectively. The group proposed a therapeutic algorithm for the treatment of HEHE, advocating the adoption of a mandatory 120 day waiting time prior to transplantation to monitor tumour behaviour arguing that such approach would prevent the futile transplantation of aggressive Angiosarcomas masquerading as HEHE. The group also recommended the use of tailored immunosuppression and targeted therapy post-

transplantation for patients in the high risk bracket. A marked improvement in disease-free survival was noted in patients transplanted after 1999 compared to the previous period which the authors ascribed to a growing approach of early transplantation for HEHE.

The administration of neoadjuvant therapies is recommended in the presence of extrahepatic disease [96]. However, there is no standardised approach to this to date. The anti VEGF antibody bevacizumab has been used as monotherapy or in combination with various chemotherapy regimens with mixed results [97]. Other novel therapies have also been investigated in recent years including the tyrosine kinase inhibitors sorafenib and the m-TOR inhibitor sirolimus [98–100]. The role of these agents as adjuvant therapies is yet to be clarified. It is worth noting that combined and sequential liver and lung transplantation has been reported for multifocal disease with acceptable results [101,102].

The recent identification of the pathognomonic fusion protein WWTR1-CAMTA1 in EHE has been a breakthrough in understanding the biology of this tumour. This fusion protein results from the translocation of chromosomes 1 and 3 and is present in the majority of cases of EHE therefore providing great diagnostic potential [103,104]. The analysis of variant fusion transcripts has demonstrated the monoclonal nature of multifocal HEHE, confirming these as metastatic implants of the same clone rather than synchronous tumours [105]. This discovery is likely to facilitate the delivery of effective adjuvant therapies for multifocal EHE in the future.

Other primary liver malignancies

A retrospective review of liver transplantation for Angiosarcomas reported to ELTR demonstrated dismal results. Of 22 patients transplanted during the period between 1986 and 2004, all died within 22 months of transplantation, and 77% developed recurrent disease within an average of 5 months post-transplantation [106]. Similar poor results have been shown in other studies [31,107] and Angiosarcomas are currently viewed as an absolute contraindication for liver transplantation.

Liver transplantation for primary hepatic lymphoma has been reported in a few cases presenting initially with fulminant liver failure of unclear aetiology. Results from these reports have been mixed [108]. Although transplantation can been life-saving in such obscure cases, systemic chemotherapy should be commenced as soon as the correct diagnosis is reached.

Secondary liver malignancies

Colorectal liver metastases (CRLM)

Colorectal cancer is the second leading cause of cancer deaths worldwide [109]. Approximately 20% of new cases diagnosed with colorectal cancer will present with liver metastases, and at least a further 25% will develop liver metastases through the course of the disease [110]. Liver resection remains the gold standard treatment as it offers the greatest likelihood of cure amongst currently available therapeutic options [111,112], particularly when negative margins are achieved [113]. However, despite advances in surgical and medical oncology that have pushed the boundaries on the definition of CRLM resectability, less than 30% of patients present with disease amenable to surgical resection due to factors including tumour size, location, number and background hepatic reserve [110,114–116]. It would therefore seem rational to consider transplantation for patients with unresectable large volume or progressive colorectal metastases confined to the liver that would otherwise not be suitable for resection, given that transplantation achieves negative margins by definition. In fact, liver transplantation had been considered a treatment option for this indication up until 1994 [117]. Results from the ELTR report in the years that followed highlighted a 5-year survival rate of 18% with a significant proportion of data provided by an Austrian group [117,118]. Interestingly, despite poor results, the group argued that a significant proportion of mortalities were perioperative and that liver transplantation still provided the best available therapeutic option for CRLM at that time [118]. However, due to these poor historic results in the face of worldwide organ shortages, CRLM became widely considered as a contraindication for liver transplantation.

The landscape has significantly changed since the 1990s with advances in imaging techniques, surgical procedures, immunosuppression and chemotherapy paving the way for a resurgence in interest in liver transplantation for unresectable CRLM. In particular, a landmark Norwegian pilot study (SECA-I study) published in 2013 showed promising results in 21 patients receiving liver transplants for unresectable CRLM using the m-TOR inhibitor Sirolimus for immunosuppression from the first postoperative day. Inclusion criteria were resection of the colorectal primary tumour, completion of at least 6 weeks of chemotherapy and exclusion of extrahepatic disease by a staging CT scan and diagnostic laparoscopy with hilar node sampling. The reported 5-year overall survival rate was 56%; significantly exceeding the current survival rate of around 9% for unresectable disease on modern first-line chemotherapy [119,120]. It is important to mention that the vast majority of patients (90%) experienced recurrent disease, a third of whom had pulmonary-only metastases. The group acknowledged that, in retrospect, at least 41% of these were likely to be due to missed staging rather than true recurrence [121]. In addition, the group demonstrated that pulmonary recurrences were usually of an indolent nature and were not associated with reduced survival in comparison to liver or other non-pulmonary recurrences [122]. Nevertheless, a significant proportion of recurrent disease was amenable to further interventions including surgical resection, ablation or radiotherapy resulting in a third of patients showing no residual disease upon last follow up [119]. This may explain the higher overall relative to disease-free survival demonstrated in this study.

The authors identified four prognostic factors associated with poor survival outcomes: Largest tumour diameter measuring >5.5 cm, less than 2 years from primary tumour resection to transplantation, CEA levels higher than 80 μg/L and progressive disease on pre-transplant chemotherapy. Given that the availability of donor organs in Norway contrasts with the significant organ shortage worldwide, the group suggested the use of the above prognostic factors as a scoring system for patient selection (OSLO score) with each factor contributing one point to the total score [121]. Indeed, a recent analysis of the SECA cohort by the same group identified that patients with CRLM and an OSLO score of 3 or less (classed as a low-risk group) demonstrated a 5-year overall survival rate of 75%, comparable to a cohort of patients transplanted for HCC within the Milan criteria (76%) despite having a considerably higher tumour load (Median: 8 lesions, largest measuring 35 mm versus 1 lesion with a median measurement of 27 mm respectively) [123]. Unsurprisingly, selection of low risk patients was also shown to be more cost effective [124].

In addition to the above factors, nodal status of the primary colonic tumour may also be of prognostic significance. Although this factor only showed a trend towards prognostic value in the SECA study, it is worth noting that the previously cited Austrian group had noted an improvement in survival outcomes when transplants were restricted to node-negative primary disease. This prompted a pathology review and DNA analysis of historic colorectal specimens for those patients that had undergone liver

transplantation in that institute. Their analysis identified a subgroup of patients with micrometastases (initially thought to have node-negative disease) that had inferior survival outcomes. Lymph node micrometastases were shown to have a significant correlation with both overall and disease-free survival [125].

PET CT imaging was part of the preoperative workup protocol in the SECA-I study. In addition to its superiority over contrast enhanced CT in identifying extrahepatic disease [126], in a recent study, the Norwegian group demonstrated its prognostic value through calculation of metabolic tumour volume (MTV) and total lesion glycolysis (TLG) which were shown to be significantly associated with overall survival [127]. It is expected that PET CT may become a mandatory step in the workup for transplantation in unresectable CRLM in the future [128].

The positive results obtained from the SECA-1 trial were supported in a recently published retrospective multicentre study by the Compagnons Hépato-Bilaires group [129]. Twelve patients transplanted for CRLM at centres in Lisbon, Coimbra, Paris and Geneva between 1995 and 2015 were included in this study. Most patients had prior liver resections and chemotherapy although this was by no means standardised. The 5-year overall and disease-free survival was 50% and 38% respectively. Similar to the Norwegian study, a large proportion of recurrent deposits were in the lungs but recurrences were managed mostly with palliative chemotherapy. The group found that transplants which were preceded by liver resection and chemotherapy as part of a long-term treatment strategy demonstrated lower recurrence rates compared to "compassionate" transplants performed upfront or as salvage procedures.

