Update on liver transplantation for cholangiocarcinoma : a review of the recent literature

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Abstract

Cholangiocarcinoma (CC) represent 3% of all gastrointestinal tumours and can be classified anatomically in 3 types: intrahepatic (ICC), perihilar (PCC) and distal (DCC) cholangiocarcinomas. Resection is the treatment of choice but is only achieved in a few cases (< 20%) because of invasion of the biliary tract and/or vascular structures. The outcome of advanced CC is poor with an overall survival (OS) of maximum 15 months with chemotherapy. In the 1990s, CC was regarded as a contraindication for liver transplantation (LT). LT has recently been proposed as potentially curative option for ICC and PCC. Careful patient selection has changed OS. This article provides an update on current status of LT for patients with unresectable CC. (Acta gastroenterol. belg., **2019**, 82, **417-420**).

Key words : cholangiocarcinoma, liver transplantation, intrahepatic, peri hilar

Diagnosis and staging of cholangiocarcinoma

CC is cancer of the biliary tract which can be classified in 3 types: intrahepatic (ICC), perihilar (PCC) and distal (DCC) cholangiocarcinomas (1). CC represent 3% of all gastrointestinal tumors. Fig. 1A illustrates the distribution of the CCs and Fig. 1B the Bismuth classification of PCC (2). The risk factors for the development of CCA include primary sclerosing cholangitis (PSC), with a prevalence of PCC ranging 5% to 15%, choledocal cystic disease, hepatolithiasis, genetic or epigenetic alterations, infection, metabolic factors and inflammatory status (3). Guidelines for the diagnosis of CC have been proposed (4, 5). Here, we wanted to provide updated data in this field and optimal guidance for our daily practice in accordance with the goal of our national medical Journal (6).

Computed Tomography (CT) might be more accurate than Magnetic Resonance Imaging (MRI) in predicting the resectability of ICC, with an accuracy of up to 88% and a negative predictive value of 85-100% (7). In comparison with MRI, CT seems to be more sensitive in detecting vascular involvement and extrahepatic invasion; therefore, it may be advantageous in the primary staging of ICC (7).

Histological confirmation of malignancy is obtained by percutaneous biopsy of ICC.

PCC is an aggressive malignancy accounting for approximately 60% of CCs (8). For PCC and DCC, endoscopic retrograde cholangiopancreaticography (ERCP) with brushing is used for histological diagnosis.

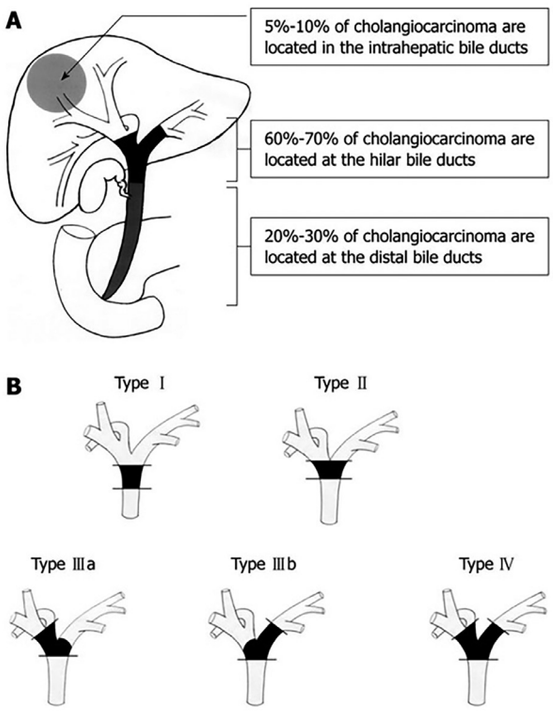

Fig. 1. — Classification of cholangiocarcinoma. (adapted from Akamatsu et al. (2))
A : The majority of cholangiocarcinoma (60%-70%) are perihilar (PCC). The distal bile duct is involved in 20% to 30% of cases, while ICC represent 5% to 10% of the tumors. B : Bismuth-Corlette classification of PCC. Type I, cholangiocarcinoma concerns the common bile duct ; Type II, involves the bifurcation of the common bile duct ; Type IIIa, the bifurcation and the right hepatic duct ; Type IIIb, involves the bifurcation and the left hepatic duct ; Type IV, involves the bifurcation and extends to both the right and left hepatic ducts.