Interestingly, almost 20% of patients in the SECA-1 trial developed arterial complications and half of these patients lost their grafts due to hepatic artery thrombosis, prompting more intensive anticoagulation therapy in this study. Although the authors attributed some of these incidents to the quality of donor hepatic artery or to technical errors, it is plausible that preoperative chemotherapy and the use of Sirolimus as immunosuppressant may have potentially contributed to such complications [130]. That said, no vascular complications were reported in the Compagnons Hépato-Bilaires study despite the majority of this cohort receiving comparable preoperative chemotherapy and immunosuppression.

Both the SECA-I and the Compagnons Hépato-Bilaires study were considered proof of concept studies. These have since been followed through with successive studies by both groups. The SECA-II study (NCT01479608) has been underway since 2011, initially designed as a randomised control trial to compare liver transplantation to best available chemotherapy. However, given the potential advantage shown with transplantation over chemotherapy in the SECA-I study, the objective was shortly amended into an RCT comparing transplantation with liver resection for large volume albeit resectable CRLM (arm A) and two further non-randomised arms investigating the role of patient selection for liver transplantation in metachronous (arm B) and synchronous (arm C) unresectable CRLM with favourable prognostic factors and no extrahepatic disease. Preliminary results from the SECA-II study have been recently presented at the 2018 International Liver Transplant Society congress in Lisbon. Five-year overall survival for 15 patients transplanted with an Oslo score of 0–1 were shown to be comparable to HCC patients transplanted within the Milan criteria and to patients transplanted for non-malignant indications [128]. The Porto Alegre protocol is another ongoing study by the Compagnons Hépato-Bilaires group exploring the survival benefit of patient selection using criteria similar to the SECA-II study but also excludes BRAF-mutant tumours [128].

The apparent survival advantage that liver transplantation confers over modern chemotherapy in unresectable CRLM, is thus far based on a retrospective comparison of data from the SECA-I and the NORDIC VII trial [120,131]. An ongoing French multicentre RCT; the TRANSMET trial (NCT02597348) aims to address this question by comparing chemotherapy alone versus chemotherapy and liver transplantation in unresectable BRAF-wildtype CRLM with no evidence of disease progression on chemotherapy. Furthermore, the SECA-III trial (NCT03494946) currently underway aims to build on the data from the SECA-I study, through a randomised control trial comparing liver transplantation versus chemotherapy or other treatment options (such as TACE or SIRT) in unresectable CRLM with progressive disease on -or intolerance of-first-line chemotherapy. Results from these trials will hopefully provide further clarification on this matter.

In addition to the optimisation of patient selection, various other approaches are currently being considered in order to expand the application of liver transplantation in CRLM and address the issue of organ shortage. One such approach is the utilisation of living donor grafts. A Canadian study (NCT02864485) is currently investigating the role of living donor grafts in unresectable CRLM in patients with stable disease on chemotherapy. Moreover, there has been recent interest in the RAPID concept (resection and partial liver segment 2/3 transplantation with delayed hepatectomy) introduced by the Norwegian group through a case report published in 2015. The technique takes advantage of the normal functioning parenchyma within the tumour liver and involves resection of segments 1–3 in the recipient and orthotopic replacement of these by a segment 2 and 3 allograft. This is subsequently followed by resection of the remnant native liver once the allograft has grown to a sufficient size. A study is currently underway investigating the safety of this procedure and the feasibility of completion hepatectomy within 4 weeks of transplantation for unresectable CRLM (NCT02215889).

Variations of the RAPID concept have also been described by other groups such as the anastomosis of allograft inflow to splenic vessels and outflow to IVC or left renal vein via a conduit following splenectomy without initial partial hepatectomy in order to minimise manipulation of native liver and reduce the number of resection surfaces (RAVAS) [132] or the use of living donor left lateral allograft after recipient full left hepatectomy (segments 1–4) (LD-RAPID) [133]. The German LIVERT(W)OHEAL study has recently commenced recruitment investigating the feasibility and benefit of the RAPID concept using living donors (NCT03488953).

Although pre-transplant chemotherapy is a prerequisite for all the above mentioned completed and ongoing studies on CRLM, the role of chemotherapy post-transplantation remains unclear due to the lack of data. In addition, despite the predominant use of Sirolimus as immunosuppressant in these studies and the limited retrospect data suggesting that immunosuppression does not accelerate metastatic growth [134], the optimal immunosuppression regime for liver transplantation for CRLM is yet to be determined.

It is anticipated that the outcomes from currently ongoing trials over the coming years will demonstrate superiority of liver transplantation over any currently available therapeutic options for unresectable CRLM [128]. It must be stressed that there is currently no evidence to support the use of liver transplant in resectable CRLM although results from the awaited SECA-II trial may shed further light on this topic.

Neuroendocrine liver metastases

The incidence of neuroendocrine neoplasms (NEN) has increased more than six-fold over the past four decades to almost 7 per 100,000 probably due to improved diagnostic methods [135]. About 40–50% of newly diagnosed cases present with distant

metastases, commonly to the liver [136]. Liver metastases are most common in patients with small bowel or pancreatic NEN [137]. Furthermore, around 5–10% of patients present with liver NEN of unknown primary source [89]. The presence of liver metastases has a negative effect on survival, with 5-year overall survival rates reducing dramatically from 75 to 99% in localised disease to 13–54% in the presence of liver metastases [89].

A number of treatment options are available for the management of NEN liver metastases including liver surgery and locoregional or systemic therapies, depending on the number, pattern and pathology of metastatic deposits [136]. Of these options, surgical resection with clear margins is the only means to potentially achieving cure. In reality, only 10–20% of patients with liver metastases are eligible for resection with curative intent. Moreover, cure is seldom realised due to the high incidence of recurrence [137]. Indeed, based on a systematic review in 2012, median 5-year overall and disease-free survival rates were 70.5% and 29% respectively following liver resection with curative intent with a median R0 resection rate of 63% [138].

Distant NEN spread is often confined to the liver [15]. Given that R0 resection confers a better prognosis and that liver resection alone is rarely curative as detailed histological examination frequently reveals more microscopic lesions [139], it follows logically that researchers would turn their attention to liver transplantation as a potential alternative therapeutic option in selected unresectable cases. A recent systematic review eloquently summarises the published evidence on the role of transplantation in NEN liver metastases reporting 5-year survival rates that ranged from 47 to 70.7% (up to 97.2% in single centre series [140]) and recurrence rates between 31.3 and 56.8% [141]. Earlier evidence on this subject was limited to small sample studies in single centres to which the wide variation in outcomes is likely attributed (Supplementary Table 5). Cumulative results from data registries in recent years have shown an improvement in survival outcomes over time [142,143]. The poor results from earlier studies were likely due to suboptimal patient selection.

In 2007, the Milan group proposed a stringent set of criteria for liver transplantation in patients with NEN liver metastases based on experience from previous studies [144]. The Milan NET criteria include a confirmed histological diagnosis of low grade NEN (Ki67 index of less than 10%) regardless of function, a primary tumour (with venous drainage via the portal system) which has been completely resected prior to transplantation, no more than 50% involvement of hepatic parenchyma, responsive or stable disease for at least 6 months prior to transplantation and a recipient age of 55 years or younger (limit later increased to 60 years). Although the evidence underpinning the proposed Milan NET criteria was based largely on non-controlled studies with significant heterogeneity, the group validated the selection criteria through a propensity score-matched prospective study published in 2016 which demonstrated superior survival and disease control in the group transplanted within the set criteria (88.8% 10-year overall survival and 13.1% disease progression compared to 22.4% and 89% respectively in the non-transplant group) [140]. Other reports have also underscored the prognostic value of various components of the Milan NET criteria such as tumour differentiation [145–148], need/extent of extrahepatic resection at the time of transplantation [146,149] and patient age [149], although the significance of some of these factors has been challenged in other reports [150]. Additional factors such as serum bilirubin level [143,151] and vascular or nodal involvement [146] have been suggested as negative prognostic indicators worthy of further validation in future studies.

Notably, a retrospective ELTR-based multicentre study that included 213 metastatic NEN transplant recipients from 35 European transplant centres also showed that poor tumour differentiation and concomitant resection of primary tumour were risk factors associated with reduced survival as was hepatomegaly -a surrogate of parenchymal involvement [142]. Interestingly, the study showed that transplants after 2000 were associated with a significant improvement in 5-year survival (59% compared to 46% before 2000), an observation likely related to progress in patient selection. Consequent to the inclusion of patients with less risk factors in the latter years, recipient age over 45 (rather than tumour differentiation) emerged as a significant poor prognostic factor in the cohort of patients transplanted after 2000. Although survival rates in this study were much lower than those recently reported by the Milan group (59% 5-year overall survival after 2000 compared to 97.2%), the authors advocated a more liberal approach to patient selection wherein isolated risk factors are tolerated arguing that the more strict approach would have denied transplantation to more than one third of their low-risk cohort with no tangible improvement to survival rates. The 5-year overall and disease-free survival rates for recipients with no more than one risk factor were remarkably 79% and 57% respectively. Moreover, a Swedish study that included older patients (up to 64 years) with relatively higher Ki67 index and tumour burden in a small cohort reported an excellent 5-year survival rate of 90%, further questioning the need for strict inclusion criteria [150]. Future prospective studies will be necessary to shed further light on the optimal patient selection criteria for transplantation.

The role of neoadjuvant and/or adjuvant therapy with liver transplantation for NEN metastases remains unclear. No controlled studies addressing this issue have been published to date. A German trial investigating neoadjuvant ^{177}Lutetium-labelled peptide receptor radiotherapy prior to transplantation is currently registered under the ClinicalTrials.gov identifier NCT01201096 but no results from this trial are thus far available.

Currently the role of liver transplantation in NEN liver metastasis remains limited. The most recent ENETS guidelines state that liver transplantation “is an option in highly selected patients, preferably in young patients with functional syndromes demonstrating early resistance to medical therapy” [136]. This is echoed in NANETS guidelines, describing transplantation as “controversial, but may be an option for some patients if the Milan and ENETS criteria are met” [152]. In the US, applications for non-standardised UNOS/OPTN MELD exception points are considered on a case by case basis with guidance largely based on the Milan NET criteria. The restricted role for transplantation is unsurprising given the indolent nature of this disease. No prospective controlled comparison exists between liver transplantation and other treatment modalities for NEN liver metastases to date and the definition of unresectable disease remains unclear particularly in the face of modern surgical approaches and downstaging therapies [137]. Cohort studies of patients within the Milan NET criteria undergoing liver resection demonstrate survival outcomes comparable to liver transplantation and some evidence suggests that current standard multimodal therapy for metastatic NEN is superior to transplantation in younger patients [153,154]. Given that 10-year overall survival rates in such low risk groups exceed 70% in recent studies irrespective of whether resected or transplanted, the advantage of liver transplantation in this setting remains questionable. With the emergence of new and effective therapies, prospective trials comparing transplantation with other therapeutic strategies will be necessary to define the future role of transplantation for this indication.

Liver metastases from other tumours

Few case reports have been published on liver transplantation for metastases from breast [155], gastric [156]and pancreatic pseudopapillary tumours [157–161] in addition to uveal malignant

melanoma [161]and GIST [107,162,163]. The paucity of evidence for liver transplantation for these pathologies precludes any meaningful recommendations being made.

Future challenges

The era of transplant oncology has well and truly begun. And with it, a number of challenges have emerged. One major challenge to transplantation for liver malignancies is the risk of disease progression beyond transplantation whilst on the waiting list particularly in the face of limited availability of deceased donor organs. Given that the background liver function is usually well reserved in many of these patients, they are inherently disadvantaged in current UKELD/MELD-based allocation systems when exception criteria are not applied. This is more evident in liver tumours where transplantation remains an experimental option. Allocation systems will have to adapt in the future as more evidence emerges in this field.

One way of overcoming the challenge of organ availability is through the living donation route. This has a further advantage of optimising the timing of transplantation with the completion of neoadjuvant therapies. However, these advantages should be counterweight by the potential to perform transplants in more aggressive disease in the absence of an appropriate waiting period resulting in lower survival outcomes. From a surgical point of view, innovative methods such as the RAPID technique have been described with the aim of optimising donor organ utilisation in both the deceased and living donor settings. Variations and refinements in some of methods continue to be reported and it will be interesting to see the long term outcomes of these techniques.

As evident from this review, criteria for liver transplantation are continuously changing for various liver malignancies as more evidence becomes available. Optimisation of case selection will likely improve survival outcomes in the future and address many of the ethical considerations in this field, with obvious implications on the evolution of some malignant indications for transplantation from experimental to mainstream application.

A recent meta-analysis has identified a clear recurrence-free survival advantage for using m-TOR inhibitors (sirolimus or everolimus) over calcineurin inhibitors as maintenance immunosuppression after liver transplantation for HCC [164]. However, beyond HCC, there is little evidence to make any recommendation on the superiority of one immunosuppression regime over another in reducing disease recurrence. In particular, the antineoplastic role of m-TOR inhibitors remains unclear. Although m-TOR inhibitors are the predominant immunosuppressants used in liver transplantation for colorectal liver metastases, this has not been based on clinical comparison against standard immunosuppression regimes. Nevertheless, previous concerns regarding the risk of hepatic artery thrombosis with the use of m-TOR inhibitors has not been demonstrated in recent studies [130,164]. On the other hand, calcineurin inhibitors remain commonly used for non-HCC malignant indications and, despite the lack of data, a minimisation strategy is justifiable given the dose dependent risk of recurrence in the case of HCC [165]. The ability to effectively induce immune tolerance in the future will facilitate minimisation or even complete withdrawal of immunosuppressive drugs and further reduce the risk of recurrence.

A number of clinical trials highlighted in this review are currently underway investigating various malignant indications for liver transplantation. In addition, collaborative registries have been setup to improve data collection for rarer tumours. Data from these registries and trials will enable a better understanding of disease process and other aspects such as risk stratification and treatment efficacy which will undoubtedly help to shape the future of transplant oncology.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.07.024.

Declaration of interest

None.

Conflict of interest statement

The authors confirm that there are no known conflicts of interest associated with the submitted manuscript and that it was not influenced as a result of the abovementioned financial support.