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However, the sensitivity does not exceed 70% despite a specificity of almost 100% when positive (9). Diagnostic procedures for extrahepatic CC include also snare biopsy or Spyscope guided biopsy (Spybite), that reach higher sensitivities (10). Diagnosis and correct staging is complex to establish, especially in case of primary sclerosing cholangitis (PSC). Patients with PSC require close monitoring to detect developing CC (11,12). Many patients with PSC are on the waiting list for LT due to PSC-based cirrhosis formation, unbearable jaundice and itching or recurrent cholangitis. Model for End-Stage Liver Disease (MELD) scores of these patients are usually low, and graft availability may be distant (13). Chest and abdominal imaging by CT and MRI are widely used (14-15). CT and MRI are of equal value regarding the detection of satellite lesions and arterial, portal vein infiltration and LN metastases. CT is performed to exclude systemic disease (16). When both are performed, the accuracy of MRI and CT in predicting resectability exceeds 75% (5). Endoscopic ultrasound (EUS) with sampling of the LN is valuable in the diagnosis and staging of PCC (1).

Laboratory testing including liver function tests and cancer markers such as carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) may help to confirm the diagnosis but a normal value cannot rule out the disease. In addition, high levels often correlate with non resectability, tumor stage, and OS. Level of CA19-9 can be used as prognostic biomarker (17).

18F-Fluorodeoxyglucose-Positron Emission Tomography (18F-FDG-PET) and PET/CT were found to be accurate in the evaluation of primary tumors, lymph node metastasis, and distant metastasis in patients with CCA. 80-90% of ICC are PET avid (18).

Surgery

The preferred modality of treatment is surgery. The goal is to obtain a negative margin (R0) with preservation of adequate size liver remnant and function (19). Extensive surgery protocols have been established.

Routine lymph nodes dissection (LND) should complete the resection of ICC and provide accurate staging to inform discussions about adjuvant therapy (20,21). Excellent outcomes were obtained in negative lymph node (LN) and R0 resections (22). Resection of ICC ≤ 5 cm can achieve 5-year survival rates up to 71% (23).

In PCC, surgery can be performed by the incorporation of extended lobectomy, vascular reconstruction, and preoperative portal vein embolization (24). Surgery is not appropriate in contralateral or bilateral vascular encasement and extension bilaterally to the level of the secondary biliary branches. If the remnant lobe has limited volume, the resectability is achieved by preoperative relief of biliary obstruction and portal vein embolization which leads to compensatory hyperplasia of the contralateral unaffected lobe (15). Careful multi-disciplinary planning from the onset is essential to increase the chances of resectability. However, in many cases, surgical resection is not possible because of the invasion of a main biliary tract or of vascular structure (22).

In general, CA 19-9 > 100 U/mL is associated with higher recurrence risk (16). From time of recurrence, OS was worse among patients who had early versus late recurrence (25).

Long-term survival remains limited despite the development of perioperative radiochemotherapy for PCC (18).

Liver transplantation as a therapeutic option for intrahepatic cholangiocarcinoma (ICC)

LT for CC remains controversial. ICC has been considered as an absolute contraindication (26). LT may become an option for patients with very early stage ICC (27). Identifying the right patients for whom acceptable results are possible becomes the challenge (23). A large multicenter international retrospective study in a cohort from 17 large institutions worldwide confirmed that patients who are diagnosed with a very early ICC (< 2cm) at explant pathology have an acceptable 5-year OS and a low recurrence rate after LT (28). Further investigations regarding the genetic polymorphisms and the risk of ICC are mandatory (1). Cirrhotic patients with ICC ≤2 cm achieved excellent 5-year OS, and validation of these findings by other groups may change the current exclusion of such patients from transplant programs (29**).**

Statistically significant independent predictors of diminished survival include multifocal tumors, perineural invasion, infiltrative subtype, and lack of neoadjuvant/adjuvant therapies (27) Moreover, tumor exceeding 3 cm, positive regional LN, or other metastases remain absolute contraindications (24). Also, it is unclear if by using chemoradiation protocols, LT could be offered to patients with a >2 cm ICC (28). The ubiquitous organ shortage has prompted graft allocation to patients with potentially higher survival chances (11).

Liver transplantation as a therapeutic option for Perihilar cholangiocarcinoma (PCC)

No prospective or randomized trial exists over the benefit of LT for PCC. However, excellent results of LT for selected patients has been described (30, 31).