References

[1] Durand F. How to improve long-term outcome after liver transplantation? Liver Int 2018;38(Suppl 1):134–8.
[2] Andrassy J, Wolf S, Lauseker M, Angele M, van Rosmalen MD, Samuel U, et al. Higher retransplantation rate following extended right split-liver transplantation: an analysis from the eurotransplant liver follow-up registry. Liver Transplant 2018;24:26–34.
[3] Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Harper AM, et al. OPTN/SRTR 2016 annual data report: liver. Am J Transplant 2018;18(Suppl 1):172–253.
[4] Neuberger J. Liver transplantation in the United Kingdom. Liver Transplant 2016;22:1129–35.
[5] Farkas S, Hackl C, Schlitt HJ. Overview of the indications and contraindications for liver transplantation. Cold Spring Harb Perspect Med 2014;4.
[6] Hibi T, Itano O, Shinoda M, Kitagawa Y. Liver transplantation for hepatobiliary malignancies: a new era of "Transplant Oncology" has begun. Surg Today 2017;47:403–15.
[7] Starzl TE, Groth CG, Brettschneider L, Penn I, Fulginiti VA, Moon JB, et al. Orthotopic homotransplantation of the human liver. Ann Surg 1968;168:392–415.
[8] Pichlmayr R, Weimann A, Oldhafer KJ, Schlitt HJ, Klempnauer J, Bornscheuer A, et al. Role of liver transplantation in the treatment of unresectable liver cancer. World J Surg 1995;19:807–13.
[9] Olthoff KM, Millis JM, Rosove MH, Goldstein LI, Ramming KP, Busuttil RW. Is liver transplantation justified for the treatment of hepatic malignancies? Arch Surg 1990;125:1261–6. discussion 6-8.
[10] Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–9.
[11] Xu X, Lu D, Ling Q, Wei X, Wu J, Zhou L, et al. Liver transplantation for hepatocellular carcinoma beyond the Milan criteria. Gut 2016;65:1035–41.
[12] Silva M, Moya A, Berenguer M, Sanjuan F, Lopez-Andujar R, Pareja E, et al. Expanded criteria for liver transplantation in patients with cirrhosis and hepatocellular carcinoma. Liver Transplant 2008;14:1449–60.
[13] Rea DJ, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. Ann Surg 2005;242:451–8. discussion 8-61.
[14] Andersen MH, Dueland S, Hagness M, Vidnes T, Finstad ED, Wahl AK, et al. Quality of life following liver transplantation in patients with liver metastases from colorectal carcinoma. Scand J Caring Sci 2012;26:713–9.
[15] Lerut J, Foss A. Liver transplantation for secondary liver tumours. Br J Surg 2015;102:1589–90.
[16] Rizvi S, Khan SA, Hallemeier CL, Kelley RK, Gores GJ. Cholangiocarcinoma - evolving concepts and therapeutic strategies. Nat Rev Clin Oncol 2018;15:95–111.
[17] Banales JM, Cardinale V, Carpino G, Marzioni M, Andersen JB, Invernizzi P, et al. Expert consensus document: cholangiocarcinoma: current knowledge and future perspectives consensus statement from the European Network for the Study of Cholangiocarcinoma (ENS-CCA). Nat Rev Gastroenterol