Selection and application of the Mayo protocol led to a better OS. LT became an option for selected patients with very early stage unresectable PCC. Neoadjuvant chemoradiotherapy followed by LT offered the best outcomes for selected patients with PCC following the Mayo protocol. (32-34). 5-year survival rates of approximately 65% to 70% have been described (35-37). However, from the beginning, the question has emerged in the literature whether the strict selection that is applied to enter the protocol is more important for the success of the program than the neo-adjuvant chemoradiotherapy

Table 1. — **Mayo clinic criteria for inclusion in the transplantation protocol for hilar cholangiocarcinoma adapted from Mantel *et al.* (39)**

Diagnosis	Pathologically confirmed hilar cholangiocarcinoma or CA19-9 >100 ng/ml in the presence of a radiographically malignant stricture
Tumor	Tumor size < 3 cm
Distant metastases	Absence of distant metastases on CT (and/or MRI) and isotope bone scan
Lymph node metastases	Negative EUS-FNA of regional lymph nodes and negative staging laparotomy/hand-assisted-laparoscopy with biopsy of regional lymph nodes

Table 2. — **1-, 3-, 5-year survival from Retrospective Studies Including Patients Transplanted for Both ICC and PCC, adapted from Goldaracena *et al.* (35)**

Ref	Center	Study Type	Total Number of Patients	1-Year Os (%)	3-Year OS (%)	5-Year OS (%)	Neoadjuvant Chemotherapy with or without Radiation Therapy
O'Grady *et al.* 52 (1988)	King's College	Retrospective	13 PCC 13 ICC	38	10	10	No
Yokayama *et al.* 57 (1990)	University of Pittsburgh	Retrospective	19 PCC 2 ICC	24 50	24 0	0 -	No
Meyer *et al.* 58 (2000)	Cincinnati Transplant Tumor Registry	Retrospective Multicenter	207	72	48	23	No
Shimoda *et al.* 59 (2001)	UCLA	Retrospective	9 PCC 16 ICC	86 62	31 39	-	4 patients
Robles *et al.* 56 (2004)	Spain	Retrospective Multicenter	36 PCC 23 ICC	82 77	53 65	30 42	No
Ghali *et al.* 60 (2005)	Canada	Retrospective Multicenter	10	-	30	-	No
Hong *et al.* 9 (2011)	UCLA	Retrospective comparing resection x LT	132	-	38	32	Yes
Panjala *et al.* 61 (2012)	Mayo	Retrospective	22	90	63	-	Yes
Duignan *et al.* 19 (2014)	Dublin	Retrospective	27	73	73	61 (4 years)	Yes

itself. One of the unanswered questions is if as with PCC and the Mayo protocol, these patients will require neoadjuvant chemoradiation. The guidelines of the European Association for the Study of the Liver (EASL) recommend LT for perihilar cholangiocarcinoma that could be offered in centres with clinical research protocols employing adjuvant or neoadjuvant therapy (38). The strict selection of the patients is mandatory and this study suggests that, with strict selection alone (28 patients from initially 153 patients out the European Liver Transplant Registery (ELTR)) following the Mayo Clinic protocol (Table 1) (39), improved survival after transplantation can be achieved. Patients who complied with the Mayo Clinic criteria showed a significant better survival compared to patients not complying with the Mayo selection criteria. The 5-year survival rate was 59% in group A versus 21% in group B (P = 0.001).

Although the results should be cautiously interpreted, this study suggests that with strict selection alone, improved survival after transplantation can be achieved, approaching the Mayo Clinic experience. An arbitrary threshold of >50% 5-year overall survival (OS) is broadly considered a minimum standard for LT (40). This will need to be studied in the near future to better understand and improve the management of patients with cirrhosis diagnosed with CCA.

Conclusion

ICC and PCC can be cured by surgery. However, in many cases of PCC, complete surgical resection cannot be achieved because of local invasion. LT is an option in highly selected patients, if the staging excludes extrahepatic metastases, vascular invasion and absence of LN invasion. Measurement of CA 19.9 and CEA has a prognostic value. Some patients with early stage PCC may be suitable candidates for LT, but selection criteria similar to the modified treatment protocol of the Mayo group should be adopted. The results of ongoing prospective studies will be of great interest. Although a subgroup of patients with CC can benefit from LT, patients with ICC > 2cm, PCC ≥ 3cm, multifocal disease, metastatic extension or LN extension should not be considered for LT. In view of the resectability of small CC and the donor shortage, resection will remain the first choice.