Hepatol 2016;13:261–80.
[18] Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BJ, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001;234:507–17. discussion 17-9.
[19] Nagino M, Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, et al. Evolution of surgical treatment for perihilar cholangiocarcinoma: a single-center 34-year review of 574 consecutive resections. Ann Surg 2013;258:129–40.
[20] Rocha FG, Matsuo K, Blumgart LH, Jarnagin WR. Hilar cholangiocarcinoma: the memorial sloan-Kettering cancer center experience. J Hepato-Biliary-Pancreatic Sci 2010;17:490–6.
[21] Ringe B, Wittekind C, Bechstein WO, Bunzendahl H, Pichlmayr R. The role of liver transplantation in hepatobiliary malignancy. A retrospective analysis of 95 patients with particular regard to tumor stage and recurrence. Ann Surg 1989;209:88–98.
[22] Goldstein RM, Stone M, Tillery GW, Senzer N, Levy M, Husberg BS, et al. Is liver transplantation indicated for cholangiocarcinoma? Am J Surg 1993;166:768–71. discussion 71-2.
[23] Stieber AC, Marino IR, Iwatsuki S, Starzl TE. Cholangiocarcinoma in sclerosing cholangitis. The role of liver transplantation. Int Surg 1989;74:1–3.
[24] Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. Transplantation 2000;69:1633–7.
[25] O'Grady JG, Polson RJ, Rolles K, Calne RY, Williams R. Liver transplantation for malignant disease. Results in 93 consecutive patients. Ann Surg 1988;207:373–9.
[26] Abu-Elmagd KM, Selby R, Iwatsuki S, Fung J, Tzakis A, Todo S, et al. Cholangiocarcinoma and sclerosing cholangitis: clinical characteristics and effect on survival after liver transplantation. Transplant Proc 1993;25:1124–5.
[27] Jonas S, Kling N, Guckelberger O, Keck H, Bechstein WO, Neuhaus P. Orthotopic liver transplantation after extended bile duct resection as treatment of hilar cholangiocarcinoma. First long-terms results. Transpl Int 1998;11(Suppl 1):S206–8.
[28] Seehofer D, Thelen A, Neumann UP, Veltzke-Schlieker W, Denecke T, Kamphues C, et al. Extended bile duct resection and [corrected] liver and transplantation in patients with hilar cholangiocarcinoma: long-term results. Liver Transplant 2009;15:1499–507.
[29] Sansalone CV, Colella G, Caccamo L, Rondinara GF, Fassati LR, Rossetti O, et al. Orthotopic liver transplantation for primary biliary tumors: milan multicenter experience. Transplant Proc 1994;26:3561–3.
[30] Calne R, Yamanoi A, Oura S, Kawamura M. Liver transplantation for hepatocarcinoma. Surg Today 1993;23:1–3.
[31] Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. Surgery 1991;110:726–34. discussion 34-5.
[32] Yokoyama I, Todo S, Iwatsuki S, Starzl TE. Liver transplantation in the treatment of primary liver cancer. Hepato-Gastroenterology 1990;37:188–93.
[33] Shimoda M, Farmer DG, Colquhoun SD, Rosove M, Ghobrial RM, Yersiz H, et al. Liver transplantation for cholangiocellular carcinoma: analysis of a single-center experience and review of the literature. Liver Transplant 2001;7:1023–33.
[34] Pichlmayr R, Weimann A, Klempnauer J, Oldhafer KJ, Maschek H, Tusch G, et al. Surgical treatment in proximal bile duct cancer. A single-center experience. Ann Surg 1996;224:628–38.
[35] Iwatsuki S, Todo S, Marsh JW, Madariaga JR, Lee RG, Dvorchik I, et al. Treatment of hilar cholangiocarcinoma (Klatskin tumors) with hepatic resection or transplantation. J Am Coll Surg 1998;187:358–64.
[36] De Vreede I, Steers JL, Burch PA, Rosen CB, Gunderson LL, Haddock MG, et al. Prolonged disease-free survival after orthotopic liver transplantation plus adjuvant chemoirradiation for cholangiocarcinoma. Liver Transplant 2000;6:309–16.
[37] Zamora-Valdes D, Heimbach JK. Liver transplant for cholangiocarcinoma. Gastroenterol Clin N Am 2018;47:267–80.
[38] Ethun CG, Lopez-Aguiar AG, Anderson DJ, Adams AB, Fields RC, Doyle MB, et al. Transplantation versus resection for hilar cholangiocarcinoma: an argument for shifting treatment paradigms for resectable disease. Ann Surg 2018;267:797–805.
[39] Hong JC, Jones CM, Duffy JP, Petrowsky H, Farmer DG, French S, et al. Comparative analysis of resection and liver transplantation for intrahepatic and hilar cholangiocarcinoma: a 24-year experience in a single center. Arch Surg 2011;146:683–9.
[40] Friman S, Foss A, Isoniemi H, Olausson M, Hockerstedt K, Yamamoto S, et al. Liver transplantation for cholangiocarcinoma: selection is essential for acceptable results. Scand J Gastroenterol 2011;46:370–5.
[41] Mantel HT, Westerkamp AC, Adam R, Bennet WF, Seehofer D, Settmacher U, et al. Strict selection alone of patients undergoing liver transplantation for hilar cholangiocarcinoma is associated with improved survival. PLoS One 2016;11:e0156127.
[42] Welling TH, Feng M, Wan S, Hwang SY, Volk ML, Lawrence TS, et al. Neoadjuvant stereotactic body radiation therapy, capecitabine, and liver transplantation for unresectable hilar cholangiocarcinoma. Liver Transplant 2014;20:81–8.
[43] Mantel HT, Rosen CB, Heimbach JK, Nyberg SL, Ishitani MB, Andrews JC, et al. Vascular complications after orthotopic liver transplantation after neoadjuvant therapy for hilar cholangiocarcinoma. Liver Transplant 2007;13:1372–81.
[44] Rosen CB, Heimbach JK, Gores GJ. Liver transplantation for cholangiocarcinoma. Transpl Int 2010;23:692–7.
[45] Darwish Murad S, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. Gastroenterology 2012;143:88–98. e3; quiz e14.
[46] Rosen CB. Transplantation versus resection for hilar cholangiocarcinoma: an argument for shifting paradigms for resectable disease in annals of surgery 2018. Ann Surg 2018;267:808–9.
[47] Croome KP, Rosen CB, Heimbach JK, Nagorney DM. Is liver transplantation appropriate for patients with potentially resectable de novo hilar cholangiocarcinoma? J Am Coll Surg 2015;221:130–9.
[48] Organ Procurement and Transplantation Network. Policy 9: allocation of livers and liver-intestines. 2018. City.
[49] Hackl C, Schlitt HJ, Kirchner GI, Knoppke B, Loss M. Liver transplantation for malignancy: current treatment strategies and future perspectives. World J Gastroenterol 2014;20:5331–44.
[50] Sapisochin G, Rodriguez de Lope C, Gastaca M, Ortiz de Urbina J, Suarez MA, Santoyo J, et al. Very early" intrahepatic cholangiocarcinoma in cirrhotic patients: should liver transplantation be reconsidered in these patients? Am J Transplant 2014;14:660–7.
[51] Sapisochin G, Facciuto M, Rubbia-Brandt L, Marti J, Mehta N, Yao FY, et al. Liver transplantation for "very early" intrahepatic cholangiocarcinoma: international retrospective study supporting a prospective assessment. Hepatology 2016;64:1178–88.
[52] Facciuto ME, Singh MK, Lubezky N, Selim MA, Robinson D, Kim-Schluger L, et al. Tumors with intrahepatic bile duct differentiation in cirrhosis: implications on outcomes after liver transplantation. Transplantation 2015;99:151–7.
[53] Hu XX, Yan LN. Retrospective analysis of prognostic factors after liver transplantation for intrahepatic cholangiocarcinoma in China: a single-center experience. Hepato-Gastroenterology 2011;58:1255–9.
[54] Takahashi K, Obeid J, Burmeister CS, Bruno DA, Kazimi MM, Yoshida A, et al. Intrahepatic cholangiocarcinoma in the liver explant after liver transplantation: histological differentiation and prognosis. Ann Transplant 2016;21:208–15.
[55] Lunsford KE, Javle M, Heyne K, Shroff RT, Abdel-Wahab R, Gupta N, et al. Liver transplantation for locally advanced intrahepatic cholangiocarcinoma treated with neoadjuvant therapy: a prospective case-series. Lancet Gastroenterol Hepatol 2018;3:337–48.
[56] Lee DD, Croome KP, Musto KR, Melendez J, Tranesh G, Nakhleh R, et al. Liver transplantation for intrahepatic cholangiocarcinoma. Liver Transplant 2018;24:634–44.
[57] Sakamoto Y, Kokudo N, Matsuyama Y, Sakamoto M, Izumi N, Kadoya M, et al. Proposal of a new staging system for intrahepatic cholangiocarcinoma: analysis of surgical patients from a nationwide survey of the Liver Cancer Study Group of Japan. Cancer 2016;122:61–70.
[58] Chang CC, Chen YJ, Huang TH, Chen CH, Kuo FY, Eng HL, et al. Living donor liver transplantation for combined hepatocellular carcinoma and cholangiocarcinoma: experience of a single center. Ann Transplant 2017;22:115–20.
[59] Sapisochin G, de Lope CR, Gastaca M, de Urbina JO, Lopez-Andujar R, Palacios F, et al. Intrahepatic cholangiocarcinoma or mixed hepatocellular-cholangiocarcinoma in patients undergoing liver transplantation: a Spanish matched cohort multicenter study. Ann Surg 2014;259:944–52.
[60] Lunsford KE, Court C, Lee YS, Lu DS, Naini BV, Harlander-Locke MP, et al. Propensity matched analysis of patients with mixed hepatocellular-cholangiocarcinoma and hepatocellular carcinoma undergoing liver transplantation. Liver Transplant 2018;24:1384–97.
[61] Wu D, Shen ZY, Zhang YM, Wang J, Zheng H, Deng YL, et al. Effect of liver transplantation in combined hepatocellular and cholangiocellular carcinoma: a case series. BMC Canc 2015;15:232.
[62] Spector LG, Birch J. The epidemiology of hepatoblastoma. Pediatr Blood Cancer 2012;59:776–9.
[63] Sharma D, Subbarao G, Saxena R. Hepatoblastoma. Semin Diagn Pathol 2017;34:192–200.
[64] Quinn JJ, Altman AJ, Robinson HT, Cooke RW, Hight DW, Foster JH. Adriamycin and cisplatin for hepatoblastoma. Cancer 1985;56:1926–9.
[65] Douglass EC, Green AA, Wrenn E, Champion J, Shipp M, Pratt CB. Effective cisplatin (DDP) based chemotherapy in the treatment of hepatoblastoma. Med Pediatr Oncol 1985;13:187–90.
[66] Czauderna P, Garnier H. Hepatoblastoma: current understanding, recent advances, and controversies. F1000Res 2018;7:53.
[67] Otte JB, de Ville de Goyet J, Reding R. Liver transplantation for hepatoblastoma: indications and contraindications in the modern era. Pediatr Transplant 2005;9:557–65.
[68] Busweiler LA, Wijnen MH, Wilde JC, Sieders E, Terwisscha van Scheltinga SE, van Heurn LW, et al. Surgical treatment of childhood hepatoblastoma in The Netherlands (1990-2013). Pediatr Surg Int 2017;33:23–31.
[69] Trobaugh-Lotrario AD, Meyers RL, Tiao GM, Feusner JH. Pediatric liver transplantation for hepatoblastoma. Transl Gastroenterol Hepatol 2016;1:44.
[70] Czauderna P, Otte JB, Aronson DC, Gauthier F, Mackinlay G, Roebuck D, et al. Guidelines for surgical treatment of hepatoblastoma in the modern era–recommendations from the childhood liver tumour strategy group of the international society of paediatric oncology (SIOPEL). Eur J Cancer 2005;41:1031–6.

[71] Koneru B, Flye MW, Busuttil RW, Shaw BW, Lorber MI, Emond JC, et al. Liver transplantation for hepatoblastoma. The American experience. Ann Surg 1991;213:118–21.
[72] Pham TA, Gallo AM, Concepcion W, Esquivel CO, Bonham CA. Effect of liver transplant on long-term disease-free survival in children with hepatoblastoma and hepatocellular cancer. JAMA Surg 2015;150:1150–8.
[73] Otte JB, Pritchard J, Aronson DC, Brown J, Czauderna P, Maibach R, et al. Liver transplantation for hepatoblastoma: results from the International Society of Pediatric Oncology (SIOP) study SIOPEL-1 and review of the world experience. Pediatr Blood Cancer 2004;42:74–83.
[74] Lautz TB, Ben-Ami T, Tantemsapya N, Gosiengfiao Y, Superina RA. Successful nontransplant resection of POST-TEXT III and IV hepatoblastoma. Cancer 2011;117:1976–83.
[75] Fuchs J, Cavdar S, Blumenstock G, Ebinger M, Schafer JF, Sipos B, et al. POST-TEXT III and IV hepatoblastoma: extended hepatic resection avoids liver transplantation in selected cases. Ann Surg 2017;266:318–23.
[76] Browne M, Sher D, Grant D, Deluca E, Alonso E, Whitington PF, et al. Survival after liver transplantation for hepatoblastoma: a 2-center experience. J Pediatr Surg 2008;43:1973–81.
[77] Srinivasan P, McCall J, Pritchard J, Dhawan A, Baker A, Vergani GM, et al. Orthotopic liver transplantation for unresectable hepatoblastoma. Transplantation 2002;74:652–5.
[78] Otte JB. Pediatric liver transplantation: personal perspectives on historical achievements and future challenges. Liver Transplant 2016;22:1284–94.
[79] Meyers RL, Tiao GM, Dunn SP, Langham Jr MR. Liver transplantation in the management of unresectable hepatoblastoma in children. Front Biosci (Elite Ed) 2012;4:1293–302.
[80] Cheng EY, Busuttil RW. Liver transplantation for pediatric hepatoblastoma and hepatocellular carcinoma: out of the unknown. JAMA Surg 2015;150:1158–9.
[81] Weiss SW, Enzinger FM. Epithelioid hemangioendothelioma: a vascular tumor often mistaken for a carcinoma. Cancer 1982;50:970–81.
[82] Lau K, Massad M, Pollak C, Rubin C, Yeh J, Wang J, et al. Clinical patterns and outcome in epithelioid hemangioendothelioma with or without pulmonary involvement: insights from an internet registry in the study of a rare cancer. Chest 2011;140:1312–8.
[83] Ishak KG, Sesterhenn IA, Goodman ZD, Rabin L, Stromeyer FW. Epithelioid hemangioendothelioma of the liver: a clinicopathologic and follow-up study of 32 cases. Hum Pathol 1984;15:839–52.
[84] Mistry AM, Gorden DL, Busler JF, Coogan AC, Kelly BS. Diagnostic and therapeutic challenges in hepatic epithelioid hemangioendothelioma. J Gastrointest Cancer 2012;43:521–5.
[85] Mehrabi A, Kashfi A, Fonouni H, Schemmer P, Schmied BM, Hallscheidt P, et al. Primary malignant hepatic epithelioid hemangioendothelioma: a comprehensive review of the literature with emphasis on the surgical therapy. Cancer 2006;107:2108–21.
[86] Otrock ZK, Al-Kutoubi A, Kattar MM, Zaatari G, Soweid A. Spontaneous complete regression of hepatic epithelioid haemangioendothelioma. Lancet Oncol 2006;7:439–41.
[87] Makhlouf HR, Ishak KG, Goodman ZD. Epithelioid hemangioendothelioma of the liver: a clinicopathologic study of 137 cases. Cancer 1999;85:562–82.
[88] Ercolani G, Grazi GL, Pinna AD. Liver transplantation for benign hepatic tumors: a systematic review. Dig Surg 2010;27:68–75.
[89] Eghtesad B, Aucejo F. Liver transplantation for malignancies. J Gastrointest Cancer 2014;45:353–62.
[90] Grotz TE, Nagorney D, Donohue J, Que F, Kendrick M, Farnell M, et al. Hepatic epithelioid haemangioendothelioma: is transplantation the only treatment option? HPB (Oxford) 2010;12:546–53.
[91] Ben-Haim M, Roayaie S, Ye MQ, Thung SN, Emre S, Fishbein TA, et al. Hepatic epithelioid hemangioendothelioma: resection or transplantation, which and when? Liver Transplant Surg 1999;5:526–31.
[92] Lerut JP, Orlando G, Adam R, Schiavo M, Klempnauer J, Mirza D, et al. The place of liver transplantation in the treatment of hepatic epitheloid hemangioendothelioma: report of the European liver transplant registry. Ann Surg 2007;246:949–57. discussion 57.
[93] Haberal Reyhan N. Liver transplant for nonhepatocellular carcinoma malignancy. Exp Clin Transplant Off J Middle East Soc Organ Transplant 2017;15:69–73.
[94] Madariaga JR, Marino IR, Karavias DD, Nalesnik MA, Doyle HR, Iwatsuki S, et al. Long-term results after liver transplantation for primary hepatic epithelioid hemangioendothelioma. Ann Surg Oncol 1995;2:483–7.
[95] Rodriguez JA, Becker NS, O'Mahony CA, Goss JA, Aloia TA. Long-term outcomes following liver transplantation for hepatic hemangioendothelioma: the UNOS experience from 1987 to 2005. J Gastrointest Surg 2008;12:110–6.
[96] Lai Q, Feys E, Karam V, Adam R, Klempnauer J, Oliverius M, et al. Hepatic epithelioid hemangioendothelioma and adult liver transplantation: proposal for a prognostic score based on the analysis of the ELTR-ELITA registry. Transplantation 2017;101:555–64.
[97] Rosenberg A, Agulnik M. Epithelioid hemangioendothelioma: update on diagnosis and treatment. Curr Treat Options Oncol 2018;19:19.