Conflict of interest

None

References

1. RIZVI S., GORES G.J. Pathogenesis, diagnosis, and management of cholangiocarcinoma. *Gastroenterology*, 2013, **145** : 1215-1229.
2. AKAMATSU N., SUGAWARA Y., HASHIMOTO D. Surgical strategy for bile duct cancer: Advances and current limitations. *World J. Clin. Oncol.,* 2011, **2** : 94-107.
3. FORNER A., VIDILI G., RENGO M. *et al.* A. Clinicalpresentation, diagnosis and staging of cholangiocarcinoma. *Liver Int.*, 2019, **00** : 1-10.
4. BRIDGEWATER J., GALLE P.R., KHAN S.A. *et al.* Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J. Hepatol.,* 2014, **60** : 1268-89.
5. MANSOUR J.C., ALOIA T.A., CRANE C.H. *et al.* Hilar cholangiocarcinoma : expert consensus statement. *HPB*, 2015, **17** : 691-9.
6. MOREELS T.G., LANTHIER N. Editorial : the quest for quality. *Acta Gastroenterol. Belgica,* 2018, **81** : 3-4
7. OLTHOF S.C., OTHMAN A., CLASEN S. *et al.* Imaging of cholangiocarcinoma. *Visc. Med.*, 2016, **32** : 402-410.
8. ETHUN C.G., LOPEZ-AGUIAR A.G., ANDERSON D.J. *et al.* Transplantation versus Resection for Hilar Cholangiocarcinoma : An Argument for Shifting Treatment Paradigms for Resectable Disease. *Ann. Surg*., 2018, **267** : 797-805.
9. BRANDI G., VENTURI M., PANTALEO M.A. *et al.* Cholangiocarcinoma : Current opinion on clinical practice diagnostic and therapeutic algorithms : A review of the literature and a long-standing experience of a referral center. *Dig. Liver Dis*., 2016, **48** : 231-41
10. OGAWA T., ITO K., KOSHITA S. *et al.* Usefulness of cholangioscopic-guided mapping biopsy using SpyGlass DS for preoperative evaluation of extrahepatic cholangiocarcinoma : a pilot study. *Endosc. Int. Open*., 2018, **6** : E199-E204.
11. RIZVI S., EATON J.E., GORES G.J. Primary Sclerosing Cholangitis as a Premalignant Biliary Tract Disease : Surveillance and Management. *Clin. Gastroenterol. Hepatol*., 2015, **13** : 2152-65.
12. QUINN L.M., DUNNE D.F.J., JONES R.P. *et al.* Optimal perioperative care in peri-hilar cholangiocarcinoma resection. *Eur. Surg.,* 2018, **50** : 93-99.
13. RAZUMILAVA N., GORES G.J. Surveillance for Cholangiocarcinoma in Patients with Primary Sclerosing Cholangitis: Effective and Justified? *Clin. Liver Dis*., 2016, **8** : 43-47.
14. TRILIANOS P., SELARU F., LIZ. *et al.* Trends in pre-liver transplantscreening for cholangiocarcinoma among patients with primary sclerosing cholangitis. *Digestion,* 2014, **89** : 165-73.
15. RAZUMILAVA N., GORES G.J. Cholangiocarcinoma. *Lancet,* 2014, **383** : 2168-79.
16. BARTELLA I., DUFOUR J.F. Clinical Diagnosis and Staging of Intrahepatic Cholangiocarcinoma. *J. Gastrointestin. Liver Dis.,* 2015, **24** : 481-9.
17. ZHI-HENG L., ZHONG C., LONG-LE M. *et al.* Factors influencing the prognosis of patients with intrahepatic cholangiocarcinoma. *Acta Gastroenterol. Belgica*., 2012, **75** : 215-18
18. HU J.H., TANG J.H., LIN C.H. *et al.* Preoperative staging of cholangiocarcinoma and biliary carcinoma using 18F-fluorodeoxyglucose positron emission tomography : a meta-analysis. J. *Investig. Med*., 2018, **66** : 52-61.
19. WAISBERG D.R., PINHEIRO R.S., NACIF L.S. *et al.* Resection for intrahepatic cholangiocellular cancer: new advances. *Transl. Gastroenterol. Hepatol*., 2018, **3** : 60.
20. SQUIRES M.H., CLOYD J.M., DILLHOFF M. *et al.* Challenges of surgical management of intrahepatic cholangiocarcinoma. *Expert Rev. Gastroenterol. Hepatol.,* 2018, **12** : 671-681.