[98] Chevreau C, Le Cesne A, Ray-Coquard I, Italiano A, Cioffi A, Isambert N, et al. Sorafenib in patients with progressive epithelioid hemangioendothelioma: a phase 2 study by the French Sarcoma Group (GSF/GETO). Cancer 2013;119:2639–44.
[99] Agulnik M, Yarber JL, Okuno SH, von Mehren M, Jovanovic BD, Brockstein BE, et al. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. Ann Oncol 2013;24:257–63.
[100] Stacchiotti S, Provenzano S, Dagrada G, Negri T, Brich S, Basso U, et al. Sirolimus in advanced epithelioid hemangioendothelioma: a retrospective case-series analysis from the Italian rare cancer network database. Ann Surg Oncol 2016;23:2735–44.
[101] Ceulemans LJ, Strypstein S, Neyrinck A, Verleden S, Ruttens D, Monbaliu D, et al. Combined liver-thoracic transplantation: single-center experience with introduction of the 'Liver-first' principle. Transpl Int 2016;29:715–26.
[102] Desie N, Van Raemdonck DE, Ceulemans LJ, Nevens F, Verslype C, Vansteenbergen W, et al. Combined or serial liver and lung transplantation for epithelioid hemangioendothelioma: a case series. Am J Transplant 2015;15:3247–54.
[103] Tanas MR, Sboner A, Oliveira AM, Erickson-Johnson MR, Hespelt J, Hanwright PJ, et al. Identification of a disease-defining gene fusion in epithelioid hemangioendothelioma. Sci Transl Med 2011;3. 98ra82.
[104] Errani C, Zhang L, Sung YS, Hajdu M, Singer S, Maki RG, et al. A novel WWTR1-CAMTA1 gene fusion is a consistent abnormality in epithelioid hemangioendothelioma of different anatomic sites. Genes Chromosomes Cancer 2011;50:644–53.
[105] Errani C, Sung YS, Zhang L, Healey JH, Antonescu CR. Monoclonality of multifocal epithelioid hemangioendothelioma of the liver by analysis of WWTR1-CAMTA1 breakpoints. Cancer Genet 2012;205:12–7.
[106] Orlando G, Adam R, Mirza D, Soderdahl G, Porte RJ, Paul A, et al. Hepatic hemangiosarcoma: an absolute contraindication to liver transplantation–the European Liver Transplant Registry experience. Transplantation 2013;95:872–7.
[107] Husted TL, Neff G, Thomas MJ, Gross TG, Woodle ES, Buell JF. Liver transplantation for primary or metastatic sarcoma to the liver. Am J Transplant 2006;6:392–7.
[108] Cameron AM, Truty J, Truell J, Lassman C, Zimmerman MA, Kelly Jr BS, et al. Fulminant hepatic failure from primary hepatic lymphoma: successful treatment with orthotopic liver transplantation and chemotherapy. Transplantation 2005;80:993–6.
[109] Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol 2017;3:524–48.
[110] Sun Z, Thacker JM. Contemporary surgical options for metastatic colorectal cancer. Curr Oncol Rep 2015;17:13.
[111] de Haas RJ, Wicherts DA, Andreani P, Pascal G, Saliba F, Ichai P, et al. Impact of expanding criteria for resectability of colorectal metastases on short- and long-term outcomes after hepatic resection. Ann Surg 2011;253:1069–79.
[112] Vigano L, Russolillo N, Ferrero A, Langella S, Sperti E, Capussotti L. Evolution of long-term outcome of liver resection for colorectal metastases: analysis of actual 5-year survival rates over two decades. Ann Surg Oncol 2012;19:2035–44.
[113] Margonis GA, Sergentanis TN, Ntanasis-Stathopoulos I, Andreatos N, Tzanninis IG, Sasaki K, et al. Impact of surgical margin width on recurrence and overall survival following R0 hepatic resection of colorectal metastases: a systematic review and meta-analysis. Ann Surg 2018;267:1047–55.
[114] Little K. Is a surgical CURE in the future for colorectal cancer liver metastasis? Int J Surg Oncol (N Y) 2017;2:e34.
[115] Passot G, Soubrane O, Giuliante F, Zimmitti G, Goere D, Yamashita S, et al. Recent advances in chemotherapy and surgery for colorectal liver metastases. Liver Cancer 2016;6:72–9.
[116] Kopetz S, Chang GJ, Overman MJ, Eng C, Sargent DJ, Larson DW, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol 2009;27:3677–83.
[117] Hoti E, Adam R. Liver transplantation for primary and metastatic liver cancers. Transpl Int 2008;21:1107–17.
[118] Muhlbacher F, Huk I, Steininger R, Gnant M, Gotzinger P, Wamser P, et al. Is orthotopic liver transplantation a feasible treatment for secondary cancer of the liver? Transplant Proc 1991;23:1567–8.
[119] Hagness M, Foss A, Line PD, Scholz T, Jorgensen PF, Fosby B, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg 2013;257:800–6.
[120] Dueland S, Guren TK, Hagness M, Glimelius B, Line PD, Pfeiffer P, et al. Chemotherapy or liver transplantation for nonresectable liver metastases from colorectal cancer? Ann Surg 2015;261:956–60.
[121] Line PD, Hagness M, Dueland S. The potential role of liver transplantation as a treatment option in colorectal liver metastases. Chin J Gastroenterol Hepatol 2018;2018:8547940.
[122] Hagness M, Foss A, Egge TS, Dueland S. Patterns of recurrence after liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg Oncol 2014;21:1323–9.
[123] Dueland S, Foss A, Solheim JM, Hagness M, Line PD. Survival following liver transplantation for liver-only colorectal metastases compared with hepatocellular carcinoma. Br J Surg 2018;105:736–42.
[124] Bjornelv GMW, Dueland S, Line PD, Joranger P, Fretland AA, Edwin B, et al. Cost-effectiveness of liver transplantation in patients with colorectal metastases confined to the liver. Br J Surg 2019;106:132–41.
[125] Kappel S, Kandioler D, Steininger R, Langle F, Wrba F, Ploder M, et al. Genetic