21. ZHANG X.F., CHAKEDIS J., BAGANTE F. *et al.* Trends in use of lymphadenectomy in surgery with curative intent for intrahepatic cholangiocarcinoma. *Br. J. Surg.,* 2018, **105** : 857-866.
22. SCHMEDING M., NEUMANN U.P. Liver Transplant for Cholangiocarcinoma : A Comeback? *Exp. Clin. Transplant*., 2015, **13** : 301-8. Review.
23. TARCHI P., TABRIZIAN P., PRIGOFF J. *et al.* Outcomes of resection for solitary ≤5 cm intrahepatic cholangiocarcinoma. *Surgery,* 2018, **163** : 698-702.
24. RAZUMILAVA N., GORES G.J. Cholangiocarcinoma. *Lancet*, 2014, **383** : 2168-79
25. ZHANG X.F., BEAL E.W., BAGANTE F. *et al.* Early versus late recurrence of intrahepatic cholangiocarcinoma after resection with curative intent. *Br. J. Surg*., 2018, **105** : 848-856
26. HASHIMOTO K., MILLER C.M. Liver transplantation for intrahepatic cholangiocarcinoma. *J. Hepatobiliary Pancreat. Sci.,* 2015, **22** : 138-43.
27. ZAMORA-VALDES D., HEIMBACH J.K. Liver Transplant for Cholangiocarcinoma. *Gastroenterol. Clin. North Am.,* 2018, **47** : 267-280.
28. SALGIA R.J., SINGAL A.G., FU S. *et al.* Improved post-transplant survival in the United States for patients with cholangiocarcinoma after 2000. *Dig. Dis. Sci.,* 2014, **59** : 1048-54.
29. SAPISOCHIN G., FACCIUTO M., RUBBIA-BRANDT L. *et al.* Liver transplantation for "very early" intrahepatic cholangiocarcinoma : International retrospective study supporting a prospective assessment. *Hepatology,* 2016, **64** : 1178-88.
30. RIZVI S., KHAN S.A., HALLEMEIER C.L. *et al.* Cholangiocarcinoma-evolving concepts and therapeutic strategies. *Nat. Rev. Clin. Oncol*., 2018, **15** : 95-111.
31. ROBLES R., SÁNCHEZ-BUENO F., RAMÍREZ P. *et al.* Liver transplantation for hilar cholangiocarcinoma. *World J. Gastroenterol.*, 2013, **19** : 9209-15.
32. BLECHACZ B. Cholangiocarcinoma : Current Knowledge and New Developments. *Gut Liver,* 2017, **11** : 13-26.
33. WELLING T.H., FENG M., WAN S. *et al.* Neoadjuvant stereotactic body radiation therapy, capecitabine, and liver transplantation for unresectable hilar cholangiocarcinoma. *Liver Transplant*., 2014, **20** : 81-8.
34. DUIGNAN S., MAGUIRE D., RAVICHAND C.S. *et al.* Neoadjuvant chemoradio-therapy followed by liver transplantation for unresectable cholangiocarcinoma : a single-centre national experience. *HPB (Oxford),* 2014, **16** : 91-8.
35. GOLDARACENA N., GORGEN A., SAPISOCHIN G. Current status of liver transplantation for cholangiocarcinoma. *Liver Transpl*., 2018, **24** : 294-303.
36. ZILBERT N., SAPISOCHIN G. Time to reconsider liver transplantation for intrahepatic cholangiocarcinoma? *Lancet Gastroenterol. Hepatol*., 2018, **3** : 294-295.
37. DEOLIVEIRA M.L., KAMBAKAMBA P., CLAVIEN P.A. Advances in liver surgery for cholangiocarcinoma. *Curr. Opin. Gastroenterol.,* 2013, **29**: 293-8.
38. European Association for the Study of the Liver. EASL Clinical Practice Guidelines : Liver transplantation. *J. Hepatol.*, 2015.
39. MANTEL H.T., WESTERKAMP A.C., ADAM R. *et al.* European Liver and Intestine Transplant Association (ELITA). Strict Selection Alone of Patients Undergoing Liver Transplantation for Hilar Cholangiocarcinoma is Associated with Improved Survival. *PLoS One*, 2016, **11** : e0156127.
40. SCHAEFER B., ZOLLER H., SCHNEEBERGER S. Con : Liver transplantation for expanded criteria malignant diseases. *Liver Transpl*., 2018, **24** : 104-111.