detection of lymph node micrometastases: a selection criterion for liver transplantation in patients with liver metastases after colorectal cancer. Transplantation 2006;81:64–70.
[126] Patel S, McCall M, Ohinmaa A, Bigam D, Dryden DM. Positron emission tomography/computed tomographic scans compared to computed tomographic scans for detecting colorectal liver metastases: a systematic review. Ann Surg 2011;253:666–71.
[127] Grut H, Dueland S, Line PD, Revheim ME. The prognostic value of (18)F-FDG PET/CT prior to liver transplantation for nonresectable colorectal liver metastases. Eur J Nucl Med Mol Imaging 2018;45:218–25.
[128] Andres A, Oldani G, Berney T, Compagnon P, Line PD, Toso C. Transplantation for colorectal metastases: on the edge of a revolution. Transl Gastroenterol Hepatol 2018;3:74.
[129] Toso C, Pinto Marques H, Andres A, Castro Sousa F, Adam R, Kalil A, et al. Liver transplantation for colorectal liver metastasis: survival without recurrence can be achieved. Liver Transplant 2017;23:1073–6.
[130] Massoud O, Wiesner RH. The use of sirolimus should be restricted in liver transplantation. J Hepatol 2012;56:288–90.
[131] Tveit KM, Guren T, Glimelius B, Pfeiffer P, Sorbye H, Pyrhonen S, et al. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. J Clin Oncol 2012;30:1755–62.
[132] Ravaioli M, Fallani G, Cescon M, Prosperi E, De Pace V, Siniscalchi A, et al. Heterotopic auxiliary segment 2-3 liver transplantation with delayed total hepatectomy: new strategies for nonresectable colorectal liver metastases. Surgery 2018;164:601–3.
[133] Konigsrainer A, Templin S, Capobianco I, Konigsrainer I, Bitzer M, Zender L, et al. Paradigm shift in the management of irresectable colorectal liver metastases: living donor auxiliary partial orthotopic liver transplantation in combination with two-stage hepatectomy (LD-RAPID). Ann Surg 2019;270:327–32.
[134] Grut H, Solberg S, Seierstad T, Revheim ME, Egge TS, Larsen SG, et al. Growth rates of pulmonary metastases after liver transplantation for unresectable colorectal liver metastases. Br J Surg 2018;105:295–301.
[135] Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol 2017;3:1335–42.
[136] Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. Neuroendocrinology 2016;103:172–85.
[137] Frilling A, Clift AK. Surgical approaches to the management of neuroendocrine liver metastases. Endocrinol Metab Clin N Am 2018;47:627–43.
[138] Saxena A, Chua TC, Perera M, Chu F, Morris DL. Surgical resection of hepatic metastases from neuroendocrine neoplasms: a systematic review. Surgical oncology 2012;21:e131–41.
[139] Elias D, Lefevre JH, Duvillard P, Goere D, Dromain C, Dumont F, et al. Hepatic metastases from neuroendocrine tumors with a "thin slice" pathological examination: they are many more than you think. Ann Surg 2010;251:307–10.
[140] Mazzaferro V, Sposito C, Coppa J, Miceli R, Bhoori S, Bongini M, et al. The long-term benefit of liver transplantation for hepatic metastases from neuroendocrine tumors. Am J Transplant 2016;16:2892–902.
[141] Moris D, Tsilimigras DI, Ntanasis-Stathopoulos I, Beal EW, Felekouras E, Vernadakis S, et al. Liver transplantation in patients with liver metastases from neuroendocrine tumors: a systematic review. Surgery 2017;162:525–36.
[142] Le Treut YP, Gregoire E, Klempnauer J, Belghiti J, Jouve E, Lerut J, et al. Liver transplantation for neuroendocrine tumors in Europe-results and trends in patient selection: a 213-case European liver transplant registry study. Ann Surg 2013;257:807–15.
[143] Nguyen NT, Harring TR, Goss JA, O'Mahony CA. Neuroendocrine liver metastases and orthotopic liver transplantation: the US experience. Int J Hepatol 2011;2011:742890.
[144] Mazzaferro V, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? J Hepatol 2007;47:460–6.
[145] Frilling A, Malago M, Weber F, Paul A, Nadalin S, Sotiropoulos GC, et al. Liver transplantation for patients with metastatic endocrine tumors: single-center experience with 15 patients. Liver Transplant 2006;12:1089–96.
[146] Sher LS, Levi DM, Wecsler JS, Lo M, Petrovic LM, Groshen S, et al. Liver transplantation for metastatic neuroendocrine tumors: outcomes and prognostic variables. J Surg Oncol 2015;112:125–32.
[147] Rosenau J, Bahr MJ, von Wasielewski R, Mengel M, Schmidt HH, Nashan B, et al. Ki67, E-cadherin, and p53 as prognostic indicators of long-term outcome after liver transplantation for metastatic neuroendocrine tumors. Transplantation 2002;73:386–94.
[148] Grat M, Remiszewski P, Smoter P, Wronka KM, Grat K, Lewandowski Z, et al. Outcomes following liver transplantation for metastatic neuroendocrine tumors. Transplant Proc 2014;46:2766–9.
[149] Mathe Z, Tagkalos E, Paul A, Molmenti EP, Kobori L, Fouzas I, et al. Liver transplantation for hepatic metastases of neuroendocrine pancreatic tumors: a survival-based analysis. Transplantation 2011;91:575–82.
[150] Olausson M, Friman S, Herlenius G, Cahlin C, Nilsson O, Jansson S, et al. Orthotopic liver or multivisceral transplantation as treatment of metastatic neuroendocrine tumors. Liver Transplant 2007;13:327–33.
[151] Nobel YR, Goldberg DS. Variable use of model for end-stage liver disease exception points in patients with neuroendocrine tumors metastatic to the liver and its impact on patient outcomes. Transplantation 2015;99:2341–6.
[152] Howe JR, Cardona K, Fraker DL, Kebebew E, Untch BR, Wang YZ, et al. The surgical management of small bowel neuroendocrine tumors: consensus guidelines of the north American neuroendocrine tumor society. Pancreas 2017;46:715–31.
[153] Norlen O, Daskalakis K, Oberg K, Akerstrom G, Stalberg P, Hellman P. Indication for liver transplantation in young patients with small intestinal NETs is rare? World J Surg 2014;38:742–7.
[154] Ruzzenente A, Bagante F, Bertuzzo F, Aldrighetti L, Campagnaro T, Ercolani G, et al. Liver resection for neuroendocrine tumor liver metastases within milan criteria for liver transplantation. J Gastrointest Surg 2019;23:93–100.
[155] Wilson JM, Carder P, Downey S, Davies MH, Wyatt JI, Brennan TG. Treatment of metastatic breast cancer with liver transplantation. Breast J 2003;9:126–8.
[156] Song XM, Zhan WH, Wang JP, Lan P, He XS, Cai SR, et al. [Radical resection of gastric or colorectal carcinoma combined with liver transplantation for gastric or colorectal carcinoma with multiple hepatic metastases]. Zhonghua Wei Chang Wai Ke Za Zhi 2005;8:419–21.
[157] Lagiewska B, Pacholczyk M, Lisik W, Cichocki A, Nawrocki G, Trzebicki J, et al. Liver transplantation for nonresectable metastatic solid pseudopapillary pancreatic cancer. Ann Transplant 2013;18:651–3.
[158] Dovigo AG, Diaz MB, Gutierrez MG, Selles CF, Grobas JP, Valladares M, et al. Liver transplantation as treatment in a massive metastasis from Gruber-Frantz pancreatic tumor: a case report. Transplant Proc 2011;43:2272–3.
[159] Kocman B, Jadrijevic S, Skopljanac A, Mikulic D, Gustin D, Buhin M, et al. Living donor liver transplantation for unresectable liver metastases from solid pseudo-papillary tumor of the pancreas: a case report. Transplant Proc 2008;40:3787–90.
[160] Sumida W, Kaneko K, Tainaka T, Ono Y, Kiuchi T, Ando H. Liver transplantation for multiple liver metastases from solid pseudopapillary tumor of the pancreas. J Pediatr Surg 2007;42:e27–31.
[161] Zhao J, Yan LN, Li B. Adult-to-adult living donor liver transplantation for malignant metastatic melanoma to the liver. Hepatobiliary Pancreat Dis Int : HBPD INT 2010;9:329–32.
[162] Serralta AS, Sanjuan FR, Moya AH, Orbis FC, Lopez-Andujar R, Pareja EI, et al. Combined liver transplantation plus imatinib for unresectable metastases of gastrointestinal stromal tumours. Eur J Gastroenterol Hepatol 2004;16:1237–9.
[163] Cameron S, Ramadori G, Fuzesi L, Sattler B, Gunawan B, Muller D, et al. Successful liver transplantation in two cases of metastatic gastrointestinal stromal tumors. Transplantation 2005;80:283–4.
[164] Grigg SE, Sarri GL, Gow PJ, Yeomans ND. Systematic review with meta-analysis: sirolimus- or everolimus-based immunosuppression following liver transplantation for hepatocellular carcinoma. Aliment Pharmacol Ther 2019;49:1260–73.
[165] Rodriguez-Peralvarez M, Tsochatzis E, Naveas MC, Pieri G, Garcia-Caparros C, O'Beirne J, et al. Reduced exposure to calcineurin inhibitors early after liver transplantation prevents recurrence of hepatocellular carcinoma. J Hepatol 2013;59:1193–9.
[166] Czauderna P, Haeberle B, Hiyama E, Rangaswami A, Krailo M, Maibach R, et al. The Children's Hepatic tumors International Collaboration (CHIC): novel global rare tumor database yields new prognostic factors in hepatoblastoma and becomes a research model. Eur J Cancer 2016;52:92–101.
[167] Umeda K, Okajima H, Kawaguchi K, Nodomi S, Saida S, Kato I, et al. Prognostic and therapeutic factors influencing the clinical outcome of hepatoblastoma after liver transplantation: a single-institute experience. Pediatr Transplant 2018;22.
[168] Uchida H, Sakamoto S, Sasaki K, Takeda M, Hirata Y, Fukuda A, et al. Surgical treatment strategy for advanced hepatoblastoma: resection versus transplantation. Pediatr Blood Cancer 2018;65. e27383.
[169] Brown J, Perilongo G, Shafford E, Keeling J, Pritchard J, Brock P, et al. Pretreatment prognostic factors for children with hepatoblastoma– results from the International Society of Paediatric Oncology (SIOP) study SIOPEL 1. Eur J Cancer 2000;36:1418–25.
[170] Cruz Jr RJ, Ranganathan S, Mazariegos G, Soltys K, Nayyar N, Sun Q, et al. Analysis of national and single-center incidence and survival after liver transplantation for hepatoblastoma: new trends and future opportunities. Surgery 2013;153:150–9.
[171] Zsiros J, Maibach R, Shafford E, Brugieres L, Brock P, Czauderna P, et al. Successful treatment of childhood high-risk hepatoblastoma with dose-intensive multiagent chemotherapy and surgery: final results of the SIOPEL-3HR study. J Clin Oncol 2010;28:2584–90.
[172] Sakamoto S, Kasahara M, Mizuta K, Kuroda T, Yagi T, Taguchi T, et al. Nationwide survey of the outcomes of living donor liver transplantation for hepatoblastoma in Japan. Liver Transplant 2014;20:333–46.
[173] Pimpalwar AP, Sharif K, Ramani P, Stevens M, Grundy R, Morland B, et al. Strategy for hepatoblastoma management: transplant versus nontransplant surgery. J Pediatr Surg 2002;37:240–5.
[174] Isono K, Ohya Y, Lee KJ, Hashimoto S, Kadohisa M, Sakisaka M, et al. Pretransplant trends in alpha-fetoprotein levels as a predictor of recurrence after living donor liver transplantation for unresectable hepatoblastoma: a single-institution experience. Pediatr Transplant 2018;22. e13221.